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Iron intake with the risk of breast cancer among Chinese women: a case–control study

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Abstract

Objective: The current study evaluated the associations between different forms and sources of Fe and breast cancer risk in Southern Chinese women.

Design: Case–control study. We collected data on the consumption of Fe from different forms and food sources by using a validated FFQ. Multivariable logistic regression and restricted cubic spline (RCS) analysis was used to reveal potential associations between Fe intake and breast cancer risk.

Setting: A case-control study of women at three major hospitals in Guangzhou, China.

Participants: From June 2007 to March 2019, 1591 breast cancer cases and 1622 age-matched controls were recruited.

Results: In quartile analyses, Fe from plants and Fe from white meat intake were inversely associated with breast cancer risk, with OR of 0·65 (95 % CI 0·47, 0·89, $P_{trend} = 0·006$) and 0·76 (95 % CI 0·61, 0·96, $P_{trend} = 0·014$), respectively, comparing the highest with the lowest quartile. No associations were observed between total dietary Fe, heme or non-heme Fe, Fe from meat or red meat and breast cancer risk. RCS analysis demonstrated J-shaped associations between total dietary Fe, non-heme Fe and breast cancer, and reverse L-shaped associations between heme Fe, Fe from meat and Fe from red meat and breast cancer.

Conclusion: Fe from plants and white meat were inversely associated with breast cancer risk. Significant non-linear J-shaped associations were found between total dietary Fe, non-heme Fe and breast cancer risk, and reverse L-shaped associations were found between heme Fe, Fe from meat or red meat and breast cancer risk.

Keywords
Iron
Heme iron
Non-heme iron
Iron from plants
Breast cancer

Breast cancer is the most common cancer among women worldwide with the incidence and mortality varying from countries and regions[1]. Environmental factors, especially diet, may play important roles in its tissue growth and tumour progression[2].

Fe, obtained almost from the diets[3] and necessary for body growth and metabolism, has strong pro-oxidant properties[4] and thus, Fe has a pivotal role in oxidative stress, inducing DNA damage and lipid peroxidation[5]. Furthermore, the interaction between Fe and estrogen in oxidative stress and other pathways has been suggested to implicate breast cancer development[6,7]. As such, Fe has been hypothesised to have the risk of breast cancer[8,9].

Epidemiological studies concerning the association between dietary Fe intake and breast cancer have reported negative association[10–12], positive association[13–15] and no association[16–25]. Of the studies[11,14,20,22,24–26] examining the relationships between different forms of Fe intake and breast cancer risk, only one study[26] found positive association of heme Fe while other studies[11,14,20,22,24,25] reported null association, and two studies[20,25] assessing non-heme Fe reported no association, but a recent meta-analysis reported a modest but statistically significant positive association between heme Fe intake, serum Fe levels and breast cancer risk[27]. Some studies examined the association between different food sources of Fe intake and breast cancer risk and found no significant association

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between Fe from plants[21], Fe from meat[14,20,22], Fe from red meat[15,20,22] and breast cancer risk, with the exception of a case–control study[21] claiming that Fe from animal food sources was positively associated with breast cancer risk. To our knowledge, no study has reported the association between Fe from white meat and breast cancer risk.

Most of the studies have been performed in Western countries, where lifestyle and dietary habits differ from China. To date, only two studies have been conducted in Shanghai, China, which reported positive associations between dietary Fe[13], animal-derived Fe[21] and breast cancer risk. The prior studies generally had limited adjustment for dietary factors and other subtypes of Fe variables in the model. Moreover, most of the previous studies did not evaluate the linear or non-linear dose–response relation between dietary Fe and breast cancer risk. Therefore, the objective of the current study was to evaluate the associations between total dietary Fe, different forms and sources of Fe intake and breast cancer risk in Southern Chinese women. Given that Fe is a pro-oxidant, our hypothesis was that dietary Fe intake was positively associated with breast cancer risk.

Materials and methods

Study population

The details of this ongoing two-stage case–control study have been reported previously[28,29]. Briefly, potential case subjects were recruited in the first stage during June 2007 to August 2008 and the second stage from September 2011 to March 2019 from patients admitted to three major teaching and general hospitals of the study areas in Guangzhou. The inclusion criteria included females aged 25–70 years, natives in Guangdong or having lived in Guangdong for at least 5 years, with incident, primary, histologically confirmed breast cancer diagnosed no more than 3 months before the interview. Patients were excluded if they could not understand or speak Mandarin/Cantonese or had a prior cancer history. Overall, a total of 1778 eligible cases were identified and 1600 were successfully interviewed, with a response rate of 90·0 %. Additionally, subjects with an energy intake <2510 or >14 644 kJ/d (<600 or >3500 kcal/d)[30] were excluded from the analysis (*n* 9). Ultimately, 1591 eligible cases were included in the current study.

Control subjects were admitted to the same hospitals during the same time period as cases, and frequency matched to the cases by 5-year age interval. The controls were females aged 25–70 years old who have never been diagnosed with any cancer and otherwise shared the same eligibility criteria as the cases. They were selected from the Departments of Ophthalmology, Plastic and Reconstructive Surgery, Vascular Surgery, Ear-Nose-Throat, and Orthopedics and Microsurgery. In total, 1622 out of 1786 eligible controls participated in the current study, yielding a response rate of 90·8 %.

Data collection

The recruited patients were interviewed face-to-face by trained interviewers using a structured questionnaire, which was used to collect information on socio-demographic characteristics, anthropometry factors, lifestyle factors, menstrual and reproductive history, history of benign breast disease and family history of cancers. Relevant medical information, medical diagnosis, histological findings, and estrogen receptor (ER) and progesterone receptor (PR) status were obtained from hospital medical records.

Measurement of dietary exposure

Study subjects reported their usual dietary consumption for the past year via a validated eight-one-item FFQ[31]. The daily consumption of each FFQ food item was collected and portion size was quantified with the help of photographs of commonly consumed foods. For the current analysis, plants included cereal, legumes, vegetables and fruits. Meats were grouped into red meat and white meat. Red meat consisted of pork, beef, lamb, organ meat and processed meat. White meat primarily constituted poultry (chickens, ducks and geese) and fish (freshwater and salt-water fish, crab, shrimp and shellfish). Energy and nutrients in foods were computed by using the 2002 Chinese Food Composition Table[32].

