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Dietary Iron Intake and Risk of Endometrial Cancer: A Population-based Case-Control Study in Shanghai, China

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Abstract

Dietary red meat and animal fat have been linked to endometrial cancer (EC) risk, but the impact of bioavailable iron in animal-derived foods has been less well studied. Our objective was to investigate the effects of iron and fats on the risk of EC in a large, population-based, case-control study. The Shanghai Endometrial Cancer Study enrolled 1,204 EC cases and 1,212 controls who completed in-person interviews, including a food frequency questionnaire. Animal-derived iron and fat intakes were calculated from dietary intakes and food composition tables. Logistic regression models were used to evaluate independent and joint effects of iron and fat on EC risk.

Animal-derived iron intake was positively associated with EC risk [adjusted OR = 1.9; 95% CI = 1.4–2.7, $P_{\text{trend}} < 0.01$, highest vs. lowest quartile], predominantly after menopause (OR = 2.2; 95% CI = 1.4–3.4, $P_{\text{trend}} < 0.01$) and in women with BMI ≥ 25 kg/m² (OR = 3.2; 95% CI = 1.4–7.5 in postmenopausal obese women, $P_{\text{trend}} < 0.01$). Animal-derived fat was also associated with postmenopausal EC risk (OR = 1.7; 95% CI = 1.2–2.5, $P_{\text{trend}} < 0.01$). Multiplicative interactions between animal-derived iron and BMI or animal-derived fat intake were not observed. Animal-derived iron intake is associated with increased risk of EC after menopause and among obese women. Avoidance of animal-derived (heme) iron may reduce the risk of EC in these women.

INTRODUCTION

Well-recognized risk factors for endometrial cancer reflect the central importance of an estrogen-progesterone imbalance in its pathogenesis. These risk factors include early menarche or later menopause, exogenous estrogen use, nulliparity, anovulation, and the polycystic ovary syndrome (1–3). The mechanisms underlying these effects are incompletely understood, however. Activation of inflammatory pathways in the endometrium by estrogen exposure during the menstrual cycle, mediated in part by macrophages and leading to compensatory endometrial hyperplasia, has recently been postulated to play a role (4). Obesity, insulin resistance, and diabetes mellitus, which may impact circulating estrogen levels as well as inflammation and oxidative stress, have also emerged as important risk factors in this disease (5–9). Ecologic and other epidemiologic studies have also suggested that dietary and lifestyle factors such as physical activity significantly influence endometrial cancer risk (10–17). Specifically, endometrial cancer has been associated with consumption of animal-derived foods, particularly red meat and animal fat, whereas a high intake of vegetables and fruits have been inversely associated with risk, although the published data are not entirely consistent (18–24). Follow-up studies have focused on animal fats, protein, and even amino acids in meat such as methionine as possible etiologic agents (25–26), but the potential effects of iron in animal foods have received less attention (27). Animal-derived iron intake, together with a high intake of animal fats, has been reported recently to increase the risk of breast cancer among Chinese women (27).

Iron is an essential micronutrient, but it also acts as a potent Fenton reagent, catalyzing the formation of toxic free radicals (28,29). Hence, the cellular uptake and transport of iron are tightly regulated in living organisms to maintain iron in non-reactive forms and minimize oxidative damage. Despite some studies showing that elevated body iron stores are associated with increased rates of cancer and cancer mortality in both men and women, many epidemiological studies have yielded conflicting results with regard to the link between dietary iron or measures of body iron status and cancer risk (29). These prior studies have been limited, however, in their ability to detect an iron effect because analyses were focused on total dietary iron intake, which consists largely of non-heme iron of low bioavailability, and potential interactions of iron with fats or other food constituents were not considered (27). Most of these studies were also conducted in the United States, where mandatory fortification of cereals and grains with non-heme iron may confound studies evaluating the association of more bioavailable forms of iron in the diet with cancer risk.

Heme iron, which is the principal form of iron contained in red meat, makes up a smaller proportion of total dietary iron intake but is efficiently absorbed following ingestion (30–33). Since iron has been suggested to play a role in the pathogenesis of estrogen-inducible cancers such as breast cancer (34), we hypothesized that iron derived from animal foods, largely heme iron, may influence the risk of endometrial cancer. We tested this hypothesis in women who participated in a large, population-based, case-control study of endometrial cancer in Shanghai, China, where a vegetable-rich and varied diet is consumed, foods are not fortified with iron, and the incidence of endometrial cancer is significantly lower than in the United States (35–38).

PATIENTS AND METHODS

Participants and Study Design

The Shanghai Endometrial Cancer Study (SECS) was a population-based, case-control study conducted in Shanghai, China, between January 1997 and December 2003 (39). Eligibility criteria for inclusion of women in the study included permanent residency in urban Shanghai, 30–69 yr of age, and no hysterectomy prior to diagnosis (cases) or study enrollment (controls). Cases, identified through the Cancer Registry, were newly diagnosed with endometrial cancer during the study period, and this diagnosis was confirmed by review of the pathology and/or review of the medical chart. Controls were randomly selected from the general population using files from the Shanghai Resident Registry, which contains demographic information on all adult residents in Shanghai. Eligibility criteria for controls were identical to those for cases with the exception of an endometrial cancer diagnosis, and controls were frequency matched to cases on age (within 5-yr intervals). Of 1,454 eligible cases, 1,204 (82.8%) were recruited to the study and completed an in-person interview. Reasons for exclusion were as follows: 135 (9.3%) refused, 65 (4.5%) died prior to interview, 23 (1.6%) could not be located, 12 (0.8%) no longer resided in Shanghai, and 15 (1.0%) could not participate due to illness or miscellaneous reasons. Of 1,629 eligible controls, 1,212 (74.4%) were recruited and completed the interview. Exclusions among the control group occurred for the following reasons: 8.0% refused, 63 (3.9%) had undergone hysterectomy, 60 (3.7%) were out-side the study area, and 163 (10.0%) could not participate due to illness or other factors. The study was approved by committees for the use of human subjects at both collaborating institutions.

