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The preventable burden of endometrial and ovarian cancers in Australia: A pooled cohort study

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HIGHLIGHTS

- Contemporary estimates of endometrial cancer burden attributable to body fatness.
- Overweight and obesity explain 42%, and obesity alone explains 35% of endometrial cancers.
- First estimates of future endometrial cancer burden for population subgroups.
- Overweight and obesity explain 49–87% of the endometrial cancer burden for some subgroups of women.

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ABSTRACT

Objective. Evidence on the endometrial and ovarian cancer burden preventable through modifications to current causal behavioural and hormonal exposures is limited. Whether the burden differs by population subgroup is unknown.

Methods. We linked pooled data from six Australian cohort studies to national cancer and death registries, and quantified exposure-cancer associations using adjusted proportional hazards models. We estimated exposure prevalence from representative health surveys. We then calculated Population Attributable Fractions (PAFs) with 95% confidence intervals (CIs), accounting for competing risk of death, and compared PAFs for population subgroups.

Results. During a median 4.9 years follow-up, 510 incident endometrial and 303 ovarian cancers were diagnosed. Overweight and obesity explained 41.9% (95% CI 32.3–50.1) of the endometrial cancer burden and obesity alone 34.5% (95% CI 27.5–40.9). This translates to 12,800 and 10,500 endometrial cancers in Australia in the next 10 years, respectively. The body fatness-related endometrial cancer burden was highest (49–87%) among women with diabetes, living remotely, of older age, lower socio-economic status or educational attainment and born in Australia. Never use of oral contraceptives (OCs) explained 8.1% (95% CI 1.8–14.1) or 2500 endometrial cancers. A higher BMI and current long-term MHT use increased, and long-term OC use decreased, the risk of ovarian cancer, but the burden attributable to overweight, obesity or exogenous hormonal factors was not statistically significant.

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Conclusions. Excess body fatness, a trait that is of high and increasing prevalence globally, is responsible for a large proportion of the endometrial cancer burden, indicating the need for effective strategies to reduce adiposity.

1. Introduction

Endometrial cancer is the fifth and ovarian cancer the eighth most common cancer in Australian women [1]. Several potentially modifiable behavioural and hormonal exposures are related to endometrial and ovarian cancer risk.

Considering endometrial cancer, body fatness is an established risk factor [2,3]. Use of menopausal hormone therapy (MHT), either oestrogen-only MHT or oestrogen-progestogen MHT, where progestogen is taken for <15 days per month, has been convincingly shown to increase the risk, with risk increasing with duration of use and remaining elevated for at least 10 years after ceasing treatment [4]. There is also convincing evidence that the risk of endometrial cancer is reduced for women who use combined oestrogen-progestogen oral contraceptives (OCs); the risk reduction is greater with longer duration of use and persists for at least 15 years after ceasing use [4]. Physical activity and coffee consumption are probable protective factors, high glycaemic load is a probable risk factor, and sedentary time is a suggestive risk factor [3].

Considering ovarian cancer, the use of OCs has been convincingly shown to reduce the risk, whereas the use of oestrogen-only MHT increases the risk [4]. A causal association between cigarette smoking and risk of mucinous ovarian tumours has also been established [5]. Body fatness is a probable risk factor [2,6] and breastfeeding is a suggestive protective factor [6].

Several studies have estimated population attributable fractions (PAFs) for the burden of endometrial [7–20] and ovarian [7,8,10,12,13,15–18,20,21] cancer attributable to behavioural or exogenous hormonal exposures in various countries. Each of these estimates was based on non-contemporary exposure distributions, and confidence intervals (CIs) were typically not reported. Additionally, no prior study has statistically compared the burden across population subgroups, which is potentially useful for targeting prevention.

We quantified the future burden of endometrial and ovarian cancer that could be avoided by changes to the current distribution of potentially modifiable behavioural and hormonal exposures in Australia, for all women and for subgroups.

2. Methods

2.1. Cohort data

We used individual-level data from the Australian cancer-PAF cohort consortium [22], which comprises seven well-established Australian prospective cohort studies, six of which included women: Melbourne Collaborative Cohort Study (MCCS), Blue Mountains Eye Study (BMES), Australian Longitudinal Study on Women's Health (ALSWH), Australian Diabetes, Obesity and Lifestyle Study (AusDiab), North West Adelaide Health Study (NWAHS), and the 45 and Up Study (45&Up). We excluded 1959 women who enrolled in more than one cohort and 1820 who did not consent to record linkage. The final study sample for endometrial cancer comprised 160,555 women after further excluding 841 with a history of endometrial cancer and 53,140 with a self-reported history of hysterectomy (Table 1). For ovarian cancer, we studied 194,864 women after excluding 346 with a history of ovarian cancer and 19,326 with self-reported bilateral oophorectomy (Table 1).

The Australian Institute of Health and Welfare Ethics Committee approved the study (EC2013/4/62).

2.2. Prevalence data

We obtained the most recent available risk factor exposure prevalence estimates from the Australian National Health Surveys (NHS 2014–2015 and 2001) [23,24], the LADY (Learning how Australians Deal with menopause sYmptoms) Survey (2013) [25], sampled to be

Table 1
Characteristics of the individual and pooled cohort and external data sources.