In the current study, total dietary Fe contained only Fe from diet but not from supplements. Heme Fe intake was calculated based on meat-specific heme Fe proportions such as 65 % for beef, 39 % for pork and pork products, 26 % for chicken and fish, and 21 % for liver[33]. Dietary non-heme Fe intake was determined by subtracting dietary heme Fe from total dietary Fe intake. Fe from plants, Fe from meat, Fe from red meat and Fe from white meat were derived as the sum of dietary Fe for all of the plant foods, all of the meat, all of the red meat and all of the white meat intake, respectively.

Statistical analysis

Characteristics between cases and controls were compared by using *t* test or Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. The dietary intake data were adjusted for total energy intake using the residual method[34]. Dietary Fe intake was categorised into quartiles (Q1-Q4) based on the distribution among the controls. Multivariable logistic regression models were used to estimate the OR and 95 % CI for the associations, with the lowest quartile as the reference group. Tests for trend were performed by entering the categorical variables as continuous variables in the regression models.

Covariates in the multivariable models were selected by a significant level of $P < 0{\cdot}05$ in univariable analysis, changing the OR by 10 % for the main variables of interest or based on

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known risk factors for breast cancer. The following variables were included in the multivariable models: age, age at menarche, educational level, income, occupational activity, first-degree relative with cancer, history of benign breast disease, regular smoking, passive smoking, regular drinking, ever used an oral contraceptive and BMI. Models were adjusted for covariates in a stepwise procedure. The values of model 1 were shown as crude OR and 95 % CI. Model 2 was adjusted for above-mentioned non-dietary factors. Model 3 was further adjusted for dietary intake of fat, fibre, vitamin A, C and E which were reported having influence on Fe metabolism[21,35]. Additional adjustment for Ca, Se, Mg or flavonoids was also conducted. Mutual adjustment was performed for dietary heme Fe and non-heme Fe, Fe from plants and Fe from meat. Fe from red meat and Fe from white meat were adjusted for each other, and simultaneously adjusted for Fe from plants.

Restricted cubic spline (RCS) model was used to reveal the potential non-linear associations in model 3. Based on Akaike information criteria, three knots (at 10th, 50th and 90th percentiles of total dietary Fe, non-heme Fe and Fe from white meat intake) or four knots (at 5th, 35th, 65th, and 95th percentiles of heme Fe, Fe from plants, Fe from meat and Fe from red meat intake) were suggested to fit the models better[36]. The lowest dietary Fe intake was used as the reference value. Owing to the effect of sparse data on the RCS curve, the subjects with dietary intake > 99 % were excluded in cases and controls. $P_{\text{non-linearity}}$ was calculated by using a Wald test.

Stratified analysis by menopausal status assessed the interactions by adding the multiplicative interaction terms (dietary Fe intake × menopausal status) to the multivariable models as indicator variables. Subgroup analysis by sex hormone receptor status (ER+, ER− *v.* controls and PR+, PR− *v.* controls) was performed using polytomous logistic regression. Possible heterogeneity was examined in a case-only analysis where ER/PR status was used as the dependent variable (outcome) and dietary Fe (categorical) as independent variable in the logistic regression model. Sensitivity analysis was performed by excluding nutrient supplement users or restricting to invasive breast cancer cases to see whether the results remained consistent. All data analyses were conducted using SPSS 25.0 and Stata 15.1. All *P* values were two sided, and *P* values < 0·05 were considered as statistically significant.

Results

Baseline characteristics and dietary factors compared between cases and controls are shown in Tables 1 and 2, respectively. Overall, breast cancer cases had younger age at menarche, less education, lower income, more occupational activities and higher BMI and were more likely to drink and smoke regularly, be exposed to second-hand smoke, have a first-degree relative with cancer, suffer from benign breast disease and use oral contraceptive. Compared with the controls, cases had a lower intake of total dietary Fe, non-heme Fe, Fe from plants and Fe from white meat, while red meat intake was significantly higher in the cases than the controls.

As shown in Table 3, higher intake of total dietary Fe was associated with a lower risk of breast cancer in model 2 (OR = 0·54, 95 % CI 0·44, 0·66, $P_{\text{trend}} < 0·001$). However, this inverse association became null after adjusting for dietary factors in model 3, with an adjusted OR of 1·06 (95 % CI 0·79, 1·43) comparing the highest with the lowest quartile ($P_{\text{trend}} = 0·995$).

Heme Fe and non-heme Fe intakes were not significantly associated with breast cancer risk in quartile analyses (Table 3). Comparing the highest with the lowest quartile, the multivariable OR in model 3 was 1·00 (95 % CI 0·79, 1·28, $P_{\text{trend}} = 0·874$) for heme Fe and 0·73 (95 % CI 0·53, 1·01, $P_{\text{trend}} = 0·032$) for non-heme Fe, respectively.

Intakes of Fe from meat and Fe from red meat were not significantly related to breast cancer risk, whereas Fe from plants and Fe from white meat were inversely associated with breast cancer risk (Table 3). These associations were consistent in all models. The adjusted OR in model 3 was 1·02 (95 % CI 0·80, 1·29, $P_{\text{trend}} = 0·990$) for Fe from meat, 1·09 (95 % CI 0·86, 1·37, $P_{\text{trend}} = 0·346$) for Fe from red meat, 0·65 (95 % CI 0·47, 0·89, $P_{\text{trend}} = 0·006$) for Fe from plants and 0·76 (95 % CI 0·61, 0·96, $P_{\text{trend}} = 0·014$) for Fe from white meat, respectively. Additional adjustment for Ca, Se, Mg or flavonoids did not change the results significantly (data not shown).

As shown in Fig. 1, RCS models showed no significant non-linear associations between Fe from plants, Fe from white meat and breast cancer risk ($P_{\text{non-linearity}} > 0·05$). However, a significant J-shaped relationship was observed between total dietary Fe and breast cancer risk, of which with increasing total dietary Fe intake, the risk of breast cancer first decreased and reached the lowest risk at around 17·96 mg/d, and then increased rapidly afterwards. The trend for non-heme Fe was similar with total dietary Fe. A lower intake of non-heme Fe was associated with decreased breast cancer risk, whereas higher non-heme Fe intake (>17·84 mg/d) was associated with increased risk of breast cancer. A reverse L-shaped curve with threshold effect for heme Fe intake and breast cancer risk was found. The breast cancer risk was relatively flat until 1·45 mg/d of heme Fe intake and significantly increased beyond 2·20 mg/d. Similar trends were observed for Fe from meat and Fe from red meat of which breast cancer risk increased significantly when Fe from meat exceeded 6·45 mg/d or Fe from red meat exceeded 4·24 mg/d.