Dietary Assessment

All study participants completed a detailed in-person interview at enrollment. Anthropometric measurements were taken, and a structured questionnaire was administered by trained personnel (retired physicians and nurses). Dietary intakes were assessed using a previously validated 76-item food frequency questionnaire (FFQ) that captured over 85% of the commonly consumed foods in Shanghai including 19 animal foods comprising 10 food categories (red meat, organ meat, shrimp or crab, eel, marine fish, freshwater fish, poultry, eggs, shellfish, and milk) (40). Subjects were asked to report their usual in-take frequency for individual food items (per day/wk/mo/year or never) and serving sizes in lians (where 1 lian equals 50 g) or jins (where 1 jin equals 500 g) over the past 5 yr, ignoring any recent changes. For seasonal foods, subjects were asked to describe their consumption based on

market availability and total months of consumption per year. Iron and fat or fatty acid intakes were estimated by summing the products of the amounts of foods consumed and the (micro)nutrient content of each food using Chinese food composition tables. Animal-derived iron in-take was estimated by calculating iron intake exclusively derived from nondairy animal foods.

Statistical Analysis

Quartile distributions of dietary intakes among controls were used to categorize intakes of total iron, vegetable-derived iron, and animal-derived iron as well as the intakes of saturated, monounsaturated fatty acids (SFA, MUFA, respectively) and polyunsaturated fatty acids (PUFA) from these foods. Unconditional logistic regression models were used to compute odds ratios (ORs) and their 95% confidence intervals (CIs) for the risk of endometrial cancer across quartiles of iron or fatty acids intake, adjusting for potential confounders and using the lowest quartile as the referent category. The following recognized risk factors for endometrial cancer and factors distinguishing cases and controls in this study were included in all regression models: age at recruitment; age at menarche; age at menopause if postmenopausal; education (or > high school level); body mass index (BMI); number of pregnancies; family history of breast, colorectal, or endometrial cancer; regular physical exercise (yes–no); ever use of oral contraceptive pills (OCP; yes–no); hormone replacement therapy (HRT; yes–no); and total energy intake in kcal/day. ORs incorporating additional adjustment for the following covariates were also computed: vitamin A, C, and E (antioxidant vitamin) intake; soy isoflavone (41) and folic acid intake; regular use of vitamin or other supplements; and for analyses involving iron, SFA and MUFA intake. Stratified regression analyses were performed to evaluate the effects of menopausal status and BMI on associations between iron or fat intakes on endometrial cancer risk. All statistical tests were based on 2-sided probabilities with a level of significance of 0.05 and were carried out using SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Endometrial cancer cases and controls were similar with respect to age and level of education but differed in the expected directions with regard to known risk factors for endometrial cancer, as shown in Table 1. Cases were significantly younger at menarche, older at menopause, had higher BMI, and were more likely to have positive family history of endometrial, breast, and/or colorectal cancer in a first-degree relative. Controls, in contrast, had higher parity; they reported more combination oral contraceptive use, fewer years of menstruation, and tended to have more regular physical exercise. Fewer cases were postmenopausal at the time of the study as compared with controls (58% vs. 63%, respectively). The prevalence of HRT use in Chinese women overall is very low and was nonsignificantly higher among cases than controls in this study. Finally, total energy intake and meat intake were significantly greater among women with endometrial cancer than among controls. Intake of fruits and vegetables was similar in the two groups.

Adjusted ORs for the association of iron from different food sources with the risk of endometrial cancer are shown in Table 2. After adjustment for potential confounding factors

[age at enrollment, age at menarche (and if postmenopausal, age at menopause), education, BMI, number of pregnancies, family history of cancer, regular physical activity, OCP and HRT use, total energy intake, antioxidant vitamin, folic acid and soy isoflavone intakes, and vitamin supplement use], animal-derived iron intake was significantly and independently associated with the risk of endometrial cancer (adjusted OR = 1.9; 95% CI = 1.4–2.7, $P_{\text{trend}} < 0.01$). Further adjustment for the intake of SFA and MUFA, which are present in many of the same animal foods, did not significantly diminish the effect of iron (OR = 1.9; 95% CI = 1.2–2.9, $P_{\text{trend}} < 0.01$). Although the risk of endometrial cancer also increased with total iron intake, this trend did not reach statistical significance after adjustment for other factors.

Analyses stratified by menopausal status revealed that the risk associated with animal-derived iron intake occurred primarily in postmenopausal women (OR = 2.2 in the highest vs. lowest quartile of intake; 95% CI = 1.4–3.4, $P_{\text{trend}} < 0.01$), and this result was not changed significantly by further adjustment for animal fat (SFA and MUFA) intake (Table 2). Total iron intake, comprised mainly of nonbioavailable vegetable-derived iron, was not significantly associated with endometrial cancer risk in this group despite a trend toward increasing risk in the third and fourth quartiles. An apparent protective effect noted with increasing consumption of iron from vegetable sources became statistically insignificant after additional adjustment for SFA and MUFA intake.

