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Endometrioid and clear cell ovarian cancers – A comparative analysis of risk factors ☆

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ABSTRACT

Endometrioid and clear cell subtypes of ovarian cancer are both known to be closely associated with endometriosis and endometrial pathology, and so have often been combined in studies of causation. We have examined these ovarian cancers separately for potentially distinct risk factors in our population-based, Australia-wide case control study of 142 women with incident invasive endometrioid, 90 with clear cell ovarian cancers and 1508 population controls. Multivariate logistic regression was used to calculated odds ratios (ORs) and 95% confidence intervals (CIs). Increasing parity, and hormonal contraceptive use for $\geqslant$5 years, strongly decreased the risks of both subtypes. Breast feeding and tubal ligation were also inversely associated, but significantly so only for the endometrioid subtype. As expected endometriosis increased the risk of both subtypes (OR 2.2, 95%CI 1.2–3.9 for endometrioid and OR 3.0, 95%CI 1.5–5.9 for clear cell). Obesity was associated only with clear cell cancers, where we observed a two-fold increased risk (OR 2.2, 95%CI 1.2–4.1). Also a significant trend of decreasing risk with increasing intensity of smoking (p trend 0.02) and education beyond high school was associated with decreased development of clear cell cancers only. Endometrioid and clear cell ovarian cancers have some shared as well as some distinct risk factors, and therefore should be considered separately in studies of ovarian cancer.

1. Introduction

Ovarian cancer is a morphologically and biologically heterogenous disease.[1] The most common subtypes are serous and endometrioid, accounting for about 50% and 10–20%, respectively, of all malignant ovarian neoplasms, and less common are the mucinous (~5–10%) and clear cell (~5–10%) subtypes.[2] Cancers of both the ovary and uterus have histological classification schemes that include (amongst others) endometrioid and clear cell subtypes.[3,4] It has long been noted that both the endometrioid and clear cell subtypes of ovarian tumours are strongly associated with endometriosis[5,6] and with endometrial pathology.[7–9] These shared associations, combined with the difficulties associated with obtaining large numbers of

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clear cell ovarian cases, have often led researchers to group endometrioid and clear cell ovarian subtypes together when investigating causal factors. Yet these types of ovarian cancer have distinct histological,[1] clinical,[10] and prognostic profiles,[11] and so the approach of combining the endometrioid and clear cell subtypes in previous studies has most likely introduced errors and limited our understanding of these potentially distinct subtypes.

In an effort to characterise distinct aetiologies for endometrioid and clear cell ovarian cancers, we have evaluated an array of personal, lifestyle, reproductive and hormonal exposures as potential risk factors for each of these subtypes separately, using data from a large Australian population-based case–control study.

2. Materials and methods

A detailed description of the study population and data collected had been provided previously.[12] A flow chart detailing recruitment of cases and controls is provided in Fig. 1. Briefly, 3550 women with suspected ovarian (or fallopian tube or peritoneal) cancer were identified by trained nurses through the major treatment centres and state-based cancer registries throughout Australia. Of these, 307 died before contact could be made, physicians refused to give consent to contact 133, and 194 women could not be contacted. A further 171 women were excluded on the basis of language difficulties (70), mental incapacity (35) and illness (66). The remaining 2745 women with a clinically suspected diagnosis of ovarian cancer were invited to participate (prior to surgery, to facilitate fresh tissue collection) and, of these, 2319 (85%) agreed to take part. After surgery, pathology reports were obtained for all women and a further 608 women were excluded because their final diagnosis was a benign, non-epithelial or metastatic tumour and not primary epithelial ovarian cancer, 25 because their cancer was first diagnosed before the start of the study period and one woman was excluded because she was not an Australian resident at the time of her initial diagnosis. Two researchers independently abstracted information on tumour site, histological subtype and tumour behaviour (invasive versus borderline) from the diagnostic histopathology reports. Discrepancies were resolved by consensus. To check the quality of the abstracted data the pathology reports and full set of diagnostic slides for a sample of 200 women were reviewed by a gynaecological pathologist; agreement with the abstracted data was >95% for tumour subtype and site, and 99% for tumour behaviour. Of the final 1685 eligible participants, 1591 (94%) returned a questionnaire.

