Heme iron from meat and risk of adenocarcinoma of the esophagus and stomach

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Iron can cause oxidative stress and DNA damage, and heme iron can catalyze endogenous formation of *N*-nitroso compounds, which are potent carcinogens. Dietary iron promotes esophageal cancer incidence in animal studies and has been identified as a growth factor for *Helicobacter pylori*, an established risk factor for stomach cancer. We conducted a population-based case–control study of adenocarcinoma of the esophagus ($n=124$) and stomach ($n=154$) and 449 controls in Nebraska. Heme iron and total iron intake were estimated from a food frequency questionnaire and databases of heme and total iron. We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for known risk factors. Esophageal cancer was positively associated with higher intakes of heme iron ($OR_{Q4\ vs.\ Q1}=3.04$, 95% CI: 1.20–7.72; *P* trend = 0.009) and total iron from meat sources ($OR_{Q4\ vs.\ Q1}=2.67$, 95% CI: 0.99–7.16; *P* trend = 0.050). Risk of stomach cancer was elevated among those with higher intakes of heme iron ($OR_{Q4\ vs.Q1}=1.99$, 95% CI: 1.00–3.95; *P* trend = 0.17) and total iron from meat (OR = 2.26, 95% CI: 1.14–4.46; *P* trend = 0.11). Iron intake from all dietary sources was not significantly associated with risk of either cancer. Our results suggest that high intakes of heme and iron from meat may be important dietary risk factors for esophageal and stomach cancer and may partly explain associations with red meat. *European Journal of Cancer Prevention* 21:134–138 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The incidence of esophageal adenocarcinoma has risen rapidly in developed countries and the reasons for the increase are not well explained. Esophageal cancer predominantly afflicts men; however, the known risk factors, including obesity, reflux, and smoking cannot explain the strong male excess. Although the incidence of stomach cancer has decreased over the past 50 years in the United States and other Western countries (Shibata and Parsonnet, 2006), stomach cancer still ranks fourth in cancer incidence and second in mortality worldwide. Infection with *Helicobacter pylori* is an established risk factor for noncardia stomach cancer; however, only a small proportion of those infected go on to develop stomach cancer (Shibata and Parsonnet, 2006).

Iron status is typically higher in men, and animal models of esophageal cancer indicate that oxidative damage caused by a combination of gastroesophageal reflux and high iron intake promotes tumorigenesis (Chen and Yang, 2001). Iron may also play a role in stomach cancer risk by causing oxidative damage and it is thought to be an essential growth factor for *H. pylori* (Perez-Perez and Israel, 2000). Another potential mechanism involves endogenous formation of carcinogenic *N*-nitroso compounds (NOC), which is increased after ingestion of heme iron (Cross *et al.*, 2003) and red and processed meats (Lunn *et al.*, 2007), the primary sources of intake.

Only a few epidemiologic studies have estimated iron intake from meat and risk of esophageal or stomach cancer. An index for endogenously formed NOC was developed from human studies of iron intake from meats and was associated with an increased risk of stomach cancer in a European cohort study (Jakszyn *et al.*, 2006). A cohort study in Iowa (Lee *et al.*, 2005) found elevated incidence of esophageal and stomach cancer associated with high intake of heme iron but not total dietary iron.

We previously reported increased risks of esophageal and stomach adenocarcinomas associated with higher intake of red and processed meat, well-done red meat, and dietary nitrate and nitrite from animal sources (Ward *et al.*, 1997, 2008). Here we estimate intake of heme and total iron from meat in relation to risk of these cancers using a new database of heme iron levels developed at the National Cancer Institute (NCI).

