

## RESEARCH ARTICLE

# No Effect of Energy Intake Overall on Risk of Endometrial Cancers: a Meta-analysis

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### Abstract

**Background:** Previous epidemiologic studies on the association between energy intake and endometrial cancer risk have only generated contradictory results. The role of energy intake in endometrial carcinogenesis thus remains unclear. To quantitatively assess the potential association between energy intake and endometrial cancer, a meta-analysis of case-control and cohort studies was here conducted. **Materials and Methods:** Eligible studies were retrieved via both computerized searches and review of references. Fixed-or random-effect models were used to summarize the estimates of OR with 95% CIs. Stratified analyses on study design, region and macronutrients' calorie were performed. **Results:** Sixteen studies met the inclusion criteria of the meta-analysis. No association between total energy intake and endometrial cancer was observed in either overall group (OR=1.11, 95% CI 0.92-1.30) or subgroups stratified by study design and region. In the specific macronutrients' calorie analysis, higher fat energy intake was found to be associated with increased endometrial risk (OR=1.72, 95% CI 1.12-2.32) while energy from carbohydrate and protein was not related to endometrial cancer risk. **Conclusions:** Our analysis did not support that total energy intake is related to endometrial cancer risk, in contrast to fat energy.

**Keywords:** Endometrial cancer - energy - meta-analysis - overall intake - fat intake

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### Introduction

Endometrial cancer, which is one of the most common gynecological cancers in the world, is increasing in populations over the past 2 decades (Jamison et al., 2013). The rising incidence of endometrial cancer is alarming and there are limited effective preventive strategies towards it. However, little is known about the exact mechanisms involved in its development. One of best risk factors for endometrial cancer are exposure to estrogens not counterbalanced by progesterone and obesity, which may increase risk by increasing endometrial cell proliferation and peripheral production of estrogens (Kaaks et al., 2002; Tinelli et al., 2008). Recently, growing epidemiological evidences along with molecular researches have suggested that dietary would be a potential cofactor for endometrial cancer development (Biel et al., 2011a; Nordeen et al., 2013).

Dietary energy intake is one of the major focuses of dietary. The association between energy intake and cancer risk has received much attention since 1909. It is reported that higher dietary energy intake may affect several biological pathways involved in cancer initiation such as insulin resistance, elevated levels of insulin-like and other growth factors, elevated levels of sex steroid hormones, pro-inflammatory state, and

altered adipokines. Experimental studies have clearly demonstrated a protective effect of calorie restriction and cancer risk (Kritchevsky, 1999). For endometrial cancer, the role of dietary energy intake is still controversial from epidemiological prospective. In a case-control study conducted in Shanghai, the increased risk of endometrial cancer was related to the higher intake of energy (Shu et al., 1993). However, the study by Petridou et al. (2002) revealed that cases with endometrial cancer showed a significantly lower total energy intake than controls. We therefore summarize the epidemiologic evidence to verify the role of energy in the etiology of endometrial cancer.

### Materials and Methods

#### *Literature search*

We initially identified publications in PubMed database up to Dec 2013 using keywords "diet", "energy" and "endometrial cancer". Furthermore, additional studies were identified from references lists of retrieved articles. Eligible studies should fulfill all the following inclusion criteria: (a) studies evaluating the energy intake and endometrial cancer risk, (b) adequate classification of calories intake was recorded, (c) the outcome of interest should be an incidence of endometrial cancer, (d) odds ratio (OR) or relative risk (RR) estimates with

corresponding 95% CIs (or sufficient data allowing us to calculate them) were provided. In studies with overlapping patients or controls, the latest study with the largest sample size should be included.

#### Data extraction

Two investigators independently extracted the name of the first author, the year of publication, the regions where the study was conducted, study design, the maximally adjusted effects estimates and exposure assessment. Disagreement was resolved by either discussion or the third-party resolution. Considering that endometrial cancer was a rare disease, the RR was assumed approximately the same as OR, and the OR was used as the study outcome. All the studies provided stratified energy intake level with the exception of the study conducted by Petridou et al. (2002), which offered risk estimate for 1 SD increment only. For the studies provided stratified energy intake level, the maximally adjusted ORs/RRs and the corresponding 95% CIs for highest versus lowest energy intake levels were recorded.