Controls were randomly selected from the national electoral roll (enrolment is compulsory) and were frequency matched by age (in 5-year age bands) and state of residence to the case group. Selected women were mailed an invitation letter and information brochure explaining the study and then, where possible, followed up by telephone. Of the 3613 women contacted and invited to participate, 171 women were excluded due to illness (63) and language difficulties (97), and 11 women had died after initial contact. Of the remaining 3442 women, 1613 agreed to participate and returned a questionnaire (47%). Six of them reported a history of ovarian cancer and 99 reported a previous bilateral oophorectomy, and thus were excluded from this study leaving 1508 population controls.

All study participants (cases and controls) completed a comprehensive health and lifestyle questionnaire, which included questions about demographic factors, physical characteristics, family history of cancer, lifestyle habits, reproductive and hormonal factors and other potential risk factors. Exposures that occurred in the 12 months before diagnosis in cases (or date of first approach for controls) were excluded because they were not considered aetiologically relevant. It was also considered that for cases recent behaviours may have been affected by preclinical disease. The variables of particular interest in this study were those related to oestrogenic effects, in particular smoking, body mass index (BMI) and oestrogen replacement therapy. We also examined self-reported history of gynaecologic conditions (endometriosis, fibroids) and menstrual characteristics variously reported to be associated with endometrioid and clear cell ovarian cancers and/or hormonal exposures.

Ethics approval was received from the Human Research Ethics Committees at the Queensland Institute of Medical Research, Peter MacCallum Cancer Centre, University of Melbourne, all participating hospitals and cancer registries.

Case–control comparisons were used to assess the main effects on ovarian cancer risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from univariate and multivariate logistic regression models adjusting for age (in 10-year age-groups), education (secondary school, technical college/apprenticeship, university), parity (0, 1–2, 3 or more full term births), hormonal contraceptive use (none, <60 months, $\geqslant$60 months use) and body mass index, 1 year prior to diagnosis/recruitment (BMI). BMI was classified using the World Health Organisation (WHO) definitions of obesity: <18.5 'underweight', 18.5–24.9 'normal weight', 25–29.9 'overweight' and $\geqslant$30 kg/m^2 'obese'. Further adjustment for factors including perineal talc use, history of hysterectomy or tubal ligation, menopausal status, use of hormone replacement therapy (HRT), family history of breast or ovarian cancer in a first degree relative, breast feeding and state of residence did not substantially alter risk estimates (changed point estimates 10% or less), thus these factors were not routinely included in the final models. Tests for linear trend were performed using the maximum likelihood test, with the ordinal categorical variables of interest entered as a continuous term. All analyses were performed using the SAS system V 9.1 (SAS Institute Inc., Cary, NC).

3. Results

Cases for the current analysis included 142 women with invasive endometrioid cancer, 90 women with invasive clear cell ovarian cancer and 1508 population controls. Women with endometrioid ovarian cancers were on average a little younger at diagnosis than women with clear cell cancers (mean age 57.4 compared with 58.5 years), and the mean age of control women was 56.4 years (Table 1). There was a decreased risk of clear cell ovarian cancer amongst those with a post-school education (OR 0.5, 95% CI 0.3–0.8 and OR 0.4, 95% CI 0.2–0.9, for women who had a technical college and university

