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Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2)

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Background: Nulliparity is an endometrial cancer risk factor, but whether or not this association is due to infertility is unclear. Although there are many underlying infertility causes, few studies have assessed risk relations by specific causes.

Methods: We conducted a pooled analysis of 8153 cases and 11 713 controls from 2 cohort and 12 case-control studies. All studies provided self-reported infertility and its causes, except for one study that relied on data from national registries. Logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: Nulliparous women had an elevated endometrial cancer risk compared with parous women, even after adjusting for infertility (OR = 1.76; 95% CI: 1.59–1.94). Women who reported infertility had an increased risk compared with those without infertility concerns, even after adjusting for nulliparity (OR = 1.22; 95% CI: 1.13–1.33). Among women who reported infertility, none of the individual infertility causes were substantially related to endometrial cancer.

Conclusions: Based on mainly self-reported infertility data that used study-specific definitions of infertility, nulliparity and infertility appeared to independently contribute to endometrial cancer risk. Understanding residual endometrial cancer risk related to infertility, its causes and its treatments may benefit from large studies involving detailed data on various infertility parameters.

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Epidemiologic studies have consistently observed that nulliparity is associated with an elevated risk of endometrial cancer, with increasing number of births associated with reduction in risk (Cook *et al*, 2006). The extent to which these associations are explained by infertility, which has also been related to increased risk (Escobedo *et al*, 1991; Venn *et al*, 1995; Modan *et al*, 1998; Althuis *et al*, 2005; Silva Idos *et al*, 2009; Lerner-Geva *et al*, 2012), remains unclear. It is plausible that increased endometrial cancer risk associated with infertility is simply attributable to relatively higher proportions of nulliparous women among those who report infertility concerns or *vice versa*. Many previous studies that reported on nulliparity in relation to endometrial cancer risk did not account for infertility (Mcpherson *et al*, 1996; Parazzini *et al*, 1998; Wernli *et al*, 2006; Brinton *et al*, 2007; Dossus *et al*, 2010; Setiawan *et al*, 2013); others showed that the inverse association between higher parity and endometrial cancer risk remained after adjustment for infertility (Henderson *et al*, 1983) or that that increased risk was limited to nulliparous women who sought medical advice for infertility-related issues (Brinton *et al*, 1992). Furthermore, most previous cohort studies estimated standardized incidence ratios, unadjusted for nulliparity, to measure infertility-associated endometrial cancer risk, comparing cancer risk in infertile women to the general population (Ron *et al*, 1987; Brinton *et al*, 1989; Venn *et al*, 1995; Modan *et al*, 1998; Dor *et al*, 2002; Doyle *et al*, 2002; Lerner-Geva *et al*, 2012). One previous cohort study found that a borderline-significant 29% increased risk associated with infertility was no longer apparent after adjustment for parity (Jensen *et al*, 2008). Thus, questions about the independence of nulliparity and infertility on endometrial cancer risk have not been adequately addressed.

Infertility can be attributable to number of different disorders (Cetin *et al*, 2008). Studies have suggested that infertility-associated endometrial cancer risk may be attributable to underlying reasons for infertility, however, a limited number of studies have assessed whether there are distinctive endometrial cancer risk relationships according to different infertility causes. Anovulatory problems, including polycystic ovary syndrome (PCOS), have been associated in a number of studies to elevated endometrial cancer risk, with a recent meta-analysis of four studies reporting an odds ratio (OR) for PCOS of 2.70 (95% confidence interval (CI): 1.00–7.29) (Chittenden *et al*, 2009). Relationships of endometrial cancer risk with other infertility causes such as endometriosis, fibroids and male infertility are less certain (Ron *et al*, 1987; Escobedo *et al*, 1991; Brinton *et al*, 2005a,b; Zucchetto *et al*, 2009; Rowlands *et al*, 2011; Pollacco *et al*, 2012).

To increase the understanding of these putative associations, we conducted an investigation within a consortial context to evaluate endometrial cancer risk and: (1) the independent contribution of parity and infertility and (2) specific infertility diagnoses.