Characteristic	Cohort data							Prevalence data		
	MCCS	BMES	ALSWH	AusDiab	NWAHS	45&Up	Pooled	AusDiab[a]	LADY[b]	NHS[c]
Baseline year(s)	1990–1994	1992–1993	1996	1999–2000	1999–2003	2006–2009	1990–2008	1999–2000	2013	2014–2015
State/territory	VIC	NSW	All	All	SA	NSW	All	All	All	All
Endometrial cancer analysis										
Population (n)	19,169	1452	31,412	4874	2101	101,547	160,555	6197	3571	7907
Incident cancer cases (n)[d]	91	10	79	17	5	308	510	–	–	–
Deaths (n)[d]	667	231	1857	280	116	3605	6756	–	–	–
Age in years at baseline, mean (range)	54 (31–76)	66 (49–97)	42[e] (18-75)	49 (25-91)	50 (18–89)	60 (45–106)	55 (18–106)	50 (25–91)	63 (50–71)	47 (18–85)
Ovarian cancer analysis										
Population (n)	22,116	1851	35,577	5763	2108	127,449	194,864	6197	3571	7907
Incident cancer cases (n)[d]	56	6	70	7	4	160	303	–	–	–
Deaths (n)[d]	762	297	2274	351	117	4786	8587	–	–	–
Age in years at baseline, mean (range)	54 (31–76)	66 (49–97)	44[e] (18-75)	49 (25-91)	46 (18–89)	61 (45- > 100)	57 (18- > 100)	50 (25–91)	63 (50–71)	47 (18–85)

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); LADY (Learning how Australians Deal with menopause sYmptoms) survey; MCCS (Melbourne Collaborative Cohort Study); NHS (National Health Survey); NSW (New South Wales); NWAHS (North West Adelaide Health Study); SA (South Australia); VIC (Victoria).

[a] The AusDiab Study is the primary source of exposure prevalence for OC use. The study population differs from that used for the cohort analyses as there are no exclusions.

[b] The LADY Survey is the primary source of exposure prevalence for MHT use in postmenopausal women.

[c] The NHS is the primary source of exposure prevalence for body fatness and physical activity.

[d] During the first 10-years follow-up.

[e] The ALSWH recruited three cohorts aged 18–23, 45–50 and 70–75 so the age distribution is not continuous.

representative for use of MHT, and the national population-based AusDiab Study (1999–2000) [26] (Table 1, Supplementary Table 1).

2.3. Data collection and harmonisation

We examined potentially modifiable hormonal and behavioural exposures with convincing, probable or suggestive evidence of a causal association with endometrial or ovarian cancer [2–6] if they were measured in our cohort and there were available sources of prevalence data. These exposures were body fatness (approximated by body mass index, BMI), OC use, MHT use, smoking, physical activity, and breastfeeding, ascertained at baseline. For OC and MHT use, we also examined duration of use and time since cessation, but we did not have information on type of MHT. We harmonised these exposures across the cohort studies and external prevalence data sources (Supplementary Table 1), both as continuous variables and by classifying them in accordance with current Australian recommendations for healthy living [22]. These recommendations are to maintain a healthy weight (BMI < 25 kg/m^2), to not smoke, to do at least 150 min of moderate or 75 min of vigorous physical activity per week (≥15 MET-hours/week), and to breastfeed exclusively for around six months and continue breastfeeding until 12 months if possible. MHT use was evaluated for postmenopausal women, with menopausal status defined as previously described [27].

We also harmonised non-modifiable exposures associated with endometrial or ovarian cancer risk [3,6,28]: age, height, nulliparity and diabetes mellitus (available from all or most cohorts); as well as first-degree family history of ovarian cancer, age at menarche, and age at menopause (collected in at least one cohort) to allow adjustment for potential confounders (Supplementary Table 1) [27]. We further harmonised data on country of birth, marital status, educational attainment, socio-economic status and residential location (rurality) for subgroup analyses.

2.4. Data linkage and ascertainment of outcomes

The Australian Institute of Health and Welfare performed the linkage of the pooled cohort to the Australian Cancer Database and National Death Index using probabilistic matching to identify cancers and deaths. These records were available until 31st December 2012, providing a maximum of 8–22 years follow-up (Table 1).

We classified primary invasive endometrial and ovarian cancers of epithelial origin according to the International Classification of Diseases for Oncology (ICD-O-3; topography C54-C55 and C56, respectively), excluding all sarcomas, and separately identifying cancers of corpus uteri (C54) and mucinous ovarian cancers (morphology 8470–8490, 9015) [29].

2.5. Statistical methods

We performed separate analyses for endometrial and ovarian cancers. We defined follow-up as the time from baseline to the date of cancer diagnosis, death or end of follow-up, whichever occurred first. We estimated the strength of exposure-cancer and exposure-death associations using a parametric piecewise constant exponential hazards model, and expressed them as hazard ratios (HR) and their 95% confidence intervals (CI). We included the first 10 years of follow-up to generate comparable estimates across the cohorts, and tested heterogeneity between cohorts using the asymptotic DerSimonian and Laird Q statistic.