Stratified analyses by menopausal status (2034 premenopausal and 1179 postmenopausal) showed that inverse relationships between non-heme Fe, Fe from plants and Fe from white meat intake and breast cancer risk were restricted to premenopausal women (Table 4). However, there were no statistically significant interactions ($P_{\text{interaction}} > 0·05$). No significant association was found

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Table 1 Socio-demographic and selected characteristics of breast cancer in the studied population*

	Cases (*n* 1591)				Controls (*n* 1622)				
Variables	*n*	%	Mean	SD	*n*	%	Mean	SD	*P*
Age (years)			47·8	9·6			47·7	9·9	0·851
Age at menarche (years)			14·5	1·9			14·8	1·8	< 0·001
Age at first live birth (years)			25·6	3·7			25·4	3·6	0·146
BMI (kg/m^2)			23·1	3·4			22·6	3·2	< 0·001
Age categories									0·628
25–30	38	2·4			50	3·1			
31–35	113	7·1			123	7·6			
36–40	234	14·7			238	14·7			
41–45	312	19·6			318	19·6			
46–50	314	19·7			273	16·8			
51–55	208	13·1			225	13·9			
56–60	192	12·1			203	12·5			
61–65	122	7·7			133	8·2			
66–70	58	3·6			59	3·6			
Marital status									0·999
Married	1488	93·5			1517	93·5			
Unmarried/divorced/widowed	103	6·5			105	6·5			
Educational level									0·001
Primary school or below	395	24·8			444	27·4			
Junior high school	454	28·6			392	24·2			
Senior high school	389	24·5			379	23·4			
Secondary technical school	199	12·5			187	11·5			
College or above	153	9·6			219	13·5			
Occupation									0·299
Blue collar worker	634	39·8			654	40·3			
Administrator/other white-collar worker	398	25·0			436	26·9			
Unemployed/other	559	35·1			532	32·8			
Income level (yuan/month)									0·003
≤ 2000	306	19·2			248	15·3			
2001–5000	491	30·9			467	28·8			
5001–8000	433	27·2			498	30·7			
≥ 8001	361	22·7			409	25·2			
Occupational activity									0·027
Non-working	505	31·7			440	27·1			
Sedentary	514	32·3			545	33·6			
Standing	323	20·3			374	23·1			
Manual	136	8·5			159	9·8			
Heavy manual	113	7·1			104	6·4			
Parity									0·323
0	51	3·2			57	3·5			
1–2	1021	64·2			1075	66·3			
≥ 3	519	32·6			490	30·2			
Menopausal status									0·312
Premenopausal	1021	64·2			1013	62·5			
Postmenopausal	570	35·8			609	37·5			
Breast-feeding history	1345	88·3			1394	89·9			0·149
Regular drinker	195	12·3			114	7·0			< 0·001
Regular smoker	18	1·1			8	0·5			0·044
Passive smoking	946	59·5			831	51·2			< 0·001
First-degree relative with cancer	238	15·0			158	9·7			< 0·001
History of benign breast disease	608	38·2			371	22·9			< 0·001
Ever used an oral contraceptive	134	8·4			100	6·2			0·014
Sex hormone receptor status									
ER+	1049	65·9							
ER–	282	17·7							
PR+	1061	66·7							
PR–	269	16·9							
Unknown	261	16·4							
Breast cancer subtype									
Luminal	1134	71·3							
Human epidermal growth factor receptor 2 positive	61	3·8							
Basal-like	12	0·8							
Unknown	384	24·1							
Breast cancer pathological type									
Carcinoma *in situ*	178	11·2							
Invasive tumour	1408	88·5							
Unknown	5	0·3							

ER, estrogen receptor; PR, progesterone receptor.
*Continuous variables were evaluated using *t* test and categorical variables were evaluated using χ^2 test.

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Table 2 Intakes of total dietary Fe and different types of Fe and selected dietary variables among cases and controls*,†

	Cases (*n* 1591)					Controls (*n* 1622)					
Variables	Mean	SD	25th	Median	75th	Mean	SD	25th	Median	75th	*P*
Energy intake (kJ/d)	5957	1602	4832	5704	6840	5932	1611	4872	5672	6758	0·455
Total dietary Fe (mg/d)	17·3	3·4	15·0	17·0	19·3	18·1	3·3	15·8	17·9	20·1	< 0·001
Heme Fe (mg/d)	1·2	0·6	0·7	1·1	1·5	1·1	0·6	0·7	1·1	1·5	0·677
Non-heme Fe (mg/d)	16·1	3·1	14·0	15·8	18·0	16·9	3·1	14·9	16·7	18·8	< 0·001
Fe from plants (mg/d)	12·6	2·8	10·7	12·2	14·0	13·4	3·0	11·4	13·2	15·1	< 0·001
Fe from meat (mg/d)	3·4	1·8	2·1	3·1	4·3	3·3	1·6	2·2	3·1	4·3	0·875
Fe from red meat (mg/d)	2·3	1·6	1·2	1·9	3·0	2·2	1·4	1·2	1·9	2·9	0·135
Fe from white meat (mg/d)	1·1	0·9	0·5	0·9	1·4	1·2	0·9	0·6	1·0	1·5	0·017
Total fat (g/d)	30·0	10·9	22·3	28·9	36·1	29·6	10·2	22·9	28·9	35·2	0·550
Dietary fibre (g/d)	8·7	2·6	6·8	8·3	9·9	9·5	2·9	7·5	9·1	10·8	< 0·001
Vitamin A (μgRE/d)	771·8	356·6	527·4	706·6	938·7	863·9	368·5	623·9	810·7	1026·1	< 0·001
Vitamin C (mg/d)	140·6	69·3	94·1	128·7	171·4	160·0	70·9	113·7	149·2	193·4	< 0·001
Vitamin E (mg/d)	10·1	3·7	7·5	9·3	11·9	11·1	4·3	8·3	10·4	13·1	< 0·001
Total meat (g/d)	192·9	87·3	131·3	186·4	242·6	193·0	88·1	132·7	185·1	241·0	0·936
Red meat (g/d)	103·6	58·7	62·4	93·4	134·7	97·2	54·8	57·7	89·7	130·4	0·008
White meat (g/d)	89·2	69·6	42·5	73·1	115·4	95·9	74·9	48·9	77·7	121·8	0·009
Poultry (g/d)	25·5	24·2	9·2	19·8	33·9	27·5	24·7	10·8	21·8	36·5	0·004
Fish (g/d)	63·6	63·9	21·4	45·7	81·7	68·3	69·0	25·6	47·0	85·1	0·048
Plants (g/d)	837·5	227·6	682·0	799·5	934·4	910·8	247·5	747·9	873·2	1030·1	< 0·001

*The consumption was adjusted for total energy intake by the residual method.
†Wilcoxon rank-sum test was used to compare the median consumption levels between cases and controls.

between total dietary Fe, heme Fe, Fe form meat and Fe from red meat intake and breast cancer risk in pre- and postmenopausal women.