MATERIALS AND METHODS

Study population. In response to an invitation to principal investigators of studies in the Epidemiology of Endometrial Cancer Consortium (E2C2; (Olson *et al*, 2009; Setiawan *et al*, 2012)), 14 studies with information on ≥ 1 infertility factors contributed individual-level data for this pooled analysis. Cohort studies were analysed as nested case-control studies, with up to four controls randomly selected among women at risk within each cohort (i.e., women alive with intact uteri and without endometrial cancer before the date of diagnosis of the index case) for each case based on the same year of birth, date of cohort entry (± 6 months) and other criteria as appropriate for each study (e.g., race/ethnicity, study area). Cases in the cohort studies were identified through annual linkage to state or national cancer registries (Iowa Women

Health Study (IWHS), Swedish Women's Lifestyle Health Study (WLHS)) or through a combination of self-report confirmed through medical records review, linkage to cancer registries or the National Death Index (New York University Women's Health Study (NYU)). One cohort study (NYU) collected infertility and parity information from a case-control interview and is henceforth labelled as a case-control study. In the case-control studies, hospital-based controls (Patient Epidemiologic Data System (PEDS), Turin Case-Control Study (TURIN)) or population-based controls were selected within each source population (Alberta Case-Control Study on Endometrial Cancer (ALBERTA), Australian National Endometrial Cancer Study (ANECs), Connecticut Endometrial Cancer Study (CECS), Estrogen, Diet, Genetics and Endometrial Cancer (EDGE), Hawaii Endometrial Cancer Study (HAW), Polish Endometrial Cancer Study (PECS), Shanghai Endometrial Cancer Study (SECS), US Endometrial Cancer Study (US) and USC LA Case-Control Study (USC)).

Informed consent was obtained from all study participants as part of the original studies in accordance with the requirements of each study's institutional review board. In addition, NCI received approval from the Office of Human Subjects Research as the receiver of the pooled data set.

Data collection. De-identified data from the participating studies were centrally collected and initially harmonised at Memorial Sloan Kettering Cancer Center (MSKCC). Data on infertility (ever/never) were collected from all participating studies. Each study assessed a study participant's infertility using a study-specific questionnaire with questions such as: 'have you ever tried to become pregnant but were unable to'; 'was there any time when you could have become pregnant but did not'; and 'have you ever had regular sexual intercourse without any kind of birth control without getting pregnant', except for one study (WLHS) which relied on clinical data from population-based national registries with complete coverage of the Swedish population. The duration of trying to become pregnant ranged from ≥ 6 months to ≥ 2 years across studies, while some studies did not specify such a time frame. The information on infertility presumably combined primary and secondary infertility, respectively, the inability to conceive or to get pregnant at all *vs* the inability after having been successful at least once.

We also requested from each study the following additional infertility variables: sought medical attention for infertility (yes/no, age at doctor visit), cause of infertility identified (yes/no, specific causes identified and age diagnosed with specific causes) and fertility treatment (yes/no, specific types of treatment, age start/stop treatment and number of cycles). For causes of infertility, we examined data for: (a) endometriosis, (b) anovulation or PCOS, (c) structural defects (e.g., fibroids, cervical stricture, tubal occlusion), (d) male factor and (e) other causes of infertility. For these causes, we did not have information on how the diagnoses were made (e.g. no information on whether endometriosis diagnosis was surgically confirmed). We employed a wider definition of PCOS, in which we included women with anovulation problems. This was based on a previous analysis of 12 193 women evaluated for infertility in 5 large US clinics, which found that a large number of women were anovulatory, although few women had hyperandrogenism or polycystic ovaries (Brinton *et al*, 2010). For infertility treatment, we collected data for: (a) *in vitro* fertilisation (IVF), (b) selective oestrogen receptor modulator (SERM, i.e., anti-oestrogen), (c) gonadotropin, (d) progesterone, (e) oestrogen and (f) other drug. Supplementary Table 1 lists the common infertility drugs by infertility treatment categories.

Each study also provided information regarding age at diagnosis (cases), age at interview or reference date (controls), interview year, race/ethnicity, anthropometric measures, reproductive and menstrual characteristics, menopausal hormone use, oral contraceptive

use, smoking history and history of diabetes, in accordance with the E2C2 core data dictionary.

Case definition. Incident cases of endometrial cancer (primary site codes C54 and C55.9) were included in this analysis. All studies provided the International Classification of Diseases for Oncology, Third Edition, histology codes for each case, except for three studies (PECS, SECS and TURIN), which provided a summary histologic type for each case (i.e., endometrioid, serous, clear cell, adenocarcinoma not otherwise specified, etc.).

Exclusion criteria. For the analysis of the treatments of infertility, treatments identified in non-infertility sections of the questionnaire (SECS, USC) were excluded. The primary reason for this exclusion was the possibility that hormonal treatments were used for reasons unrelated to infertility concerns. Several infertility variables with >15% missing data, such as age at doctor visit for infertility and use of progesterone for infertility treatment, are not presented.

