Research Article

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Heme Iron Intake, Dietary Antioxidant Capacity, and Risk of Colorectal Adenomas in a Large Cohort Study of French Women

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Abstract

Background: Nitrosylated and non-nitrosylated heme iron from red processed and nonprocessed meat have been associated with increased colorectal carcinogenesis. Mechanisms include oxidative processes. It has been hypothesized that dietary antioxidants could counteract the effects of heme iron. We investigated the relationships between heme iron intake and the risk of colorectal adenomas, and a potential interaction with the dietary antioxidant capacity, in the E3N prospective cohort study.

Methods: The study included 17,397 women, who underwent at least one colonoscopy. Among them, 1,409 were diagnosed with at least one first colorectal adenoma during the 103,253 person-years of follow-up. Dietary intake was measured by a semiquantitative food history questionnaire. HR estimates and 95% confidence intervals (CI) were obtained from Cox proportional hazards models, adjusted for potential confounders.

Results: Heme iron intake was positively associated with colorectal and colon adenoma risks [HR for the fourth vs. first quartile: $HR_4 = 1.36$ (1.13–1.65), $P_{trend} = 0.001$ and $HR_4 = 1.49$; 95% CI, 1.19–1.87; $P_{trend} = 0.0003$, respectively]. Nonnitrosylated and nitrosylated heme iron intakes were, respectively, associated with advanced distal and proximal adenoma risks. There was a dose–effect relationship between the heme iron to total dietary antioxidant capacity ratio and colorectal adenoma risk.

Conclusion: In this prospective cohort study, the association between heme iron and colorectal adenoma risk was found to depend on site, nitrosylation or not, and the ratio with the NEAC.

Impact: These results emphasize the need for a global assessment of diet when considering nutritional prevention of colorectal carcinogenesis. *Cancer Epidemiol Biomarkers Prev; 25(4); 640–7. ©2016 AACR.*

Introduction

Colorectal cancer is the second most common type of cancer and the second cause of cancer-related death among French women after breast cancer (1). Environmental factors, particularly food habits, are believed to play a major role in its development (2). Many epidemiologic studies have shown an increased risk of colorectal cancer and adenomas with high red and processed meat intake (3, 4). The World Cancer Research Fund panel considers the evidence relating the consumption of red and processed meat to the risk of colorectal cancer convincing and therefore recommends avoiding the consumption of processed meat and eating less than 500 grams of red meat per week (2, 4).

Among the factors present in red and processed meat, most epidemiologic and experimental evidence support a major role of heme iron, abundant in red meat but far less in poultry, in the promotion of colorectal cancer by red and processed meat (5, 6, 7). In processed red meat, heme iron is nitrosylated because curing salt contains nitrate or nitrite (5), and the International Agency for Research on Cancer recently classified processed red meat as a carcinogen (8). As most colorectal cancers are thought to arise through an adenoma–carcinoma sequence, studying dietary risk factors of colorectal adenomas could enhance our understanding of the early stages of colorectal carcinogenesis (9). However, only four prospective studies and two case–control studies investigated the relationship between colorectal adenoma risk and heme iron intake (10–14) and none separately investigated associations with nitrosylated and non-nitrosylated heme iron.

One of the main hypotheses explaining the promotion of colorectal carcinogenesis by heme iron is that its prooxidative properties could induce the oxidation of dietary polyunsaturated fatty acids. Oxidation leads to the formation of secondary reactive end products, such as malondialdehyde or 4-hydroxynonenal, that are cytotoxic and genotoxic (5). The heme-induced lipid peroxidation can be inhibited in the gastrointestinal tract by some polyphenols and vitamins, redox components of plant origin, that are able to hamper the damaging effect of free radicals (15–21). To consider the global antioxidant capacity as well as synergistic interactions between dietary antioxidants, the assessment of dietary non-enzymatic antioxidant capacity (NEAC) has

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been applied to epidemiologic studies as well as human intervention trials (22, 23).

The aim of this study was to investigate the relationship between nitrosylated and non-nitrosylated heme iron intake and the risk of colorectal adenomas in the Etude Epidémiologique de femmes de la MGEN: Mutuelle Générale de l'Education Nationale (E3N) study and to test potential interactions with the NEAC.

Materials and Methods

The E3N cohort study

The E3N prospective cohort was initiated in France in 1990 to study the main risk factors of cancer and severe chronic conditions in women (24). It includes 98,995 French women born between 1925 and 1950 and covered by the MGEN, a national teacher's health insurance plan. All women signed an informed consent in compliance with the rules of the French National Commission for Data Protection and Individual Freedom (Commission National Informatique et Libertés), from which approval was obtained.

Medical and lifestyle data

In each questionnaire, women declared all medical events, including cancer occurrence, screening examinations, and findings of colonoscopies, as well as information on lifestyle, including lifetime use of hormonal treatments, height and weight, and smoking status.