Methods

Study population

We conducted a population-based case–control study of adenocarcinoma of the esophagus and stomach in 66

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counties in eastern Nebraska as previously described (Ward *et al.*, 1997; Chen *et al.*, 2002). Patients were white men and women aged 21 years or above, newly diagnosed between 1 July 1988 and 30 June 1993, identified from the Nebraska Cancer Registry and confirmed by histological review. Controls were randomly selected from a previous population-based case–control study in the same geographic region of Nebraska (Zahm *et al.*, 1990) and were matched to patients by race, age, sex, and vital status. We selected a random sample of previous controls with oversampling of living controls to provide more power for analyses by respondent type. Of the 606 eligible controls, 503 (83%) were successfully interviewed for this study in 1992–1994. The response rate in the original study was 87%, giving an overall control response rate of 72%. Response rates were 88 and 79% for patients with esophageal and stomach cancer, respectively. Telephone interviews were conducted with the patients or their proxies for those who were deceased or too ill to participate. Proxy interviews were conducted for 76, 80, and 61% of patients with esophageal and stomach cancer and controls, respectively. The majority ($\geq 79\%$) of proxies were the spouse or child. The study was approved by the Institutional Review Boards at the NCI and University of Nebraska Medical Center.

Interviews and dietary database

Interviewers obtained information about dietary intakes, tobacco, alcohol, and other factors. We used the short Health Habits and History Questionnaire (Block *et al.*, 1990) with addition of foods high in nitrate/nitrite and questions about meat cooking methods and doneness preferences for beef, pork, and chicken (Ward *et al.*, 1997). The short questionnaire was developed from the full 100-item questionnaire after dropping questions that resulted in little reduction in nutrient intake correlations (correlations were ≥ 0.94 for macronutrients and micronutrients) (Block *et al.*, 1990). The full questionnaire contains foods that represented at least 90% of each of the 18 nutrients in the Second National Health and Nutrition Examination Survey database, including iron (Block *et al.*, 1985). Age-specific and sex-specific portion sizes and iron values came from the DIETSYS database (HHHQ-DIETSYS, 1993) with nutrient values appropriate for the food supply in the 1980s. Iron intake from supplements was not obtained. Heme iron in meats was determined from a database developed at the NCI, that was created from measured values of heme iron in meat samples (bacon, chicken, cold cuts, hamburgers, hot dogs, pork chops, roast beef, sausages, and steak) cooked by different methods to varying degrees of doneness (Sinha *et al.*, 2005). The US Department of Agriculture value for iron was used for liver (beef liver, pan fried) (USDA, 2008).

Data analysis

We limited analyses to those with adequate dietary data, defined as having fewer than 20% line items missing or unknown food items (124 patients with esophageal and 154 with stomach cancer, and 449 controls). We investigated distal stomach cancer separately [excluding cardia cases, $n = 30$ (19%)] and the results were similar to those for all stomach cancers and are not presented. We evaluated quartiles of intake of heme and total iron on the basis of distribution among controls, as well as intake on the continuous scale. We evaluated processed, nonprocessed, and total red meat intake on a grams per day basis simultaneously adjusting for white meat intake (chicken and fish). Previously, intake was evaluated in servings per week and was not adjusted for other meat types and macronutrients and micronutrients. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression, adjusting for the study matching factors of sex and year of birth, and risk factors for esophageal (smoking, alcohol, BMI) and stomach cancer (education, smoking, alcohol) in this study population that changed the ORs more than 10%. Analyses were additionally adjusted for total calories and several nutrients associated with these cancers (Chen *et al.*, 2002); details are given in the tables. We tested for trend across quartiles by including the median level of each quartile in the model as a continuous variable. Additional adjustment for animal nitrite/nitrate, saturated fat, or beef doneness preference did not change the ORs by at least 10% and, therefore, these were not included as covariates in the final models. We evaluated risk separately for self and proxy respondents and observed similar associations so combined results are presented. We assessed effect modification by vitamin C and alcohol because vitamin C inhibits endogenous nitrosation and has other beneficial effects, and alcohol influences iron homeostasis (Fletcher *et al.*, 1999) and nitrosamine metabolism (Anderson *et al.*, 1995, 1996). To evaluate the consistency of the association, we stratified by sex, BMI, and smoking status.