Statistical analysis. Except for the main infertility variable (ever/never), all other analyses were analysed as one combined data set rather than performing a meta-analysis of study-specific estimates given the small numbers of exposed cases and controls for each study. Associations between infertility factors and endometrial cancer risk were assessed by estimating pooled ORs and 95% CIs using unconditional logistic regression adjusted for age (continuous), study site, race (White, Black, Asian, mixed, other), oral contraceptive use (never, ever), menopausal hormone use (never, ever), parity (no births, one or more births), interview year (continuous) and body mass index (<25, 25–29, ≥30 kg m²). Missing values were coded as a separate category for each variable. Sensitivity analysis stratifying by study site was performed and the results did not appreciably change.

We also performed stratified analyses by histological subtype (endometrioid vs others), study design (case-control vs cohort), study location (North America, Europe, vs others), by study period (before vs after 2000) and by the various limited definitions of infertility (e.g., tried to conceive without success for <1 + year, 1 + year, 2 + years, vs time period not specified).

Tests for trend were performed by entering the ordinal values representing categories of variables as a continuous variable in the models. Tests for interaction were assessed using log-likelihood test statistics, where models with and without interaction terms were compared. For all analyses, *P*-values <0.05 were considered statistically significant. All statistical tests (*P*-values quoted) were two sided. Statistical analyses were performed in Stata 13 (StataCorp, College Station, TX, USA).

RESULTS

Table 1 describes the characteristics of the 12 case-control and two cohort studies that contributed 8153 cases and 11 713 controls to the pooled analysis. Comparison of established endometrial cancer risk factors in this study population generally reflected those found in a previous E2C2 pooling study (Setiawan *et al*, 2013). Across studies, the prevalence of infertility among controls ranged from 5 to 60%, according to their varying definitions of infertility as presented in Table 1.

Table 2 describes the risks associated with parity and infertility. Based on mainly self-reported infertility data that used study-specific definitions of infertility, nulliparous women had an elevated endometrial cancer risk compared with parous women (OR = 1.82; 95% CI: 1.65–2.00), with a similar risk after adjustment for infertility (OR = 1.76; 95% CI: 1.59–1.94). Relative to women who gave birth to three or more children,

there were significantly elevated risks associated with having had fewer births that was greatest in magnitude for nulliparous women.

Based on 7877 cases and 11 466 controls with infertility data, the OR for ever infertility and endometrial cancer risk was 1.31 (95% CI: 1.21–1.42), with risk slightly attenuated after adjustment for parity (adjusted for nulliparity: OR = 1.22; 95% CI: 1.13–1.33; adjusted for number of births: OR = 1.20; 95% CI: 1.11–1.30). Infertility was associated with similar risks among parous (OR = 1.22; 95% CI: 1.12–1.34) and nulliparous (OR = 1.26; 95% CI: 1.03–1.55) women (*P*-interaction = 0.44; Table 3). In additional analyses evaluating the infertility–endometrial cancer association stratified by number of births (nulliparous, 1, 2, 3 +), the only significantly increased risk associated with infertility was for those who gave birth to less than three children (*P*-interaction = 0.001; *P*-interaction remained significant with the addition of an interaction term for nulliparity and infertility; Table 3).

When parity and infertility were examined jointly and risks compared with women who were parous and did not report infertility, a significantly elevated risk was observed among nulliparous women who reported infertility (OR = 2.21, 95% CI: 1.90–2.56), a risk that was somewhat higher than that among nulliparous women without infertility problems (OR = 1.68, 95% CI: 1.48–1.92) and parous women who reported infertility (OR = 1.21, 95% CI: 1.11–1.32; data not tabled). Further, using as a referent group women who had given birth to three or more children and did not report fertility problems, we observed that the adjusted OR for nulliparous women who reported infertility was 2.44 (95% CI: 2.09–2.86), a risk somewhat higher than that of nulliparous women without infertility problems (adjusted OR = 1.86, 95% CI: 1.61–2.14; data not tabled). We further assessed whether the infertility associations were modified by other endometrial cancer risk factors (Supplementary Table 2) and we did not observe any significant interactions (*P*-interaction ≥ 0.10).

