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ORIGINAL CONTRIBUTION

Glycemic index, glycemic load and endometrial cancer risk: results from the Australian National Endometrial Cancer study and an updated systematic review and meta-analysis

Christina M. Nagle · Catherine M. Olsen · Torukiri I. Ibiebele · Amanda B. Spurdle · Penelope M. Webb · The Australian National Endometrial Cancer Study Group · The Australian Ovarian Cancer Study Group

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Abstract
Purpose The relationship between habitual consumption of foods with a high glycemic index (GI) and/or a diet with a high glycemic load (GL) and risk of endometrial cancer is uncertain, and relatively few studies have investigated these associations. The objectives of this study were to examine the association between GI/GL and risk of endometrial cancer using data from an Australian population-based case–control study and systematically review all the available evidence to quantify the magnitude of the association using meta-analysis.
Methods The case–control study included 1,290 women aged 18–79 years with newly diagnosed, histologically confirmed endometrial cancer and 1,436 population controls. Controls were selected to match the expected Australian state of residence and age distribution (in 5-year bands) of cases. For the systematic review, relevant studies were identified by searching PubMed and Embase databases through to July 2011. Random-effects models were used to calculate the summary risk estimates, overall and dose–response.
Results In our case–control study, we observed a modest positive association between high dietary GI (OR 1.43, 95 % CI 1.11–1.83) and risk of endometrial cancer, but no association with high dietary GL (OR 1.15, 95 % CI 0.90–1.48). For the meta-analysis, we collated information from six cohort and two case–control studies, involving a total of 5,569 cases. The pooled OR for the highest versus the lowest intake category of GI was 1.15 (0.95–1.40); however, there was significant heterogeneity (p 0.004) by study design (RR 1.00 [95 % CI 0.87–1.14] for cohort studies and 1.56 [95 % CI 1.21–2.02] for case–control studies). There was no association in the dose–response meta-analysis of GI (RR per 5 unit/day increment of GI 1.00, 95 % CI 0.97–1.03). GL was positively associated with endometrial cancer. The pooled RR for the highest versus the lowest GL intake was 1.21 (95 % CI 1.09–1.33) and 1.06 (95 % CI 1.01–1.11) per 50 unit/day increment of GL in the dose–response meta-analysis.
Conclusion The pooled results from observational studies, including our case–control results, provide evidence of a modest positive association between high GL, but not GI, and endometrial cancer risk.

Keywords Glycemic load · Glycemic index · Case–control · Dose–response meta-analysis · Endometrial cancer

The details of The Australian National Endometrial Cancer Study Group and The Australian Ovarian Cancer Study Group are given "Appendix".

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C. M. Nagle (✉) · C. M. Olsen · T. I. Ibiebele · P. M. Webb · The Australian National Endometrial Cancer Study Group · The Australian Ovarian Cancer Study Group
Gynaecological Cancers, Population Health Research Department, Queensland Institute of Medical Research, Locked Bag 2000, Royal Brisbane Hospital, Herston, Brisbane, QLD 4029, Australia
e-mail: Christina.Nagle@qimr.edu.au

A. B. Spurdle
Molecular Cancer Epidemiology, Genetics Research Department, Queensland Institute of Medical Research, Locked Bag 2000, Royal Brisbane Hospital, Herston, Brisbane, QLD, Australia

Introduction

Insulin resistance and hyperinsulinemia are widely hypothesised to play a role in the aetiology of endometrial cancer [1–4]. Obesity, hypertension and impaired glucose tolerance, which are known risk factors for endometrial cancer, are all associated with insulin resistance and hyperinsulinemia [1, 4]. Several biologically plausible mechanisms have been put forward to explain the potential association between hyperinsulinemia/insulin resistance and the development of endometrial cancer [1, 3, 4]. For example, insulin is thought to influence endometrial cancer risk via direct actions on endometrial tissue as a mitogenic and antiapoptotic growth factor. It is also thought to influence risk indirectly by increasing insulin-like growth factor (IGF)-1 activity and levels of bioavailable oestrogens [1, 3, 4].

Circulating insulin levels are directly influenced by the type, amount and the rate of digestion of dietary carbohydrates, so measures that quantify this variation, such as glycemic index (GI) and glycemic load (GL), are thought to be relevant [5–7]. Dietary GI values rank carbohydrate-containing foods according to the 2-hour blood glucose level after, and hence insulin response to the consumption of a set portion of food, in comparison with that induced by a standard food, usually glucose or white bread. An additional measure, the GL, combines the GI value and the quantity of carbohydrates consumed to quantify the overall glycemic effect of a portion of food.

The results of previous studies that have investigated the association between GI, GL and endometrial cancer risk have been mixed. Several studies have reported positive associations between high GI [8] or GL [9] and endometrial cancer risk, whereas other studies found no association [10–14]. Three separate meta-analyses (two included the same five studies [15, 16] and one included three of the studies [17]) all published in 2008 found positive associations between the highest versus the lowest category of GL, although one pooled estimate was of borderline significance [17, 18]; however, only one of these meta-analyses reported a positive association with high GI [15].