Dietary data

The food frequency questionnaire was sent to 95,644 women (with two reminders for non-answering women) between June 1993 and July 1995. It was composed of questions about (i) quantity and frequency of food groups and (ii) qualitative data to detail food groups into single foods. The questionnaire was sent with a booklet of pictures to facilitate the estimation of portion sizes (25). The questionnaire provided data on the intake of 208 food and drink items. It was validated with twelve monthly 24-hour recalls, and reproducibility was evaluated after one year (26). In all, 77,613 questionnaires were collected, and the response rate was 81.1%. Among them, we excluded 985 women because they failed to sign a consent file for external health follow-up by the health insurer in the case of dropout of the study and 2,106 women because of miscoded or double answers. Therefore, 74,522 questionnaires were available for the analysis of dietary factors. Mean daily intake of nutrients was evaluated using a food composition table derived from the French food composition table of the French Information Center on Food Quality (27). The table was completed with the NEAC of foods, evaluated with two different assays: ferric ion–reducing antioxidant power (FRAP), based on the single-electron transfer method, and total radical-trapping antioxidant parameter (TRAP), based on the hydrogen atom transfer method, calculated using an Italian database (28, 29). Because the correlation between FRAP and TRAP was high ($r_{\text{Pearson}} = 0.999$) and because FRAP is directly related to the reduction of iron oxidation, we chose to present only results with FRAP in the main text (results with TRAP are listed in Supplementary Tables). For four food items (apple, melon, beer, and vinegar), two values were available, and we used an average value. If there was no exactly matching food item in the database, we used the value of a similar item, based on the similarity of botanical group and in vitamin E and polyphenol contents. The NEAC intake from coffee was not considered in this study due to (i) uncertainty about the *in vivo* absorption of its main antioxidant compounds and (ii) the fact that coffee could act as an important confounder, considering its associations with multiple negative lifestyle factors (30). For each food item, the heme iron content was calculated by multiplying the iron content (in mg/g) of the food by the type-specific percentage of heme iron (e.g., 65%, 39%, and 26% for cooked beef, pork, and chicken or fish, respectively), as described by Balder and colleagues (31). For processed meat items, the nitrosylated heme iron content was calculated by multiplying the heme iron content of each type of processed meat by 0.67 (32), a coefficient provided by the French Pork Institute (Paris, France) since in France, most processed meat is pork meat, especially at the time of the questionnaire (1993–1995). These data were included in the food composition table and enabled us to obtain daily intakes of total heme iron and nitrosylated and non-nitrosylated heme iron intakes. Information on antioxidant dietary supplement intake was provided in the 1994 and 2000 questionnaires.

Identification of cases

The polyp database has been described previously (33). Briefly, we requested pathology and colonoscopy reports from the women who reported intestinal polyps in the questionnaires and from their physicians to code the polyp histologic features, size, number, and site. Advanced lesions were defined as adenomas over 1 cm in diameter, or with high-grade dysplasia (severe or *in situ* adenocarcinoma), or with over 20% villous component. Women simultaneously diagnosed with advanced and nonadvanced adenomas were classified in the "advanced adenoma" category. Right colon included the caecum, ascending colon, hepatic flexure, and transverse colon; left colon included the splenic flexure, descending colon, and sigmoid colon; and rectum included the rectosigmoid junction and the rectal ampulla.

Population and follow-up

Because adenomas are only diagnosed with colonoscopy, we restricted our population to women who underwent at least one colonoscopy during follow-up; women with polyp-free colonoscopies were defined as non-cases. Women with only hyperplastic polyps or with polyps of unknown histology were excluded from the study population.

Baseline was defined as the date of response to the food frequency questionnaire (1993). Participants contributed person-years of follow-up until the date of adenoma diagnosis, the date of the questionnaire with normal colonoscopy prior to any cancer diagnosis, the date the last questionnaire with normal colonoscopy was returned, or July 2002 (date of the 2002 questionnaire mailing) if the 2002 questionnaire was the last questionnaire with normal colonoscopy, whichever occurred first.

From the initial 74,522 women who answered the 1993 questionnaire, we excluded 4,654 with prevalent cancer, 810 lost to follow-up after the baseline questionnaire, and 1,364 with extreme values of energy intake [individuals in the top and bottom 1% of the ratio of energy intake to basal metabolic rate computed on the basis of age, height, and weight (34)]. In the remaining cohort, 20,922 women underwent a colonoscopy during follow-up; we further excluded 193 women with inflammatory bowel disease, 9 with colectomy, one with familial adenomatous polyposis, 1,953 with a colorectal adenoma or unspecified polyp diagnosed before baseline, 840 with only hyperplastic polyps at first polyp diagnosis (i.e., first colonoscopy with a polyp), 114 whose removed polyp was not analyzed, and 415 with no available histologic report

despite repeated mailings to women and/or their physicians (33). Therefore, 17,397 women were available for the adenoma study.

Statistical analysis

HR estimates and 95% confidence intervals (CI) were obtained using Cox proportional hazards model with the ages of individuals used as the time scale (35). HRs were determined by comparison with the lowest quartile of intake. To test for linear trends across categories, we modeled semiquantitative variables, considering the median value of each category. In multivariable analyses, models were simultaneously adjusted for colorectal cancer in first-degree relatives (yes or no), education level (less or more than 14 years of schooling), smoking status (never smoker vs. ever smoker), menopausal status (yes or no), physical activity (semiquantitative considering the median value of each quartile in METs), body mass index (BMI; semiquantitative considering the median value of each quartile in kg/m^2), total energy intake (semiquantitative considering the median value of each quartile in kcal/day), alcohol intake (semiquantitative considering the median value of each quartile in mL/day), dietary fiber intake (semiquantitative considering the median value of each quartile in g/day), dietary and supplemental calcium intakes (quartiles, time dependent), and dietary zinc intake (semiquantitative considering the median value of each quartile in mg/day). Nitrosylated and non-nitrosylated heme iron were simultaneously included in the model. Additional adjustment for FRAP, TRAP, menopausal hormone therapy, or number of colonoscopies did not modify the observed associations and was therefore not included in the main models. Data were missing for less than 5% of adjustment variables; we therefore replaced missing values with the modal value.