For each cancer, we first modelled each risk factor separately, adjusted for age and study. We then modelled all risk factors together, retaining significant factors in the final model. We computed the corresponding exposure prevalence (PR) estimates from the health surveys, and combined them with the strength of association estimates to calculate PAFs and their 95% CIs, accounting for potential competing risk of death [27,30,31]. This PAF method allows a flexible choice of the risk and reference level for the hypothetical exposure modification, and we evaluated scenarios in which the exposure was completely removed or only reduced. The method also allows testing for potential PAF effect modification, by including an interaction term between the risk factor and the potential effect modifying factor in the model and calculating the 95% confidence interval for the difference in PAF estimates between the categories of the effect modifying factor. We tested for potential differences in the distribution of the endometrial and ovarian cancer burden by other exposures and socio-demographic factors.

We conducted sensitivity analyses adjusting for potential confounding factors only available for subsets of participants and excluding the first year of follow-up, to assess the potential effect of reverse causality.

We estimated the number of endometrial and ovarian cancers in Australia over the next 10 years that could be attributed to the current risk factors by multiplying the PAF estimates by the projected numbers of these cancers during 2017–2026 [32].

We used SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and our publicly available PAF program [31].

3. Results

During a median 4.9 years (interquartile range 4.4–10.0) follow-up, we observed 510 incident endometrial cancers (495 corpus uteri) and 6756 deaths from any cause (Table 1). The corresponding figures for the ovarian cancer analyses were 303 cancers (18 mucinous carcinomas) and 8587 deaths.

3.1. Endometrial cancer risk and burden

3.1.1. All women

We found no significant heterogeneity between the cohort-specific HRs for endometrial cancer in relation to the non-modifiable or modifiable risk factors (Supplementary Table 2).

Older age at baseline, greater height, nulliparity and older age at menopause were associated with an increased risk of endometrial cancer (Table 2). No exposure, other than age, was associated with a greater risk of death than of endometrial cancer (data not shown).

Body fatness was positively associated with endometrial cancer (HR 1.10, 95% CI 1.09, 1.12 per kg/m^2; Table 2). Obese women (BMI ≥ 30 kg/m^2) had a 3-fold risk of endometrial cancer (HR 3.17, 95% CI 2.52, 3.98) compared with women of healthy weight. In 2014–2015, more than half of Australian women were either overweight (29%) or obese (27%). Overweight and obesity combined were estimated to be responsible for 41.9% (95% CI 32.3%, 50.1%) of endometrial cancers, and obesity alone was responsible for 34.5% (95% CI 27.5%, 40.9%). In the next 10 years this translates to 12,800 endometrial cancers attributable to overweight and obesity combined and 10,500 attributable to obesity alone at the national level. Were all obese women instead only overweight, 27.9% or 8500 endometrial cancers could be prevented. The results for the risk and burden of cancer of corpus uteri in relation to body fatness were very similar to those for all endometrial cancers (data not shown).

Ever use of OCs was inversely associated with endometrial cancer risk (HR 0.73, 95% CI 0.59, 0.91; Table 2). The protective effect appeared to last for up to 30 years since ceasing use, irrespective of the duration of use (Supplementary Table 3). Women who used OCs for a shorter duration were more likely to have ceased longer ago (median of 31 versus 22 years ago for those who used OCs < 5 versus ≥5 years; p-difference < 0.001). Three quarters of women had used OCs (Table 2). Were all women to ever use OCs, the endometrial cancer burden would potentially be lower by 8.1% (2500 cancers).

In this analysis, MHT use was not associated with endometrial cancer risk (Table 2), irrespective of duration of use or time since cessation (data not shown). Similarly, physical activity was not associated with endometrial cancer risk.

Table 2
Risk factor frequencies, hazard ratios, population exposure prevalences and attributable fractions for endometrial cancer incidence by exposure level over 10-years follow-up.

Risk factors	n/N (%)[a]	HR (95% CI)[b]	PR[c]	Risk factor category change	PAF (95% CI)[b]
Non-modifiable risk factors					
Age (per year)	448/143,529	1.04 (1.03, 1.05)			
Height (per 5 cm)	448/143,529	1.07 (1.00, 1.14)			
Nulliparity					
1. No	373/116,702 (81%)	1	69%		
2. Yes	75/26,827 (19%)	1.33 (1.03, 1.72)	31%		
Diabetes mellitus					
1. No	402/136,049 (95%)	1	94%		
2. Yes	44/7294 (5%)	1.31 (0.95, 1.80)	6%		
Age at menarche (per year)[d]	98/20,312	0.95 (0.84, 1.08)			
Age at menopause (per year)[d]	246/69,481	1.07 (1.04, 1.10)			
Age at menopause[d]					
1. <55 years	210/64,200 (92%)	1	NA		
2. ≥55 years	36/5281 (8%)	1.81 (1.27, 2.59)	NA		
Modifiable risk factors					
Body fatness (per kg/m^2)	448/143,529	1.10 (1.09, 1.12)			NA
Body fatness (BMI; kg/m^2)					
1. <25.0	139/71,137 (50%)	1	44%	2,3 → 1	41.9 (32.3, 50.1)
				3 → 1	34.5 (27.5, 40.9)
2. 25–29.9	136/44,540 (31%)	1.44 (1.13, 1.83)	29%	3 → 2	27.6 (19.6, 34.7)
3. ≥30.0	173/27,852 (19%)	3.17 (2.52, 3.98)	27%		
Oral contraceptive use					
1. Never	188/36,540 (25%)	1	24%		
2. Ever	260/106,989 (75%)	0.73 (0.59, 0.91)	76%	1 → 2	8.1 (1.8, 14.1)
Menopausal hormone therapy use[e]					
1. Never	232/54,410 (64%)	1	56%		
2. Former	67/21,566 (26%)	0.86 (0.65, 1.14)	32%		
3. Current	32/8498 (10%)	1.08 (0.74, 1.58)	12%		
Physical activity					
Moderate activity (per hour/week)	242/86,801	1.01 (0.99, 1.02)			
Vigorous activity (per hour/week)	204/71,891	1.02 (0.99, 1.05)			
Australian recommendation[f]					
1. < 150 min/week	94/30,258 (34%)	1	79%		
2. ≥ 150 min/week	156/59,211 (66%)	1.07 (0.82, 1.39)	21%		