To help clarify the association between GI, GL and endometrial cancer, we present our results from a large, population-based, case–control study of Australian women. Unlike previous studies, our case–control study examined endometrial cancer by histological subtype allowing us to additionally explore whether any association differs between the more common low-grade endometrioid tumours (type 1) and the more aggressive high-grade tumours (type 2). We have also included our data in an updated systemic review and meta-analysis with the following objectives: (1) to review and summarise the epidemiological evidence of the association between GI, GL and endometrial cancer; (2) to more precisely quantify the associations using a dose–response meta-analysis and (3) to examine whether heterogeneity between results was due to differences in study design.

Materials and methods

Case–control study

Study participants

The Australian National Endometrial Cancer study (ANECS) was an Australia-wide, population-based, case–control study of endometrial cancer conducted between July 2005 and December 2007. The study methods have been described in detail elsewhere [19]. Women aged 18–79 years, who were diagnosed with incident endometrial cancer during this period, were recruited by nurses who liaised with the treatment clinics, physicians and state-based cancer registries across Australia. Of 2,707 women identified, 394 women were excluded because of language difficulties, mental incapacity or because they were too sick ($n = 220$); they could not be contacted ($n = 66$) or the physicians refused permission to contact ($n = 108$). The remaining 2,313 women were invited to participate and, of these, 1,497 (67 %) agreed to take part in the study. Information on tumour site and histological subtype was abstracted from the diagnostic histopathology reports for consenting women. We excluded 39 women (not primary endometrial cancer; diagnosed outside the study period) leaving a final sample of 1,458 eligible women, 1,399 (96 %) of whom completed an interview.

Cases were compared to control women without endometrial cancer, sampled in two groups, using identical methods from the national electoral role (enrolment to vote in Australia is compulsory).

The first group of controls was recruited specifically for the ANECS study between 2005 and 2007. The women were randomly selected from the Australian electoral role to match the state of residence and age distribution (in 5-year bands) of the cases. Women with prior hysterectomy or endometrial cancer were excluded. Of 1,496 eligible women contacted, 92 women were excluded due to illness, language difficulties or inability to give informed consent. Of the remaining 1,404 women, 740 (53 %) participated in the study. To increase the power of our study, we included a second group of controls recruited between 2003 and 2006 as part of study of ovarian cancer [20]. Of 3,442 women contacted, 1,612 (47 %) agreed to participate. After exclusion of women who reported a prior hysterectomy or endometrial cancer, a random sub-sample of 799 women was selected to match the state of residence and age

distribution of the endometrial cancer case group. Combining women from both groups gave a total control group of 1,539 women. The two groups of controls were very similar with regard to parity, oral contraceptive (OC) use, smoking, body mass index (BMI), diabetes, GI and GL (all $p > 0.1$).

The study was approved by the Human Research Ethics Committees at Queensland Institute of Medical Research and all participating hospitals and cancer registries.

Data collection

After obtaining written informed consent, detailed health and lifestyle information were collected using a standard questionnaire that was administered by telephone interview for the cases and the first group of controls and self-administered for the second group of controls. Dietary information was obtained using a 139-item semi-quantitative food frequency questionnaire (FFQ) based on the instrument developed by Willett et al. [21] but modified and validated for use in Australia [22, 23]. Controls were asked to report how often they consumed a specified amount of each food item in the previous year. Cases were asked to report their usual frequency of consumption in the year before their diagnosis or, if their diet had changed in the last 6–12 months, their usual diet. To calculate GL and GI, we used an Australian GI database (FoodWorks: Professional Edition, 2007) that compiled GI values based on carbohydrate-containing food items to reflect their blood glucose response. Data not available in FoodWorks were supplemented with GI values obtained from tables compiled by Atkinson et al. 2008 [24]. We calculated total dietary GL of a food item by multiplying the amount of carbohydrate contained in a specified serving size of the food by the quantity of that food item consumed per day and its corresponding GI value (using glucose as the reference food) [24]. We then summed the values for all carbohydrate-containing foods reported on the FFQ to estimate total GL. The overall GI was calculated by dividing the total dietary GL by the total available carbohydrate intake.

For the present analyses, we excluded 33 cases and 42 controls who did not return the FFQ, 15 cases and 15 controls with more than 10 % of FFQ items missing and 61 cases and 46 controls whose estimated calorie intake was extreme (< 700 or >4,000 kcal), leaving a final group of 1,290 cases and 1,436 controls for analysis.