Infertility was a risk factor regardless of whether medical attention for infertility was sought (OR = 1.24; 95% CI: 1.13–1.37) or not (OR = 1.16; 95% CI: 1.02–1.31) (Table 4). Among women whose cause of infertility was investigated, both those with self-identified causes and those without identified causes showed increased risks, OR = 1.31 and 1.22, respectively, whereas women who were not investigated showed no altered risk. When women with identified causes were compared for each cause of infertility with women who never reported having infertility concerns, we observed significant risks for women both with and without endometriosis, although the risk was substantially higher for those with endometriosis (OR = 1.80 vs 1.28; *P*-het < 0.0001) (Table 4). Significantly elevated risks were also observed for both those with and without structural defects (OR = 1.35 vs 1.15; *P*-het = 0.001). However endometriosis and structural defects were no longer associated with endometrial cancer risk when we limited our analysis to women reporting infertility concerns and used women who did not have the indicated cause of infertility as the referent group (data not tabled).

We further assessed whether associations with infertility causes were modified by endometrial cancer risk factors (Supplementary Table 3). Although an interaction with parity was not significant, we found that the significant risk associated with anovulation/PCOS was limited to nulliparous women (*P*-interaction = 0.27). In addition, we found that the non-significant positive association between endometriosis and endometrial cancer was limited to oral contraceptive users (*P*-interaction = 0.02).

We had relatively small number of women who reported ever having used fertility treatments (*n* = 203 cases with any fertility treatment). We found that fertility treatment overall was not

Table 1. Characteristics of 14 studies included in the E2C2 pooled analysis

Study	Location	Period of ascertainment	Cases (n)	Controls (n)	Age range (years) ^a	Matching parameters	Infertility ^b prevalence in controls	Study-specific infertility definition ^b
Case-control								
Alberta Case-Control Study on Endometrial Cancer (ALBERTA)	Canada	2002–2006	542	1032	28–79	Age (± 5 years)	39%	Before the reference date, were there any periods of 12 months or longer when you could have become pregnant but did not?
Australian National Endometrial Cancer Study (ANECS)	Australia	2005–2007	1444	741	26–80	Age (5-year group), state	24%	Have you ever had regular sexual intercourse without any kind of birth control for more than 1 year without getting pregnant?
Connecticut Endometrial Cancer Study (CECS)	USA	2004–2009	668	665	35–80	Age (5-year group)	30%	Have you ever tried for at least 6 months to become pregnant, but were unable to (i.e., when you didn't use any contraception)?
Estrogen, Diet, Genetics, and Endometrial Cancer (EDGE)	USA	2001–2005	469	467	23–97	Age (5-year group)	45%	Did you ever have unprotected intercourse, once a week or more often, for a period of 6 months or longer without getting pregnant?
Hawaii Endometrial Cancer Study (HAW)	USA	1988–1993	332	511	27–80	Age (± 2.5 years), ethnicity	12%	Have you ever tried to become pregnant for 2 straight years or more, and not been able to get pregnant during that time?
New York University Women's Health Study (NYU) ^c	USA	1985–1990	128	340	39–89	Birth year, cohort entry	13%	Have you ever tried to get pregnant for ≥ 2 years, and during this time not become pregnant?
Polish Endometrial Cancer Study (PECS)	Poland	2000–2003	551	1925	24–75	Age (± 5 years), site	13%	Have you ever tried to become pregnant for two straight years or more, and during that time, not become pregnant?
Patient Epidemiologic Data System (PEDS)	USA	1982–1998	541	541	26–94	Age (± 5 years)	13%	Have you ever had difficulty getting pregnant? Did this problem last for > 1 year?
Shanghai Endometrial Cancer Study (SECS)	China	1997–2004	1199	1212	30–69	Age (± 5 years)	5%	If you have never been pregnant, the reason is: (includes your husband is infertile, you are infertile)
Turin Case-Control Study (TURIN)	Italy	1998–1999	297	307	40–75	None	8%	Did you ask for a doctor visit because of difficulty in becoming pregnant?
US Endometrial Cancer Study (US)	USA	1987–1990	433	320	25–78	Age (± 5 years), race, telephone exchange	15%	Have you ever tried to become pregnant for 2 straight years or more, and during that time, not become pregnant?
USC LA Case-Control Study (USC)	USA	1987–1993	833	791	50–74	Age (± 5 years)	60%	Did you not get pregnant for 7 or months while trying to get pregnant or while sexually active and making no effort to avoid getting pregnant?
Cohort								
Iowa Women Health Study (IWHS)	USA	1986–2007	553	2212	55–90	Birth year, cohort entry, race, area	18%	Did you ever try for 1 straight year or more to become pregnant and during that time not become pregnant?
Women's Lifestyle Health Study (WLHS)	Sweden	1991–2011	163	649	31–66	Birth year, cohort entry	19%	Clinical data from population-based national registries
Pooled studies	—	—	8153	11 713	—	—	22%	
Abbreviation: E2C2 = Epidemiology of Endometrial Cancer Consortium.								
^a Age at diagnosis for cases and at reference date for controls.								
^b Study-specific infertility definition.								
^c Cohort study with infertility data collected in case-control interviews.								