Since endogenous estrogen levels are increased in obesity, and iron may interact with estrogen exposure in endometrial cancer, we performed stratified analyses of the iron effect on endometrial cancer by BMI. These results are presented in Table 3, with adjustment of all ORs for SFA and MUFA intake. A statistically significant increase in risk of endometrial cancer was observed for animal-derived iron in women with BMI $< 25 \text{ kg/m}^2$ (OR = 1.8, 95% CI = 1.02–3.3, $P_{\text{trend}} = 0.03$), but the effect was greater in women with BMI $\geq 25 \text{ kg/m}^2$ (OR = 2.5, 95% CI = 1.3–4.8, $P_{\text{trend}} < 0.01$). Postmenopausal obese women were predictably at highest risk (adjusted OR = 3.3, 95% CI = 1.4–7.5, $P_{\text{trend}} < 0.01$). A similar but statistically insignificant trend was observed in obese premenopausal women. Among postmenopausal women with BMI $< 25 \text{ kg/m}^2$, the association of animal-derived iron with endometrial cancer risk lost statistical significance (OR = 1.6, 95% CI = 0.72–3.7, $P_{\text{trend}} = 0.15$).

Dietary intake of animal-derived fats was positively associated with the risk of endometrial cancer among Chinese women in this study (Table 4), and the association was limited to postmenopausal women (OR = 1.7; 95% CI = 1.2–2.5, $P_{\text{trend}} < 0.01$). When dietary fats were subcategorized by fatty acid composition, a positive association with postmenopausal endometrial cancer risk was observed only with MUFA intake (adjusted OR = 1.9, 95% CI = 1.3–2.8, $P_{\text{trend}} < 0.01$); the adjusted OR for SFA intake was 1.2 (95% CI = 0.8–1.8) in postmenopausal women. Vegetable-derived fat was inversely associated with risk in postmenopausal women (adjusted OR = 0.4, 95% CI = 0.3–0.6, $P_{\text{trend}} < 0.01$). Intake of total and polyunsaturated fats was not associated with endometrial cancer risk.

The joint effects of animal-derived iron and animal fats on endometrial cancer risk are presented in Table 5. Summary ORs for the effects of animal-derived iron intake, additionally adjusted for animal fat intake and for the effects of animal fat intake

additionally adjusted for animal-derived iron are shown. Mutual adjustment for the effects of animal-derived iron and animal fat intakes had little effect on the association between animal-derived iron and endometrial cancer risk; the association with animal fat was slightly diminished but also remained statistically significant. Animal-derived iron and fat intake did not show a statistically significant multiplicative interaction effect, but very small numbers of women in low-iron and high-fat and high-iron and low-fat cells may have resulted in inadequate power to detect an interaction.

DISCUSSION

A steady rise in the population of elderly women underscores the need for a clearer understanding of the pathophysiology of endometrial cancer. The incidence of endometrial cancer has risen steadily over the past 30 years among all racial/ethnic groups, most notably among immigrants to the United States and Europe from regions characterized by historically low rates of this malignancy, such as Asia (10,11,14). Changes in diet and lifestyle have been implicated as modifiers of the risk of this malignancy. Endometrial cancer actually comprises many tumor histologies that differ in their epidemiology, natural history, and pathophysiology. Endometrioid carcinomas make up the majority (80% or more) of these cancers, however, and this sub-type is strongly associated with estrogen exposure (1,2,42,43). Published data implicate downstream prooxidant and proinflammatory effects of estrogen in endometrial carcinogenesis; progesterone opposes these effects (4). In this large, case-control study of urban Chinese women, iron derived from animal foods emerged as an independent risk factor for endometrial cancer among postmenopausal women and particularly among women who are overweight. Consistent with many previous studies (24), we also found that a higher consumption of animal-derived fats was associated with endometrial cancer risk. No statistically significant multiplicative interaction between animal-derived iron and fat was observed, possibly due to low numbers in some intake categories. This is the first and largest case-control study, to our knowledge, to evaluate the role of iron from different food sources as well as its potential interactions with animal fat intake, menopausal status, or BMI in endometrial cancer risk.

Most ingested iron in all human diets (80–95% of typical Western diets) consists of non-heme iron from vegetable sources. Non-heme iron, present in vegetables and some animal foods, is largely nonabsorbed, whereas iron in the highly bioavailable heme form makes up approximately 40% of the iron contained in red or processed meats. Elimination of meat from the diet therefore has little impact on total dietary iron content but significantly decreases the quantity of iron absorbed (30). A meta-analysis of published case-control studies concluded that the weight of evidence favors a link between red meat intake and an increased risk of endometrial cancer (19). Summary estimates of the association between dietary fat intake and this malignancy from a meta-analysis of case-control and cohort studies suggested a weaker positive association (24). Other studies have focused on the possible effects of animal protein per se, specific amino acids such as methionine, or other nutrients that are present in animal foods such as B vitamins, but the role of bioavailable iron, an important constituent of many animal foods and a potent prooxidant, has rarely been addressed (16,25,26). Kabat et al. (44) very recently reported data from a cohort study of Canadian women, showing no association of total meat intake, dietary iron intake, or heme

iron intake with risk of endometrial cancer in that population. Although the data were not shown, the authors reported no associations between heme iron intake and endometrial cancer risk within strata of BMI, HRT, and menopausal status; but the power to discern associations, if they existed, in stratified analyses may have been insufficient, and only baseline exposure data were analyzed. However, their results were consistent with those of one prior cohort study of postmenopausal women (216 cases) in the United States that showed no increased risk of endometrial cancer associated with total and red meat intake (relative risks 1.0 and 1.1, respectively) (22).