Statistical analyses

Tests for trend were performed over categories of GI/GL, modelling the median values of each category as a single continuous variable. Analysis of variance was used to test for differences in means for continuous variables, and the Chi-square test was used for categorical variables. Unconditional multivariate logistic regression models were used to assess the relative risks of endometrial cancer associated with GI and GL, adjusted for potential confounders including age (years), age at menarche ($\leq$12, 13 and $\geq$14 years), educational level (high school only, technical college and university), BMI last year (kg/m^2), smoking status (never smoked, ex-smoker and current smoker), parity (0, 1 or 2, $\geq$3), OC use (never use, <6 months, 6–59 months and $\geq$60 months), hormone replacement therapy (HRT) use (never or <3 months of use and $\geq$3 months of use), menopausal status, history of diabetes (never and ever), physical activity level (low, moderate and high) and energy (kJ/day, log transformed). Other potential confounders which did not change risk estimates by more than 10 % were not included in the final models. Results are presented as odds ratios (ORs) and 95 % confidence intervals (CI) compared to the lowest intake category. All tests were two-sided, and p values <0.05 were considered statistically significant. Using the criteria specified by Silverberg and colleagues [25], we defined type 1 endometrial cancer as low-grade endometrioid and mucinous endometrial cancers, and type 2 as all other epithelial subtypes including serous and clear cell cancers, high-grade endometrioid cancers and carcinosarcomas. We analysed data for all cases combined, as well as for type 1 and type 2 cases separately. We also conducted subgroup analyses to examine whether the associations between GL and GI were modified by BMI (<25 and $\geq$25). The statistical significance of any observed stratum differences was assessed by including a cross-product term in regression models. All statistical analyses were performed using SAS version 9·1 (SAS Institute Inc., Cary, NC, USA).

Meta-analysis

Search strategy

We updated the meta-analyses published in 2008 by searching Medline 1950 (U.S. National Library of Medicine, Bethesda, MD, USA), Embase 1966 (Elsevier Science, Amsterdam, Holland), Conference Papers Index 1982 (CSA, Bethesda, MD, USA) and ISI Science Citation Index. The following MeSH terms and text words were used 'glyc(a)emic index', 'glyc(a)emic load' or 'carbohydrates' or 'dietary carbohydrates' combined with 'endometrial cancer', 'endometrial neoplasms' or 'endometrial malignancy'. Searches were limited to studies conducted on humans, published up to the end of July 2011. No language restriction was specified. We included prospective cohort and case–control studies that reported a

quantitative assessment of the association between GI, GL and risk of endometrial cancer. We (CMN and CMO) read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine whether they met the study inclusion criteria. The reference lists of the identified publications were also reviewed to identify any additional studies. Relevant studies identified were also included as citation search terms in the ISI Science Citation Index (1990-present) to identify subsequent studies that had referenced them.

Data extraction

Data extraction was conducted independently by two reviewers (CMN, CMO). We extracted publication data (first author's last name, publication year, country where the study was performed and study period), number of subjects, effect estimates with corresponding 95 % confidence intervals (CIs) and variables controlled for in multivariable models. From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounders. All studies provided risk estimates adjusted for energy intake and BMI, and all but two studies adjusted for smoking. Other covariates were less consistently included in adjusted models. Where essential information was missing (e.g. person-years for the dose–response meta-analysis), the authors of these studies were contacted personally to obtain this information.

Meta-analysis

We performed a meta-analysis comparing the risk of endometrial cancer in the highest reported category of GI and GL to the lowest reported category within each study. To pool OR/RR estimates, a weighted average of the log OR/RR was calculated, taking into account random effects using the method of DerSimonian and Laird [26]. We also conducted a dose–response meta-analysis using the method of generalised least squares for trend estimation proposed by Greenland and Longnecker [27] and Orsini et al. [28]. The main advantages of the dose–response approach are that all the available data relating to the exposure can be used, which in turn improves the precision of the estimates [27]. The value assigned to each category of GI/GL was the median where reported, or the mid-point for closed categories and an assigned value for open-ended categories based upon the range of the adjacent category. Dose–response relationships were expressed per increment of 5 and 50 units for GI and GL, respectively. We performed subgroup analyses to examine heterogeneity by study design (cohort and case–control). Statistical heterogeneity between studies was assessed with the Chi-square statistic and quantified by I^2. Significant heterogeneity was defined as a p value <0.05. We evaluated publication bias by assessing the funnel plot asymmetry [29, 30]. All statistical analyses were carried out using SAS (version 9.2: SAS institute Inc., Cary, NC, USA) and Stata Statistical software (version 10.1, StataCorp LP, College station, TX, USA).

Results

Case–control results

Cases and controls were similar in age, and there was no significant difference in educational, menopausal and physical activity status (Table 1). Cases were more likely to be younger at menarche, nulliparous, obese and have a history of diabetes. Controls were more likely to have used OC's and HRT for longer, and to be ex-smokers.

GI was positively associated with the risk of endometrial cancer (Table 2). Compared to women in the lowest quartile, those in the highest quartile had a 43 % increased risk of endometrial cancer (95 % CI 1.11–1.83, p for trend $= 0.02$) and a 13 % increase in risk (95 % CI 1.03–1.24) per 5 units/day (Table 2). There was no association between high dietary GL and risk of endometrial cancer. Analyses by subtype showed that the increase in risk associated with GI was statistically significant for both type 1 and type 2 endometrial cancers; however, there was no significant association between GL and either cancer type (results not shown). We found no evidence that BMI modified the associations between GI, GL and risk of endometrial cancer.