Results

In this population, intake of red meat (control median: 111 g/day, interquartile range: 74–157) was about four-fold higher than intake of white meat (chicken and fish) (median: 24 g/day, interquartile range: 16–37). High intake of red meat was associated with increased risk of both esophageal and stomach cancer (highest vs. lowest quartile OR = 2.85, 95% CI: 1.00–8.16; P trend = 0.03; OR = 2.16, 95% CI: 1.06–4.38; P trend = 0.04, respectively) (Table 1). For stomach cancer, this association was primarily due to the intake of nonprocessed red meat.

We observed an increased risk of esophageal cancer with increasing quartiles of heme and total iron from meat, with a stronger association for heme iron (highest vs. lowest quartile OR = 3.04, 95% CI: 1.20–7.72; P trend = 0.01) (Table 2). Risk of stomach cancer was elevated about two-fold in all intake quartiles compared with the lowest for both heme and total iron from meat. Iron intake from all dietary sources was not significantly associated with risk of either cancer.

Table 1 Odds ratios and 95% confidence intervals for esophageal and stomach adenocarcinoma associated with intake of total red meat, processed meat, and red nonprocessed meat.

	Esophageal[a]			Stomach[b]	
g/day	Controls	Patients	OR 95% CI	Patients	OR 95% CI
Total red meat					
≤ 73.8	113	19	1.0	25	1.0
73.9–111.3	111	22	1.10 (0.50–2.44)	36	1.64 (0.88–3.05)
111.4–157.2	113	36	1.44 (0.63–3.28)	44	1.95 (1.03–3.70)
>157.2	112	47	2.85 (1.00–8.16)	49	2.16 (1.06–4.38)
P trend	–	–	0.034	–	0.043
OR per 10 g/day	–	–	1.03 (0.95–1.12)	–	1.02 (0.99–1.06)
Processed red meat					
≤ 16.1	113	20	1.0	30	1.0
16.2–29.6	112	26	0.81 (0.38–1.72)	38	0.81 (0.45–1.46)
29.7–52.3	111	31	1.07 (0.52–2.21)	40	1.17 (0.66–2.10)
>52.3	113	47	1.40 (0.62–3.15)	46	0.97 (0.51–1.85)
P trend	–	–	0.23	–	0.87
OR per 10 g/day	–	–	1.06 (0.97–1.17)	–	1.03 (0.97–1.10)
Nonprocessed red meat					
≤ 50.4	113	19	1.0	24	1.0
50.5–75.1	112	25	0.86 (0.40–1.85)	42	1.46 (0.78–2.70)
75.2–111.2	112	33	1.82 (0.84–3.93)	35	1.90 (1.03–3.51)
>111.2	112	47	1.92 (0.73–5.06)	53	1.94 (1.00–3.76)
P trend	–	–	0.10	–	0.055
OR per 10 g/day	–	–	1.01 (0.92–1.10)	–	1.02 (0.98–1.06)

All models are additionally adjusted for other meat so that the variables in the model sum to total intake (red and white meats).
CI, confidence interval; OR, odds ratio.
[a]Adjusted for year of birth, sex, cigarettes/day (none, <30/day, 30+/day), quartiles of BMI, continuous intake of retinoic acid, folate, riboflavin, zinc, carbohydrate, protein, total calories.
[b]Adjusted for year of birth, sex, cigarettes (never, <30/day, 30+/day), education (<high school, high school graduate, some college/vocational school, college graduate/postgraduate), vitamin C, fiber, carbohydrate, total calories.

Adjustment of the models for animal sources of nitrite did not change the ORs (not shown). The association of esophageal and stomach cancer with heme and total iron from meat was similar among those with below the median (< 114.7 mg/day) and above the median (≥ 114.7 mg/day) intake of vitamin C. Stratification by alcohol consumption was limited by small numbers of nondrinkers among patients (26 esophageal, 66 stomach). Among consumers of alcohol (past or current), we observed significant positive trends with intake of heme iron for esophageal and stomach cancers (*P* trend = 0.02 and < 0.001, respectively) and total iron from meat (*P* trend = 0.03 and 0.01, respectively). Among nondrinkers, ORs for esophageal cancer were nonsignificantly elevated among those with high intake of heme and meat iron; however, we observed no association with stomach cancer (not shown).