#### Statistical analysis

The ORs/RRs and the corresponding 95% CIs were pooled. Between-study heterogeneity across the eligible comparisons was measured using the chi-square-based Q test and I-square test (Lau et al., 1997). Heterogeneity was considered significant while  $p < 0.05$  or  $I^2 > 50\%$ . According to the significance of heterogeneity, the data from single study were combined using either fixed-effect or random-effect models (Mantel et al., 1959; DerSimonian et al., 1986). In addition, subgroups in terms of study region and study design were stratified. The potential publication bias was assessed graphically by funnel plot and estimated statistically by both Begg's and Egger's test (Egger et al., 1997).  $p < 0.05$  was considered significant for publication bias. If any publication bias appeared to exist, Duval and Tweedie nonparametric "trim and fill" method would be

used to account for publication bias (Duval et al., 2000). In the overall study, sensitivity analysis would be performed to evaluate the effect of a single study contributing to overall summary. All statistical analyses were performed with STATA (version 8.0, StataCorp, College Station, TX). All  $p$  values were two-sided.

## Results

#### Eligible studies

A total of 16 published articles reporting risk factor of endometrial cancer satisfied the inclusion criteria and were included in our meta-analysis (Levi et al., 1993; Potischman et al., 1993; Shu et al., 1993; Tzonou et al., 1996; Goodman et al., 1997; Jain et al., 2000; McCann et al., 2000; Littman et al., 2001; Petridou et al., 2002; Folsom et al., 2003; Furberg et al., 2003; Xu et al., 2007; Bravi et al., 2009; Yeh et al., 2009; Biel et al., 2011b; Cui et al., 2011). The characteristics of the included studies were shown in Table 1. The publication dates in this study ranged between 1993 and 2011. Among them, 4 studies were cohort studies, while the remainders were all in case-control design. Based on regional feature, 2 studies were conducted in Asia (China), while 5 were the results from Europe (Italy, Greece, Switzerland and Norway) and 9 were from North America (USA and Canada). Furthermore, 3 studies providing statistics on macronutrient-calorie's effect were also summarized as an intensive analysis.

#### Risk assessment

The overall result, presented in Figure 1, showed no statistically significant association between total energy intake and endometrial cancer (OR=1.11, 95%CI 0.92-1.30). Simultaneously, sensitivity analysis was performed to evaluate the effect of a single study on the overall estimate by sequentially excluding each study. We found that most studies could possibly not influence the overall

**Table 1. Summary Characteristics of Included Studies**

Authors	Publication year	Study Period	Country	Region	Design	Comparison	OR/RR	95%CI
Shu et al.	1993	1988-1990	China	Asia	Case-control	$\geq 2462.70$ vs $\leq 1832.7$ Kcals	2.1	1.2-3.4
Levi et al.	1993	1988-1991	Switzerland & Northern Italy	Europe	Case-control	Highest vs lowest quartile	2.7	1.8-3.9
Potischman et al.	1993	1987-1990	USA	North America	Case-control	Highest vs lowest quartile	1.5	0.9-2.5
Tzonou et al.	1996	1992-1994	Greece	Europe	Case-control	Highest vs lowest quartile	0.72	0.42-1.25
Goodman et al.	1997	1985-1993	USA	North America	Case-control	Highest vs lowest quartile	1.6	0.99-2.59
Jain et al.	2000	1980-1985	Canada	North America	Cohort	Highest vs lowest quartile	0.88	0.6-1.28
McCann et al.	2000	1986-1991	USA	North America	Case-control	$> 2598$ vs $\leq 1710$ Kcals	0.9	0.6-1.5
Littman et al.	2001	1985-1991	USA	North America	Case-control	$> 2112.3$ vs $< 1083.6$ Kcals	0.91	0.64-1.3
Petridou et al.	2002	1999	Greece	Europe	Case-control	1 SD increment	0.6	0.4-0.88
Furberg et al.	2003	1974-1976	Norway	Europe	Cohort	$\geq 6402$ vs $< 4266$ Kcals	1.36	0.75-2.48
Folsom et al.	2003	1986-1992	USA	North America	Cohort	$> 9403$ vs $< 5473$ Kcals	0.87	0.63-1.19
Xu et al.	2007	1997-2003	China	Asia	Case-control	Highest vs lowest quintile	1.2	1-1.7
Yeh et al.	2009	1982-1998	USA	North America	Case-control	$\geq 9258$ vs $\leq 5694$ Kcals	1.27	0.89-1.82
Bravi et al.	2009	1992-2006	Italy	Europe	Case-control	$\geq 2554.1$ vs $< 1597.9$ Kcals	1.47	1.02-2.13
Cui et al.	2011	1976	USA	North America	Cohort	Highest vs lowest quintile	1.22	0.95-1.57
Biel et al.	2011	2002-2006	Canada	North America	Case-control	$7875.1-19318.4$ vs $\leq 4880.6$ Kcals	1.08	0.56-2.09