Systematic review

A flowchart of the identification of relevant studies is shown in Fig. 1. The literature search identified 440 studies. After review of the abstracts, we retrieved 12 full articles for further assessment, of which 6 reports from cohort studies [9–14] and 1 case–control study [8] met the criteria for inclusion. We also included the results (described above) from our population-based case–control study (ANECS). The studies were conducted in the United States [10, 12, 13], Canada [9], Sweden [14], Europe [11], Italy [8] and Australia (ANECS) (Supplementary Table 1). The number of cases ranged from 410 to 1,290. All studies used self-administered food frequency questionnaires (FFQ) to assess diet, and three of the cohort studies updated the information with additional FFQs after baseline [10, 11, 14] (Supplementary Table 2). All but two studies sourced GI values from international tables [31]. Flosom et al. [12] primarily used values from the Harvard database of listed foods calculated as described by Salmerón [32, 33] and in our ANECS study, we used an Australian GI database

Table 1 Non-dietary and dietary characteristics of 1,290 cases and 1,436 controls included in Australian endometrial cancer study

Characteristics n (%)	Cases	Controls	*p* value
Age, years (mean ± SD)	61.3 ± 9.4	60.8 ± 9.8	0.17[a]
Age at menarche			
≤12 years	593 (46.0)	515 (35.9)	
13 years	318 (24.7)	427 (29.8)	
≥14 years	379 (29.4)	493 (34.4)	<0.0001[c]
Education			
High school only	667 (51.7)	702 (48.9)	
Technical college	425 (32.9)	530 (36.9)	
University	198 (15.4)	204 (14.2)	0.55[c]
Body mass index (kg/m^2)			
<25	325 (26.0)	653 (46.3)	
25–29.9	322 (25.7)	458 (32.5)	
≥30	604 (48.3)	300 (21.3)	<0.0001[c]
Smoking status			
Never smoked	836 (64.8)	861 (60.0)	
Ex-smoker	333 (25.8)	442 (30.8)	
Current smoker	121 (9.4)	132 (9.2)	0.07[c]
Parity			
0	230 (17.8)	124 (8.6)	
1 or 2	502 (38.9)	619 (43.1)	
≥3	558 (43.3)	693 (48.3)	<0.0001[c]
Oral contraceptive use			
Never use	416 (32.7)	291 (20.5)	
<6 months	137 (10.8)	85 (6.0)	
6–59 months	316 (24.8)	296 (20.9)	
≥60 months	404 (31.7)	745 (52.6)	<0.0001[c]
Hormone replacement therapy use			
Never use or <3 months of use	927 (72.2)	906 (63.4)	
At least 3 months of use	357 (27.8)	523 (36.6)	<0.0001[b]
Menopausal status			
Pre-menopausal	257 (19.9)	272 (18.9)	
Post-menopausal	1,033 (80.1)	1,164 (81.1)	0.52[b]
History of diabetes			
Never	1,121 (86.9)	1,363 (94.9)	
Ever	169 (13.1)	73 (5.1)	<0.0001[b]
Physical activity level			
Low	212 (16.7)	227 (15.9)	
Moderate	515 (40.5)	561 (39.2)	
High	543 (42.8)	643 (44.9)	0.28
Daily energy intake, kJ (mean ± SD)	9,046 ± 2,556	9,006 ± 2,523	0.68[a]

[a] From ANOVA

[b] From Pearson's Chi-square statistic

[c] From Chi-square statistic test for trend

(FoodWorks: Professional Edition, 2007), supplemented with GI values obtained from tables compiled by Atkinson and colleagues [24]. In the studies, total dietary GL was calculated by multiplying the digestible carbohydrate content of a given food item (g/100 g) by the quantity of that food item consumed per day and its GI value and then summing the values for all food items reported [31]. The overall GI was calculated by dividing the total dietary GL by the daily total carbohydrate intake [31]. All studies provided risk estimates adjusted for energy intake and BMI, and all but two studies adjusted for smoking. Other covariates were less consistently included (Supplementary Table 2). For the dose–response meta-analysis, additional information regarding the number of cases and persons-years of observation was obtained from the authors of four studies [10–13].

Table 2 Odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between glycemic load, glycemic index and risk of endometrial cancer overall, and stratified by BMI, from the Australian Endometrial Cancer Study

	Quartiles of intake					
	Q1	Q2	Q3	Q4	P trend	P for interaction
Glycemic index						
Median (range)	45 (27–47)	49 (47–50)	52 (50–53)	55 (53–70)		
Number of cases/controls	230/374	330/348	306/343	348/349		
OR (95 % CI)[a]	1.0	1.43 (1.11–1.82)	1.29 (1.00–1.65)	1.43 (1.11–1.83)	0.02	
Energy-adjusted glycemic index per 5 units/day[a]			1.13 (1.03–1.24)		0.01	
Glycemic load						
Median (range)	92 (21–101)	108 (101–114)	120 (114–128)	138 (128–233)		
Number of cases/controls	250/341	292/347	340/340	332/351		
OR (95 % CI)[a]	1.0	1.14 (0.89–1.46)	1.28 (1.00–1.63)	1.15 (0.90–1.48)	0.19	
Energy-adjusted glycemic load per 50 units/day[a]			1.14 (0.93–1.40)		0.20	