Discussion

We previously reported that high red meat intake and animal sources of nitrate and nitrite were associated with increased risk of esophageal and stomach cancers (Ward *et al.*, 1997, 2008). Here, we report risk for grams of daily red and processed meat intake adjusted for total meat intake and micronutrients. For both esophageal and stomach cancer, we observed significantly increased risk with high intake of red meat. High intake of heme and meat iron were associated with increased risk of esophageal and stomach cancers, whereas iron intake from all foods was not associated with risk of these cancers.

Most previous case–control studies observed a positive association between red meat intake and risk of esophageal and stomach cancers, whereas cohort studies are less consistent (Gonzalez *et al.*, 2006; Jakszyn and Gonzalez, 2006; World Cancer Research Fund/American Institute for Cancer Research, 2007; Cross *et al.*, 2010). Few studies have investigated potential mechanisms for these associations.

Several prior studies evaluated heme or meat iron and risk of these cancers. In a Danish cohort study, esophageal cancer was more common than expected in patients with hemochromatosis, a condition associated with iron overload (Hsing *et al.*, 1995). A cohort study of older women in Iowa (Lee *et al.*, 2005) found a positive trend in risk of upper aerodigestive cancer (esophageal and stomach cancers) with increasing heme iron intake. Risks were similar among nondrinkers and drinkers, although stomach and esophageal cancers were not evaluated separately. In an analysis of heme iron intake in the NIH-AARP Diet and Health Study cohort (Cross *et al.*, 2010) using the same database, heme iron was positively associated with esophageal adenocarcinoma (highest vs. lowest quartile hazard ratio = 1.47, 95% CI: 0.99–2.20; *P* for trend = 0.063). A case–control study in Ireland (O'Doherty *et al.*, 2010) found a three-fold risk of esophageal adenocarcinoma among those in the highest quartile of heme iron intake. The distribution of intake and the magnitude of the association were very similar to our study. However, in contrast to our findings, total dietary iron was associated with decreased risk of

Table 2 Odds ratios and 95% confidence intervals for esophageal and stomach adenocarcinoma associated with heme, meat iron, and total dietary iron intake

	Esophageal[a]			Stomach[b]	
	Controls	Patients	OR 95% CI	Patients	OR 95% CI
Heme iron (mcg/day)					
98 to <660	112	19	1.0	21	1.0
660 to <1038	112	26	1.20 (0.56–2.55)	40	2.15 (1.15–4.02)
1038 to <1440	112	35	1.89 (0.88–4.08)	47	2.38 (1.26–4.52)
1440+	113	44	3.04 (1.20–7.72)	46	1.99 (1.00–3.95)
P trend	–	–	0.01	–	0.17
OR per mg/day	–	–	1.25 (0.70–2.23)	–	1.24 (0.97–1.58)
Meat iron (mcg/day)					
589 to <2489	113	19	1.0	23	1.0
2489 to <3802	112	29	1.38 (0.66–2.90)	44	2.32 (1.26–4.25)
3802 to <5309	112	32	1.64 (0.74–3.61)	37	1.66 (0.87–3.15)
5309+	112	44	2.67 (0.99–7.16)	50	2.26 (1.14–4.46)
P trend	–	–	0.05	–	0.11
OR per mg/day	–	–	1.07 (0.86–1.34)	–	1.06 (0.98–1.16)
Total iron (mg/day)					
<10.6	113	26	1.0	29	1.0
10.6 to <13.4	112	24	0.73 (0.35–1.53)	31	1.24 (0.66–2.32)
13.4 to <17.3	112	39	1.40 (0.62–3.20)	49	1.67 (0.87–3.18)
17.3+	112	35	1.67 (0.51–5.44)	45	1.71 (0.75–3.18)
P trend	–	–	0.31	–	0.21
OR per mg/day	–	–	1.03 (0.91–1.19)	–	1.03 (0.98–1.08)