Other than the obvious differences between case-control and cohort study designs, some important population differences between the two mentioned cohort studies and this Chinese study may account for the disparate results observed. In the United States and other Western countries, consumption of meat, red meat, and processed meats is considerably higher and intake of vegetables and unrefined grains much lower than in China (45). Phytates present in legumes and whole grains, polyphenols present in tea, soy isoflavones, and eggs, which inhibit the absorption of dietary non-heme iron, are also abundant in the Chinese diet (45,46). Urbanization of China has led in recent years to increases in the intake of meat, particularly among more affluent individuals, and endometrial cancer risk among urban Chinese women is rising (47,48). Furthermore, cereals, grains, and many other commonly consumed food items in the United States and Canada are heavily fortified with non-heme iron (49,50). Although iron fortification may appear to have little impact on iron stores due to the poor bioavailability of non-heme iron, co-ingestion of both heme iron and animal protein in Western diets has been shown to greatly enhance non-heme iron absorption, thereby increasing the potential for iron-mediated oxidative stress and DNA damage (50–52). Total bioavailable iron in the diet may therefore be significantly greater and interindividual variation in iron absorption may be much less in the West than in Asian countries like China; indeed, one study showed that the proportion of heme iron in the typical American diet is 16% vs. 3.3% of the Chinese diet (33). These factors, as well as the very low prevalence of vitamin supplement use in China, may have enabled us to detect an association between animal-derived iron and endometrial cancer risk in our study (22,39,48). We also adjusted for the intakes of animal fat, intake of antioxidant vitamins (e.g., vitamin C), and vitamin supplement use. In addition, estrogen exposure is perhaps the strongest risk factor for endometrial cancer, and endogenous estrogen levels are known to be higher and HRT use much more prevalent in Western women (53). The impact of estrogen on endometrial cancer risk may therefore predominate in Western populations, making any effects of dietary iron, particularly heme iron, difficult to detect. Lastly, non-heme iron absorption is highly regulated and strongly influenced by body iron status and the presence of anemia, with increased absorption in individuals with low body iron status or iron-deficiency anemia. Non-heme iron absorption in populations with low iron stores (a high prevalence of iron deficiency) may therefore be enhanced to a greater extent by co-ingested red meat than non-heme iron absorption in populations that are relatively iron replete (30). Although the body iron status of participants in this study was unknown, previous studies among women in urban Shanghai have suggested that the prevalence of iron-deficiency anemia may be as high as 25%, much higher than in Western countries (33,34). Overall, the

large sample size, population-based design, and very high response rate in this study are significant strengths favoring the validity of our findings in Chinese women.

The positive association of animal-source iron intake with endometrial cancer risk may be due to the prooxidative effects of iron or to modification by iron of estrogenic proinflammatory effects in the endometrium (43,51,54). Dietary iron lactate supplementation in rats has been reported to induce endometrial hyperplasia, a common antecedent to endometrial cancer, although endometrial cancer rates were not increased in this model (55). Some studies have suggested that animal-derived saturated and monounsaturated fats may facilitate the transport of iron in its reactive ferrous (+2) form across cell membranes, augmenting the oxidative effects of iron in vivo (56). Heme iron contained in red meat may also differ from non-heme iron in its ability to activate specific inflammatory pathways such as the release of tumor necrosis factor (TNF)- α via toll-like receptor 4 activation (57). Substantial epidemiologic evidence supports a role for mediators of inflammation such as TNF- α in endometrial carcinogenesis (4). Our study may have lacked sufficient power to detect an interaction of iron and fat from animal foods due to very small numbers of women in high-iron and low-fat and high-fat and low-iron intake categories. Since exogenous sex steroids are not added to animal feed in China as they are in the United States, we believe an estrogenic effect of meat is unlikely. Other suggested reasons for the association of meat intake with cancers in general have included a possible effect of meat protein and the generally less healthy diets of individuals who consume more animal foods (11,19). It is therefore possible that dietary pattern rather than iron from meat is the factor most associated with endometrial cancer risk in this study (47). However, the association of iron from animal foods with endometrial cancer risk persisted after adjustment for intakes of vegetables, antioxidant vitamins, total energy, and animal fats. The effects of animal fats, protein, and animal-derived iron may not be completely distinguishable in this type of analysis since they are present in many of the same foods (correlation between fats and iron derived from animal sources was high in our study population; $r = .59$), but the lack of reduction in risk of endometrial cancer associated with animal-derived iron after adjusting for animal fat intake favors an independent effect of iron. Consumption of dairy products, which contain animal fats but lack heme iron content, would have provided a method of distinguishing the effects of these dietary constituents, but intake of dairy foods was too low among the women we studied to be helpful in this analysis.

Cooking temperatures and methods affect heme iron absorption and the generation of carcinogenic heterocyclic amines in meats (58,59). We did not control for differences in cooking methods in this study, but another study of women in Shanghai previously reported that cooking methods had little influence on the association between animal foods and endometrial cancer risk (45).

Differences between premenopausal and postmenopausal women with regard to the observed effects of animal-derived iron and to a lesser extent, animal fat on endometrial cancer risk, may be due to several factors. Despite similar increases in risk in the higher quartiles of animal-derived iron intake before menopause, there were 35% fewer premenopausal than post-menopausal women in the study, resulting in reduced power to detect associations. Variation in body iron stores and/or differences in the inflammatory

milieu in the endometrium before and after menopause may also account for some of the observed differences. Although premenopausal women may absorb non-heme iron more avidly than postmenopausal women due to menstrual iron losses and lower iron stores, absorbed iron rapidly exits the circulation for use in red cell production in this setting and may not be available to impact inflammation. Regardless of endogenous estrogen levels, the systemic inflammatory state known to be associated with obesity may enhance the adverse effects of dietary iron on endometrial inflammation in both premenopausal and postmenopausal women (4). In postmenopausal women, endometrial estrogen exposure is low, but dietary iron may have a greater impact on inflammation since iron stores are also higher, particularly in over-weight or obese women (37,60). In this study, postmenopausal women with BMI ≥ 25 kg/m² experienced a much higher risk of endometrial cancer associated with animal-derived iron in-take than their nonoverweight counterparts. The mechanisms underlying the effect modification by BMI in this study remain speculative, however, as we did not measure estrogen levels, iron stores, or biomarkers of inflammation directly in study participants.