	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]	OR (95 % CI)[a]		
Glycemic index						
BMI (kg/m^2)						0.30
<25	1.0	1.30 (0.86–1.98)	1.35 (0.88–2.07)	1.48 (0.97–2.24)	0.08	
25–<30	1.0	1.41 (0.91–2.18)	1.25 (0.79–1.98)	1.43 (0.91–2.26)	0.23	
≥30	1.0	1.66 (1.06–2.59)	1.23 (0.80–1.90)	1.43 (0.91–0.35)	0.35	
Glycemic load						
BMI (kg/m^2)						0.52
<25	1.0	1.06 (0.70–1.59)	1.13 (0.74–1.71)	0.92 (0.61–1.40)	0.77	
25–<30	1.0	1.31 (0.84–2.03)	1.21 (0.79–1.87)	1.10 (0.71–1.69)	0.79	
≥30	1.0	0.98 (0.63–1.51)	1.45 (0.95–2.24)	1.34 (0.86–2.07)	0.07	

[a] Multivariate odds ratios and 95 % CI adjusted for age (years), age at menarche (≤12, 13, ≥14), educational level (high school only, technical college and university), BMI last year (kg/m^2), smoking status (never smoked, ex-smoker and current smoker), parity (0, 1 or 2, ≥3), oral contraceptive use (never use, <6 months, 6–59 months and ≥60 months), HRT use (Never or <3 months of use, at least 3 months of use), menopausal status, history of diabetes (never and ever), physical activity level (low, moderate and high), and energy (kJ/day, log transformed)

Meta-analysis

Glycemic index

Seven studies [8, 9, 11–14] including our ANECS study reported risk estimates for the highest versus lowest quintile/quartile of GI and these are summarized in Fig. 2. For all the identified studies, the pooled RR for endometrial cancer among women in the highest versus the lowest GI category was 1.15 (95 % CI 0.95–1.40); however, there was evidence of significant heterogeneity (I^2 68.9 %, p 0.004). After stratifying by study design, the pooled RR for the highest versus the lowest category of GI was 1.00 (95 % CI 0.87–1.14, $p_{heterogeneity}$ 0.28) for the five cohort studies and 1.56 (95 % CI 1.21–2.02, $p_{heterogeneity}$ 0.26) for the two case–control studies.

Seven studies [8, 9, 11–14] including our ANECS study were included in the dose–response meta-analysis for GI. For all studies, the summary RR per 5-unit increment of GI was 1.00 (95 % CI 0.97–1.03), with no indication of heterogeneity (p 0.10) (Table 3). When we stratified by study design, the dose–response estimates per 5-unit increment of GI was 0.98 (95 % CI 0.95–1.01) for the cohort studies and 1.18 (95 % CI 0.52–2.69) for the case–control studies.

The funnel plots of the effect estimates for the risk of endometrial cancer related to GI were close to symmetrical, and there was no evidence of publication bias using the Egger weighted regression method (p for bias 0.08) or the Begg rank correlation method (p for bias 0.13).

Glycemic load

Eight studies [8–14], including our ANECS study, reported risk estimates for the highest versus the lowest quintile/quartile of GL and these are summarized in Fig. 2. The overall comparison of the highest versus the lowest