Among 1332 (83·7 %) cases with information on hormone receptor status, the cases with ER+, ER−, PR+ and PR− accounted for 1049 (78·8 %), 282 (21·2 %), 1061 (79·7 %) and 269 (20·2 %), respectively. As shown in Table 5, there was no evidence of heterogeneity ($P_{heterogeneity} > 0·05$).

The prevalence of nutritional supplement users was not significantly different among breast cancer cases and controls (27·3 % in cases *v.* 24·7 % in controls, $P = 0·099$). Sensitivity analysis by excluding all nutrient supplement users did not materially change the results (data not shown). Analysis restricted to invasive breast cancer cases did not materially change the results (data not shown).

Discussion

The quartile analyses of the current study showed that the intakes of Fe from plants and Fe from white meat were inversely associated with breast cancer risk. Furthermore, RCS analysis showed significant non-linear J-shaped associations between total dietary Fe, non-heme Fe and breast cancer risk, and reverse L-shaped associations between heme Fe, Fe from meat and Fe from red meat and breast cancer risk.

The association between total dietary Fe intake and breast cancer risk has been examined in some epidemiological studies, but the results were inconsistent. In line with the present study, three prospective studies[20,22,24] and ten case–control studies[10,12,13,16–19,21,23,25] did not support a significant association between total dietary Fe intake and breast cancer risk. However, two prospective studies conducted in the USA[14] and France[15], respectively, found a positive association between dietary Fe intake and breast cancer risk by means of quartile analyses. In the RCS model, the present study showed a significant J-shaped association between total dietary Fe intake and breast cancer risk. Consistent with our result, a meta-analysis showed a significant J-shaped relationship between serum Fe level and breast cancer risk[27]. In contrast, a case-control study in Canada did not support a non-linear relationship between dietary Fe intake and breast cancer risk[25].

Some possible biological explanations might account for this J-shaped non-linear association between total dietary Fe and breast cancer risk. First, Fe is a necessary micronutrient in human body and it is a component of various metabolic substances, such as Hb, cytochromes and tissue enzymes[37]. An appropriate amount of Fe *in vivo* plays an essential role in transport of oxygen and carbon dioxide, energy production and immune system functioning[37]. Therefore, an appropriate consumption of dietary Fe would help body metabolism and growth development. Second, due to its redox potential, Fe might cause oxidative stress through productions of free radicals and peroxide by catalysing the Fenton and Haber-Weiss reactions[38]. Excess Fe could be harmful to DNA, protein and lipid[4]. Animal experimental studies have shown that low-Fe diet could suppress 1-methyl-1-nitrosourea-induced mammary carcinogenesis, whereas high intakes might promote tumour occurrence[39,40]. This could partially explain the lower risk of breast cancer at relatively lower intake of total

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Table 3 OR and 95 % CI of breast cancer according to quartiles (Q) of different types of Fe

		Q2		Q3		Q4		
	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
Total dietary Fe (mg/d)	< 15·8	15·8–17·9		17·9–20·1		≥ 20·1		
Cases/controls (*n*)	561/405	411/406		317/406		302/405		
Model 1*	1·00	0·73	0·61, 0·88	0·56	0·46, 0·69	0·54	0·44, 0·66	< 0·001
Model 2†	1·00	0·74	0·60, 0·90	0·59	0·48, 0·72	0·54	0·44, 0·66	< 0·001
Model 3‡	1·00	0·92	0·74, 1·13	0·86	0·68, 1·09	1·06	0·79, 1·43	0·995
Heme Fe (mg/d)	< 0·7	0·7–1·1		1·1–1·5		≥ 1·5		
Cases/controls (*n*)	407/406	388/405		401/406		395/405		
Model 1*	1·00	0·96	0·79, 1·16	0·99	0·81, 1·20	0·97	0·80, 1·18	0·867
Model 2†	1·00	0·94	0·76, 1·15	0·98	0·80, 1·20	1·05	0·85, 1·30	0·574
Model 3‡	1·00	0·90	0·72, 1·12	0·95	0·76, 1·18	1·00	0·79, 1·28	0·874
Non-heme Fe (mg/d)	< 14·9	14·9–16·7		16·7–18·8		≥ 18·8		
Cases/controls (*n*)	594/405	389/406		335/406		273/405		
Model 1*	1·00	0·65	0·54, 0·79	0·56	0·46, 0·68	0·46	0·38, 0·56	< 0·001
Model 2†	1·00	0·68	0·55, 0·82	0·57	0·47, 0·70	0·45	0·37, 0·56	< 0·001
Model 3‡	1·00	0·77	0·62, 0·95	0·71	0·55, 0·91	0·73	0·53, 1·01	0·032
Fe from plants (mg/d)	< 11·4	11·4–13·2		13·2–15·1		≥ 15·1		
Cases/controls (*n*)	566/405	454/406		343/406		228/405		
Model 1*	1·00	0·80	0·67, 0·96	0·61	0·50, 0·73	0·40	0·33, 0·50	< 0·001
Model 2†	1·00	0·80	0·66, 0·97	0·63	0·51, 0·77	0·40	0·32, 0·50	< 0·001
Model 3‡	1·00	0·90	0·73, 1·11	0·79	0·62, 1·00	0·65	0·47, 0·89	0·006
Fe from meat (mg/d)	< 2·2	2·2–3·1		3·1–4·3		≥ 4·3		
Cases/controls (*n*)	412/405	405/406		364/406		410/405		
Model 1*	1·00	0·98	0·81, 1·19	0·88	0·72, 1·07	1·00	0·82, 1·21	0·710
Model 2†	1·00	0·95	0·77, 1·16	0·88	0·72, 1·09	1·05	0·85, 1·29	0·821
Model 3‡	1·00	0·91	0·73, 1·12	0·87	0·70, 1·08	1·02	0·80, 1·29	0·990
Fe from red meat (mg/d)	< 1·2	1·2–1·9		1·9–2·9		≥ 2·9		
Cases/controls (*n*)	393/405	374/406		407/406		417/405		
Model 1*	1·00	0·95	0·78, 1·16	1·03	0·85, 1·26	1·06	0·87, 1·29	0·404
Model 2†	1·00	0·95	0·78, 1·17	1·07	0·87, 1·32	1·21	0·98, 1·49	0·043
Model 3‡	1·00	0·87	0·70, 1·08	0·97	0·78, 1·20	1·09	0·86, 1·37	0·346
Fe from white meat (mg/d)	< 0·6	0·6–1·0		1·0–1·5		≥ 1·5		
Cases/controls (*n*)	451/405	417/406		369/406		354/405		
Model 1*	1·00	0·92	0·76, 1·12	0·82	0·67, 0·99	0·79	0·65, 0·96	0·007
Model 2†	1·00	0·85	0·69, 1·04	0·77	0·62, 0·94	0·69	0·56, 0·85	< 0·001
Model 3‡	1·00	0·87	0·71, 1·08	0·81	0·65, 1·00	0·76	0·61, 0·96	0·014

