FULL PAPER

BJC

British Journal of Cancer (2013) 108, 727–734 | doi: 10.1038/bjc.2013.2

Keywords: risk factors; uterine sarcoma; pooled analysis; obesity; diabetes

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) $\geqslant 30$ *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 ($\geqslant 15$ 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.

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Received 8 October 2012; revised 13 December 2012; accepted 16 December 2012; published online 24 January 2013

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 most 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 progestin, 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 metaplastic 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 aetiologic 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 (SECS)). 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 coordinating 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 progestin 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 $\geqslant$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 adenocarcinoma, NOS cases and were excluded from analysis.

Statistical methods. Categories for exposure variables were created including age ($\leqslant$54, 55–59, 60–64, 65–69, $\geqslant$70 years), race (White, Black, Asian, other), BMI ($<$25, 25–30, $\geqslant$30 kg m^{-2}), age at menarche ($<$11, 11–12, 13–14, $\geqslant$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, $\geqslant$5 live births), smoking status (never, former, current), menopausal hormone use (never, ever), menopausal oestrogen use (never, ever), menopausal oestrogen plus progestin 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.

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, race, clinic
Nurses' Health Study (NHS)[a]	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 (BWHS)[b]	7	6	—	52	1995	Birth year, cohort entry, menopausal status, 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)[c]	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).
[a]The NHS combined endometrioid endometrial carcinoma and adenocarcinoma cases in one group.
[b]The BWHS only submitted patients with uterine sarcoma, malignant mixed mullerian tumours and matched controls to the Epidemiology of Endometrial Cancer Consortium (E2C2).
[c]The CTS data include only participants in a nested case–control study of endometrial cancer.

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 < 0.05 indicated the magnitude of effect for a particular risk factor was significantly different between case groups. Between-study 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 α 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).

RESULTS

A total of 229 uterine sarcomas, 244 MMMTs, 7623 EECs, and 28 829 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 tabled), 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 tabled). 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 $\geqslant 15$ 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 tabled), whereas median age at diagnosis was similar (61.8 and 63.6 years, respectively, data not tabled). 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).

DISCUSSION

The present pooled analysis examined the association between previously identified endometrial carcinoma risk factors—including reproductive, hormonal, and anthropometric factors—and uterine sarcoma, a rare yet fatal uterine cancer subtype. Our data suggest that uterine sarcoma shares certain risk factors with EECs but less so with MMMTs. Similar to EEC, obesity and history of diabetes were linked with an increased risk of uterine sarcoma, while older age at menarche was associated with decreased risk. Subtype analyses of endometrial stromal sarcoma and leiomyosarcoma generally revealed risk factor associations similar to those observed for all uterine sarcomas combined.

Uterine sarcomas fall under the broad category of soft tissue sarcomas, which are extremely rare regardless of the site of origin. Previously documented risk factors for this heterogeneous group of tumours include ionising radiation, exposure to certain chemicals, and genetic syndromes, such as neurofibromatosis type 1 and Li-Fraumeni syndrome (Skubitz and D'Adamo, 2007). Uterine sarcomas have been particularly difficult to examine owing to changes in classification over time, histological diversity, and low incidence rates. In 2009, the International Federation of Gynaecology and Obstetrics reclassified MMMTs, which at the time was the most common uterine sarcoma histology subtype (40%), as a metaplastic endometrial carcinoma. Moreover, the remaining uterine sarcoma subtypes—leiomyosarcoma, endometrial stromal sarcoma, adenosarcoma, and undifferentiated sarcoma—are a heterogeneous group, which complicates the study of their aetiology. The two most common subtypes now, leiomyosarcoma and endometrial stromal sarcoma, can be distinguished by their sarcomatous appearance during histology examination. However, expert pathologists are needed for the correct classification of these subtypes (Chu *et al*, 2001).

Our results support findings from some previous studies on risk factors for specific histological subtypes of uterine sarcoma. In a case–control study (167 cases, 208 controls), Schwartz *et al* (1991, 1996) reported on uterine sarcoma subtype risks associated with exogenous hormone use, obesity, smoking, and menstrual and reproductive characteristics. As in our study, high BMI was associated with increased risks of endometrial stromal sarcoma ($n = 26$), while the risk of leiomyosarcoma ($n = 56$) was lower among cigarette smokers than never smokers. Although we observed inverse associations with current smoking status for uterine sarcoma overall (OR: 0.88) and for leiomyosarcoma (OR: 0.75), these associations did not achieve statistical significance. Prior reports also suggest decreased uterine sarcoma risk associated with older age at menarche (Kvale *et al*, 1988; Schwartz *et al*, 1991), which was apparent in our study for uterine sarcoma risk overall and of the endometrial stromal sarcoma subtype. Parity was associated with decreased uterine sarcoma risk in a prior study (Kvale *et al*, 1988); however, our results concur with two other reports that did not observe clear associations with any live births, the number of live births, and uterine sarcoma risk (Schwartz and Thomas, 1989; Schwartz *et al*, 1991).