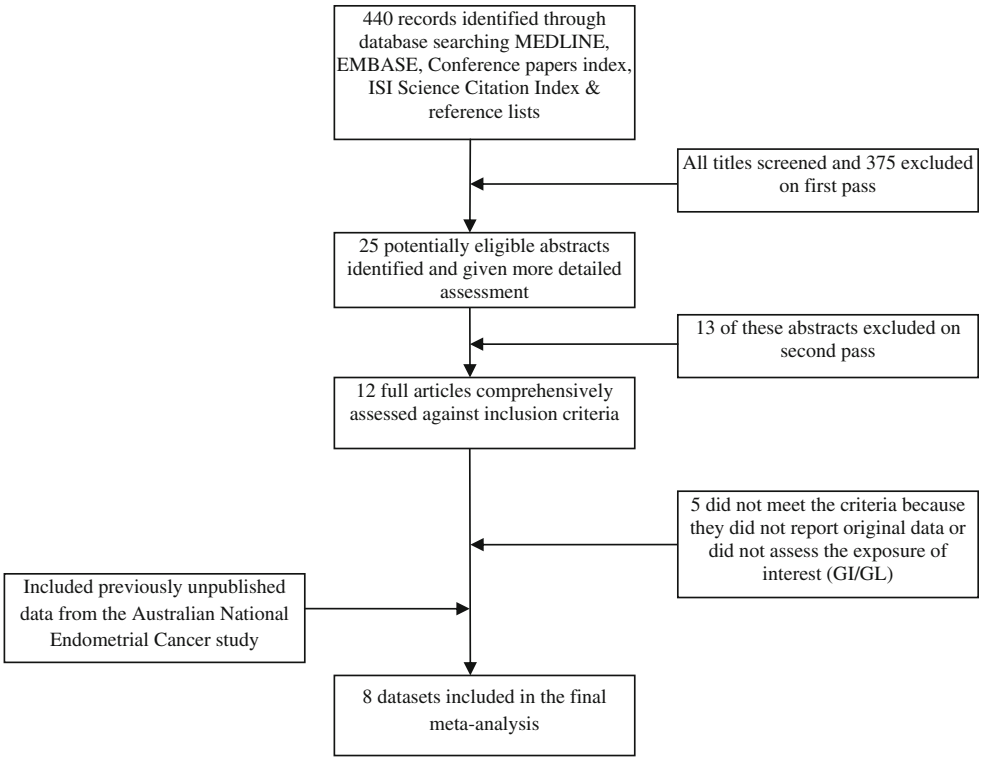

Fig. 1 Flowchart of selection of studies for inclusion in the meta-analysis

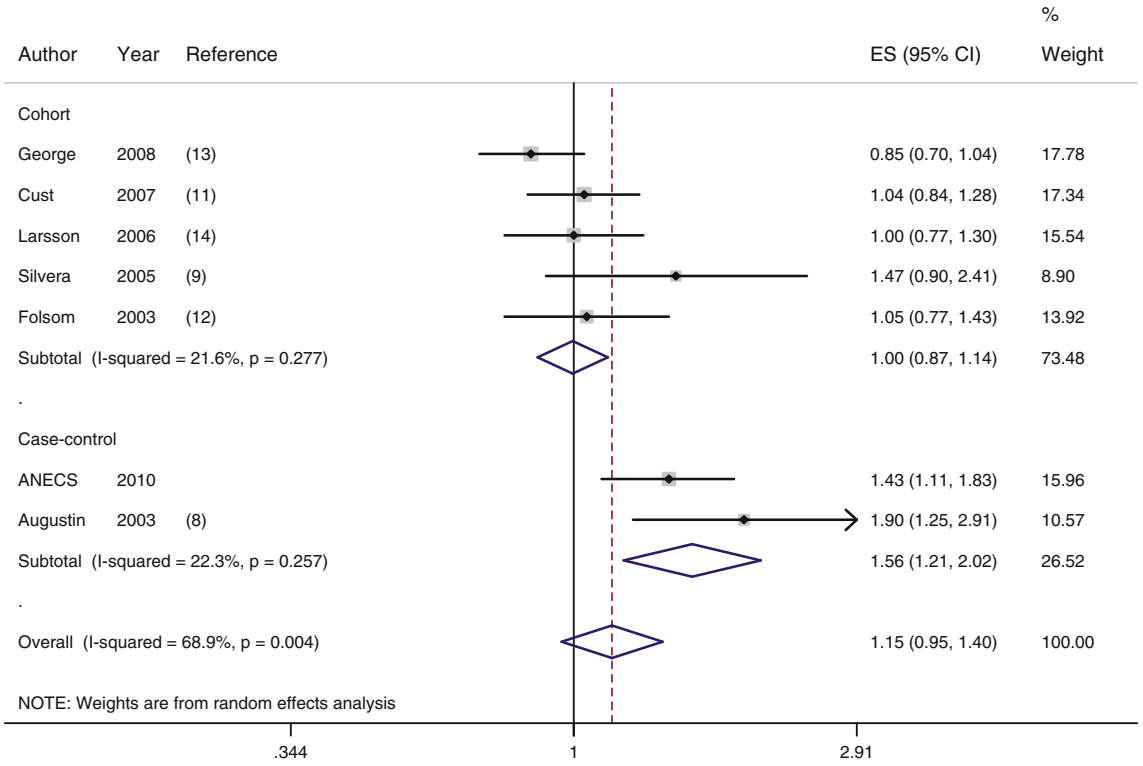

Fig. 2 Forest plot of the association between endometrial cancer and glycemic index (highest vs. lowest category) using a random-effects model, stratified by study design. Each *line* represents an individual study result with the width of the *horizontal line* indicating 95 % CI, the position of the *box* representing the point estimate and the size of the *box* being proportional to the weight of the study

Table 3 Results of the dose–response meta-analysis for risk of endometrial cancer associated with a 5-unit increase in glycemic index and 50-unit increase in glycemic load

	No. of studies	Pooled RR	95 % CI
Glycemic index (per 5-unit increment)			
Main analysis [8, 9, 11–14], ANECS	7	1.00	0.97–1.03
Cohort studies [9, 11–14]	5	0.98	0.95–1.01
Case–control studies [8], ANECS	2	1.18	0.52–2.69
Glycemic load (per 50-unit increment)			
Main analysis [8–14], ANECS	8	1.06	1.01–1.11
Cohort studies [9–14]	6	1.06	1.02–1.11
Case–control studies [8], ANECS	2	1.03	0.88–1.22

category showed a significant increase in risk (pooled RR 1.21 and 95 % CI 1.09–1.33), and there was no evidence of statistical heterogeneity (p 0.98). After stratifying by study design, the pooled RR for the highest versus the lowest category of GL was 1.22 (95 % CI 1.09–1.37, $p_{heterogeneity}$ 0.94) for the six cohort studies and 1.14 (95 % CI 0.91–1.44, $p_{heterogeneity}$ 0.90) for the two case–control studies.

Results from eight studies [8–14], including ANECS, were included in the dose–response meta-analysis for GL, and the summary RR per 50-unit increment of GL was 1.06 (95 % CI 1.01–1.11), with no evidence of heterogeneity (p 0.84) (Table 3). Stratifying by study design, we found a significant increase in risk per 50-unit increment of GL in the cohort studies (RR 1.06, 95 % CI 1.02–1.11), but no significant association in the case–control studies (RR 1.03, 95 % CI 0.88–1.22).