Selective participation and recall bias are concerns in our study as in other epidemiologic studies of this kind. Although the response rate among controls was lower than that among cases, the hypotheses in this study were not known to interviewers and study subjects (61). Hence, biases of this type are unlikely to explain our results. Disease-associated changes in iron intake, if they occurred, would lead to an underestimate of the risk, as cancer patients are commonly advised to reduce animal sources of food. Finally, we did not collect data on the intake of Chinese medicines, red dates, coagulated blood products, or other possible sources of iron that are sometimes used to supplement the Chinese diet, and this may have affected our results. Not including this information, however, would be expected to lead to random misclassification error and to attenuate any effect of iron that we found.

In conclusion, dietary iron as well as fat from animal sources significantly increases the risk of endometrial cancer among postmenopausal and obese Chinese women. These results may be due to the oxidative and/or proinflammatory effects of iron in the endometrium, but further studies are needed to determine the mechanisms underlying the observed associations and whether estrogen augments these effects.

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TABLE 1

Comparison of general demographic and lifestyle characteristics between cases and controls in the SECS^a

Variable	Cases (n = 1,165)	Controls (n = 1,147)	P Value
Age (yr, mean $\pm$ SD)	54.9 $\pm$ 8.5	55.0 $\pm$ 8.5	0.86
Education (>high school, %)	40.9	40.2	0.71
Family history of cancer (yes, %) ^b	8.5	4.4	<0.01
Age at menarche (yr, mean $\pm$ SD)	14.4 $\pm$ 1.7	14.8 $\pm$ 1.8	<0.01
Postmenopausal women (%)	58.3	63.2	0.02
Age at menopause (yr, mean $\pm$ SD)	50.2 $\pm$ 3.6	49.0 $\pm$ 3.7	<0.01
No. of pregnancies (mean $\pm$ SD)	2.6 $\pm$ 1.4	2.8 $\pm$ 1.4	<0.01
Yr of menstruation (mean $\pm$ SD)	32.8 $\pm$ 5.0	30.7 $\pm$ 5.4	<0.01
Hormone replacement therapy (yes, %)	4.5	4.1	0.66
Oral contraceptive use (yes, %)	18.2	24.7	<0.01
Body mass index (kg/m ² , mean $\pm$ SD)	25.7 $\pm$ 4.1	23.8 $\pm$ 3.5	<0.01
Regular exerciser (%)	20.3	23.6	0.06
Total energy intake (kcal/day, mean $\pm$ SD)	1,794 $\pm$ 464	1,754 $\pm$ 465	0.04
Total meat intake (g/day, mean $\pm$ SD)	133.6 $\pm$ 81.8	114.2 $\pm$ 75.6	<0.01
Total vegetable intake (g/day, mean $\pm$ SD)	1,024 $\pm$ 379	1,018 $\pm$ 387	0.69
Total fruit intake (g/day, mean $\pm$ SD)	220.3 $\pm$ 169.9	216.4 $\pm$ 191.8	0.61

^a Abbreviation is as follows: SECS, Shanghai Endometrial Cancer (Case-Control) Study. *P* values: Student *t*-test for continuous variables and χ^2 test for categorical variables; *P* < 0.05 is considered significant.

^b Family history of colorectal, breast, and/or endometrial cancer among first-degree relatives.

TABLE 2

Association of endometrial cancer risk with dietary iron intake^a

	Cases (%)	Controls (%)	OR1 (95% CI)	OR2 (95% CI)
All women (cases: 1,165; controls: 1,147)				
Total iron (mg/day)				
Quartile 1 (<15.8)	22.83	24.93	1.0	1.0
Quartile 2 (15.9–19.2)	24.12	25.11	0.91 (0.65–1.28)	0.90 (0.64–1.28)
Quartile 3 (19.3–23.2)	25.67	25.02	1.14 (0.72–1.80)	1.13 (0.71–1.79)
Quartile 4 (>23.2)	27.38	24.93	1.54 (0.85–2.77)	1.47 (0.81–2.66)
			<i>P</i> _{trend} = 0.12	<i>P</i> _{trend} = 0.16
Animal iron (mg/day)				
Quartile 1 (<1.92)	19.23	25.02	1.0	1.0
Quartile 2 (1.93–2.86)	22.58	24.93	1.24 (0.95–1.63)	1.23 (0.91–1.66)
Quartile 3 (2.87–4.14)	29.18	25.02	1.83 (1.36–2.45)	1.80 (1.26–2.58)
Quartile 4 (>4.14)	29.01	25.02	1.91 (1.37–2.66)	1.86 (1.22–2.85)
			<i>P</i> _{trend} < 0.01	<i>P</i> _{trend} < 0.01
Vegetable iron (mg/day)				
Quartile 1 (<13.24)	24.38	24.93	1.0	1.0
Quartile 2 (13.25–16.09)	25.32	25.11	0.76 (0.56–1.04)	0.80 (0.58–1.10)
Quartile 3 (16.10–19.50)	24.55	25.02	0.66 (0.44–0.97)	0.73 (0.48–1.10)
Quartile 4 (>19.50)	25.75	24.93	0.70 (0.42–1.15)	0.79 (0.64–1.25)
			<i>P</i> _{trend} = 0.14	<i>P</i> _{trend} = 0.37
Premenopausal women (cases: 502; controls: 447)				
Total iron (mg/day)				
Quartile 1 (<15.8)	22.43	24.88	1.0	1.0
Quartile 2 (15.9–19.2)	22.63	25.12	0.91 (0.52–1.60)	0.91 (0.52–1.62)
Quartile 3 (19.3–23.2)	27.57	23.93	1.19 (0.57–2.49)	1.19 (0.57–2.50)
Quartile 4 (>23.2)	27.37	26.07	1.52 (0.60–3.83)	1.52 (0.60–3.86)
			<i>P</i> _{trend} = 0.30	<i>P</i> _{trend} = 0.32
Animal iron (mg/day)				
Quartile 1 (<1.92)	15.64	18.72	1.0	1.0
Quartile 2 (1.93–2.86)	21.19	21.80	1.18 (0.74–1.89)	1.24 (0.74–2.08)
Quartile 3 (2.87–4.14)	30.04	29.38	1.43 (0.87–2.34)	1.70 (0.92–3.13)
Quartile 4 (>4.14)	33.13	30.09	1.54 (0.88–2.68)	1.62 (0.80–3.29)
			<i>P</i> _{trend} = 0.11	<i>P</i> _{trend} = 0.16
Vegetable iron (mg/day)				
Quartile 1 (<13.24)	24.49	27.25	1.0	1.0
Quartile 2 (13.25–16.09)	24.90	26.07	0.86 (0.52–1.43)	0.89 (0.53–1.49)
Quartile 3 (16.10–19.50)	25.72	23.46	0.90 (0.47–1.73)	0.95 (0.48–1.86)
Quartile 4 (>19.50)	24.90	23.22	1.16 (0.52–2.56)	1.27 (0.56–2.91)
			<i>P</i> _{trend} = 0.68	<i>P</i> _{trend} = 0.54
Postmenopausal women (cases: 702; controls: 765)				