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 aetiologic 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

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

Characteristics[a]	Controls *n* = 28 829		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*-heterogeneity[c]
Body mass index												0.01
Normal weight (<25 kg m^{-2})	14 244	49.4	96	41.9	1.00	75	30.7	1.00	2675	35.1	1.00	
Overweight (25–30 kg m^{-2})	9044	31.4	62	27.1	1.04 (0.75, 1.45)	75	30.7	1.34 (0.97, 1.87)	2246	29.5	1.37 (1.28, 1.46)	
Obese (⩾30 kg m^{-2})	4932	17.1	60	26.2	1.73 (1.22, 2.46)	84	34.4	2.25 (1.60, 3.15)	2479	32.5	3.03 (2.82, 3.26)	
P-trend[d]					0.008			0.0001			0.0001	
Age at menarche												0.68
<11	1252	4.3	13	5.7	1.00	10	4.1	1.00	434	5.7	1.00	
11–12	10 408	36.1	98	42.8	1.14 (0.63, 2.06)	109	44.7	1.52 (0.79, 2.93)	2807	36.8	0.86 (0.76, 0.98)	
13–14	12 808	44.4	88	38.4	0.87 (0.47, 1.59)	103	42.2	1.34 (0.69, 2.60)	3190	41.8	0.78 (0.69, 0.89)	
⩾15	4103	14.2	23	10.0	0.70 (0.34, 1.44)	19	7.8	0.88 (0.40, 1.91)	1136	14.9	0.63 (0.54, 0.72)	
P-trend[d]					0.04			0.18			0.0001	
Parity												0.61
Nulliparous	3234	11.2	32	14.0	1.00	40	16.4	1.00	1266	16.6	1.00	
Parous	24 912	86.4	186	81.2	0.87 (0.58, 1.30)	198	81.1	0.67 (0.47, 0.96)	6152	80.7	0.64 (0.59, 0.69)	
Number of live births (among parous women)												0.10
1	3621	15.4	30	16.1	1.00	15	7.6	1.00	1351	22.0	1.00	
2	7805	31.3	58	31.2	1.06 (0.66, 1.70)	59	29.8	1.76 (0.99, 3.14)	2061	33.5	0.87 (0.79, 0.95)	
3–4	10 040	40.3	80	43.0	1.12 (0.70, 1.78)	88	44.4	1.66 (0.95, 2.91)	2169	35.3	0.72 (0.65, 0.78)	
⩾5	3446	13.8	18	9.7	0.62 (0.33, 1.17)	36	18.2	1.31 (0.71, 2.44)	571	9.3	0.52 (0.46, 0.58)	
P-trend[d]					0.31			0.78			0.0001	
Menopausal status												0.33
Premenopausal	4015	13.9	54	23.6	1.00	14	5.7	1.00	1189	15.6	1.00	
Peri-menopausal	281	1.0	2	0.9	0.66 (0.13, 3.28)	1	0.4	0.50 (0.06, 4.01)	92	1.2	1.00 (0.76, 1.31)	
Postmenopausal	23 826	82.6	154	67.2	0.84 (0.54, 1.31)	221	90.6	1.46 (0.75, 2.87)	6152	80.7	0.94 (0.84, 1.04)	
Menopausal hormone use[e]												0.002
Never	14 179	59.5	68	44.2	1.00	133	60.2	1.00	3497	56.8	1.00	
Ever	9375	39.3	78	50.6	1.54 (0.82, 2.87)	84	38.0	0.98 (0.59, 1.62)	2605	42.3	1.64 (1.47, 1.84)	
Menopausal oestrogen-alone use[f]												0.88
Never	15 019	76.9	95	68.8	1.00	132	74.6	1.00	3740	73.8	1.00	
Ever	2878	14.7	23	16.7	1.13 (0.56, 2.28)	31	17.5	1.43 (0.66, 3.10)	931	18.4	1.13 (0.95, 1.33)	

Table 2. (Continued)