The funnel plots of the effect estimates for the risk of endometrial cancer related to GL were close to symmetrical, and there was no evidence of publication bias using the Egger weighted regression method (p for bias 0.67) or the Begg rank correlation method (P for bias 0.27).

Discussion

In this large population-based study of Australian women, higher dietary GI was associated with an increased risk of endometrial cancer, but we found no evidence of an association with GL. In contrast, our meta-analysis shows a modest positive association between a diet high in GL and risk of endometrial cancer, but no association with GI. Although our meta-analysis found no association with GI overall, it should be noted that we did find significant between-study heterogeneity that appeared to be driven by differences in study design. Whilst none of the individual cohort studies in the meta-analysis found a significant association with GI, both case–control studies reported a statistically significant increased risk associated with high dietary GI. The different results in the cohort compared to the case–control studies may reflect the presence of greater bias in the case–control studies if disease status or other covariates affect the dietary reporting in cancer cases. Compared to case–control studies, well-conducted prospective cohort studies provide a higher level of evidence because they are less prone to recall and selection bias.

Despite finding no association between a high dietary GL and risk of endometrial cancer in our case–control study, it is apparent graphically (Fig. 3) that all the studies in the meta-analysis show a consistent pattern of increased risk associated with higher levels of GL, leading to a summary estimate of 1.06 (95 % CI 1.01–1.11) per 50 unit/day increment. Interestingly, only one of the individual studies included in this meta-analysis reported a statistically significant association with GL [9]. However, as identified by other authors [15, 16], the narrow range of observed GL values, particularly in the cohort studies, probably explains the lack of a significant association in individual studies. The finding of an association with GL, but not GI, in our meta-analysis suggests that GL is perhaps a better indicator of physiological response to carbohydrates because it takes into account both the quantity of carbohydrate intake and the carbohydrate quality [34, 35].

Several mechanisms may relate high GL diets to endometrial cancer. Long-term consumption of high glycemic diet results in hyperinsulinemia [36]. Hyperinsulinemia down-regulates IGF-binding proteins, which in turn increase bioavailability of free IGF-1 [37–39]. Biologic evidence from in vitro studies has shown that IGF-1 directly promotes cellular proliferation and reduces apoptosis [40] and stimulates mitogenesis in endometrial cancer cell lines [41, 42]. Insulin and IGF-1 are also powerful negative regulators of sex hormone-binding globulin synthesis in vitro and thus may stimulate endometrial cancer risk through a hormonal pathway. It has also been postulated that high glycemic diets may influence the risk of endometrial cancer by increasing oxidative stress [43].

As the magnitude of the insulin response to carbohydrate intake is substantially greater in the presence of insulin resistance [44], it has been suggested that positive associations between GI/GL might be stronger among overweight and obese women. Whilst subset analyses