BMI (body mass index); CI (confidence interval); HR (hazard ratio); NA (not able to be computed); PAF (population attributable fraction); PR (prevalence).
[a] Number of cancer cases/total N (%) per risk factor category.
[b] Adjusted for age, study, body fatness, oral contraceptive use, height, and nulliparity.
[c] Population prevalence for nulliparity from National Health Survey (NHS) 2001, for diabetes mellitus, body fatness and physical activity from NHS 2014–2015, for OC use from Australian Diabetes, Obesity and Lifestyle (AusDiab) Study 1999–2000, and for MHT use from Learning how Australians Deal with menopause sYmptoms (LADY) Survey 2013.
[d] Only used in sensitivity analyses.
[e] Analyses restricted to postmenopausal women with intact uterus.
[f] ≥150 min/week of moderate physical activity or ≥75 min/week of vigorous physical activity or a combination of the two.

The strength of these associations did not change materially after excluding the first year of follow-up, nor after adjusting for age at menopause in sensitivity analyses (data not shown).

3.1.2. Subgroups of women

The burden of endometrial cancer attributable to overweight and obesity was higher for women with, than without, a history of diabetes (86.8% compared with 37.6%, p-difference < 0.001), women who lived in regional or remote areas compared with major cities (61.5% compared with 25.4%; p-difference < 0.001), women 70 years or older or 55–69 years compared with those <55 years (59.8% and 45.5% compared with 20.9% respectively; p-difference < 0.001 and 0.03), women with lower compared with higher socio-economic status (56.0% for SES quintile 2 compared with 15.6% for SES quintile 5, p-difference = 0.005), women of low compared with high educational attainment (50.0% compared with 26.5%, p-difference = 0.03), and women born in Australia compared with elsewhere (49.3% compared with 16.9%, p-difference = 0.004), due to both a higher body fatness prevalence and stronger association (Table 3). Further, the obesity-attributable endometrial cancer burden was higher for women who did not meet the Australian guidelines for physical activity compared with those who did (43.4% compared with 25.7% respectively; p-difference = 0.04), due to a higher prevalence of obesity for physically inactive women. There were no subgroup differences in the distribution of endometrial cancer burden attributable to non-OC use (data not shown).

3.2. Ovarian cancer risk and burden

3.2.1. All women

We identified no significant between-cohort heterogeneity for ovarian cancer in relation to non-modifiable or modifiable risk factors (Supplementary Table 4).

Older age at baseline, nulliparity and having a first-degree relative diagnosed with ovarian cancer were associated with a higher risk of ovarian cancer (Table 4). Age was the only exposure associated with a greater risk of death than of ovarian cancer (data not shown).

Body fatness was positively associated with ovarian cancer when evaluated as a continuous exposure (HR 1.02, 95% CI 1.00, 1.05 per kg/m^2) but not when categorised into overweight and obesity (Table 4). The respective PAF estimates for ovarian cancer attributable to overweight or obesity were also not significant.

Ever use of OCs for five or more years compared to never use was inversely associated with ovarian cancer risk (HR 0.72, 95% CI 0.52, 0.99; Table 4). This protective effect appeared to last for up to 30 years, and shorter duration of use did not show an association (Supplementary Table 3). The respective reduction in the ovarian cancer burden attributable to long-term OC use was 8.3% (95% CI -0.4%, 16.2%).

Current use of MHT for five or more years compared to never use was associated with an increased risk of ovarian cancer (HR1.74, 95% CI 1.06, 2.85); long-term MHT use was reported in 11% of postmenopausal Australian women in 2013 (Table 4). The corresponding ovarian

Table 3
Exposure prevalence, hazard ratios and fractions of endometrial cancer attributable to overweight and obesity by effect modifying factors.