*Values in model 1 were showed as crude OR and 95 % CI.
†Model 2 was adjusted for age, age at menarche, educational level, income, occupational activity, first-degree relative with cancer, history of benign breast disease, ever used an oral contraceptive, regular smoking, passive smoking, regular drinking and BMI.
‡Model 3 was adjusted for confounders from model 2 plus intakes of dietary fat, fibre, vitamin A, C and E. Mutual adjustment was performed for dietary heme Fe and non-heme Fe, Fe from plants and Fe from meat. Fe from red meat and Fe from white meat were adjusted for each other and simultaneously adjusted for Fe from plants.

dietary Fe and the higher risk of breast cancer at relatively higher intake of total dietary Fe in our study.

In the present study, the quartile analysis did not show significant association between heme Fe intake and breast cancer risk. However, a reverse L-shaped association was found between heme Fe intake and breast cancer risk. Higher heme Fe intake (> 2·20 mg/d) was significantly associated with an increased risk of breast cancer. So far, most epidemiological studies[11,14,15,20,22,24,25] have reported a null association between heme Fe intake and breast cancer risk, but the National Institutes of Health-American Association of Retired Persons Diet and Health Study[26] and a recent meta-analysis[27] reported a positive association in quartile analyses. A threshold effect in non-linear dose–response analysis was also found in the above-mentioned meta-analysis[27]. However, another population-based case–control study in Canada did not find a non-linear dose-response relationship between heme Fe intake and breast cancer risk[25].

The non-linear association between heme Fe intake and breast cancer risk could be explained by some plausible reasons. Heme Fe is a principal contributor to body Fe stores due to its easier absorption than non-heme Fe[21]. Red meat, the main source of heme Fe, has been reported to be linked with increased breast cancer risk[11]. Heme Fe in red meat can coordinate with biological components like nitrogen or oxygen of amino acids and then be transported to every organ and tissue[41]. Excess intracellular heme could accelerate the expression of hemeoxygenase, thus increasing the excess heme breakdown rate[42]. This reaction could lead to the intracellular accumulation of free heme and labile Fe. An animal study indicated that mice fed with high heme diet showed acute oxidative stress[43]. Due to its involvement in endogenous *N*-nitroso compound formation, lipid peroxidation and cellular oxidative damage, heme Fe was considered to have a positive association with cancer risk[41,44].

So far, only two studies conducted in Canada[20,25] evaluated the association between non-heme Fe intake

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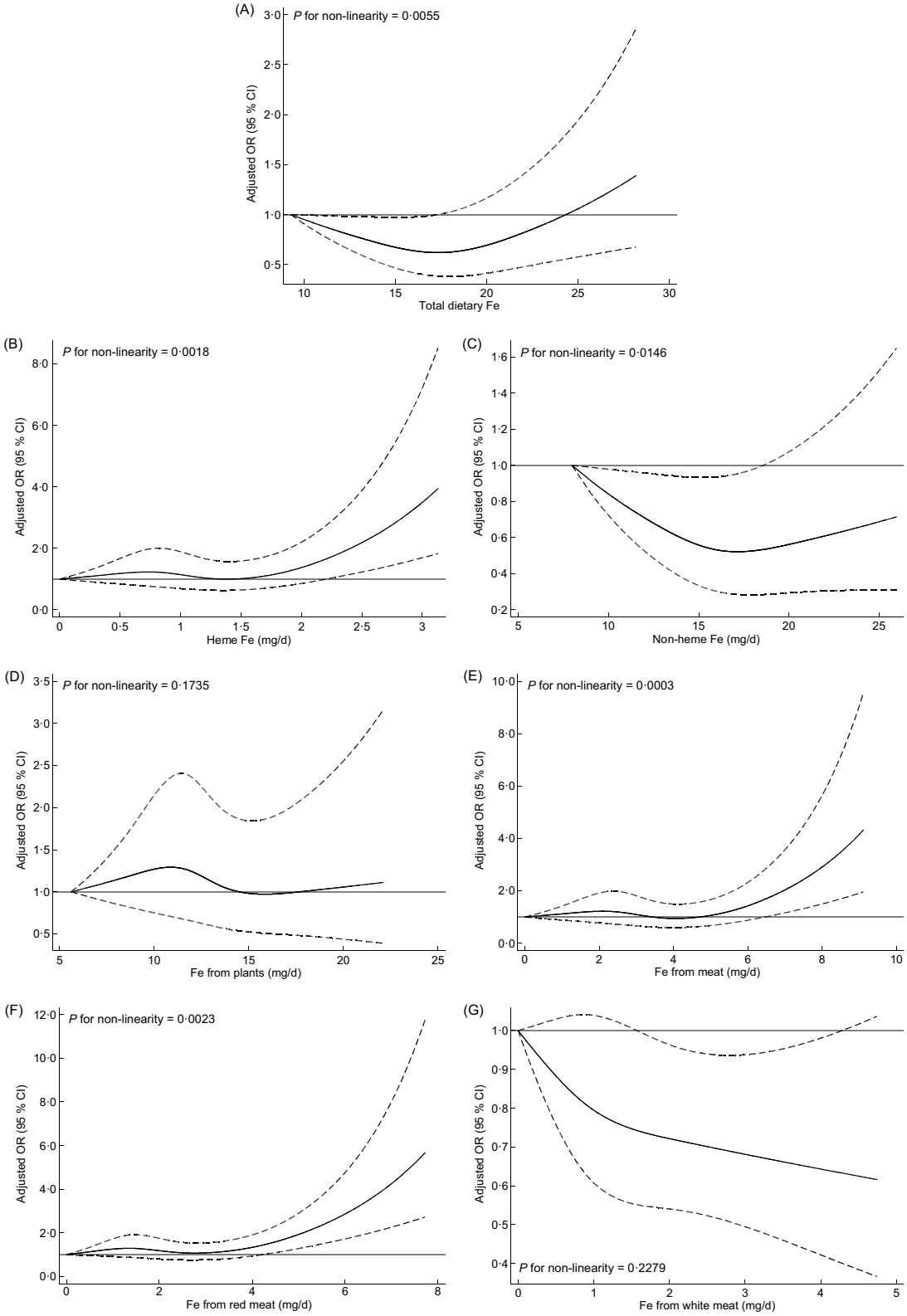