Table 2. Adjusted odds ratio and 95% confidence interval for endometrial cancer in relation to parity and infertility in the E2C2 pooled analysis

	Cases N ^a (%)	Controls N ^a (%)	OR (95% CI) ^b	Additionally adjusted for infertility	Additionally adjusted for nulliparity	Additionally adjusted for no. of live births
Nulliparity						
Parous	6591 (84)	10 366 (90)	1.00	1.00	—	—
Nulliparous	1272 (16)	1168 (10)	1.82 (1.65–2.00)	1.76 (1.59–1.94)	—	—
Number of births						
3+	2663 (34)	4501 (39)	1.00	1.00	—	—
2	2349 (30)	3788 (33)	1.22 (1.13–1.32)	1.21 (1.12–1.31)	—	—
1	1579 (20)	2077 (18)	1.46 (1.33–1.61)	1.44 (1.30–1.58)	—	—
0	1272 (16)	1168 (10)	2.11 (1.90–2.35)	2.04 (1.83–2.27)	—	—
	—	—	P-trend ^c < 0.001	P-trend ^c < 0.001	—	—
Infertility						
Never	5573 (71)	8957 (78)	1.00	—	1.00	1.00
Ever	2304 (29)	2509 (22)	1.31 (1.21–1.42)	—	1.22 (1.13–1.33)	1.20 (1.11–1.30)

Abbreviations: CI = confidence interval; OR = odds ratio.

^aNumbers do not add to the total because of missingness.^bAdjusted for age, study site, race, ever oral contraceptive use, ever menopausal hormone therapy use, interview year and body mass index. Missing set as a separate category for each covariate.^cP-trend calculated by entering the ordinal values representing categories of parity as a continuous variable in the model.**Table 3. Adjusted odds ratio and 95% confidence interval for endometrial cancer in relation to infertility by nulliparity and number of live births in the E2C2 pooled analysis**

	Infertility							
	Never			Ever				P-interaction ^b
	Case (n = 5573)	Control (n = 8957)	OR ^a	Case (n = 2304)	Control (n = 2509)	OR ^a	95% CI	
Nulliparity								
Parous	4830	8177	1.00 ^c	1662	2054	1.22	(1.12–1.34)	—
Nulliparous	615	695	1.00 ^c	556	401	1.26	(1.03–1.55)	0.44
Number of births								
3 +	2006	3536	1.00 ^c	612	886	1.08	(0.93–1.25)	—
2	1687	2987	1.00 ^c	632	766	1.19	(1.03–1.37)	—
1	1137	1654	1.00 ^c	418	402	1.44	(1.18–1.75)	—
Nulliparous	615	695	1.00 ^c	556	401	1.26	(1.03–1.55)	0.001

Abbreviations: CI = confidence interval; E2C2 = Epidemiology of Endometrial Cancer Consortium; OR = odds ratio. Numbers due are not added to the total due to missingness.

^aAdjusted for age, study site, race, ever oral contraceptive use, ever menopausal hormone therapy use, interview year, body mass index. Missing set as separate category for each covariate.^bEffect modification was assessed using the likelihood ratio test statistic.^cReferent category.

associated with endometrial cancer risk after adjustment for other risk factors (data not tabled). Based on even smaller numbers ($n = 3$ –71 cases using individual treatments), none of the individual treatments (IVF, SERMs, gonadotropins and oestrogen) were substantially related to risk when compared with women who did not report infertility concerns or those with infertility concerns who had not been treated.

Sensitivity analyses. Given that infertility definition varied across individual studies, we created a forest plot of the endometrial cancer risk estimates for infertility adjusted for nulliparity stratified by study (Figure 1). Estimates of this association were not significantly heterogeneous between studies ($P < 0.22$; $I^2 = 20.7\%$), with ORs ranging between 1.03 (95% CI: 0.80–1.34) and 2.30 (95% CI: 1.50–3.55). We also conducted sensitivity analyses using varying definitions of infertility (i.e., tried to conceive without success for < 1 + year, 1 + year, 2 + years, time frame of trying not specified) and we found the strongest associations among studies that defined infertility as unsuccessfully trying to conceive for ≥ 2 years (OR = 1.33, 95% CI: 1.09–1.63) and for an unspecified time frame (OR = 1.72, 95% CI: 1.33–2.21; Supplementary Figure 1). Subsequently, we examined the

association between nulliparity, number of births and infertility in eight studies that defined infertility as trying to get pregnant for 1 + year and found that the results did not appreciably change, although the associations were slightly attenuated towards the null (data not tabled).