	Cases (%)	Controls (%)	OR1 (95% CI)	OR2 (95% CI)
Total iron (mg/day)				
Quartile 1 (<15.8)	23.12	24.97	1.0	1.0
Quartile 2 (15.9–19.2)	25.18	25.10	0.93 (0.59–1.45)	0.92 (0.58–1.45)
Quartile 3 (19.3–23.2)	24.30	25.66	1.14 (0.62–2.10)	1.15 (0.62–2.14)
Quartile 4 (>23.2)	27.39	24.28	1.54 (0.69–3.46)	1.47 (0.66–3.32)
			$P_{\text{trend}} = 0.19$	$P_{\text{trend}} = 0.22$
Animal iron (mg/day)				
Quartile 1 (<1.92)	21.80	28.69	1.0	1.0
Quartile 2 (1.93–2.86)	23.56	26.76	1.26 (0.89–1.79)	1.15 (0.78–1.71)
Quartile 3 (2.87–4.14)	28.57	22.48	2.22 (1.51–3.26)	1.98 (1.23–3.17)
Quartile 4 (>4.14)	26.07	22.07	2.18 (1.41–3.38)	2.02 (1.15–3.55)
			$P_{\text{trend}} < 0.01$	$P_{\text{trend}} < 0.01$
Vegetable iron (mg/d)				
Quartile 1 (<13.24)	24.30	23.59	1.0	1.0
Quartile 2 (13.25–16.09)	25.63	24.55	0.69 (0.46–1.04)	0.75 (0.49–1.14)
Quartile 3 (16.10–19.50)	23.71	25.93	0.52 (0.31–0.88)	0.60 (0.35–1.05)
Quartile 4 (>19.50)	26.36	25.93	0.42 (0.21–0.84)	0.51 (0.25–1.05)
			$P_{\text{trend}} = 0.02$	$P_{\text{trend}} = 0.08$

^a Abbreviations are as follows: odds ratio, OR; CI, confidence interval. OR1: Adjusted for age; education; body mass index; age at menarche; age at menopause (in postmenopausal women); number of pregnancies; family history of colorectal, breast, and/or endometrial cancer; regular exercise; total energy intake; vitamin A, C, and E intake; folic acid and isoflavone intake; vitamin supplement use; oral contraceptive pill; and hormone replacement therapy. OR2: Adjusted for saturated fat and monounsaturated fat intake in addition to variables for OR1.

TABLE 3

Adjusted ORs for endometrial cancer associated with total and animal-derived iron intake, stratified by BMI and menopausal status

	BMI < 25 kg/m ² OR (95% CI) (cases: 565, controls: 761)	BMI ≥ 25 kg/m ² OR (95% CI) (cases: 600, controls: 386)
All women		
Total iron (mg/day)		
Quartile 1 (<15.8)	1.0	1.0
Quartile 2 (15.9–19.2)	0.94 (0.59–1.49)	0.91 (0.52–1.58)
Quartile 3 (19.3–23.2)	1.00 (0.54–1.88)	1.34 (0.66–2.74)
Quartile 4 (>23.2)	1.36 (0.61–3.03)	1.69 (0.66–4.31)
	$P_{\text{trend}} = 0.44$	$P_{\text{trend}} = 0.20$
		$P_{\text{interaction}} = 0.60$
Animal iron (mg/day)		
Quartile 1 (<1.92)	1.0	1.0
Quartile 2 (1.93–2.86)	1.28 (0.83–1.99)	1.19 (0.76–1.85)
Quartile 3 (2.87–4.14)	1.70 (1.03–2.82)	2.32 (1.33–4.05)
Quartile 4 (>4.14)	1.84 (1.02–3.32)	2.48 (1.28–4.80)
	$P_{\text{trend}} = 0.03$	$P_{\text{trend}} < 0.01$
		$P_{\text{interaction}} = 0.52$
	(cases: 259; controls: 321)	(cases: 227; controls: 101)
Premenopausal women		
Total iron (mg/day)		
Quartile 1 (<15.8)	1.0	1.0
Quartile 2 (15.9–19.2)	1.03 (0.50–2.13)	0.66 (0.22–1.95)
Quartile 3 (19.3–23.2)	1.04 (0.39–2.74)	1.37 (0.35–5.31)
Quartile 4 (>23.2)	1.08 (0.33–3.56)	2.72 (0.44–16.9)
	$P_{\text{trend}} = 0.90$	$P_{\text{trend}} = 0.24$
		$P_{\text{interaction}} = 0.46$
Animal iron (mg/d)		
Quartile 1 (<1.92)	1.0	1.0
Quartile 2 (1.93–2.86)	1.53 (0.77–3.05)	0.74 (0.30–1.82)
Quartile 3 (2.87–4.14)	1.93 (0.86–4.32)	1.55 (0.51–4.75)
Quartile 4 (>4.14)	2.01 (0.78–5.13)	1.32 (0.37–4.68)
	$P_{\text{trend}} = 0.17$	$P_{\text{trend}} = 0.49$
		$P_{\text{interaction}} = 0.27$
	(cases: 306; controls: 440)	(cases: 373; controls: 285)
Postmenopausal women		
Total iron (mg/d)		
Quartile 1 (<15.8)	1.0	1.0
Quartile 2 (15.9–19.2)	0.92 (0.48–1.76)	1.10 (0.56–2.16)
Quartile 3 (19.3–23.2)	1.15 (0.47–2.83)	1.41 (0.58–3.44)