Effect modifier	BMI categories						PAF (2,3 → 1)[c]	PAF (3 → 1)[c]
	1. <25.0 kg/m^2		2. 25.0–29.9 kg/m^2		3. ≥30.0 kg/m^2			
	PR[a]	HR (95% CI)[b]	PR[a]	HR (95% CI)[b]	PR[a]	HR (95% CI)[b]		
Oral contraceptive use								
Never	41%	1	35%	1.44 (1.00, 2.07)	24%	3.09 (2.17, 4.39)	39.6 (23.5, 52.4)	30.2 (19.9, 39.2)
Ever	49%	1	29%	1.44 (1.05, 1.96)	22%	3.23 (2.40, 4.33)	38.4 (25.8, 48.9)	30.6 (22.0, 38.2)
Menopausal hormone therapy use[d]								
Never	41%	1	33%	1.37 (1.03, 1.82)	26%	3.21 (2.47, 4.18)	41.4 (29.6, 51.2)	34.1 (26.1, 41.2)
Ever	43%	1	31%	1.44 (0.93, 2.25)	26%	2.43 (1.54, 3.84)	33.9 (12.5, 50.1)	24.8 (10.5, 36.8)
Physical activity[e]								
< 150 min/week	41%	1	29%	1.11 (0.62, 2.00)	30%	3.65 (2.25, 5.92)	45.2 (21.6, 61.6)	43.4 (26.9, 56.1) *
≥ 150 min/week	54%	1	28%	2.07 (1.40, 3.06)	18%	3.49 (2.34, 5.22)	42.7 (27.0, 55.0)	25.7 (15.8, 34.5)
History of diabetes mellitus								
No	46%	1	29%	1.39 (1.09, 1.78)	26%	2.89 (2.27, 3.67)	37.6 (27.3, 46.4) *	30.6 (23.1, 37.3) *
Yes	16%	1	33%	4.49 (1.00, 20.3)	51%	11.7 (2.79, 48.8)	86.8 (47.0, 96.7)	71.4 (49.7, 83.8)
Menopausal status[f]								
Premenopausal	54%	1	24%	1.14 (0.62, 2.12)	22%	2.51 (1.42, 4.42)	26.9 (1.3, 45.9)	24.4 (6.0, 39.1)
Postmenopausal	32%	1	36%	1.58 (1.21, 2.08)	32%	3.27 (2.50, 4.27)	48.5 (37.1, 57.9)	38.2 (29.8, 45.5)
Age group (years at baseline)								
<55	50%	1	25%	0.85 (0.52, 1.38)	25%	2.21 (1.46, 3.34)	20.9 (0.9, 36.8) *	23.9 (9.6, 35.9)
55 to 69	31%	1	33%	1.41 (0.98, 2.02)	35%	2.97 (2.11, 4.18)	45.5 (29.3, 58.0)	38.0 (26.7, 47.6)
≥70	34%	1	40%	2.23 (1.42, 3.49)	27%	4.76 (3.02, 7.52)	59.8 (43.0, 71.7)	40.3 (27.7, 50.8)
Country of birth								
Australia	42%	1	28%	1.64 (1.24, 2.18)	30%	3.66 (2.80, 4.80)	49.3 (38.5, 58.2) *	40.2 (31.9, 47.4) *
Other	47%	1	31%	0.93 (0.58, 1.50)	22%	2.01 (1.29, 3.13)	16.9 (−5.4, 34.5)	18.7 (5.0, 30.4)
Marital status								
Not married	49%	1	27%	1.67 (1.08, 2.58)	26%	3.56 (2.35, 5.39)	46.1 (28.7, 59.3)	36.5 (23.5, 47.3)
Married/de facto	41%	1	30%	1.32 (0.99, 1.76)	28%	3.01 (2.29, 3.95)	39.8 (27.6, 50.0)	34.0 (25.3, 41.6)
Educational attainment								
Low	40%	1	30%	1.66 (1.21, 2.29)	30%	3.65 (2.68, 4.96)	50.0 (37.3, 60.2) #	40.1 (30.8, 48.1)
Intermediate	40%	1	30%	1.31 (0.76, 2.26)	30%	2.40 (1.40, 4.11)	33.7 (6.7, 52.9)	27.6 (8.3, 42.9)
High	53%	1	26%	0.99 (0.59, 1.67)	21%	2.75 (1.71, 4.41)	26.5 (5.2, 43.1) #	26.7 (11.5, 39.3)
Socio-economic status (SES)								
SES quintile 1 (low)	39%	1	29%	1.46 (0.87, 2.44)	32%	2.91 (1.79, 4.75)	42.8 (19.0, 59.7)	35.3 (18.5 48.6)
SES quintile 2	42%	1	28%	1.31 (0.73, 2.36)	30%	4.99 (3.04, 8.17)	56.0 (35.4, 70.1) #	52.1 (37.0, 63.6) #
SES quintile 3	41%	1	30%	1.71 (1.02, 2.87)	29%	3.14 (1.88, 5.24)	45.2 (21.8, 61.6)	33.3 (17.1, 46.5)
SES quintile 4	44%	1	30%	1.71 (1.03, 2.84)	26%	2.89 (1.72, 4.84)	41.2 (18.0, 57.9)	28.9 (12.9 41.9) #[g]
SES quintile 5 (high)	52%	1	27%	1.01 (0.58, 1.77)	21%	1.88 (1.04, 3.40)	15.6 (−10.2, 35.4) #	15.3 (−2.2, 29.8) #[g]
Residential location								
Major city	47%	1	29%	1.06 (0.78, 1.46)	25%	2.30 (1.70, 3.12)	25.4 (11.3, 37.3) *	24.1 (14.4, 32.7) *
Regional or remote	36%	1	30%	2.13 (1.47, 3.09)	34%	4.72 (3.31, 6.72)	61.5 (48.9, 71.1)	48.7 (38.7, 57.1)

BMI (body mass index); CI (confidence interval); HR (hazard ratio); PAF (population attributable fraction); PR (prevalence); SES (socio-economic status); * Burden for this subgroup differs from burden for other subgroup(s); # Burden between these two subgroups differs, i.e. the 95% confidence interval of the difference of the PAF estimates for these subgroups does not include zero.