HRs according to adenoma site or risk category (advanced or nonadvanced) were estimated by using a competing risk method in which adenoma cases, other than those under study, were censored at the date of diagnosis (36). We then tested homogeneity in associations between colon and rectum, right and left colon, and advanced and nonadvanced adenomas.

We tested for potential interactions between heme iron intake (in ordered quartiles) and NEAC (two categories according to the median value) by including an interaction term between the two variables into the fully adjusted regression model. We additionally investigated associations between colorectal adenoma risk and the total heme iron/FRAP ratio. The ratio was modeled as restricted cubic splines based on three knots in the Cox regression model. The knots were located at the 25th (reference value), 50th, and 75th percentiles (0.055, 0.084, and 0.12 g/mol). Estimates of colorectal adenoma risk associated with the ratio were extracted from the model.

In the sensitivity analyses, we restricted analyses to women who did not report any antioxidant (vitamin E, vitamin C, or β-carotene) supplement intake during follow-up. Women using supplements were censored at the date they declared antioxidant supplement intake. We also conducted a sensitivity analysis excluding the first two years of follow-up to investigate potential reverse causation bias.

All *P* values were two-tailed, and statistical significance (*P* value) was set at the 0.05 level. All analyses were performed using the SAS software, version 9.3 (SAS Institute, Inc).

Results

Among the 17,397 French women of the E3N study who were initially free of cancer or polyps and underwent colonoscopy between June 1993 and July 2002, 1,409 women were diagnosed with at least one colorectal adenoma during 103,253 person-years of follow-up (median, 5.9 years; SD, 2.4). Among them, 1,035 had exclusively colon adenomas (exclusively proximal colon, 344; exclusively distal colon, 642; both, 49), 258 had exclusively rectal adenomas, 64 had both colon and rectal adenomas, and in 52 cases, the site could not be retrieved. There were 599 advanced adenomas (42.5%), representing 40.8%, 30.2%, 45.3%, and 50.8% of total, proximal, distal colon, and rectal adenomas, respectively. The major contributors to dietary intake of heme iron and FRAP are given in Table 1. Heme iron content values in red meats varied from 0.31 mg/100 g pork filet to 3.58 mg/100 g roast beef. Nitrosylated heme iron content in processed meats ranged from 0.13 mg/100 g for some specific sausages to 1.43 mg/100 g for a sort of pâté. FRAP varied from 0 in foods like meat or fish to 3.73 mmol/100 g of spinach.

Characteristics of participants according to quartiles of heme iron intake are listed in Table 2. Compared with women in the lowest quartile of heme iron intake, those in the highest quartile were more likely to be younger at baseline and at diagnosis, to be past or current smokers, to have higher BMI, to be premenopausal, and to be in the fourth quartile of energy, total iron, nonheme iron, fiber, fruits, and vegetables, FRAP, TRAP, and calcium intake, and to be alcohol consumers; they were less likely to be physically active.

The correlations between (i) total red meat and total heme iron consumption, (ii) nonprocessed red meat and non-nitrosylated heme iron intake, and (iii) processed meat and nitrosylated heme iron intake were high ($r_{Pearson} = 0.94$, 0.94, and 0.9, respectively). Associations between heme iron intake and colorectal adenoma risk by site are reported in Table 3. In the multivariable adjusted model, total, non-nitrosylated, and nitrosylated heme iron were positively associated with the risk of colorectal and colon adenomas but not of rectal adenomas, although there was no heterogeneity between the colon and rectum (Table 3). The absolute annual detection rates for colorectal adenomas were 83, 84, and 84 in the first quartiles, and 114, 106, and 100 per 100,000 women in the fourth quartiles of total, non-nitrosylated and nitrosylated heme iron intakes, respectively. Associations between heme iron intake, and risks of proximal and distal colon, and advanced and

Table 1. Major contributors to dietary intake of heme and dietary antioxidant capacity

Nutrient	Main food contributors (% contribution)
Total heme iron	Beef (30%), sheep (11%), sausage (10%), ham (5%), other offal (5%), pâté/rillettes (5%), liver (4%), rabbit (4%), pork (4%), poultry (4%), and horse (4%)
Nonnitrosylated heme iron	Beef (35%), lamb (13%), liver (5%), other offal (6%), rabbit (5%), pork (5%), poultry (5%), horse (4%), and veal (3%)
Nitrosylated heme iron	Sausages (43%), ham (23%), pâté (22%), and salami (6%)
Dietary FRAP	Vegetables and fruits (29%), wine (15%), tea (14%), and chocolate (9%)

Table 2. Population characteristics according to quartiles of heme iron intake in the E3N study