risk estimate (Figure 2).

Additional stratified analyses were conducted to assess possible interactions. The studies were stratified by region, considering characteristic disease trend and dietary pattern (Biel et al., 2011b). In the region-stratified analysis, low energy did not reduce endometrial cancer risk in all the 3 regions (OR=1.49, 1.02 and 1.22, 95%CI 0.67-2.32, 0.89-1.16 and 0.67-1.77 for Asia, North America and Europe, respectively). Furthermore, the studies were stratified by difference of study design. The summary of 12 case-control studies indicated no association between energy intake and endometrial cancer (OR=1.18, 95%CI 0.92-1.44), and the cohort studies did not show significant risk increase (OR=1.00, 95%CI 0.83-1.18) either.

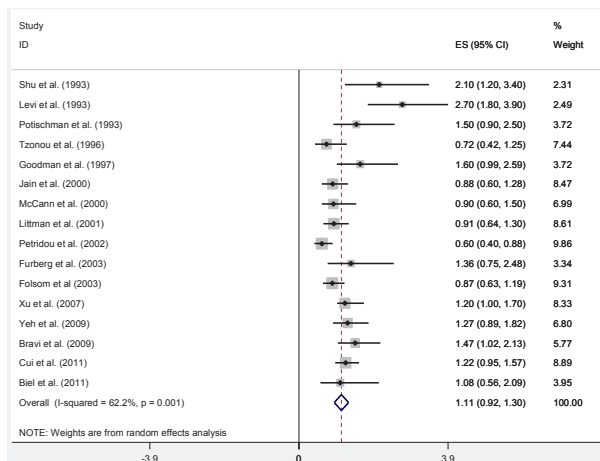


Figure 1. Forest Plot Depicting the Risk Estimates from Included Studies on the Association between total Energy Intake and Endometrial Cancer Risk

For publication bias, visual exploration of the Begg's funnel plot for overall summary revealed an asymmetry shape (Figure 3). Further statistical test with Begg's and Egger's method did not indicate existence of publication bias in the overall analysis ( $P_{Egger's}=0.78$ ,  $P_{Begg's}=0.53$ ). The North America or Case-control subgroup did not show publication either ( $P_{Egger's}=0.74$ ,  $P_{Begg's}=0.30$ , and  $P_{Begg's}=0.96$ ,  $P_{Egger's}=0.78$ , respectively).

As an intensive analysis, we also pooled the independent effect of 3 major macronutrients, i.e. fat, protein and carbohydrate. Three studies provided statistics on macronutrient-calorie's effect were summarized. The results indicated that higher fat energy intake could increase endometrial risk (OR=1.72, 95%CI 1.12-2.32), while higher protein energy showed marginal hazard effect