Pooled ORs were also not significantly heterogeneous ($P > 0.05$) by histology (endometrioid vs others), study design (case-control vs cohort studies), study location (North America, Europe vs others) or study period (before vs after 2000) (data not tabled). In addition, for the cause-specific analysis, we examined risk among women identified with only a single cause (i.e., endometriosis only, anovulation/PCOS only, structural defects only and male factor only) compared with women who never reported infertility concerns, and found similar results as the main analysis (data not tabled).

DISCUSSION

In this large pooled analysis, based on mainly self-reported infertility data that used study-specific definitions of infertility,

Table 4. Adjusted odds ratio and 95% confidence interval for endometrial cancer in relation to causes of infertility in the E2C2 pooled analysis

	Cases (n = 7877)		Control (n = 11 466)			
	N	%	N	%	OR ^a	95% CI
Sought medical attention ^b						
Never infertile	5573	72	8957	79	1.00	—
Did not seek attention for infertility issues	778	10	852	7	1.16	(1.02–1.31)
Sought medical attention for infertility issues	1398	18	1565	14	1.24	(1.13–1.37)
Unknown (among women who reported having infertility issues)	128	—	92	—	—	—
Cause investigation ^b						
Never infertile	5573	81	8957	87	1.00	—
Cause identified	953	14	851	8	1.31	(1.17–1.48)
Cause not identified	342	5	441	4	1.22	(1.03–1.44)
Cause not investigated	36	1	43	0	1.11	(0.68–1.82)
Causes found (not mutually exclusive)						
Endometriosis ^c						
Never infertile	5573	87	8957	93	1.00	—
No, infertility not due to endometriosis	731	11	546	6	1.28	(1.12–1.47)
Yes, infertility due to endometriosis	136	2	87	1	1.80	(1.34–2.42)
Anovulation/PCOS ^a						
Never infertile	5573	92	8957	95	1.00	—
No, infertility not due to anovulation/PCOS	343	6	277	3	1.07	(0.89–1.29)
Yes, infertility due to anovulation/PCOS	124	2	182	2	1.28	(0.98–1.67)
Structural defects ^e						
Never infertile	5573	87	8957	93	1.00	—
No, infertility not due to structural defects	398	6	299	3	1.15	(0.97–1.37)
Yes, infertility due to structural defects	405	6	330	3	1.35	(1.13–1.62)
Male factors ^f						
Never infertile	5573	92	8957	96	1.00	—
No, infertility not due to male factors	333	5	255	3	1.14	(0.95–1.38)
Yes, infertility due to male factors	156	3	127	1	1.21	(0.93–1.59)

Abbreviations: CI = confidence interval; OR = odds ratio; PCOS = polycystic ovary syndrome.

^aAdjusted for age, study site, race, ever oral contraceptive use, ever menopausal hormone therapy use, parity, interview year and body mass index. Missing set as separate category for each covariate.

^bBased on 13 studies.

^cBased on 9 studies.

^dBased on 8 studies.

^eBased on 9 studies.

^fBased on 8 studies.

Abbreviations: CI = confidence interval; OR = odds ratio; PCOS = polycystic ovary syndrome.

^aAdjusted for age, study site, race, ever oral contraceptive use, ever menopausal hormone therapy use, parity, interview year and body mass index. Missing set as separate category for each covariate.^bBased on 13 studies.^cBased on 9 studies.^dBased on 8 studies.^eBased on 9 studies.^fBased on 8 studies.

we observed an elevated risk of endometrial cancer in relation to history of nulliparity, even after adjusting for infertility and of infertility, even after adjusting for nulliparity. Infertility appeared to be associated with similar risks among nulliparous and parous women. Among women who reported infertility concerns, none of the individual infertility causes were substantially related to endometrial cancer risk.