		Total heme iron intake (mg/day)[a]			
Characteristics	**Total**	**<0.75**	**0.75–<1.07**	**1.07–<1.45**	**≥1.45**
Number	17,397	4,352	4,350	4,345	4,350
Number of cases	1,409	309	351	382	367
Age at baseline (y)[b]	53.2 ± 6.6	54.1 ± 6.8	53.8 ± 6.6	53.0 ± 6.5	52.1 ± 6.1
Age at diagnosis (y)[b]	58.7 ± 6.8	59.9 ± 7.1	59.2 ± 6.8	58.7 ± 7.0	57.3 ± 6.2
Heme iron intake (mg/day)[b]					
Total	1.14 ± 0.55	0.51 ± 0.17	0.91 ± 0.094	1.25 ± 0.11	1.88 ± 0.41
Nonnitrosylated	0.97 ± 0.48	0.44 ± 0.16	0.78 ± 0.12	1.07 ± 0.14	1.60 ± 0.39
Nitrosylated	0.16 ± 0.14	0.073 ± 0.06	0.13 ± 0.09	0.17 ± 0.11	0.28 ± 0.17
Red meat intake (g/day)[b]					
Total	86.7 ± 43.1	40.5 ± 16.8	70.4 ± 15.0	95.2 ± 16.7	140.6 ± 35.4
Nonprocessed	55.1 ± 31.5	23.1 ± 12.2	44.0 ± 13.1	61.4 ± 15.5	92.0 ± 29.1
Processed	31.6 ± 23.7	17.5 ± 13.3	26.4 ± 17.0	33.8 ± 19.9	48.6 ± 29.4
Other dietary intake[b]					
Total iron (mg/day)	14.5 ± 4.8	12.6 ± 4.7	13.6 ± 4.2	14.9 ± 4.4	17.1 ± 4.7
Nonheme iron (mg/day)	13.4 ± 4.6	12.1± 4.6	12.7 ± 4.2	13.7 ± 4.4	15.2 ± 4.6
FRAP (mmol/day)	13.5 ± 5.6	12.5 ± 5.3	13.0 ± 5.4	13.7± 5.5	14.9 ± 6.0
TRAP (mmol/day)	4.97 ± 2.4	4.62 ± 2.3	4.79 ± 2.3	5.03 ± 2.4	5.43 ± 2.6
Fibers (g/day)	25.2 ± 7.8	24.3 ± 8.3	24.5 ± 7.4	25.4 ± 7.5	26.7 ± 7.7
Fruits and vegetables (g/day)	535 ± 242	530 ± 253	525 ± 236	532 ± 231	552 ± 245
Calcium (mg/day)	1,081 ± 375	1,049 ± 385	1,045 ± 362	1,082 ± 364	1,146 ± 381
Total energy intake (kcal/day)[b]	2,222 ± 570	1,938 ± 497	2,105 ± 491	2,285 ± 513	2,561 ± 577
Physical activity (METs-h/week)[b]	40.7 ± 26.2	41.8 ± 26.4	40.9 ± 26.4	40.2 ± 25.6	40.0 ± 26.2
BMI (kg/m^2)[b]	22.8 ± 3.2	22.0 ± 2.9	22.6 ± 3.0	23.0 ± 3.2	23.7 ± 3.6
Alcohol consumption (g/day)[b]	11.4 ± 13.8	8.2 ± 11.3	10.0 ± 11.9	11.9 ± 13.4	15.5 ± 16.8
Ratio heme iron/FRAP (g/mol)	0.097 ± 0.06	0.037 ± 0.01	0.070 ± 0.008	0.10 ± 0.01	0.18 ± 0.07
Ratio heme iron/TRAP (g/mol)	0.28 ± 0.22	0.10 ± 0.03	0.19 ± 0.02	0.29 ± 0.04	0.55 ± 0.27
Smoking status[c]					
Never smoker	9,336 (53.7)	2,410 (55.4)	2,390 (54.9)	2,383 (54.8)	2,153 (49.5)
Past or current smoker	8,061 (46.3)	1,942 (44.6)	1,960 (45.1)	1,962 (45.2)	2,197 (50.5)
Number of years of education[c]					
<14 years	11,296 (64.9)	2,914 (67.0)	2,809 (64.6)	2,761 (63.5)	2,812 (64.6)
>14 years	6,101 (35.1)	1,438 (33.0)	1,541 (35.4)	1,584 (36.5)	1,538 (35.4)
Menopausal status[c]					
Premenopausal	7,086 (40.7)	1,555 (35.7)	1,687 (38.8)	1,848 (42.5)	1,996 (45.9)
Postmenopausal	10,311 (59.3)	2,797 (64.3)	2,663 (61.2)	2,497 (57.5)	2,354 (54.1)
Family history of colorectal cancer[c]					
No	13,329 (76.6)	3,386 (77.8)	3,334 (76.6)	3,336 (76.8)	3,273 (75.2)
Yes	4,068 (23.4)	966 (22.2)	1,016 (23.4)	1,009 (23.2)	1,077 (24.8)

Abbreviation: MET, metabolic equivalent task.
[a]Quartiles.
[b]Mean ± SD.
[c]*n* (%).

nonadvanced adenomas are reported in Table 4. Although there was no heterogeneity by site regarding the association between heme iron intake and overall adenoma risk, there was some heterogeneity between the distal and proximal colon regarding the risk of advanced adenomas ($P_{\text{homogeneity}}$ proximal vs. distal; advanced adenomas = 0.038 and 0.036 for non-nitrosylated and nitrosylated heme iron, respectively; Table 4). There was no association between total iron or nonheme iron intake and colorectal, colon, or rectal adenomas (for colorectal adenomas, $HR_4 = 1.05$; 95% CI, 0.82–1.35; $P_{\text{trend}} = 0.59$; and 1.06, 95% CI, 0.83–1.34; $P_{\text{trend}} = 0.81$, respectively, data not tabulated).