[a] Prevalence from National Health Survey 2014–2015, except for the analyses by menopausal hormone therapy (Learning how Australians Deal with menopause sYmptoms Survey 2013) and oral contraceptive use (Australian Diabetes, Obesity and Lifestyle Study 1999).

[b] Adjusted for age, study, oral contraceptive use, height, and nulliparity.

[c] PAF and 95% confidence interval for the exposure modification.

[d] Analyses restricted to postmenopausal women with intact uterus.

[e] Australian recommendation: ≥ 150 min/week of moderate physical activity or ≥ 75 min/week of vigorous physical activity or a combination of the two.

[f] Menopausal status from National Health Survey 2014–2015 according to age criteria alone (premenopausal: age < 45 years; postmenopausal: age ≥ 55 years).

[g] Burden in quintiles 4 and 5 differs statistically significantly from burden in quintile 2.

cancer burden was 7.0% (95% CI -0.7%, 14.2%). However, limiting the MHT use to less than five years could potentially reduce ovarian cancer burden by 11.5% (95% CI 2.6%, 19.6%).

Neither smoking status nor breastfeeding predicted risk of ovarian cancer (Table 4). The association between smoking status and mucinous ovarian cancer could not be evaluated separately due to the small number of cases.

The strength of these associations did not change materially after excluding the first year of follow-up, nor after adjusting for family history of ovarian cancer in sensitivity analyses (data not shown).

3.2.2. Subgroups of women

There were no notable differences in the distribution of ovarian cancer burden by population subgroups (data not shown).

4. Discussion

We found that overweight and obesity will account for 42% of the endometrial cancer burden and 12,800 of the endometrial cancers diagnosed in Australia over the next 10 years. We estimated that obesity (compared to healthy weight) was responsible for 35% of all endometrial cancers, and 28% could potentially be prevented were all obese

Table 4
Risk factor frequencies, hazard ratios, population exposure prevalences and attributable fractions for ovarian cancer incidence by exposure level over 10-years follow-up.

Risk factors	n/N (%)[a]	HR (95% CI)[b]	PR[c]	Risk factor category change	PAF (95% CI)[b]
Non-modifiable risk factors					
Age (per year)	262/168,966	1.04 (1.03, 1.05)			
Height (per 5 cm)	262/168,948	1.04 (0.96, 1.14)			
Nulliparity					
1. No	216/140,659 (83%)	1	69%		
2. Yes	46/28,307 (17%)	1.44 (1.03, 2.02)	31%		
First-degree family history of ovarian cancer					
1. No	134/106,846 (96%)	1	NA		
2. Yes	10/3882 (4%)	1.98 (1.04, 3.77)	NA		
Age at menarche (per year)[d]	55/21,458	0.91 (0.77, 1.08)			
Age at menopause (per year)[d]	129/81,262	0.99 (0.96, 1.03)			
Age at menopause[d]					
1. < 55 years	119/75,329 (93%)	1	NA		
2. ≥ 55 years	10/5933 (7%)	0.98 (0.51, 1.87)	NA		
Modifiable risk factors					
Body fatness (per kg/m^2)	262/168,966	1.02 (1.00, 1.05)			NA
Body fatness (BMI; kg/m^2)					
1. < 25.0	113/80,777 (48%)	1	44%	2,3 → 1	9.4 (−5.4, 22.1)
	89/53,541 (31%)			3 → 1	6.3 (−3.1, 15.0)
2. 25–29.9	60/34,638 (21%)	1.12 (0.84, 1.48)	29%	3 → 2	3.4 (−6.8, 12.7)
3. ≥30.0		1.26 (0.92, 1.72)	27%		
Oral contraceptive use					
1. Never	110/43,755 (26%)	1	24%		
2. Ever, < 5 years	68/47,924 (28%)	0.86 (0.62, 1.20)	32%		
3. Ever, ≥ 5 years	84/77,287 (46%)	0.72 (0.52, 0.99)	43%	1,2 → 3	14.0 (−2.4, 27.8)
				1 → 3	8.3 (−0.4, 16.2)
Menopausal hormone therapy use[e]					
1. Never	116/62,151 (61%)	1	50%		
				5 → 1	7.0 (−0.7, 14.2)
2. Former, < 5 years	22/14,634 (14%)	0.98 (0.62, 1.56)	17%		
3. Former, ≥ 5 years	26/13,138 (13%)	1.52 (0.97, 2.39)	19%		
4. Current, < 5 years	4/4092 (4%)	0.53 (0.19, 1.44)	3%	5 → 4	11.5 (2.6, 19.6)
5. Current, ≥ 5 years	19/7272 (7%)	1.74 (1.06, 2.85)	11%		
Smoking status					
1. Never smoker	171/105,833 (63%)	1	60%		
2. Former smoker	69/45,335 (27%)	1.04 (0.79, 1.38)	27%		
3. Current smoker	18/16,208 (10%)	0.89 (0.54, 1.46)	13%		
Breastfeeding[f]					
Per 6 months	160/115,427	0.96 (0.91, 1.02)			
1. Never	28/15,344 (13%)	1	14%		
2. Ever	132/100,083 (87%)	0.78 (0.52, 1.17)	86%		