Fig. 1 Multivariable-adjusted OR (black solid lines) and 95 % CI (dashed lines) for breast cancer risk according to dietary intake of total dietary Fe (A), different forms of Fe (B and C) and different sources of Fe (D–G) in model 3. The lowest intakes were set as references (gray solid lines) (OR = 1·00)

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Table 4 OR and 95 % CI of breast cancer according to quartiles (Q) of different types of Fe by menopausal status

	Premenopausal								Postmenopausal								
		Q2		Q3		Q4				Q2		Q3		Q4			
	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}	$P_{interaction}$
Total dietary Fe (mg/d)	< 16·0	16·0–18·0		18·0–20·2		≥ 20·2			< 15·7	15·7–17·9		17·9–19·9		≥ 19·9			
Cases/controls (*n*)	388/253	250/254		198/253		185/253			181/152	151/153		125/152		113/152			
Adjusted OR*	1·00	0·79	0·60, 1·03	0·76	0·56, 1·02	0·90	0·62, 1·31	0·399	1·00	1·01	0·71, 1·45	0·98	0·66, 1·45	1·16	0·70, 1·92	0·698	0·131
Heme Fe (mg/d)	<0·8	0·8–1·1		1·1–1·5		≥1·5			<0·7	0·7–1·0		1·0–1·4		≥1·4			
Cases/controls (*n*)	272/254	254/253		238/253		257/253			141/152	145/153		144/152		140/152			
Adjusted OR*	1·00	0·91	0·70, 1·20	0·89	0·68, 1·18	1·05	0·77, 1·42	0·847	1·00	0·82	0·57, 1·18	0·80	0·55, 1·17	0·83	0·55, 1·27	0·395	0·678
Non-heme Fe (mg/d)	<14·9	14·9–16·7		16·7–18·8		≥18·8			<14·8	14·8–16·7		16·7–18·6		≥18·6			
Cases/controls (*n*)	415/253	230/253		214/254		162/253			188/152	150/153		119/152		113/152			
Adjusted OR*	1·00	0·60	0·46, 0·79	0·59	0·43, 0·81	0·52	0·34, 0·78	0·002	1·00	0·93	0·64, 1·35	0·85	0·56, 1·30	1·07	0·62, 1·86	0·970	0·088
Fe from plants (mg/d)	<11·4	11·4–13·0		13·0–15·0		≥15·0			<11·6	11·6–13·4		13·4–15·2		≥15·2			
Cases/controls (*n*)	383/253	280/253		228/254		130/253			187/152	160/152		123/153		100/152			
Adjusted OR*	1·00	0·76	0·58, 0·99	0·73	0·54, 0·99	0·47	0·31, 0·70	0·001	1·00	0·99	0·70, 1·42	0·90	0·60, 1·35	1·02	0·61, 1·71	0·885	0·099
Fe from meat (mg/d)	<2·3	2·3–3·2		3·2–4·4		≥4·4			<2·0	2·0–2·9		2·9–4·0		≥4·0			
Cases/controls (*n*)	265/253	270/253		227/254		259/253			132/152	148/152		144/153		146/152			
Adjusted OR*	1·00	1·03	0·78, 1·34	0·86	0·65, 1·14	1·02	0·76, 1·37	0·763	1·00	1·00	0·70, 1·43	0·89	0·61, 1·30	1·03	0·69, 1·53	0·976	0·422
Fe from red meat (mg/d)	<1·2	1·2–1·9		1·9–3·0		≥3·0			<1·0	1·0–1·8		1·8–2·9		≥2·9			
Cases/controls (*n*)	252/253	235/253		257/254		277/253			132/152	138/152		159/153		141/152			
Adjusted OR*	1·00	0·89	0·68, 1·18	1·00	0·76, 1·32	1·14	0·85, 1·53	0·274	1·00	0·93	0·64, 1·34	1·00	0·69, 1·45	1·05	0·71, 1·56	0·729	0·954
Fe from white meat (mg/d)	<0·6	0·6–1·0		1·0–1·5		≥1·5			<0·5	0·5–0·9		0·9–1·4		≥1·4			
Cases/controls (*n*)	300/253	259/254		242/253		220/253			145/152	152/152		140/153		133/152			
Adjusted OR*	1·00	0·83	0·64, 1·08	0·84	0·64, 1·09	0·73	0·55, 0·97	0·040	1·00	0·91	0·64, 1·31	0·85	0·59, 1·23	0·79	0·54, 1·16	0·211	0·391

*OR was adjusted for age, age at menarche, educational level, income, occupational activity, first-degree relative with cancer, history of benign breast disease, ever used an oral contraceptive, regular smoking, passive smoking, regular drinking, BMI and intakes of dietary fat, fibre, vitamin A, C and E. Mutual adjustment was performed for dietary heme Fe and non-heme Fe, Fe from plants and Fe from meat. Fe from red meat and Fe from white meat were adjusted for each other and simultaneously adjusted for Fe from plants.

