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

Ke-Tan Chu, Yang Song, Jian-Hong Zhou*

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
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-squared test (Lau et al., 1997). Heterogeneity was considered significant while $p<0.05$ or $I^2 \geq 50\%$. 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 | ≥2462.70 vs ≤1832.7 Kcals | 2.1 (1.2-3.4) |
| Levi et al.      | 1993             | 1988-1991      | Switzerland      | 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 ≤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                          | Case-control | ≥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 (1.1-1.7) |
| Yeh et al.       | 2009             | 1982-1998      | USA              | North America                   | Case-control | ≥9258 vs ≤5694 Kcals | 1.27 (0.89-1.82) |
| Bravi et al.     | 2009             | 1992-2006      | Italy             | Europe                          | Case-control | ≥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 ≤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.

For publication bias, visual exploration of the Beggs funnel plot for overall summary revealed an asymmetry shape (Figure 3). Further statistical test with Beggs and Eggers 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.
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 discussion provides further context and implications of these findings.

### Discussion

Moreschi first reported that energy restriction could inhibit the growth of transplanted tumors 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 (Hurston et al., 2003; Zhu et al., 2003; Hurston 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 (Acmaz 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 provide support for an association between higher total energy intake and increased endometrial risk. It warrants further investigation.
biological and epidemiological investigations to refine the understanding of the carcinogenesis role of energy intake in endometrial cancer.

References

Acma G, Aksoy H, Albayrak E, et al (2014). Evaluation of endometrial precancerous lesions in postmenopausal obese women-a high risk group? Asian Pac J Cancer Prev, 15, 195-8.

Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML (2007). Fruits and vegetables and endometrial cancer risk: a systematic literature review and meta-analysis. Nutr Cancer, 58, 6-21.

Barbosa JC, Shultz TD, Filley SJ, Nieman DC (1990). The relationship among adiposity, diet, and hormone concentrations in vegetarian and nonvegetarian postmenopausal women. Am J Clin Nutr, 51, 798-803.

Biel RR, Csizmadi I, Cook LS, et al (2011a). Risk of endometrial cancer in relation to individual nutrients from diet and supplements. Public Health Nutr, 14, 1948-60.

Biel RR, Friedenreich CM, Csizmadi I, et al (2011b). Case-control study of dietary patterns and endometrial cancer risk. Nutr Cancer, 63, 673-86.

Bjurge T, Engeland A, Tretli S, Weiderpass E (2007). Body size in relation to cancer of the uterine corpus in 1 million Norwegian women. Int J Cancer, 120, 378-83.

Bravi F, Scotti L, Bosetti C, et al (2009). Food groups and endometrial cancer risk: a case-control study from Italy. Am J Obstet Gynecol, 200, 1-7.

Bruning PF, Bonfrer JM (1986). Free fatty acid concentrations correlated with the available fraction of estradiol in human plasma. Cancer Res, 46, 2606-9.

Cui X, Rosner B, Willett WC, Hankinson SE (2011). Dietary fat, fiber, and carbohydrate intake in relation to risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev, 20, 978-89.

Cust AE, Slimani N, Kaaks R, et al (2007). Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. Am J Epidemiol, 166, 912-23.

DerrSimonian R, Laird N (1986). Meta-analysis in clinical trials. Control Clin Trials, 7, 177-88.

Duval S, Tweedie R (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 56, 455-63.

Egger M, Davey Smith G, Schneider M, Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315, 629-34.

Folsom AR, Demissie Z, Harnack L (2003). Glycemic index, glycemic load, and endometrial cancer risk: a systematic review of data from retrospective studies of disease. J Natl Cancer Inst, 22, 719-48.

Freedman LS, Harnack L, Flynn JS, et al (2011). Dietary fat, fiber, and carbohydrate intake in relation to risk of endometrial cancer. Am J Epidemiol, 164, 691-702.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.

Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. Cancer, 71, 3575-81.
endometrial cancer. *Br J Obstet Gynaecol*, **106**, 402-6.

Sue LY, Schairer C, Ma X, et al (2009). Energy intake and risk of postmenopausal breast cancer: an expanded analysis in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. *Cancer Epidemiol Biomarkers Prev*, **18**, 2842-50.

Sun Z, Liu L, Wang PP, et al (2012). Association of total energy intake and macronutrient consumption with colorectal cancer risk: results from a large population-based case-control study in Newfoundland and Labrador and Ontario, Canada. *Nutr J*, **11**, 18.

Thompson HJ, Jiang W, Zhu Z (1999). Mechanisms by which energy restriction inhibits carcinogenesis. *Adv Exp Med Biol*, **470**, 77-84.

Tinelli A, Vergara D, Martignago R, et al (2008). Hormonal carcinogenesis and socio-biological development factors in endometrial cancer: a clinical review. *Acta Obstet Gynecol Scand*, **87**, 1101-13.

Tretli S, Gaard M (1996). Lifestyle changes during adolescence and risk of breast cancer: an ecologic study of the effect of world war II in Norway. *Cancer Causes Control*, **7**, 507-12.

Troisi R, Potischman N, Hoover RN, Siiteri P, Brinton LA (1997). Insulin and endometrial cancer. *Am J Epidemiol*, **146**, 476-82.

Tzonou A, Lipworth L, Kalandidi A, et al. (1996). Dietary factors and the risk of endometrial cancer: a case--control study in Greece. *Br J Cancer*, **73**, 1284-90.

Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE (2007). Physical activity and endometrial cancer risk, a systematic review of current evidence. *Cancer Epidemiol Biomarkers Prev*, **16**, 639-48.

Xu WH, Dai Q, Xiang YB, et al (2007). Nutritional factors in relation to endometrial cancer: a report from a population-based case-control study in Shanghai, China. *Int J Cancer*, **120**, 1776-81.

Yeh M, Moysich KB, Jayaprakash V, et al (2009). Higher intakes of vegetables and vegetable-related nutrients are associated with lower endometrial cancer risks. *J Nutr*, **139**, 317-22.

Zhang Y, Liu H, Yang S, et al (2013). Overweight, obesity and endometrial cancer risk: results from a systematic review and meta-analysis. *Int J Biol Markers*, **29**, 21-9.

Zheng W, Kushi LH, Potter JD, et al (1995). Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa women’s health study. *Am J Epidemiol*, **142**, 388-94.

Zhu Z, Jiang W, Thompson HJ (2003). Mechanisms by which energy restriction inhibits rat mammary carcinogenesis: in vivo effects of corticosterone on cell cycle machinery in mammary carcinomas. *Carcinogenesis*, **24**, 1225-31.