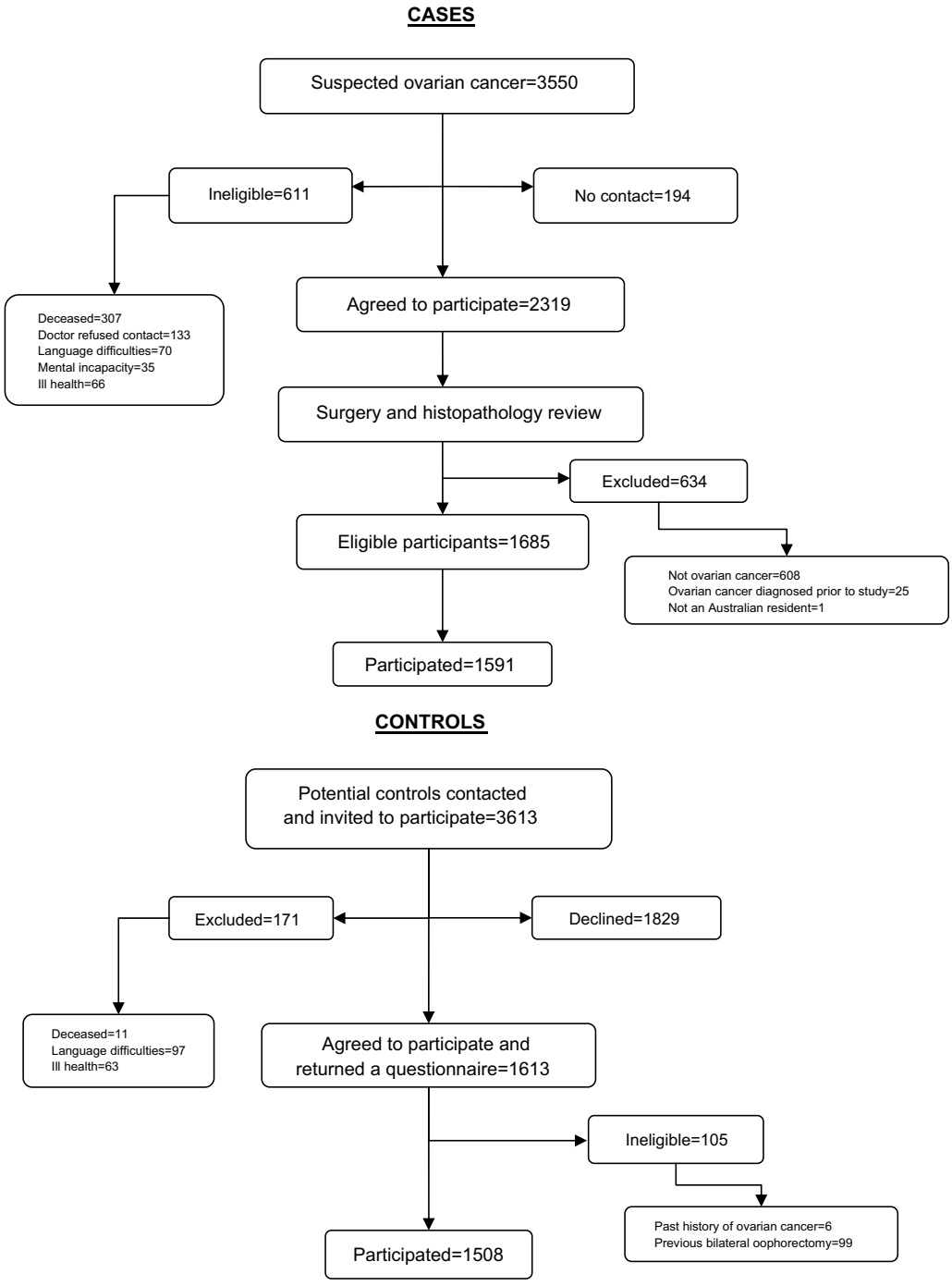

Fig. 1 – The recruitment of cases and controls for the study.

education, respectively, compared to those with only school education). Having a first degree relative with breast or ovarian cancer was not associated with risk of either subtype.

Smoking was not associated with endometrioid ovarian cancer. However, there was an inverse association with former smoking in clear cell ovarian cancers (OR 0.4, 95% CI 0.2–0.7), and a significant trend of decreasing risk associated with increasing pack-years ($p = 0.03$) (Table 1). When we examined the components of pack-years (intensity and duration of smoking) separately for the clear cell ovarian cancers we found a significant trend of decreasing risk with increasing intensity of smoking ($p = 0.02$), but there was no association with increasing duration of smoking. Obese women (BMI 30+, 1 year prior to diagnosis/recruitment) had an increased risk of both the endometrioid and clear cell subtypes, but this was significant only for clear cell cancers (OR 2.2, 95% CI 1.2–4.1). There was also a clear trend of increasing risk of clear cell cancers with increasing BMI ($p = 0.01$).

Having a term pregnancy was associated with a decreased risk of both the endometrioid and clear cell ovarian cancers,

Table 1 – Distributions, adjusted odds ratios (95% confidence intervals) for the association between selected personal and lifestyle factors and risk of endometrioid and clear cell ovarian cancers