We investigated a potential effect modification by dietary NEAC, assessed by FRAP, on colorectal adenoma risk (Table 5). Although the tests for interaction were not statistically significant, the positive association with heme iron was only observed in women with a FRAP intake below the median cohort value (12.7 mmol/day). Regarding effect modification by NEAC for distal, proximal, and rectal adenomas, results are provided in Supplementary Table S1. Although no interaction with FRAP intake was statistically significant, HRs were higher in case of low FRAP intake, especially for total and non-nitrosylated heme iron among women with proximal adenomas, but not among women with distal adenomas. For rectal adenomas, and although no individual association with heme iron was statistically significant, there was a significant interaction with FRAP intake, regarding total and non-nitrosylated heme iron with higher HRs in case of low FRAP intakes (Supplementary Table S1). Results were similar with TRAP (Supplementary Table S2).

Using spline regression curves (Fig. 1), there was a positive association between the total heme iron/FRAP ratio and colorectal adenoma risk, which became statistically significant when the ratio was 0.19 or higher. Results were similar with TRAP (Supplementary Fig. S1).

In the sensitivity analyses restricted to women who did not report any antioxidant (vitamin E, vitamin C, or β-carotene) supplementation during follow-up (95,641 person-years, 1,293 cases) or when excluding cases that occurred during the first two years of follow-up (102,884 person-years, 1,088 cases), results were not modified (data not tabulated).

Table 3. Multivariable HR (95% CI) of colorectal adenomas by site according to quartile of heme iron intake

	Colorectal adenomas (n = 1,409)			Colon adenomas						Rectal adenomas[a] (n = 258)	
				Total[a] (n = 1,035)		Proximal[b] (n = 344)		Distal[b] (n = 642)			
	Cases	HR[c] (95% CI)	HR[d] (95% CI)	Cases	HR[d] (95% CI)	Cases	HR[d] (95% CI)	Cases	HR[d] (95% CI)	Cases	HR[d] (95% CI)
Total heme iron (mg/day)											
<0.75	309	1.00	1.00	220	1.00	75	1.00	130	1.00	63	1.00
0.75–<1.07	351	1.16 (1.00–1.36)	1.17 (1.00–1.36)	253	1.20 (1.00–1.45)	83	1.18 (0.86–1.62)	158	1.25 (0.98–1.58)	64	0.99 (0.69–1.42)
1.07–<1.45	382	1.28 (1.11–1.49)	1.31 (1.11–1.54)	293	1.47 (1.21–1.78)	104	1.57 (1.13–2.18)	181	1.49 (1.16–1.90)	64	0.96 (0.66–1.41)
≥1.45	367	1.31 (1.13–1.53)	1.36 (1.13–1.65)	269	1.49 (1.19–1.87)	82	1.40 (0.94–2.07)	173	1.55 (1.16–2.07)	67	1.05 (0.67–1.62)
P_{trend}		0.0003	0.001		0.0003		0.06		0.003		0.86
Nonnitrosylated heme iron (mg/day)											
<0.63	306	1.00	1.00	220	1.00	78	1.00	129	1.00	62	1.00
0.63–<0.92	357	1.19 (1.02–1.39)	1.17 (1.00–1.37)	259	1.20 (1.00–1.44)	84	1.09 (0.79–1.49)	162	1.27 (1.00–1.61)	62	0.97 (0.67–1.39)
0.92–<1.24	385	1.29 (1.11–1.50)	1.27 (1.08–1.50)	287	1.37 (1.13–1.66)	103	1.34 (0.97–1.86)	175	1.42 (1.10–1.82)	72	1.09 (0.75–1.58)
≥1.24	361	1.27 (1.09–1.48)	1.26 (1.04–1.53)	269	1.38 (1.10–1.72)	79	1.09 (0.74–1.62)	176	1.53 (1.15–2.03)	62	0.95 (0.61–1.47)
P_{trend}		0.002	0.02		0.005		0.54		0.004		0.90
Nitrosylated heme iron (mg/day)											
<0.06	337	1.00	1.00	238	1.00	75	1.00	150	1.00	67	1.00
0.06–<0.13	338	1.04 (0.89–1.21)	1.02 (0.87–1.19)	255	1.09 (0.91–1.30)	85	1.22 (0.89–1.67)	156	1.02 (0.81–1.28)	59	0.88 (0.62–1.25)
0.13–<0.23	362	1.16 (1.00–1.35)	1.11 (0.95–1.29)	267	1.16 (0.96–1.39)	93	1.41 (1.02–1.93)	162	1.05 (0.83–1.32)	70	1.06 (0.74–1.50)
≥0.23	372	1.25 (1.08–1.45)	1.18 (1.00–1.39)	275	1.24 (1.02–1.51)	91	1.52 (1.08–2.15)	174	1.13 (0.88–1.44)	62	0.94 (0.64–1.40)
P_{trend}		0.001	0.03		0.03		0.02		0.32		0.97