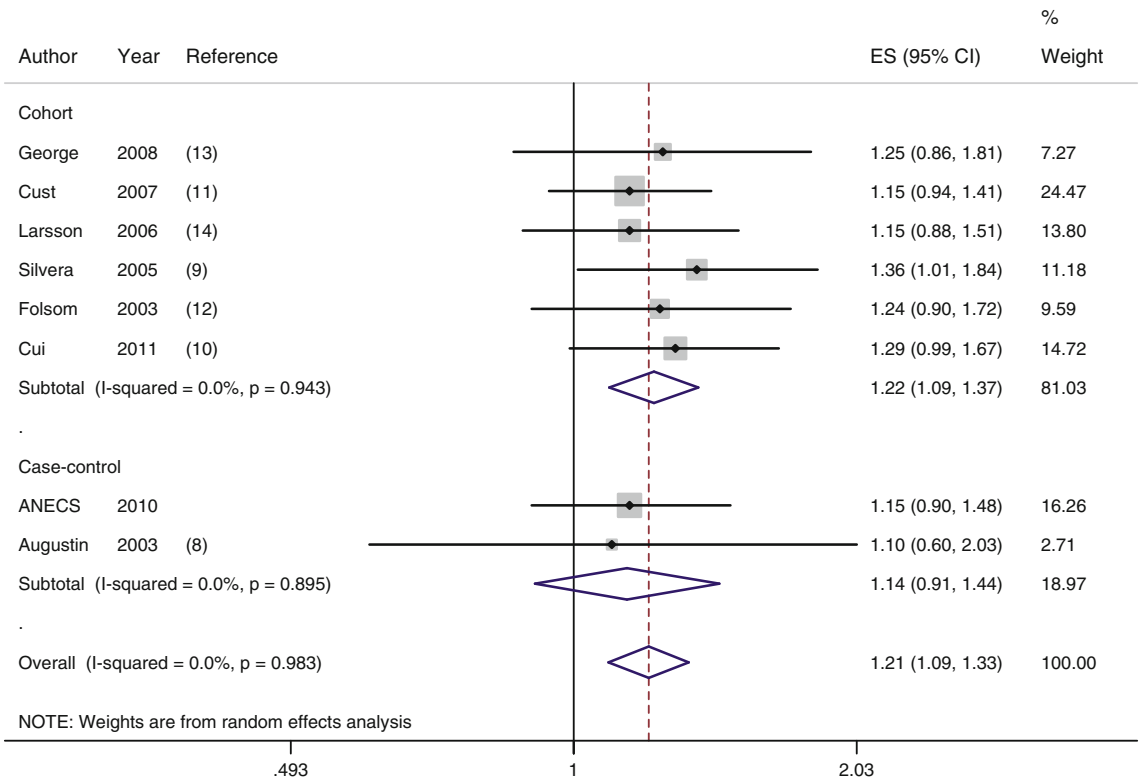

Fig. 3 Forest plot of the association between endometrial cancer and glycemic load (highest vs. lowest category) using a random-effects model, stratified by study design. Each *line* represents an individual study result with the width of the horizontal line indicating 95 % CI, the position of the *box* representing the point estimate and the size of the *box* being proportional to the weight of the study

conducted in previous studies have yielded mixed results, and our case–control study did not find any evidence that BMI modified associations, a recent meta-analysis of 4 cohort studies found that high GL diets, but not GI diets, were associated with increased risk of endometrial cancer as BMI increased [16].

Major strengths of our case–control study include its large sample size and population-based design. In addition, our detailed exposure information allowed for comprehensive adjustment for potential confounders and the FFQ we used has been shown to be a valid measure of diet when compared with weighed food measures [45]. However, it is widely recognised that estimating food and nutrients intake by questionnaires is associated with measurement error, which has been shown to attenuate effect estimates [46]. Our meta-analysis has some important strengths. The studies included a large number of cases, almost double the number compared to previous meta-analyses, so we had enhanced the power to detect significant associations. We have also extended previous meta-analyses by assessing the relationship more precisely using dose–response methodology. The result of our meta-analysis, with increased power and a more thorough approach, has confirmed the results of previous meta-analyses. This adds weight to the belief that this is a real association such that eating a diet with high GL may increase risk of endometrial cancer by 6 % (per 50 units/day of total dietary GL). Although publication bias could be of concern, we found no evidence of this. There was little heterogeneity in results between individual studies except for the high versus low analysis of GI. This was due to differences in study design, and the effect estimates for the two case–control studies were substantially higher than those from the cohort studies.

However, a meta-analysis of observational studies cannot solve inherent problems with confounding in the included studies. For example, whilst most studies adjusted for age, total energy, BMI and smoking, other factors suspected to influence the risk of endometrial cancer were less consistently included in multivariate analyses. Secondly, residual confounding due to inadequately measured confounders could also be of concern. However, in our ANECS study, the effect estimates for GI and GL adjusted for age, total energy, BMI and smoking did not differ greatly from the fully adjusted models, nor did the effects estimates differ greatly between crude and fully adjusted models. Finally, the FFQs used were quite variable in length, ranging from 37 to 130 items, and only three of the cohort studies incorporated repeat dietary assessments at different time points to account for potential changes in dietary habits during the follow-up period [10, 11, 14].

All these factors are likely to have attenuated the observed associations; therefore, our effect estimates are likely to be underestimates of the true association.

In conclusion, results from this meta-analysis suggest that a diet high in GL may modestly increase a woman's risk of endometrial cancer. Given the known association between GL and other chronic conditions including cardiovascular disease, diabetes and obesity [17], this might be yet another reason for women to reduce the overall GL of their diet.

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Appendix

The ANECS Group comprises: AB Spurdle, P Webb, J Young (Queensland Institute of Medical Research); Consumer representative: L McQuire; Clinical Collaborators: NSW: S Baron-Hay, D Bell, A Bonaventura, A Brand, S Braye, J Carter, F Chan, C Dalrymple, A Ferrier (deceased), G Gard, N Hacker, R Hogg, R Houghton, D Marsden, K McIlroy, G Otton, S Pather, A Proietto, G Robertson, J Scurry, R Sharma, G Wain, F Wong; Qld: J Armes, A Crandon, M Cummings, R Land, J Nicklin, L Perrin, A Obermair, B Ward; SA: M Davy, T Dodd, J Miller, M Oehler, S Paramasivum, J Pierides, F Whitehead; Tas: P Blomfield, D Challis; Vic: D Neesham, J Pyman, M Quinn, R Rome, M Weitzer; WA: B Brennan, I Hammond, Y Leung, A McCartney, C Stewart, J Thompson; Project Managers: S O'Brien, S Moore; Laboratory Manager: K Ferguson; Pathology Support: M Walsh; Admin Support: R Cicero, L Green, J Griffith, L Jackman, B Ranieri; Laboratory Assistants: M O'Brien, P Schultz; Research Nurses: B Alexander, C Baxter, H Croy, A Fitzgerald, E Herron, C Hill, M Jones, J Maidens, A Marshall, K Martin, J Mayhew, E Minehan, D Roffe, H Shirley, H Steane, A Stenlake, A Ward, S Webb, J White. Full membership of the Australian Ovarian Cancer Study Group is listed at http://www.aocstudy.org/.

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