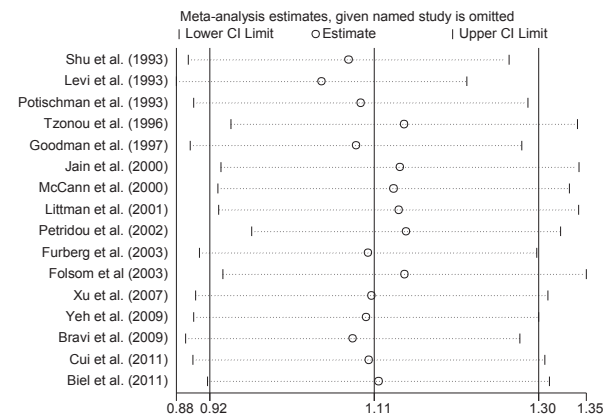


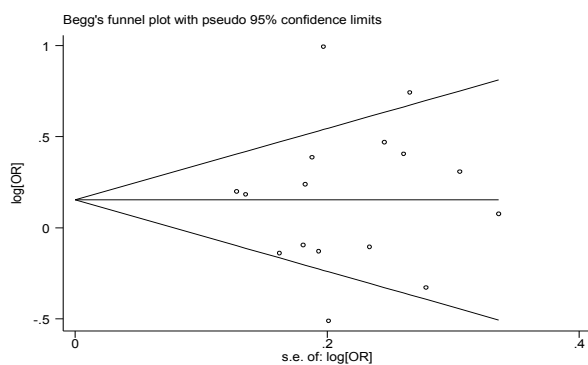
Figure 2. Sensitivity Analysis Showed the Effect of a Single Study on the Overall Estimate by Omitting the Study

Table 2. Macronutrients' Calorie and Endometrial Cancer Risk

Authors	Publication year	Macro-nutrients	Comparison	OR	95%CI
Shu et al.	1993	fat	≥659.32 vs ≤475.2 Kcals	3.9	2.2-6.8
Potischman et al.	1993	fat	≥634 vs ≤344 Kcals	1.5	0.8-2.7
Goodman et al.	1997	fat	Highest vs lowest	1.6	0.97-2.61
Shu et al.	1993	protein	≥270.87 vs ≤184 Kcals	3.1	1.8-5.3
Potischman et al.	1993	protein	>250 vs <147 Kcals	1.4	0.7-2.7
Goodman et al.	1997	protein	Highest vs lowest	1.34	0.83-2.15
Shu et al.	1993	carbohydrates	≥1588.49 vs ≤1093.38	2.1	1.2-3.4
Potischman et al.	1993	carbohydrates	>758 vs <463 Kcals	0.8	0.4-1.3
Goodman et al.	1997	carbohydrates	Highest vs lowest	1.16	0.72-1.88
Littman et al.	2001	carbohydrates	>49.9 vs <35.9%Kcal/day	0.6	0.42-0.87

Table 3. Energy Intake and Endometrial Cancer Risk

	No. of studies	OR (95% CI)	Test for heterogeneity		Test for publication bias	
			$P_{heterogeneity}$	$I^2(\%)$	$P_{egger's}$	$P_{begg's}$
Total Energy Intake						
All studies	16	1.11 (0.92-1.30)	0.001	62.2	0.784	0.528
Region						
Asia	2	1.49 (0.67-2.32)	0.126	57.2	-	-
North America	9	1.02 (0.89-1.16)	0.379	6.8	0.738	0.297
Europe	5	1.22 (0.67-1.77)	<0.001	82.2	-	-
Study design						
Cohort studies	4	1.00 (0.83-1.18)	0.272	23.2	-	-
Case-control studies	12	1.18 (0.92-1.44)	<0.001	69.2	0.957	0.784
Macronutrients						
Fat	3	1.72 (1.12-2.32)	0.154	46.5	-	-
Protein	3	1.52 (0.99-2.04)	0.176	42.4	-	-
Carbohydrates	3	0.96 (0.52-1.40)	0.024	68.2	-	-



**Figure 3. Funnel Plot of total Energy Intake and Endometrial Cancer Risk with Pseudo-95% CI**

(OR=1.52, 95%CI 0.99-2.04) and no apparent association was detected for energy derived from carbohydrate (OR=0.96, 95%CI 0.52-1.40).