[a]$P_{homogeneity}$ colon vs. rectum = 0.16, 0.17, and 0.34 for total heme iron, non-nitrosylated heme iron, and nitrosylated heme iron, respectively.
[b]$P_{homogeneity}$ proximal vs. distal = 0.68, 0.24, and 0.19 for total heme iron, non-nitrosylated heme iron, and nitrosylated heme iron, respectively.
[c]Cox proportional hazards model with individuals' ages as the time scale.
[d]Cox proportional hazards model with individuals' ages as the time scale and adjusted by colorectal cancer in first-degree relatives, educational level, smoking status, menopausal status, physical activity, BMI, total energy, intake of alcohol, fibers, dietary and supplemental calcium, and dietary zinc. Nitrosylated and non-nitrosylated heme iron were simultaneously included in the model.

Discussion

In this prospective cohort of French middle-aged women, heme iron intake was associated with colorectal, especially colon, adenoma risk. Nonnitrosylated heme iron was associated with advanced distal adenoma risk, whereas nitrosylated heme iron was associated with proximal adenoma risk.

Six studies investigated potential associations between dietary heme iron and adenoma risk (10–14); only one prospective study (11) reported a positive association between heme iron intake and the risk of colorectal adenomas, restricted to distal adenomas. To our knowledge, this is the first cohort study to examine relationships between nitrosylated and non-nitrosylated heme iron consumption, and colorectal adenoma risk, considering sites

Table 4. Multivariable HR (95% CI) of colon adenomas by site and stage according to quartile of heme iron intake

	Proximal colon adenomas (n = 344)				Distal colon adenomas (n = 622)			
	Nonadvanced (n = 240)[a]		Advanced (n = 104)[b]		Nonadvanced (n = 351)[a]		Advanced (n = 291)[b]	
	Cases	HR[c] (95% CI)	Cases	HR[c] (95% CI)	Cases	HR[c] (95% CI)	Cases	HR[c] (95% CI)
Total heme iron (mg/day)								
<0.75	47	1.00	28	1.00	66	1.00	64	1.00
0.75–<1.07	61	1.39 (0.94–2.05)	22	0.82 (0.46–1.45)	91	1.39 (1.01–1.93)	67	1.09 (0.77–1.55)
1.07–<1.45	74	1.83 (1.22–2.74)	30	1.14 (0.64–2.03)	92	1.46 (1.03–2.06)	89	1.52 (1.07–2.18)
≥1.45	58	1.66 (1.03–2.69)	24	0.98 (0.49–1.95)	102	1.71 (1.16–2.54)	71	1.36 (0.89–2.10)
P_{trend}		0.03[a]		0.87		0.012		0.089
Non-nitrosylated heme-iron (mg/day)								
<0.63	48	1.00	30	1.00	67	1.00	62	1.00
0.63–<0.92	60	1.30 (0.88–1.91)	24	0.76 (0.44–1.32)	97	1.41 (1.03–1.94)	65	1.11 (0.78–1.58)
0.92–<1.24	77	1.72 (1.15–2.55)	26	0.78 (0.43–1.40)	89	1.29 (0.91–1.83)	86	1.58 (1.10–2.26)
≥1.24	55	1.35 (0.84–2.17)	24	0.71 (0.36–1.40)	98	1.46 (0.99–2.15)	78	1.63 (1.07–2.47)
P_{trend}		0.18		0.37		0.12		0.011
Nitrosylated heme iron (mg/day)								
<0.06	52	1.00	23	1.00	74	1.00	76	1.00
0.06–<0.13	64	1.30 (0.90–1.89)	21	1.01 (0.56–1.85)	86	1.14 (0.83–1.56)	70	0.91 (0.65–1.26)
0.13–<0.23	63	1.33 (0.91–1.96)	30	1.59 (0.90–2.82)	88	1.15 (0.83–1.59)	74	0.94 (0.67–1.32)
≥0.23	61	1.39 (0.92–2.12)	30	1.86 (1.00–3.46)	103	1.34 (0.95–1.88)	71	0.92 (0.63–1.33)
P_{trend}		0.18		0.024		0.10		0.75

[a]$P_{homogeneity}$ proximal vs. distal, nonadvanced adenomas = 0.96, 0.96, and 0.99 for total heme iron, non-nitrosylated heme iron, and nitrosylated heme iron, respectively.
[b]$P_{homogeneity}$ proximal vs. distal, advanced adenomas = 0.46, 0.038, and 0.036 for total heme iron, non-nitrosylated heme iron, and nitrosylated heme iron, respectively.
[c]Cox proportional hazards model with the ages of individuals as the time scale, and adjusted on colorectal cancer in first-degree relatives, educational level, smoking status, menopausal status, physical activity, BMI, total energy, intake of alcohol, fibers, dietary and supplemental calcium, and dietary zinc. Nitrosylated and non-nitrosylated heme iron were simultaneously included in the model.

