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Iron Intake and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis

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Iron Intake and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis

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An abstract of
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Abstract

Iron Intake and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis
By Kristina Van Dang

Background. Despite moderate decreases in recent years due largely to improved screening and early detection of tumors, colorectal cancer is the third most common cancer in the world. Of the risk factors still associated with risk for colorectal cancer, diet is the only modifiable one. Only recently, epidemiological and experimental evidence suggests a role of iron intake and colorectal cancer incidence.
Objective. This systematic review and meta-analysis endeavors to estimate the role of iron intake—using the indicators serum ferritin, transferrin saturation, and heme iron—and risk of colorectal cancer.
Methods. A systematic review of articles using PubMed, Web of Science, Google Scholar, MedlinePlus, and Cochrane databases was conducted, and additional articles were identified through reference harvesting.
Results. 13 prospective studies were ultimately included in the quantitative analysis, spanning from 1966 to 2006. These analyses include a total cohort of 195,681 participants, and 5,806 incident cases of colorectal cancer. The summary odds ratio for ferritin was 0.90 (0.58-1.39), transferrin saturation was 0.94 (0.80-1.12), and heme iron was 1.13 (1.02-1.25). Only the quantitative analysis of ferritin yielded significant heterogeneity (χ^2=17.20; p=0.004; I^2=71%). Publication bias was not present for any of the iron indicators.
Discussion. Much of the heterogeneity within the ferritin studies can be explained by the relatively short study period, contrasted with the induction period of colorectal cancer. Furthermore, the small number of studies in each separate analysis makes it difficult to draw definitive conclusions, and assigns a greater weight to each study.
Conclusion. The current literature does not support the hypothesis that iron intake is causally related to the risk for colorectal cancer, regardless of the methods used to assess exposure. This analysis did not find a significant association for serum ferritin and transferrin saturation, and a weak association for heme iron. Although the evidence supporting the positive relationship between meat consumption and colorectal cancer is convincing, we cannot conclude that the effect of meat is attributable to iron.

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BACKGROUND

Cancer causes one in four deaths in the United States [1]. Colorectal cancer (CRC) is the fourth most common cancer in the United States, and is the second-leading cause of cancer-related mortality, with over 50,000 CRC deaths expected to occur in 2013. Worldwide, CRC is the third most common cancer, accounting for an estimated 1,023,256 new cases and 529,020 deaths in 2013 [1]. Population-based data indicates that CRC mortality has declined moderately in recent decades [2]. These recent decreases in CRC deaths are attributable primarily to screening and early detection and treatment of the tumors [3]. While the role of screening in CRC control is important, it also clear that additional progress can be made with primary prevention efforts. The most important risk factors of CRC include age, race/ethnicity, family history of cancer and diet [4]. Of those, only diet can be modified, and thus offers a promising target for CRC prevention. Furthermore, it has been suggested that about 25% of all CRC cases could be prevented by changes in diet [5, 6].

Global incidence of CRC is affected by substantial regional variability. While the rate in more developed countries is 26.6 per 100,000 person-years in women and 40 per 100,000 person-years in men, the corresponding estimates for the developing countries are 7.7 and 10.2 per 100,000 person-years [1, 7]. Additionally, there is a strong ecologic correlation between increased CRC incidence and dietary factors, such as intakes of fiber, vegetable, and meat [8-12]. The importance of lifestyle and dietary factors is underscored by studies that show that CRC risk increases several-fold among first generation immigrants who move from low risk to high-risk countries [13, 14].

Despite the consensus that diet affects a person's risk of developing CRC little is known about specific nutrients that may confirm harmful or protective effects. One candidate nutrient that is thought to promote colorectal carcinogenesis is iron. On average, people in the United States with a Western-style diet consume more red and processed meat, the types of food that are known to contain high concentrations of iron [15]. Iron is an essential trace element, which biologically functions in gas transport, enzymes, and cell proliferation. Iron can undergo oxidation and reduction, which, in excess, can become toxic. Iron can produce reactive oxygen species via the Fenton reaction, which can lead to downstream pro-carcinogenic effects [8, 16, 17].

It is important to point out that despite convincing mechanistic evidence human population studies evaluating the association between iron intake and CRC are inconclusive [18]. One of the reasons for the lack of definitive evidence for or against the causal role of iron in colon neoplasia is the difficulty of exposure assessment. No single method is currently considered the gold standard for measuring iron intake. Food frequency questionnaire (FFQ) data can be converted to estimate dietary iron consumption [19]. However, disadvantages of FFQ include missing data [19], measurement error due to recall and inability to assess all ingredients, combinations of foods and cooking methods [20]. It has been found that FFQ may greatly over- or under-estimate certain nutrients [18, 19, 21], although not all studies observed such severe misclassification [22-25]. On the other hand, FFQs are easy to administer, non-invasive, and relatively inexpensive compared to other methods [21].