BMI (body mass index); CI (confidence interval); HR (hazard ratio); NA (not able to be computed); PAF (population attributable fraction); PR (prevalence).
[a] Number of cancer cases/total N (%) per risk factor category.
[b] Adjusted for age, study, body fatness, oral contraceptive use and nulliparity.
[c] Population prevalence for nulliparity and breastfeeding from National Health Survey (NHS) 2001, for body fatness and smoking status from NHS 2014–2015, for OC use from Australian Diabetes, Obesity and Lifestyle (AusDiab) Study 1999–2000, and for MHT use from Learning how Australians Deal with menopause sYmptoms (LADY) Survey 2013.
[d] Only used in sensitivity analyses.
[e] Analyses restricted to postmenopausal women.
[f] Among parous women.

women instead overweight. We also identified subgroups of women with the highest body fatness–related endometrial cancer burden, with overweight and obesity accounting for 49–87% of the burden for these subgroups. Additionally, we estimated that 8% of the future burden of endometrial cancers will be attributable to having never used OCs.

The prior Australian estimate for body fatness–related endometrial cancer burden in 2010 was based on a body fatness prevalence of 37% in 2001; 26% of endometrial cancers in Australia were attributed to overweight and obesity [18]. The prevalence of overweight and obesity has since increased to 56% [23], with the prevalence of obesity almost doubling in that time period (15% in 2001 compared with 27% in 2014–2015) [18,23]. Prior PAF estimates for the endometrial cancer burden attributed to overweight and obesity in other countries range from 13% to 51%, based on prevalence estimates of 21%–70% [7,8,11–13,15,16,19,20], and to obesity alone from 22% to 40%, based on prevalence estimates of 22%–39% [14,16]. As the worldwide prevalence of overweight and obesity has increased [33], and these studies are based on past prevalences, these estimates need to be updated. To our knowledge, there was no prior PAF estimate for the obesity-related endometrial cancer burden for Australia, and no previous PAF study has examined the endometrial cancer burden preventable by being overweight instead of obese; all previous studies addressed the ideal scenario where all women were healthy weight.

To the best of our knowledge, no prior study has tested for differences in endometrial cancer burden between population subgroups. We showed that women with a history of diabetes, living in regional or remote areas, of older age, lower socioeconomic status or lower educational attainment, born in Australia, and exercising less than recommended, bear the highest body fatness–related endometrial cancer burden. These differences were due to both a higher prevalence of overweight/obesity and a higher relative risk in these subgroups.

We observed a significant 2% increase in the risk of ovarian cancer per unit increase in BMI, in line with prior literature [6]. We did not, however, observe a significant association between categorised overweight or obesity and ovarian cancer risk, likely due to loss of information due to categorisation. Accordingly, our estimate of the ovarian cancer burden attributable to overweight and obesity (9%) was not

statistically significant. The only prior Australian estimate of 4% for the burden in 2010 was reported without confidence intervals [18]. Other prior studies reported PAF estimates ranging from 4% to 22% [8,12,13,16,20], that were either non-significant [12] or not accompanied by confidence intervals [8,13,16,20]. However, even the largest PAF estimate of 22% was likely to be non-significant as, similarly to our study, the hazard ratios for ovarian cancer in relation to overweight or obesity were not significant [13].

We provide the first Australian estimate of the proportion of endometrial cancers attributable to never using OCs. The only previous Australian estimate (31%) was for non-current use of OCs [34], and was higher than our study estimate (8%) due to a much higher prevalence of non-current (73%) than never (24%) users. In keeping with published evidence [4], we found that the protective effect of OCs on endometrial cancer risk persisted for up to 30 years after ceasing use, and thus both current and past use reduce the risk and burden of endometrial cancer. Other prior studies reported PAF estimates of 22% for non-current use [17] and 17% for never use [35], but without confidence intervals or the prevalence data the estimate was based on.

Our PAF estimate for the ovarian cancer burden attributable to OC use of <5 years (14%) was not significant. The statistical significance of the prior PAF estimates for non-current use, specifically 19% (Australia) [34] and 17% (France) [17], and never use, specifically 9% (UK) [35], was not reported. We found that the protective effect of long-term use of OCs for ovarian cancer persisted for up to 30 years after ceasing use, in line with prior literature [4]. Long-term OC use appeared protective of death, which is accounted for by our competing risk analysis and may explain the non-significant burden result. Our data did not include information on OC type and therefore our results describe the average protective effect of OCs. However, although the use of OCs is associated with a reduction in risk for endometrial, ovarian and colorectal cancer, and also provides reproductive health benefits, it increases the risk for breast, cervical and liver cancer [4], so any recommendation regarding the use of OCs should be made in consideration of all these effects. Additionally, the prevalence of OC use in our study was from around 2000, due to lack of newer representative prevalence data sources, although the prevalence of hormonal contraception appears to have remained stable over time in other similar countries [36].