Characteristics[a]	Controls *n* = 28 829		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*-heterogeneity[c]**
Menopausal oestrogen plus progestin[g]												0.40
Never	11 390	69.7	70	55.1	1.00	115	71.9	1.00	2975	70.1	1.00	
Ever	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)	
Oral contraceptive use												0.37
Never	17 894	62.1	127	55.5	1.00	85	34.8	1.00	5201	71.6	1.00	
Ever	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)	
Smoking status[h]												0.50
Never	14 926	52.6	122	56.2	1.00	128	55.2	1.00	4559	63.4	1.00	
Former	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)	
Current	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)	
History of diabetes[i]												0.09
No	15 889	62.8	108	57.4	1.00	128	57.9	1.00	4288	65.5	1.00	
Yes	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)	

Abbreviations: CI = confidence interval; E2C2 = 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]Polytmous 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 caluclated 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

			Histological subtypes of uteirne sarcoma						
	Controls		Endometrial stromal sarcoma			Leiomyosarcoma			
Characteristics[a]	***n* = 28 829**		***n* = 98**			***n* = 82**			
	n	**%**	***n***	**%**	**OR (95% CI)**[b]	***n***	**%**	**OR (95% CI)**[b]	***P*-heterogeneity**[c]
Body mass index									0.39
Normal weight (<25 kg m^{-2})	14 244	49.4	42	42.9	1.00	33	40.2	1.00	
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)	
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)	
P-trend[d]					0.07			0.26	
Age at menarche									0.10
<11	1252	4.3	7	7.1	1.00	6	7.3	1.00	
11–12	10 408	36.1	39	39.8	0.88 (0.39, 2.01)	38	46.3	1.10 (0.44, 2.73)	
13–14	12 808	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)	
P-trend[d]					0.41			0.44	
Parity									0.40
Nulliparous	3234	11.2	11	11.2	1.00	12	14.6	1.00	
Parous	24 912	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	10 040	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)	
P-trend[d]					0.31			0.12	
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	23 826	82.6	70	71.4	0.85 (0.42, 1.72)	50	61.0	0.35 (0.16, 0.75)	
Menopausal hormone use[e]									0.98
Never	13 412	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[f]									0.97
Never	15 019	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	1.63 (0.18, 14.95)	
Menopausal oestrogen plus progestin[g]									0.72
Never	11 390	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	17 894	62.1	52	53.1	1.00	44	53.7	1.00	
Ever	10 670	37.0	44	56.4	0.85 (0.53, 1.34)	36	43.9	0.72 (0.44, 1.19)	
Smoking status[h]									0.22
Never	14 926	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[i]									0.65
No	15 889	62.8	47	64.4	1.00	33	48.5	1.00	
Yes	1583	6.3	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.

[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, 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 endometrial stromal sarcoma cases as the 'controls'.

[d]*P*-values for trend caluclated 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.

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.

ACKNOWLEDGEMENTS

This research was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

REFERENCES

Audet-Walsh E, Lepine J, Grégoire J, Plante M, Caron P, Têtu B, Ayotte P, Brisson J, Villeneuve L, Bélanger A, Guillemette C (2011) Profiling of endogenous estrogens, their precursors, and metabolites in endometrial cancer patients: association with risk and relationship to clinical characteristics. *J Clin Endocrinol Metab* **96**(2): E330–E339.

Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, Olsen JH, Mellemkjaer L (2005) Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. *Cancer Epidemiol Biomarkers Prev* **14**(12): 2929–2935.

Brooks SE, Zhan M, Cote T, Baquet CR (2004) Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989–1999. *Gynecol Oncol* **93**(1): 204–208.

Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* **4**(8): 579–591.

Chiang S, Oliva E (2011) Cytogenetic and molecular aberrations in endometrial stromal tumors. *Hum Pathol* **42**(5): 609–617.

Chu PG, Arber DA, Weiss LM, Chang KL (2001) Utility of CD10 in distinguishing between endometrial stromal sarcoma and uterine smooth muscle tumors: an immunohistochemical comparison of 34 cases. *Mod Pathol* **14**(5): 465–471.

D'Angelo E, Prat J (2010) Uterine sarcomas: a review. *Gynecol Oncol* **116**(1): 131–139.

Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, Stegger J, Overvad K, Chabbert-Buffet N, Jimenez-Corona A, Clavel-Chapelon F, Rohrmann S, Teucher B, Boeing H, Schütze M, Trichopoulou A, Benetou V, Lagiou P, Palli D, Berrino F, Panico S, Tumino R, Sacerdote C, Redondo ML, Travier N, Sanchez MJ, Altzibar JM, Chirlaque MD, Ardanaz E, Bueno-de-Mesquita HB, van Duijnhoven FJ, Onland-Moret NC, Peeters PH, Hallmans G, Lundin E, Khaw KT, Wareham N, Allen N, Key TJ, Slimani N, Hainaut P, Romaguera D, Norat T, Riboli E, Kaaks R (2010) Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. *Endocr Relat Cancer* **17**(4): 1007–1019.

Harlow BL, Weiss NS, Lofton S (1986) The epidemiology of sarcomas of the uterus. *J Natl Cancer Inst* **76**(3): 399–402.

Hosmer DaL. Stanley (2000) *Applied Logistic Regression*. John Wiley & Sons, INC.: New York.

Jaakkola S, Lyytinen HK, Pukkala E, Ylikorkala O (2011) Use of estradiol-progestin therapy associates with increased risk for uterine sarcomas. *Gynecol Oncol* **122**(2): 260–263.

Koivisto-Korander R, Martinsen JI, Weidepass E, Leminen A, Pukkala E (2012) Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. *Maturitas* **72**(1): 56–60.

Kvale G, Heuch I, Ursin G (1988) Reproductive factors and risk of cancer of the uterine corpus: a prospective study. *Cancer Res* **48**(21): 6217–6221.

Lavie O, Barnett-Griness O, Narod SA, Rennert G (2008) The risk of developing uterine sarcoma after tamoxifen use. *Int J Gynecol Cancer* **18**(2): 352–356.

McCluggage WG (2002) Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. *Int J Gynecol Cancer* **12**(6): 687–690.

Oh JC, Wu W, Tortolero-Luna G, Broaddus R, Gershenson DM, Burke TW, Schmandt R, Lu KH (2004) Increased plasma levels of insulin-like growth factor 2 and insulin-like growth factor binding protein 3 are associated with endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev* **13**(5): 748–752.

Olson SH, Chen C, De Vivo I, Doherty JA, Hartmuller V, Horn-Ross PL, Lacey Jr JV, Lynch SM, Sansbury L, Setiawan VW, Schouten LJ, Shu XO (2009) Maximizing resources to study an uncommon cancer: E2C2–Epidemiology of Endometrial Cancer Consortium. *Cancer Causes Control* **20**(4): 491–496.

Prat J (2009) FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet* **104**(3): 177–178.

Rosato V, Zucchetto A, Bosetti C, Dal Maso L, Montella M, Pelucchi C, Negri E, Franceschi S, La Vecchia C (2011) Metabolic syndrome and endometrial cancer risk.. *Ann Oncol* **22**(4): 884–889.

Schwartz SM, Thomas DB (1989) A case-control study of risk factors for sarcomas of the uterus. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. *Cancer* **64**(12): 2487–2492.

Schwartz SM, Weiss NS (1990) Marital status and the incidence of sarcomas of the uterus. *Cancer Res* **50**(6): 1886–1889.

Schwartz SM, Weiss NS, Daling JR, Gammon MD, Liff JM, Watt J, Lynch CF, Newcomb PA, Armstrong BK, Thompson WD (1996) Exogenous sex hormone use, correlates of endogenous hormone levels, and the incidence of histologic types of sarcoma of the uterus. *Cancer* **77**(4): 717–724.

Schwartz SM, Weiss NS, Daling JR, Newcomb PA, Liff JM, Gammon MD, Thompson WD, Watt JD, Armstrong BK, Weyer P (1991) Incidence of histologic types of uterine sarcoma in relation to menstrual and reproductive history. *Int J Cancer* **49**(3): 362–367.

Sherman ME, Devesa SS (2003) Analysis of racial differences in incidence, survival, and mortality for malignant tumors of the uterine corpus. *Cancer* **98**(1): 176–186.

Skubitz KM, D'Adamo DR (2007) Sarcoma. *Mayo Clin Proc* **82**(11): 1409–1432.

Venn A, Jones P, Quinn M, Healy D (2001) Characteristics of ovarian and uterine cancers in a cohort of in vitro fertilization patients. *Gynecol Oncol* **82**(1): 64–68.

Wang T, Rohan TE, Gunter MJ, Xue X, Wactawski-Wende J, Rajpathak SN, Cushman M, Strickler HD, Kaplan RC, Wassertheil-Smoller S, Scherer PE, Ho GY (2011) A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. *Cancer Epidemiol Biomarkers Prev* **20**(5): 971–977.

Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA (2000) Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). *Cancer Causes Control* **11**(2): 185–192.