	Controls *n* (%)	Endometrioid *n* (%)	Endometrioid OR[a] (95% CI)	Clear cell *n* (%)	Clear cell OR[a] (95% CI)
Age (mean ± standard deviation)	56.4 ± 12.4	57.4 ± 10.2		58.5 ± 10.3	
Level of education					
High school	740 (49)	68 (48)	1.0	56 (62)	1.0
Technical college/trade certificate	550 (37)	51 (36)	0.9(0.6–1.4)	25 (28)	0.5 (0.3–0.8)
University	218(14)	23 (16)	1.0(0.6–1.6)	9(10)	0.4 (0.2–0.9)
Family history of ovarian or breast cancer (in first degree relative)	196(13)	24(17)	1.4(0.9–2.3)	14(16)	1.5(0.8–2.8)
Smoking status[b]					
Never	902 (60)	84 (59)	1.0	65 (72)	1.0
Ex-smoker	436 (29)	42 (29)	1.2(0.8–1.8)	12(13)	0.4 (0.2–0.7)
Current	165(11)	15(11)	0.9(0.5–1.8)	13(14)	1.1 (0.6–2.3)
			$p = 0.78$		$p = 0.32$
Total pack-years of smoking[b]					
Never smoker	902 (60)	84 (59)	1.0	65 (72)	1.0
1–14.9 years	378 (25)	34 (24)	1.2(0.8–1.8)	14(16)	0.7(0.4–1.2)
15–29.9 years	128 (8)	13(9)	1.0(0.5–2.0)	7(8)	0.6(0.2–1.6)
⩾30 years	98(7)	11 (8)	1.1 (0.6–2.3)	4(4)	0.3(0.1–1.1)
			p for trend 0.71		p for trend 0.03
BMI last year[c]					
<18.5	33(2)	2(2)	0.9 (0.2–4.0)	3(4)	2.9(0.8–11.1)
18.5–24.9	662 (44)	52 (40)	1.0	23 (30)	1.0
25–29.9	453 (30)	46 (35)	1.3(0.8–2.0)	27 (35)	1.7(0.9–3.0)
30+	341 (23)	30 (23)	1.2(0.7–1.9)	25 (32)	2.2(1.2–4.1)
			p for trend 0.41		p for trend 0.01

a Adjusted for age, education, parity, hormone contraceptive use.
b ORs additionally adjusted for BMI last year.
c ORs additionally adjusted for smoking status.

and there was a significant trend of decreasing risk of both subtypes with increasing number of pregnancies ($p \leqslant 0.001$) (Table 2). Similarly a history of breast feeding was associated with reduced risk, however the results were only significant for the endometrioid subtype (OR 0.6, 95% CI 0.4–1.0). Use of hormonal contraceptives for ⩾5 years was associated with a reduced risk of both the endometrioid and clear cell cancer subtypes, with statistically significant trends of decreasing risk with increasing duration of use ($p < 0.0001$ and $p = 0.0002$ for endometrioid and clear cell cancers, respectively).

We found no evidence that hysterectomy, perineal talc use or menopausal status was associated with either subtype. We observed modest inverse relations for both the subtypes with tubal ligation, but this association was only significant for the endometrioid subtype (OR 0.4, 95% CI 0.3–0.7). There was a suggestion of a positive association between post-menopausal status and the risk of clear cell ovarian cancer, but no association with endometrioid ovarian cancer. Whilst there appeared to be no relation between ever-use of HRT and risk of both the subtypes (results not shown), use of HRT that contained oestrogens only was associated with modest, non-significant, increase in risk of endometrioid ovarian cancer only (OR 1.4, 95% CI 0.8–2.4). We also found a reduced risk of clear cell ovarian cancer amongst users of HRT containing oestrogen and progestagens. The odds ratio comparing never HRT users to users of HRT containing oestrogen and progestagens was 0.5 (95% CI 0.2–1.0). These results were unchanged when we restricted the analyses to peri-menopausal and menopausal women.

Finally whilst there appeared to be no association between fibroids and endometrioid and clear cell cancers (Table 2), women with endometriosis had a three-fold increased risk of clear cell ovarian cancer (OR 3.0, 95% CI 1.5–5.9) and two-fold increased risk of endometrioid ovarian cancer (OR 2.2, 95% CI 1.2–3.9). Because we had excluded control women with a history of bilateral oophorectomy (who are no longer at risk of ovarian cancer) and these women were also more likely to have had endometriosis (20%), we repeated the analysis including this group ($n = 99$). In this sensitivity analysis, the associations with clear cell cancers and endometrioid cancers were maintained although somewhat attenuated (ORs, 2.3, 95% CI 1.2–4.6 and 1.7, 95% CI 1.0–3.0, respectively). Menstrual cycle characteristics (regularity and duration of periods, history of dysmenorrhoea) were not associated with either subtype.