We did not find an association between MHT use and endometrial cancer risk, but we could not evaluate MHT use by type and the prior evidence is strong for oestrogen-only MHT [4]. Women who have not had a hysterectomy are less likely to have been prescribed oestrogen-only MHT [25], and only women without hysterectomy were included in our endometrial cancer analysis. The association of oestrogen-progestogen MHT with endometrial cancer risk is dependent on how many days per month progestogen is administered [4]. We did find an increased risk of ovarian cancer in relation to current MHT use for five or more years and showed that limiting MHT use to less than five years could potentially reduce the ovarian cancer burden by 12%. A prior Australian study attributed 3% of endometrial cancers and 1.5% of ovarian cancers in 2010 to current use of oestrogen-only MHT, based on the assumption that 3% of all Australian women and 0.4% of women without hysterectomy used oestrogen-only MHT in 2004–2005, but no confidence intervals were provided [18]. The only other study reported even smaller point estimates for MHT-attributable endometrial and ovarian cancer burden (1.2% and 0.7%, respectively) in the UK [35].

We found physical activity below Australian recommendations (<15 MET-hours/week) was not associated with endometrial cancer risk. Two prior studies that used similar reference levels (≥15–20 MET-hours/week) reported PAF estimates of 3–4%, which were either non-significant [12] or not accompanied by confidence intervals [15]. A prior Australian study using a higher reference level (≥30 MET-hours/week) attributed 6% of endometrial cancers to lower physical activity levels but reported no confidence intervals; however, no women reported physical activity levels ≥30 MET-hours/week in NHS 2001 and thus such high levels are unlikely to be a realistic target for behaviour modification [18]. Three other PAF studies comparing the highest to lowest levels of physical activity reported PAF estimates of 10% [7], 22% [10] and 22% (95% CI 7.1–34.3%) [9].

We observed no association between smoking and ovarian cancer risk but were not able to evaluate mucinous ovarian cancers due to the small number of cases. A previous Australian study attributed 2% of all ovarian cancers and 17% of mucinous ovarian cancers in 2010 to ever smoking, using hazard ratios from an international meta-analysis, but did not report the statistical significance of the findings [18,37]. An earlier European study attributed 14% of mucinous ovarian cancers in 2008 to current smoking but this estimate was based on a non-significant hazard ratio [21]. Of all ovarian cancers, 1–5% were previously attributed to ever smoking [7,12,15], with the highest estimate reported as non-significant [12].

We did not find a significant association between breastfeeding and ovarian cancer risk. The only previous study attributed 18% of ovarian cancers in the UK in 2010 to not breastfeeding a minimum of 6 months, a target that 75% of parous women were unable to meet, but again did not report the significance of this finding [15].

4.1. Strengths and limitations

This is a large pooled study with harmonised individual-level cohort data matched with representative prevalence data. The advanced PAF method allowed us to assess PAF effect modification and account for potential competing risk of death, even though no strong competing risk was present.

We examined modifiable and non-modifiable exposures with convincing or probable evidence of causality according to the IARC or WCRF [2–6], except for dietary factors, family history of endometrial cancer, and tamoxifen, a hormonal therapy used for breast cancer [3]. Although information on hysterectomy and oophorectomy was self-reported, such data have been shown to be accurate [38], though the cumulative prevalence of exposure, as well as other information gathered at baseline, may have changed during follow-up. However, any hysterectomies performed for benign conditions are unlikely to be associated with the modifiable risk factors of interest and therefore are unlikely to affect our analyses. Sensitivity analyses did not indicate reverse causality or confounding but the possibility of residual confounding due to the factors mentioned above cannot be excluded. Despite the large sample size, our power for evaluating ovarian cancer risk and burden may have been inadequate. Additionally, although our maximum follow-up time was 10 years, the median follow-up time was only 5 years, which may have attenuated some of the associations. Finally, PAF estimation assumes immediate risk reduction following the hypothetical behavior modification, which is unrealistic.

5. Conclusion

In summary, a large proportion of endometrial cancer cases in Australia could be prevented if policy and interventions could successfully support weight reduction for those who are obese or overweight. In Australia, women with diabetes, living in rural areas, of older age, lower socio-economic status, lower educational attainment, born in Australia, or physically inactive, appear to have the highest body fatness–related endometrial cancer burden. Weight reduction would also likely reduce the risk of ovarian cancer. Obesity prevention measures are all the more important as the prevalence is predicted to increase, both in Australia [39] and globally [40], and is also related to many other cancers [2] and health conditions.

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Conflict of interest statement

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RJM: Has nothing to disclose

JEB: Has nothing to disclose

EB: Has nothing to disclose

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TKG: Has nothing to disclose

EK: Has nothing to disclose

LSV: Has nothing to disclose

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Author contributions

- All authors provided substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.
- MAL, MEA and CMV drafted the work and all other authors revised it critically for important intellectual content.
- All authors provided final approval of the version to be published.

Appendix A. Supplementary data

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