We found that parity and infertility independently contribute to endometrial cancer risk. Our observation that nulliparous women are at increased risk of endometrial cancer, as compared with parous women, may be related to the increased number of menstrual cycles associated with the absence of pregnancy and lactation and subsequent uninterrupted exposure to oestrogen for long durations (Ali, 2014). The magnitude of the effect estimate for the infertility-adjusted nulliparity association (OR = 1.76; 95% CI = 1.59–1.94) was greater than the effect estimate for the nulliparity-adjusted infertility association (OR = 1.22; 95% CI = 1.13–1.33). This finding suggests that nulliparity is a stronger risk predictor than infertility. In agreement with these results, a previous report from a Los Angeles case-control study, which is included in the pooled analysis, described that nulliparity remained significant after adjusting for infertility, but that the association with infertility diminished after adjusting for parity (Henderson *et al*, 1983). Other previous investigations have similarly shown that infertility associations diminished after adjustment for parity, based on relatively small number of endometrial cancer cases

(*n* = 52 (Brinton *et al*, 2007) and *n* = 64 (Jensen *et al*, 2008)) who reported having infertility concerns.

We also observed in our pooled analysis that the infertility-associated elevation in endometrial cancer risk was similar for nulliparous and parous women, although women who gave birth to three or more children had no elevation in risk. The diminished risk among these women might be a chance finding or could be related to misclassification since it is unclear what infertility means among women who sought advice for infertility but were able to have multiple births. It is also possible that women who had infertility problems and never conceived had more recalcitrant infertility that led to their higher risks. Additional information about primary vs secondary infertility might help clarify how infertility-associated endometrial cancer risk may vary by different parity categories as previous studies have reported differential risk for primary vs secondary infertility as it relates to endometrial cancer risk (Brinton *et al*, 2010). To some degree, we attempted to do this by considering nulliparity, but the number of cases with available information on age at first birth and age at seeking advice for infertility were too small to properly distinguish between primary vs secondary infertility.

Compared with women not reporting infertility concerns, increased risks were noted for those with infertility from identified causes and for those with unidentified causes. Previous investigations have shown increased endometrial cancer risk among women with unexplained infertility (Venn *et al*, 1995, 1999). This result could be

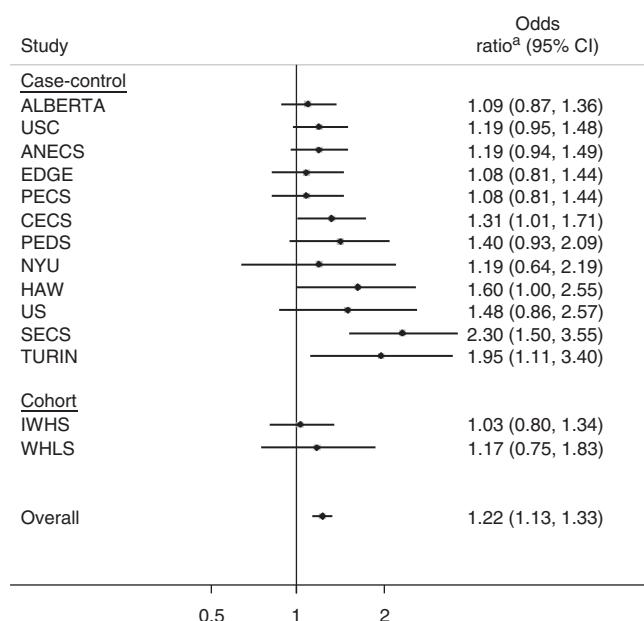


Figure 1. Study-specific adjusted odds ratio and 95% confidence interval for endometrial cancer in relation to infertility in the E2C2 pooled analysis, ordered by standard error. ^aAdjusted for age, race, ever oral contraceptive use, ever menopausal hormone therapy use, parity, interview year, body mass index, and nulliparity. Missing set as a separate category for each covariate.

explained by the fact that ~25–40% of infertile couples have no identifiable cause of infertility after standard investigations, such as tests of ovulation, tubal patency and semen analysis (Ray *et al*, 2012).

When we examined risk relations among women with identified causes of infertility, we found that the highest risk among those with diagnoses of endometriosis, although even those with other causes were at some elevated risk, suggesting that infertility *per se* may confer some predisposition towards development of endometrial cancer. In attempts to disentangle the effects of generalised infertility from that of the specific causes, we limited our analysis to women who reported ever having infertility and defined the referent group as infertile women not diagnosed with the indicated cause of infertility. Here, among women who reported being infertile, none of the individual causes were associated with endometrial cancer risk.