	BMI < 25 kg/m² OR (95% CI) (cases: 565, controls: 761)	BMI ≥ 25 kg/m² OR (95% CI) (cases: 600, controls: 386)
Quartile 4 (>23.2)	2.12 (0.66–6.82)	1.42 (0.44–4.64)
	$P_{\text{trend}} = 0.20$	$P_{\text{trend}} = 0.48$
		$P_{\text{interaction}} = 0.58$
Animal iron (mg/day)		
Quartile 1 (<1.92)	1.0	1.0
Quartile 2 (1.93–2.86)	1.03 (0.57–1.88)	1.27 (0.73–2.19)
Quartile 3 (2.87–4.14)	1.50 (0.75–3.00)	2.83 (1.42–5.64)
Quartile 4 (>4.14)	1.62 (0.72–3.66)	3.25 (1.41–7.50)
	$P_{\text{trend}} = 0.15$	$P_{\text{trend}} = 0.002$
		$P_{\text{interaction}} = 0.49$

^a Abbreviations are as follows: BMI, body mass index; OR, odds ratio; CI, confidence interval. OR adjusted for age; education; age at menarche; age at menopause (in postmenopausal women); number of pregnancies; family history of colorectal, breast, and/or endometrial cancer; regular exercise; total energy intake; vitamin A, C, and E intake; folic acid and isoflavone intake; vitamin supplement use; and intakes of saturated, monounsaturated (animal) fat, oral contraceptive pills, and hormone replacement therapy.

TABLE 4

Association of dietary fats and fatty acids with endometrial cancer risk in the SECS^a

	All Women				Premenopausal Women				Postmenopausal Women			
	Cases (n = 1,165) %	Controls (n = 1,147) %	OR (95% CI)	Cases (n = 486) %	Controls (n = 422) %	OR (95% CI)	Cases (n = 702) %	Controls (n = 765) %	OR (95% CI)			
Total fat (g/day)												
Quartile 1 (<22.34)	21.72	24.93	1.0	19.75	20.38	1.0	23.12	27.59	1.0			
Quartile 2 (22.35–30.65)	25.24	25.02	1.05 (0.81–1.36)	25.31	24.64	0.97 (0.62–1.49)	25.18	25.24	1.15 (0.82–1.63)			
Quartile 3 (30.66–40.76)	26.01	25.11	1.08 (0.81–1.44)	24.07	27.73	0.75 (0.46–1.21)	27.39	23.59	1.39 (0.96–2.03)			
Quartile 4 (>40.76)	27.04	24.93	1.09 (0.78–1.50)	30.86	27.25	1.07 (0.63–1.82)	24.30	23.59	1.15 (0.75–1.77)			
			$P_{\text{trend}} = 0.61$			$P_{\text{trend}} = 0.98$			$P_{\text{trend}} = 0.60$			
Animal source fat (g/day)												
Quartile 1 (<11.89)	18.88	24.93	1.0	16.87	18.72	1.0	20.32	28.55	1.0			
Quartile 2 (11.90–18.12)	24.38	25.02	1.28 (0.99–1.66)	23.87	25.36	1.03 (0.66–1.60)	24.74	24.83	1.37 (0.98–1.91)			
Quartile 3 (18.13–25.75)	28.15	25.02	1.55 (1.19–2.04)	27.98	26.07	1.19 (0.75–1.88)	28.28	24.41	1.85 (1.30–2.62)			
Quartile 4 (>25.75)	28.58	25.02	1.50 (1.12–2.01)	31.28	29.86	1.13 (0.69–1.86)	26.66	22.21	1.73 (1.18–2.54)			
			$P_{\text{trend}} < 0.01$			$P_{\text{trend}} = 0.51$			$P_{\text{trend}} < 0.01$			
Plant source fat (g/d)												
Quartile 1 (<8.32)	25.92	24.93	1.0	25.51	26.78	1.0	26.22	23.86	1.0			
Quartile 2 (8.33–11.54)	28.07	25.02	0.92 (0.72–1.18)	29.42	26.54	1.02 (0.68–1.52)	27.10	24.14	0.83 (0.59–1.15)			
Quartile 3 (11.55–15.64)	25.15	25.02	0.67 (0.51–0.88)	24.90	23.70	0.83 (0.53–1.30)	25.33	25.79	0.60 (0.42–0.85)			
Quartile 4 (>15.64)	20.86	25.02	0.52 (0.38–0.70)	20.16	22.99	0.66 (0.40–1.10)	21.35	26.21	0.43 (0.29–0.64)			
			$P_{\text{trend}} < 0.01$			$P_{\text{trend}} = 0.09$			$P_{\text{trend}} < 0.01$			
Saturated fatty acids (g/day)												
Quartile 1 (<6.16)	21.12	25.02	1.0	18.93	20.85	1.0	22.68	27.45	1.0			
Quartile 2 (6.17–8.94)	25.24	25.02	1.12 (0.87–1.45)	25.10	22.99	1.12 (0.73–1.73)	25.33	26.21	1.15 (0.82–1.60)			
Quartile 3 (8.95–11.93)	25.75	25.93	1.19 (0.90–1.56)	24.07	28.91	0.92 (0.58–1.44)	26.95	22.62	1.50 (1.04–2.14)			
Quartile 4 (>11.93)	27.90	25.02	1.22 (0.90–1.65)	31.89	27.25	1.24 (0.75–2.06)	25.04	23.72	1.22 (0.82–1.81)			
			$P_{\text{trend}} = 0.20$			$P_{\text{trend}} = 0.58$			$P_{\text{trend}} = 0.31$			
Monounsaturated fatty acids (g/day)												
Quartile 1 (<8.95)	19.40	24.93	1.0	17.70	19.43	1.0	20.62	28.14	1.0			