Table 5. Multivariable HR (95% CI) of colorectal adenomas by quartiles of heme iron intake according to dietary antioxidant intake

	Colorectal adenomas ($n = 1{,}409$)				
	FRAP <12.7 mmol/day		FRAP ≥12.7 mmol/day		
	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	$P_{interaction}$
Total heme iron (mg/day)					
<0.75	180	1.00	129	1.00	0.25
0.75–<1.07	186	1.15 (0.93–1.42)	165	1.18 (0.93–1.49)	
1.07–<1.45	184	1.35 (1.08–1.70)	198	1.26 (0.99–1.61)	
≥1.45	161	1.56 (1.19–2.05)	206	1.23 (0.93–1.61)	
P_{trend}		0.0009		0.20	
Nonnitrosylated heme iron (mg/day)					
<0.63	180	1.00	124	1.00	0.50
0.63–<0.92	179	1.06 (0.86–1.31)	178	1.31 (1.04–1.66)	
0.92–<1.24	191	1.25 (1.00–1.57)	194	1.31 (1.02–1.67)	
≥1.24	159	1.31 (1.00–1.72)	202	1.26 (0.96–1.66)	
P_{trend}		0.03		0.23	
Nitrosylated heme iron (mg/day)					
<0.06	193	1.00	144	1.00	0.15
0.06–<0.13	172	0.96 (0.78–1.18)	166	1.08 (0.86–1.35)	
0.13–<0.23	172	1.09 (0.88–1.34)	190	1.13 (0.90–1.42)	
≥0.23	174	1.29 (1.02–1.62)	198	1.09 (0.85–1.39)	
P_{trend}		0.01		0.82	

[a]Cox proportional hazards model with the ages of individuals as the time scale and adjusted by colorectal cancer in first-degree relatives, educational level, smoking status, menopausal status, physical activity, BMI, total energy, energy-adjusted intake alcohol, fibers, dietary and supplemental calcium, and dietary zinc. Nitrosylated and non-nitrosylated heme iron were simultaneously included in the model.

along the large bowel and to study potential interactions with NEAC. There was no heterogeneity by site regarding the associations between nitrosylated and non-nitrosylated heme iron and overall adenoma risk. However, findings of specific associations (i.e., non-nitrosylated heme iron consumption and distal colon adenomas and nitrosylated heme iron and proximal adenomas), and with high-risk rather than low-risk adenomas, suggest some relevance for colorectal carcinogenesis. These findings suggest partly different carcinogenic mechanisms in the proximal and distal colon (37). Many studies have described different associations between risk factors and colorectal adenoma risk according to site, and there is biologic plausibility in considering partly different carcinogenic pathways along the colorectum, including pathologic subtype and microbiota differences (37–41). However, the reasons why non-nitrosylated heme iron would mostly affect distal colon carcinogenesis, possibly even rectal carcinogenesis in subjects with low antioxidant intake, and why nitrosylated heme iron mostly affects proximal colon carcinogenesis in subjects with low antioxidant intake is not clear and should prompt specific experimental studies. Risks associated with nitrosylated heme iron intake appeared with lower intakes than with non-nitrosylated heme iron, suggesting a higher toxicity of nitrosylated heme iron. These findings are consistent with epidemiologic and experimental studies that show a greater carcinogenicity of processed meat, rich in nitrosylated heme iron, than fresh red meat, which only contains non-nitrosylated heme iron (3, 5, 42).

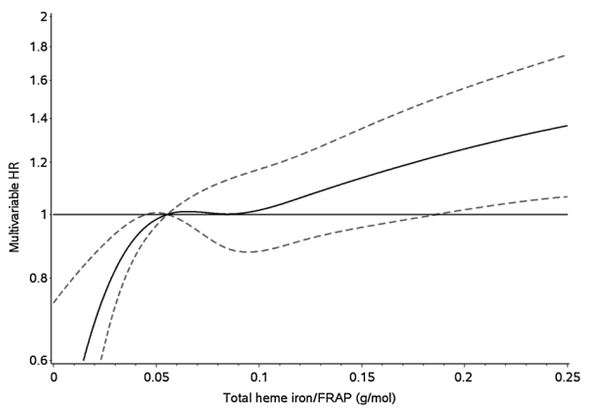

Figure 1.
Risk of colorectal adenomas according to the total heme iron/FRAP ratio. HRs were calculated from Cox proportional hazards model based on restricted cubic splines with the ages of individuals as the time scale and adjusted by colorectal cancer in first-degree relatives, educational level, smoking status, menopausal status, physical activity, BMI, total energy, and intake of alcohol, fibers, dietary and supplemental calcium, dietary zinc, and FRAP. The knots were located at the 25th, 50th, and 75th percentiles, corresponding to 0.055 g/mol, 0.084 g/mol, and 0.12 g/mol, respectively, for the heme/FRAP ratio. The 25th percentile was used as the reference value. Hatched lines represent the 95% CIs for the adjusted estimate (solid line). The vertical axis is on a log scale.