Table 5 OR and 95 % CI of breast cancer according to quartiles (Q) of different types of Fe by sex hormone receptor status

		Q2		Q3		Q4		
	Q1	OR	95 %CI	OR	95 %CI	OR	95 %CI	P_{trend}
Total dietary Fe (mg/d)	< 15·8		15·8–17·9		17·9–20·1		≥ 20·1	
ER+								
Cases/controls (*n*)	355/405		266/406		215/406		213/405	
Adjusted OR*	1·00	0·94	0·74, 1·19	0·90	0·69, 1·18	1·19	0·86, 1·64	0·515
ER–								
Cases/controls (*n*)	108/405		80/406		50/406		44/405	
Adjusted OR*	1·00	1·02	0·71, 1·46	0·78	0·51, 1·21	0·99	0·57, 1·69	0·638
$P_{heterogeneity}$	0·304							
PR+								
Cases/controls (*n*)	360/405		271/406		217/406		213/405	
Adjusted OR*	1·00	0·94	0·75, 1·19	0·90	0·69, 1·17	1·16	0·84, 1·61	0·592
PR–								
Cases/controls (*n*)	102/405		76/406		47/406		44/405	
Adjusted OR*	1·00	1·02	0·71, 1·48	0·77	0·49, 1·20	1·04	0·60, 1·80	0·713
$P_{heterogeneity}$	0·436							
Heme Fe (mg/d)	<0·7		0·7–1·1		1·1–1·5		≥1·5	
ER+								
Cases/controls (*n*)	260/406		240/405		251/406		298/405	
Adjusted OR*	1·00	0·86	0·67, 1·09	0·90	0·70, 1·15	1·09	0·83, 1·42	0·482
ER–								
Cases/controls (*n*)	85/406		76/405		74/406		47/405	
Adjusted OR*	1·00	0·90	0·62, 1·30	0·92	0·63, 1·33	0·68	0·43, 1·07	0·163
$P_{heterogeneity}$	0·080							
PR+								
Cases/controls (*n*)	266/406		252/405		250/406		293/405	
Adjusted OR*	1·00	0·89	0·70, 1·13	0·88	0·68, 1·12	1·05	0·81, 1·38	0·759
PR–								
Cases/controls (*n*)	79/406		64/405		75/406		51/405	
Adjusted OR*	1·00	0·79	0·54, 1·16	1·00	0·68, 1·46	0·77	0·49, 1·22	0·560
$P_{heterogeneity}$	0·521							
Non-heme Fe (mg/d)	<14·9		14·9–16·7		16·7–18·8		≥18·8	
ER+								
Cases/controls (*n*)	380/405		256/406		228/406		185/405	
Adjusted OR*	1·00	0·75	0·59, 0·96	0·70	0·53, 0·92	0·71	0·50, 1·02	0·043
ER–								
Cases/controls (*n*)	112/405		78/406		51/406		41/405	
Adjusted OR*	1·00	0·97	0·67, 1·40	0·71	0·45, 1·11	0·78	0·43, 1·40	0·223
$P_{heterogeneity}$	0·792							
PR+								
Cases/controls (*n*)	386/405		256/406		232/406		187/405	
Adjusted OR*	1·00	0·74	0·58, 0·95	0·71	0·54, 0·94	0·71	0·50, 1·02	0·049
PR–								
Cases/controls (*n*)	105/405		78/406		47/406		39/405	
Adjusted OR*	1·00	1·00	0·69, 1·46	0·66	0·41, 1·06	0·77	0·42, 1·40	0·170
$P_{heterogeneity}$	0·738							
Fe from plants (mg/d)	<11·4		11·4–13·2		13·2–15·1		≥15·1	
ER+								
Cases/controls (*n*)	373/405		297/406		224/406		155/405	
Adjusted OR*	1·00	0·87	0·69, 1·10	0·76	0·58, 0·99	0·67	0·47, 0·95	0·015
ER–								
Cases/controls (*n*)	107/405		73/406		68/406		34/405	
Adjusted OR*	1·00	0·79	0·55, 1·14	0·90	0·59, 1·38	0·53	0·29, 0·95	0·108
$P_{heterogeneity}$	0·733							
PR+								
Cases/controls (*n*)	375/405		299/406		230/406		157/405	
Adjusted OR*	1·00	0·88	0·70, 1·11	0·79	0·60, 1·03	0·68	0·48, 0·96	0·024
PR–								
Cases/controls (*n*)	104/405		71/406		62/406		32/405	
Adjusted OR*	1·00	0·76	0·53, 1·11	0·79	0·51, 1·21	0·47	0·26, 0·86	0·035
$P_{heterogeneity}$	0·451							
Fe from meat (mg/d)	<2·2		2·2–3·1		3·1–4·3		≥4·3	
ER+								
Cases/controls (*n*)	262/405		251/406		230/406		306/405	412/405
Adjusted OR*	1·00	0·87	0·69, 1·11	0·84	0·66, 1·08	1·11	0·86, 1·44	0·452
ER–								
Cases/controls (*n*)	87/405		78/406		67/406		50/405	
Adjusted OR*	1·00	0·90	0·63, 1·30	0·84	0·58, 1·23	0·71	0·46, 1·09	0·134
$P_{heterogeneity}$	0·070							

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Table 5 *Continued*

		Q2		Q3		Q4		
	Q1	OR	95 %CI	OR	95 %CI	OR	95 %CI	P_{trend}
PR+								
Cases/controls (*n*)	270/405		264/406		224/406		303/405	
Adjusted OR*	1·00	0·90	0·71, 1·14	0·80	0·62–1·02	1·10	0·85, 1·42	0·683
PR–								
Cases/controls (*n*)	79/405		65/406		73/406		52/405	
Adjusted OR*	1·00	0·78	0·53, –1·14	0·99	0·67–1·45	0·72	0·46, 1·12	0·361
$P_{heterogeneity}$	0·319							
Fe from red meat (mg/d)	<1·2		1·2–1·9		1·9–2·9		≥2·9	
ER+								
Cases/controls (*n*)	255/405		228/406		256/406		310/405	
Adjusted OR*	1·00	0·82	0·64, 1·05	0·93	0·73–1·18	1·17	0·91–1·50	0·145
ER–								
Cases/controls (*n*)	75/405		79/406		74/406		54/405	
Adjusted OR*	1·00	0·95	0·65, 1·37	0·95	0·65, 1·39	0·85	0·55, 1·30	0·523
$P_{heterogeneity}$	0·149							
PR+								
Cases/controls (*n*)	257/405		235/406		261/406		308/405	
Adjusted OR*	1·00	0·84	0·66, 1·08	0·95	0·74, 1·21	1·18	0·91, 1·51	0·136
PR–								
Cases/controls (*n*)	74/405		71/406		69/406		55/405	
Adjusted OR*	1·00	0·83	0·57, 1·21	0·85	0·57, 1·25	0·78	0·51, 1·21	0·319
$P_{heterogeneity}$	0·077							
Fe from white meat (mg/d)	<0·6		0·6–1·0		1·0–1·5		≥1·5	
ER+								
Cases/controls (*n*)	288/405		281/406		244/406		236/405	
Adjusted OR*	1·00	0·92	0·73, 1·17	0·85	0·67, 1·08	0·82	0·64, 1·05	0·087
ER–								
Cases/controls (*n*)	93/405		75/406		61/406		53/405	
Adjusted OR*	1·00	0·82	0·57, 1·16	0·67	0·46, 0·98	0·57	0·38, 0·85	0·004
$P_{heterogeneity}$	0·059							
PR+								
Cases/controls (*n*)	302/405		282/406		245/406		232/405	
Adjusted OR*	1·00	0·88	0·70, 1·10	0·81	0·64, 1·02	0·75	0·59, 0·97	0·020
PR–								
Cases/controls (*n*)	78/405		73/406		61/406		57/405	
Adjusted OR*	1·00	0·98	0·68, 1·42	0·82	0·55, 1·22	0·77	0·51, 1·16	0·147
$P_{heterogeneity}$	0·895							