CI, confidence interval; OR, odds ratio.
[a]Adjusted for year of birth, sex, cigarettes/day, (none, <30/day, 30+/day), quartiles of BMI, continuous intake of retinoic acid, folate, riboflavin, zinc, carbohydrate, protein, total calories.
[b]Adjusted for year of birth, sex, cigarettes (never, <30/day, 30+/day), education (<high school, high school graduate, some college/vocational school, college graduate/postgraduate), vitamin C, fiber, carbohydrate, total calories.

esophageal adenocarcinoma and toenail iron levels showed a similar inverse association with risk. A case–control study of esophageal cancer in the United States (Rogers *et al.*, 1993) found that higher concentrations of iron measured in nails were associated with increased risk of esophageal cancer; however, the authors did not evaluate esophageal tumors by histology.

Heme iron intake was not associated with stomach cancer risk in the NIH-AARP cohort (Cross *et al.*, 2010). In contrast, a cohort study in Europe (Jakszyn *et al.*, 2006) evaluated iron intake from meat as a marker of endogenous nitrosation and found a significantly increased risk of stomach cancer with increased intake. In a nested case–control study within this cohort, the positive association with endogenous NOC as estimated by meat iron was present only among individuals infected with *H. pylori* (>90% of patients) and those with plasma vitamin C levels below the median. We observed similar associations between meat and heme iron and stomach cancer risk by the median vitamin C intake level estimated from the food frequency questionnaire. Differences in our findings may be because of the different methods used to estimate vitamin C intake. We did not have information on *H. pylori* infection on the entire study population, but infection rates were high (>70%) based on 100 controls (unpublished data).

Ingestion of nitrate and nitrite from processed meats is associated with increased risk of esophageal and stomach cancers in most case–control studies (International Agency for Research on Cancer, 2007). We previously reported a significant positive trend in risk of esophageal cancer with higher intake of animal sources of nitrite and nitrate (Ward *et al.*, 2008); however, our findings for heme and meat iron intake were not altered by adjustment for nitrate/nitrite or for meat doneness levels.

A potential mechanism whereby meat iron may increase risk has been demonstrated in rodent models using surgically induced reflux, in which high dose intraperitoneal iron induced esophageal tumors (Chen and Yang, 2001). Heme iron has cytotoxic and hyperproliferative effects in the rat colon (Sesink *et al.*, 1999) and may act similarly in the specialized intestinal epithelium of Barrett's esophagus, which is associated with esophageal adenocarcinoma. Iron is thought to be an important growth factor for *H. pylori* (Perez-Perez and Israel, 2000) and infection is an established risk factor for stomach cancer. Heme iron also increases endogenous formation of NOC (Cross *et al.*, 2003; Lunn *et al.*, 2007), which cause esophageal and stomach tumors in several animal species (Mirvish, 1995).

This study was limited by a lack of information on *H. pylori* infection and a limited sample size for evaluating risks among subgroups. Some of the data were collected from proxy respondents, which may have resulted in some degree of measurement error; however, if nondifferential, the effect would be to attenuate risk estimates. However, we observed similar intake levels and consistent associations by respondent type suggesting that proxy reporting

of meat intake was similar to self-reports. The strengths of this study include the high response rates, information on important risk factors for these cancers, detailed dietary information, and a database of heme iron levels that accounted for varying levels in meats cooked by various methods and to different doneness preferences. We were also able to adjust for nitrate and nitrite levels in meats.

Our findings suggest that heme iron from red meat is a risk factor for adenocarcinoma of the esophagus and stomach. Larger and prospective studies are needed to confirm these associations and to evaluate effect modification by factors affecting iron homeostatsis and endogenous NOC production.

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Conflicts of interest

There are no conflicts of interest.

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