	All Women			Premenopausal Women			Postmenopausal Women		
	Cases (<i>n</i> = 1,165) %	Controls (<i>n</i> = 1,147) %	OR (95% CI)	Cases (<i>n</i> = 486) %	Controls (<i>n</i> = 422) %	OR (95% CI)	Cases (<i>n</i> = 702) %	Controls (<i>n</i> = 765) %	OR (95% CI)
Quartile 2 (8.96–12.51)	23.52	25.11	1.19 (0.91–1.55)	23.46	26.30	0.95 (0.61–1.47)	23.56	24.41	1.38 (0.98–1.94)
Quartile 3 (12.51–17.64)	29.01	25.02	1.53 (1.16–2.02)	28.40	24.64	1.22 (0.76–1.95)	29.46	25.24	1.80 (1.25–2.58)
Quartile 4 (>17.64)	28.07	24.93	1.49 (1.09–2.03)	30.45	29.62	1.09 (0.65–1.82)	26.36	22.21	1.88 (1.25–2.84)
			$P_{\text{trend}} < 0.01$			$P_{\text{trend}} = 0.53$			$P_{\text{trend}} < 0.01$
Polyunsaturated fatty acids (g/day)									
Quartile 1 (<5.59)	22.83	24.93	1.0	21.40	21.56	1.0	23.86	26.90	1.0
Quartile 2 (5.60–7.92)	27.73	25.20	1.07 (0.83–1.38)	28.81	29.62	0.84 (0.55–1.27)	26.95	22.62	1.28 (0.92–1.80)
Quartile 3 (7.93–10.69)	24.46	24.93	0.83 (0.62–1.09)	24.69	22.51	0.82 (0.51–1.33)	24.30	26.34	0.82 (0.57–1.18)
Quartile 4 (>10.69)	24.98	24.93	0.83 (0.60–1.14)	25.10	26.30	0.78 (0.46–1.34)	24.89	24.14	0.90 (0.59–1.32)
			$P_{\text{trend}} = 0.10$			$P_{\text{trend}} = 0.40$			$P_{\text{trend}} = 0.18$

^a Abbreviations are as follows: SECS, Shanghai Endometrial Cancer (Case-Control) Study; OR, odds ratios; CI, confidence intervals. All ORs are adjusted for age; education; body mass index; age at menarche; age at menopause (in postmenopausal women); number of pregnancies; family history of colorectal, breast, and/or endometrial cancer; regular exercise; total energy intake; oral contraceptive pills; and hormone replacement therapy.

TABLE 5

Joint effects of dietary animal-derived iron and fat on risk of endometrial cancer^a

Animal-Derived Iron Intake (mg/day)	Animal Fat Intake (g/day)			OR2 (95% CI) ^b
	Low (<14.16)	Middle (14.16–22.95)	High (>22.95)	
	227/311 ^c	76/61	6/10	
Low (<2.24)	1.0	1.69 (1.14–2.51)	0.82 (0.28–2.40)	1.0
	82/68	227/238	91/77	
Middle (2.24–3.62)	1.61 (1.09–2.37)	1.38 (1.05–1.83)	1.75 (1.19–2.58)	1.46 (1.13–1.89)
	6/3	113/85	337/294	
High (3.63)	2.44 (0.58–10.3)	1.82 (1.26–2.62)	1.60 (1.20–2.15)	1.74 (1.26–2.39)
OR1 (95% CI) ^d	1.0	1.35 (1.08–1.69)	1.40 (1.09–1.80)	<i>P</i> _{interaction} = 0.34

^a Abbreviations are as follows: OR, odds ratio; CI, confidence interval. All ORs are adjusted for age; education; body mass index; age at menarche; age at menopause (in postmenopausal women); number of pregnancies; family history of colorectal, breast, and/or endometrial cancer; regular exercise; total energy intake; oral contraceptive pills; and hormone replacement therapy. The referent category for all comparisons is the group with low animal-iron and low animal-fat intake.

^b OR2 shows the association of endometrial cancer with animal-derived iron intake, additionally adjusted for dietary fat intake.

^c The number of cases/controls in each cell is followed by the OR and 95% CI for endometrial cancer risk.

^d OR1 shows the association of endometrial cancer with animal fat intake, additionally adjusted for dietary iron intake.