4. Discussion

We have presented detailed case–control analyses comparing the aetiologies of invasive endometrioid and clear cell ovarian cancers in a large group of Australian women. Our results suggest that factors that suppress ovulation such as parity, hormonal contraceptives and breast feeding are important determinants of both subtypes, and these risk factors closely

Table 2 – Distributions, adjusted odds ratios (95% confidence intervals) for the association between reproductive and hormonal factors and risk of endometrioid and clear cell ovarian cancers

	Controls *n* (%)	Endometrioid *n* (%)	Endometrioid OR[a] (95% CI)	Clear cell *n* (%)	Clear cell OR[a] (95% CI)
Number of pregnancies					
Nulliparous	180 (12)	33 (23)	1.0	31 (34)	1.0
1–2	645 (43)	55 (39)	0.5 (0.3–0.8)	35 (39)	0.2 (0.1–0.4)
>3	683 (45)	54 (38)	0.4 (0.2–0.7)	24 (27)	0.1 (0.07–0.2)
			p for trend 0.001		*p* for trend <0.0001
Ever breastfed[b]	943 (73)	64 (63)	0.6(0.4–1.0)	33 (62)	0.8 (0.4–1.4)
Hormone contraceptive use					
Never	325 (22)	50 (35)	1.0	35 (39)	1.0
<5 years	365 (24)	42 (30)	0.7(0.4–1.1)	26 (29)	0.9 (0.5–1.5)
⩾5 years	813 (54)	49 (35)	0.3 (0.2–0.5)	28 (32)	0.4 (0.2–0.6)
			p for trend <0.0001		*p* for trend 0.0002
Previous hysterectomy	291 (20)	32 (22)	1.2 (0.8–1.9)	18 (20)	0.9 (0.5–1.6)
Previous tubal ligation	406 (27)	19(14)	0.4 (0.3–0.7)	15 (17)	0.7 (0.4–1.2)
Ever use talc in the perineal region	668 (45)	70 (49)	1.3 (0.9–1.8)	40 (45)	1.1 (0.7–1.7)
Menopausal status					
Pre-menopausal	398 (26)	35 (25)	1.0	13 (14)	1.0
Peri-menopausal	108 (7)	11 (8)	0.9 (0.4–2.0)	5 (6)	1.5 (0.5–4.8)
Post-menopausal	1002 (67)	96 (67)	0.8 (0.4–1.7)	72 (80)	2.9 (0.9–9.4)
Type of hormone replacement therapy					
No hormone replacement therapy	956 (68)	94 (69)	1.0	62 (73)	1.0
Oestrogen only	281 (20)	23 (17)	1.4 (0.8–2.4)	11 (13)	0.9 (0.5–1.9)
Oestrogen and progestagens	162 (12)	19 (14)	0.7 (0.4–1.2)	12 (14)	0.5 (0.2–1.0)
Endometriosis (ever)[c]	87 (6)	18 (13)	2.2 (1.2–3.9)	13 (15)	3.0 (1.5–5.9)
Fibriods (ever)	271 (18)	33 (23)	1.3 (0.8–2.0)	20 (23)	1.3 (0.8–2.3)

a Adjusted for age, education, parity and hormone contraceptive use.
b Restricted to parous women only.
c Additionally adjusted for BMI (last year).

parallel those for most other ovarian cancer subtypes and the serous subtype in particular.[13–16] However, the risk profile for clear cell ovarian cancer is distinctive regarding two key lifestyle factors: obesity and smoking. We found that obese women had a two-fold increased risk of clear cell ovarian cancer. We also observed an inverse association with former smoking in clear cell ovarian cancers, and a significant trend of decreasing risk associated with increasing intensity of smoking.

Our findings in relation to clear cell cancers and lifestyle factors cast doubt on the extent of a shared aetiology of these two subtypes of ovarian cancer. Since this is one of the few studies addressing this question,[13–15,17,18] we have limited context in which to embed our findings. We therefore compared our findings with the epidemiological evidence from endometrial cancers of the uterus because they also are classified into endometrioid or type I (85%) and clear cell/serous or type II (15%) histological subtypes.[19,20] Unlike their ovarian counterparts however, endometrioid cancers of the uterus appear to be strongly oestrogen dependant with clear cell/serous cancers less so.[20] Our results, contrary to these data and to our expectations, showed that clear cell ovarian cancers were associated with a greater number of oestrogen-related factors (BMI, smoking) than endometrioid ovarian cancers. Both ovarian clear cell and endometrioid cancers are strongly linked to endometriosis[21,22] (perhaps explaining the decreases in risk with tubal ligation), but beyond that our results suggest divergent paths to causation. Indeed clear cell ovarian cancers may be the subtype that is the more amenable to prevention through modulation of oestrogenic exposure. Interestingly molecular studies have shown that clear cell ovarian cancers have a remarkably similar gene expression profile to clear cell cancers in the endometrium, and it has been postulated that they may share a common transformation pathway.[23] By contrast, although similar in histological appearance, endometrioid cancers of the ovary and uterus have been shown to have different gene expression patterns.[24]