Previous epidemiological data supporting the link between endometriosis and endometrial cancer have been conflicting, with risks ranging from a decreased risk in one nested case-control study (OR = 0.58; 95% CI: 0.42, 0.81) (Borgfeldt and Andolf, 2004) to a substantially increased risk (OR = 4.0; 95% CI: 1.1, 6.4) in a large hospital-based case-control study (Zucchetto *et al*, 2009). Cohort studies based on relatively small number of endometrial cancer cases, ranging from 7 to 97, have generally found no significant associations between endometriosis and endometrial cancer (Brinton *et al*, 1997; Olson *et al*, 2002; Brinton *et al*, 2005b; Melin *et al*, 2006, 2007). A possible explanation for the conflicting results across previous studies and with our pooled analysis may relate to detection bias associated with the asymptomatic nature of endometriosis (Rowlands *et al*, 2011) or that many older women with endometriosis may subsequently have their uteri removed. Among a small subset of women for whom data on age at diagnosis of endometriosis information were available, we found that the risk association with endometriosis remained statistically significant after excluding endometriosis diagnosed in the year prior to the reference year. Furthermore, the risk was mainly limited to younger age groups (data not tabled). We also observed that the

increased risk associated with endometriosis was limited to users of oral contraceptives, which may have been taken to alleviate pelvic pain associated with more severe endometriosis (The American Congress of Obstetricians and Gynecologists (ACOG), 2010). We also found that the significant risk associated with anovulation/PCOS was limited to nulliparous women, possibly also indicating more severe forms of this disorder.

Although gynaecological diseases, such as fibroids (Escobedo *et al*, 1991; Brinton *et al*, 2005a; Zucchetto *et al*, 2009; Rowlands *et al*, 2011), and other medical conditions, such as PCOS (Navaratnarajah *et al*, 2008; Chittenden *et al*, 2009), have been previously reported as endometrial cancer risk factors in some studies, epidemiological evidence supporting their associations in the context of infertility have been limited. In a population-based case-control study, Escobedo *et al* (1991) found that self-reported ovarian factors (based on seven endometrial cancer cases with this cause) were associated with significant elevations in endometrial cancer risk as compared with fertile women. In a retrospective cohort study of infertile women, in whom 40 endometrial cancer cases developed, Brinton *et al* (2005b, 2010) found that primary infertility due to androgen excess, menstrual disorders and male factor causes of infertility were associated with an increased risk when compared with women with secondary infertility without these conditions, suggesting that only severe forms of these conditions might increase endometrial cancer risk. Thus, it is possible that previous studies with relatively small number of subjects observed risk associations with various infertility causes by chance alone or that self-reported definitions used in our analysis might have led to non-differential misclassification, tending to attenuate associations towards the null. Studies with clinically confirmed infertility causes, along with details such as the severity of the disorders, may further elucidate our understanding.

In our large pooled analysis, we were limited by the relatively small number of women using infertility treatments (<3% of study population) and even smaller number of women with information regarding specific types of infertility treatments, limiting our ability to examine and disentangle the effects associated with treatment-related factors such as treatment type, dose, duration and age at treatment. This demonstrates the need for larger studies based on samples of cases selected from groups of infertile women rather than endometrial cancer cases from the general population, as were those included in our analysis (Brinton *et al*, 2012).

Major strengths of this pooled analysis include the large sample size and the detailed reproductive and medical histories that permitted a comprehensive assessment of confounding and effect modification. The main limitation was the reliance on self-reports of infertility, which raises concern of potential recall bias and other misclassification issues. Furthermore, fertility definitions used across these studies varied widely with regard to the length of time of unsuccessful efforts to conceive, thereby complicating the comparisons across studies. We attempted to address this issue by conducting sensitivity analyses with different definitions of infertility. We observed one of the highest risks when we used the most stringent definition, although we did observe an increased risk for all definitions. Another source of misclassification could have been introduced by nulliparous women that never attempted to have children and thus that reported no difficulties with conception. However, we observed similar overall infertility–endometrial cancer risk associations for nulliparous and parous women. Our definition of infertility did not distinguish between primary and secondary infertility, which might be considered as two distinct risk factors with different pathologies (Lunenfeld *et al*, 2004; Mascarenhas *et al*, 2012). Studies with large numbers of infertile and treated women, with improved measures of infertility parameters are needed. An international pooled analysis of data from large infertility clinics, which would have well-documented information about various

parameters, including ages at pregnancies and infertility diagnosis and treatment modalities, is warranted.

In conclusion, our pooled analysis, based on mainly self-reported infertility data with varying definitions across studies, provides epidemiologic evidence that nulliparity and infertility may independently contribute to endometrial cancer risk. Our data also suggest that specific causes of infertility examined, *per se*, do not elevate endometrial cancer risk. Understanding residual endometrial cancer relationships of infertility, its causes and its treatments may benefit from large studies that utilise documented information to clarify relationships.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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