## Discussion

Moreschi first reported that energy restriction could inhibit the growth of transplanted tumor in mice in 1909. Subsequently, numerous studies have consistently demonstrated that energy restriction could inhibit the development of a variety of spontaneous and induced tumors in rats and mice as well as non-human primates (Hursting et al., 2003; Zhu et al., 2003; Hursting et al., 2010; Klement et al., 2011). The essential biological rationale for anti-cancer effect of energy restriction would be endocrine regulation of cancer by insulin-like signals, which in turn may repress cell proliferation, disturb cell cycle, induce apoptosis and impair neovascularization of tumor tissue (Jiang et al., 2002; 2003; Zhu et al., 2003). Some other mechanisms, such as increasing activities of antioxidant enzymes, enhancing DNA repair, suppressing oncogene expression and modulating level of immunological responsiveness are also involved (Loft et al., 1995; Thompson et al., 1999). However, very few studies have assessed the relationship between energy restriction and the risk of various cancer sites because of the ethical issue. Therefore, it is unclear and there is little direct evidence that such a protective effect exists in humans. A cohort of Norwegians showed acute energy restriction reduced breast cancer risk (Tretli et al., 1996). Also, published epidemiologic findings has indicated that higher energy intake was associated with increased risk of specific type of cancer, e.g. prostate (Hsieh et al., 2003), breast (Sue et al., 2009), and colorectal cancer (Sun et al., 2012). However, the association between energy and endometrial cancer were ambiguous. Theoretically, higher energy resulted in the enhancement of insulin resistance, thus increasing the risk of endometrial cancer (Troisi et al., 1997; Stoll, 1999).

We statistically summarized the previous findings. On the basis of the study results since 1993, findings on energy intake and endometrial cancer did not support the hypothesis that higher energy intake may be associated with a higher risk of endometrial cancer. The following reason may attribute our results.

First, dietary energy source largely depends on dietary

patterns, which composed with diverse macronutrients composition settings in different pattern. A healthier dietary pattern consisting primarily of plant-based foods including vegetables, fruits, and whole grains may meaningfully reduce endometrial cancer risk (Bandera et al., 2007). The association between diet and a modified hormonal milieu in vegetarians suggested a vegetarian pattern might be the most relevant for endometrial cancer risk reduction (Goldin et al., 1982; Barbosa et al., 1990). However, in the study by zheng et al. (1995), both energy from plant foods and energy from animal foods were not related to endometrial cancer risk. Thus, to further elucidate the role of different macronutrients, we performed subgroup analysis based on macronutrients' calorie intake. With exception of energy from protein and carbohydrate, a positive relation between energy from fat and endometrial cancer were found. The result was quite consistent with the theory that increased fat intake would increase the exposure to possible endogenous mitogenic factors, e.g. insulin, IGF and estrogen, which was linked to endometrial carcinogenesis (Bruning et al., 1986; Cust et al., 2007).

Second, the energy balance is a complex process, which can not be determined by energy intake alone. As modifiable lifestyle factors, physical activity, body size, and metabolic efficiency are highly related to total energy intake and expenditure. Low energy intake generally reflects low energy expenditure and, thus, low physical activity (Petridou et al., 2002). Both physical activity and BMI, the major determinants of variability in energy demand, was related to endometrial cancer (Voskuil et al., 2007). The meta-analysis has showed that physical activity is associated with a decreased risk of endometrial cancer, with a summary estimate of risk reduction (Voskuil et al., 2007). Overweight and obese was found to be associated with elevated endometrial precancerous lesion rates (Acmaaz et al., 2014). Even more, convincing and consistent evidence showed that increased BMI was an established risk factor for endometrial cancer (Zhang et al., 2013). Most studies observed a linear increase in risk of endometrial cancer with increasing BMI (Bjorge et al., 2007; Friedenreich et al., 2007). So, it is difficult to precisely assess the independent effect of energy intake on endometrial cancer risk without a comprehensive consideration of interaction with BMI and physical activity. Further studies need to be conducted with a better clarification of the interaction among energy intake, physical activity and BMI.

As is often the case with meta-analysis, several potential limitations in our study should also be acknowledged. First, even though we have used the maximal adjusted estimates, the adjusted criteria for OR/RR varied between studies. The different adjustment criteria for confounding factors probably would bias our results. Second, dietary data do not necessarily reflect absorbed or biologically active doses and measurement error would be brought in by nutritional assessment techniques, which would also bias our results.

Overall, our current meta-analysis could not provided support for an association between higher total energy intake and increased endometrial risk. It warrants further



biological and epidemiological investigations to refine the understanding of the carcinogenesis role of energy intake in endometrial cancer.

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