Our results are generally consistent with those of other studies[13–15,18,25–28] which show that parity and oral contraceptive use significantly and appreciably reduce risk of both endometrioid and clear cell subtypes of ovarian cancer. In addition to this, lactation and tubal ligation both appeared to convey protection, supporting evidence from some but not all previous studies.[13–15,18,28,29] Our results showed no association between hysterectomy and risk of either subtype which is consistent with other studies that have considered this exposure.[14,18,26,28] Our findings in relation to risk of both

subtypes of ovarian cancer and type of HRT use are interesting given the role of unopposed oestrogens in endometrial cancer risk.[30,31] We had expected to find a strong positive association between oestrogen-only HRT use and the endometrioid subtype of ovarian cancer, but instead found no association. Our finding of a decreased risk of clear cell ovarian cancer amongst users of combined oestrogen and progestagens HRT was interesting given the role of progestagens as a potential chemopreventive agent in ovarian cancer, but all these HRT results should be interpreted with caution because of the small number of cases involved, and the potential for misclassification of exposure. Like others[5,32] our results confirmed a significant association between endometriosis (self-reported) and both ovarian cancer subtypes, but as previously reported by us no association with other subtypes (serous, mucinous).[12] Although it has long been suspected that endometriosis is a precursor to ovarian cancer, a recent study has demonstrated clonal progression in 10 cases of ovarian cancer (endometrioid $n = 6$; clear cell $n = 4$) with coexisting endometriosis.[21] In the present analysis also we found a weak, but statistically significant, inverse association between higher levels of education and clear cell ovarian cancer, but no association with endometrioid cancers. A similar finding, albeit non-significant, was recently reported by Kurian and colleagues.[13] They speculate that this finding may reflect an associated reproductive factor, such as later age at first pregnancy.[13]

The strengths of our study are the population-based design, the size of the study population, particularly for the clear cell ovarian cancers, which is larger than most previous studies, and the detailed information collected on a wide range of reproductive, health and lifestyle exposures. We also undertook a thorough abstraction of the pathologic data from the diagnostic histopathology reports. We do however note a number of limitations. Despite our clear cell cancer group being large compared to previous studies, the small number of clear cell cases overall means that true modest associations may not be detected or may not reach statistical significance. Another potential limitation was the relatively low participation rate amongst controls (47%). To assess the impact of this we had previously compared the distribution of key variables in our control group with data from the Australian National Health Survey (NHS),[33] a national survey with a 90% response rate. We found that the distributions of most key exposures (education level, parity, BMI) amongst our control women were almost identical to those from the NHS.[34] Our controls were however less likely than NHS women to be current smokers, although the rates of ever- and ex-smoking were identical. We also found that hormonal contraceptive use in women younger than 50 years was 5% higher in our controls than in the population, which would have biased our estimates slightly away from null.

Another possible source of error is recall bias. Whilst it is possible that cases were more likely to recall a history of endometriosis than controls, it is unlikely to have been a major influence on our results since reporting is unlikely to differ amongst women with different subtypes of ovarian cancer and the association with endometriosis was observed for the endometrioid and clear cell cancer subtypes only, and not for any other subtypes.[12]

Finally, we had excluded 99 controls with a past history of previous bilateral oophorectomy because they were no longer at risk of developing ovarian cancer. However, endometriosis is a possible indication for oophorectomy, and the excluded controls had a higher prevalence of endometriosis than those included in the study. When we repeated our analyses including these women the associations with clear cell cancers and endometrioid cancers were maintained although somewhat attenuated.

In summary, this study provides new evidence that the endometrioid and clear cell subtypes of ovarian cancer have some common risk factors and others that are different. Although both are associated with reproductive risk factors and endometriosis, differences in the effects of BMI and intensity of smoking support the idea that these two subtypes may develop along different pathways. Our results support the notion that these two ovarian cancer subtypes, like the serous and mucinous subtypes, represent distinct disease entities as defined by traditional histopathologic classifications.

Conflict of interest statement

None declared.

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