Although carcinogenic mechanisms associated with heme iron are not fully understood, experimental studies have reported a catalytic effect of heme iron on dietary lipid peroxidation, leading to the formation of cytotoxic and genotoxic aldehydes (5). Foods of plant origin contain a wide array of redox ingredients such as polyphenols and vitamins, which are able to inhibit oxidation reactions (15). Experimental studies reported that some antioxidants could reduce the carcinogenic effect of heme iron in the colon (16–18, 20, 22). Our findings suggest that dietary antioxidants could reduce some of the carcinogenic effects of heme iron on colon adenomas and possibly on the rectum. We investigated the total NEAC rather than individual polyphenols and vitamins for several reasons; first, we wanted to assess the intake of all antioxidants, even those that are not well characterized or measured. Second, we intended to capture synergistic and cumulative interactions among antioxidant nutrients in the food matrix. Finally, we wanted to avoid multiple testing of individual nutrients (43). Our results are consistent with a recent cross-over study, in which adding α-tocopherol to cured meat given to human volunteers decreased fat lipid peroxidation in the feces, an early biomarker for colon precancerous lesions, compared with volunteers eating control cured meat without antioxidants (22). A recent case–control study reported an inverse association between

colorectal cancer and the NEAC (44). However, a potential prevention of the heme-associated risk by dietary antioxidants has never been investigated. The heme iron to FRAP ratio was associated with adenoma risk, and the HR was statistically significant with a ratio of 0.19 and above. It is of preventive interest to note that in our study, a 0.19 ratio corresponded to mean consumptions of 552 g/day of fruit and vegetables and 141 g/day of total red meat as 92 g/day of nonprocessed meat and 49 g/day of processed meat. Thus, our findings suggest that a consumption of about four times more fruit and vegetables than red meat would be associated with low risk of colorectal adenomas and agree with French national recommendations to eat at least 400 g/day of fruits and vegetables, less than 500 g/week of nonprocessed red meat and to avoid processed meat (45).

For this study, we used the best currently available data on heme iron and nitrosylated heme iron. Indeed, heme iron was not included in the French food composition (CIQUAL) database, therefore, we estimated daily intake of heme iron using data provided by Balder and colleagues (31), as well as, for comparison purposes, those reported by Cross and colleagues (46), as the latter were less relevant to our food data because of no information on meat cooking in our dietary questionnaire and because of differences between meats, especially processed meats, consumed in the United States and in Europe. However, both methods retrieved similar results. Concerning the proportion of nitrosylated heme iron in various types of processed meat, little data exist. As in France, most processed meat is pork meat preserved by smoking, curing, or salting (sausages, ham, pâté, salami, bacon, and saucisson), we calculated the nitrosylated heme iron content of each type of processed meat using the most precise available data on the total heme iron content from Balder and colleagues (31), then applying the 0.67 coefficient provided by the French Pork Institute (Paris, France) for the proportion of nitrosylated heme iron (32). More accurate estimates of various nitrosylated heme iron contents in various types of processed meats could lead to more precise estimates of risk in future epidemiologic studies.

The strengths of our study include its prospective design, limited loss to follow-up, regular updates on screening practices, including colonoscopy, and adjustment for potential confounders. Our figures of 1,400 women detected with a first ascertained adenoma among approximately 74,000 women of our cohort during a 9-year follow-up are comparable with figures provided for the same age ranges by the population-based registry of colorectal tumors of Burgundy (47). The validation of our self-administered dietary history questionnaire has shown adequate reproducibility and validity of meat and iron intake (26). Bias was limited by histologic confirmation of all cases and inclusion of polyp-free subjects as noncases. Moreover, the availability of colonoscopy and pathology reports made it possible to investigate adenoma site and stage.

Our study also has limitations. First, our population is composed of women who consumed, for 80% of them, less than 100 g/day of red meat and less than 50 g/day of processed meat. Most of the study population was highly educated, exercised regularly, and attended regular medical screenings. Therefore, extrapolation of our findings to a male population or to the general female population, especially to populations with higher meat intake, should be cautious. Second, the lower number of rectal adenomas compared with colon adenomas reduced our ability to demonstrate associations, as power calculations indicated that numbers were only sufficient for detecting HRs of 1.7 or above in stratified analyses. Third, residual confounding cannot be ruled out, especially because we lacked information on the use of aspirin and NSAIDs, which play a protective role in colorectal carcinogenesis (48). Finally, the dietary questionnaire was not designed to capture combinations of nutrients in the same meal. Antioxidants and heme are not necessarily consumed simultaneously, and we can therefore expect that a potential biologic interaction would be underestimated.

In conclusion, we have shown, in one of the largest studies to date on adenoma incidence, that a high dietary intake of heme is associated with colorectal, especially colon, adenoma risk, and that the association may depend on the ratio of heme iron to the NEAC in the diet. These results, obtained in a population of health-conscious women, highlight the importance of early nutritional prevention of colorectal cancer by increasing sources of antioxidants in the diet simultaneously with the reduction of red and processed meat consumption.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N. Bastide, F.H. Pierre, M.-C. Boutron-Ruault
Development of methodology: N. Bastide, M.-C. Boutron-Ruault
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Bastide, F. Clavel-Chapelon, M.-C. Boutron-Ruault
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Bastide, C. Cadeau, G. Gusto, L. Dossus
Writing, review, and/or revision of the manuscript: N. Bastide, S. Morois, C. Cadeau, M. Serafini, G. Gusto, L. Dossus, F.H. Pierre, M.-C. Boutron-Ruault
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Morois, C. Cadeau, S. Kangas
Study supervision: M.-C. Boutron-Ruault

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