ER, estrogen receptor; PR, progesterone receptor

*OR was adjusted for age, age at menarche, educational level, income, occupational activity, first-degree relative with cancer, history of benign breast disease, ever used an oral contraceptive, regular smoking, passive smoking, regular drinking, BMI and intakes of dietary fat, fibre, vitamin A, C and E. Mutual adjustment was performed for dietary heme Fe and non-heme Fe, Fe from plants and Fe from meat. Fe from red meat and Fe from white meat were adjusted for each other and simultaneously adjusted for Fe from plants.

and breast cancer risk. These studies demonstrated a null association, which was consistent with our results in quartile analysis. However, a significant J-shaped association was observed in the present study. Relatively, low non-heme Fe intake was associated with decreased risk and higher non-heme Fe intake (>17·84 mg/d) was associated with increased risk of breast cancer. In our population, approximately 80 % non-heme Fe intake derived from plant foods such as cereal products, legumes, vegetables and fruits. These food sources contained many beneficial substances such as antioxidant vitamins[45] and phytochemicals[46]. On the other hand, non-heme Fe was found to be associated with serum ferritin in Chinese females with a predominantly plant-based diet[47]. High level of serum ferritin was found to be associated with an elevated risk of breast cancer[48].

Consistent with our results of quartile analyses, the null associations between Fe from meat, Fe from red meat and breast cancer risk were also reported in several cohort studies[14,15,20,22]. In RCS models, the present study showed that higher intake of Fe from meat (>6·45 mg/d) and Fe from red meat (>4·24 mg/d) was significantly associated with increased risk of breast cancer. Meat, including red meat, contains essential amino acids and micronutrients, but the consumption of red meat was classified as 'probably carcinogenic to humans'[49]. The mechanism of the potential harmful effects of higher intake of Fe from meat and Fe from red meat could be partially explained by heme Fe. Other carcinogenic mediators found in red meat, such as *N*-nitroso compounds, heterocyclic amines and polycyclic aromatic hydrocarbons, might also contribute to these associations[26].

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Contrary to our hypothesis, the present study found a significant inverse association between Fe from white meat and breast cancer risk. It is known that white meat contained less heme Fe, probably 26 %, than red meat[33]. Higher intake of white meat generally indicated a healthier dietary pattern[50]. A pooled analysis in the USA showed that white meat intake was inversely associated with breast cancer risk[51]. Our observation of an inverse association between Fe from white meat and breast cancer risk persisted after further adjusting for vitamin C, vitamin E, vitamin A, fat, fibre, Ca, Se or Mg. There might be some other components of white meat attributable to the protective effect of Fe from white meat.

So far, only one population-based case–control study has reported the association between plant-derived Fe intake and breast cancer risk and found a null association[21]. This is in contrast to the inverse association between plant-derived Fe intake and breast cancer risk observed in the present study. The inverse association persisted after further adjustment for other substances contained in plant foods such as flavonoids, fibre or Ca. There might be some other reasons to explain or contribute to this inverse association. Further studies are needed to clarify this issue.

There was no significant interaction between Fe intake and menopausal status in the current study. Similarly, some studies[11,20,21,24] also found the associations between total dietary Fe[11,20,21,24], heme Fe[11,20,24], meat Fe[20], animal sources of Fe[21], plant sources of Fe[21] and breast cancer risk were not modified by menopausal status. On the other hand, no significant heterogeneity across sex hormone receptor status was observed. Two cohort studies[22,26] and a case–control study[25] have also reported null associations between dietary Fe intake and hormone receptor-defined breast cancer risk. Given the limited literature, further studies are warranted to clarify this issue.

To our knowledge, this is the first study to examine the association between two forms and four sources of Fe intake and breast cancer risk in Southern Chinese women. Strengths included the large sample size, the nutrient intakes reflecting the local level, a wide range of potential confounders and potential non-linear associations assessed by RCS models.

Some limitations also need to be considered. First, selection bias and recall bias are difficult to rule out in hospital-based case–control studies. However, cases were consecutively recruited from three major hospitals in Guangzhou and the high participation rate (90·0 % for cases and 90·8 % for controls) helped to reduce selection bias in our results. Second, Fe from dietary supplements was not calculated as part of the exposure, but sensitivity analysis excluding nutritional supplement users did not materially change the results. Third, some potential residual confounding may still exist. Fourth, due to multiple comparisons, chance findings may exist and therefore the current results should be interpreted with caution. Fifth, measurement errors and misclassification were inevitable due to the use of FFQ, but the potential misclassification was likely to be non-differential and tended to attenuate the association to null. Moreover, although the present study did not evaluate the relationship between dietary Fe intake estimated by FFQ and body Fe status, some studies have shown that dietary Fe intake was related to body Fe status[52,53].

In conclusion, Fe from plants and Fe from white meat were inversely associated with breast cancer risk in quartile analyses, whereas total dietary Fe, heme Fe, non-heme Fe, Fe from meat and Fe from red meat intake were non-linearly associated with breast cancer risk, showing J-shaped associations between total dietary Fe, non-heme Fe and breast cancer risk, and reverse L-shaped associations between heme Fe, Fe from meat and Fe from red meat and breast cancer risk.

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