A useful FFQ-based measure is heme iron intake. Heme iron is bound to a porphyrin (e.g., hemoglobin or myoglobin) ring, and for this reason, its intake specifically reflects consumption of red meat. Moreover heme iron is highly bio-available, as it is more readily absorbed in the intestine than non-heme iron, and thus it is more likely to exert systemic effects [26].

An alternative to FFQ-based measures of iron intake is the use of biomarkers. Serum ferritin, the primary iron storage protein, is thought to be a more stable and more informative indicator of iron stores [27, 28], and has been suggested to be associated both colonic adenoma and colorectal cancer when present in high concentrations [29]. Moreover, serum ferritin and transferrin are considered to be the best indicators of iron status, though there is debate about which is better [30]. Biomarkers of dietary exposures are increasingly being used to validate or substitute FFQ data [31], primarily because of the ability to take into consideration both consumption and absorption of nutrients, and the elimination of reliance on subject recall [31-33]. However, disadvantages of using biomarkers compared to using FFQ include significantly higher costs, the inability to assess long term exposures if only taken at one time point, and the relative invasiveness of blood draws [31].

Although a number of studies have examined the association between iron intake and risk of colorectal neoplasia, the differences and similarities in results across different methods of measuring iron exposure have not been assessed in a systematic fashion. For this

reason, the objective of this review and meta-analysis is to evaluate weight-of-the-evidence linking iron intake to colorectal tumor risk in prospective studies, and to compare how the results vary depending on the method of exposure assessment.

METHODS

Inclusion criteria and analysis were specified in advance, and the study was conducted according to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses [34]. No language, publication date, or publication status restrictions were imposed. All studies that measured iron exposure levels among participants of any age were considered eligible for inclusion in the current analysis. An iron exposure level was defined as serum ferritin, blood transferrin saturation (a ratio of serum iron and total iron-binding capacity), or FFQ-derived heme iron intake. Studies that focused on patients with genetic syndromes that may influence iron levels, including hereditary hemochromatosis or familial adenomatous polyposis, were excluded. The primary outcome measures were incident sporadic colorectal neoplasms including adenomas and cancers.

Studies were identified by searching electronic databases, scanning reference lists of articles and consulting experts in the field. The electronic literature search was applied to PubMed, Web of Science, Google Scholar, MedlinePlus, and Cochrane databases. We used the following search terms: iron; ferritin, transferrin; heme, colon; colorectal; neoplasia; polyp; adenoma; and cancer. The last search was run on January 31, 2013. In addition, we reviewed table of contents and reference pages of relevant journals and articles to identify eligible studies that were missed by the electronic search. One reviewer performed eligibility assessment in an unblinded, standardized manner.

We developed a data extraction sheet, based on the Cochrane Collaboration's RevMan software, pilot-tested it on three studies and refined it accordingly. One review author

(KD) extracted the relevant information from included studies and the second author (MG) checked the resulting data for accuracy. Disagreements were resolved by consensus. We contacted one original study author for further information about a study. Information extracted from each paper included: (1) study author; (2) study date; (3) characteristics of study participants (including gender, age, number, and cohort or study); (5) study design; (6) type of iron exposure measured; (7) comparison made; (8) outcome measure; (9) effect estimate and confidence interval; (10) follow-up period or average number of years followed; (11) any assessment of preclinical cases; (12) participation rate; and (13) any assumptions or adjustments used in the analysis. If multiple effect estimates were present, all were reported and included in the quantitative analysis as separate studies as long as the estimate reflected non-overlapping independent cohorts. If the estimates were not independent, the quantitative analysis was carried out with and without each estimate to determine if any significant differences were present.

The meta-analyses were performed by pooling odds ratios (ORs) and 95% confidence intervals (CI) in RevMan. A fixed effects model was used, unless significant heterogeneity suggested a random effects model was more appropriate. We tested for heterogeneity using the Cochrane Q statistic, and used the measure I^2 to measure the degree of inconsistency across studies. The symmetry of 'funnel plots' that examined the effect size against the inverse of its standard error was assessed visually, for evidence of publication bias. Subgroup analyses were performed based on gender, outliers, and studies that were weighted greater than 50%.

RESULTS

Overview of study selection and exclusions

The electronic search provided 866 total citations. In addition, 28 articles were identified through reference searching, and another 15 were found through general internet searches (e.g. using Google Scholar) or by canvassing the tables of contents of most commonly cited journals. After adjusting for duplicates, 752 titles remained. Of these, 714 studies were discarded because they did not meet the criteria for inclusion in the current review. The abstracts and the full text of 42 articles were reviewed further, and 29 papers were excluded, resulting in 13 studies left for the final quantitative analysis. Figure 1 is the flow diagram of study selection. Study quality indicators, such as participation rate, exclusion of preclinical cases, and any adjustments made by authors are included in Table 4.

Most studies were excluded because of the inappropriate design as they examined iron stores in patients with colorectal cancer using cross-sectional data [35-44]. These studies were not considered relevant because they could not assess the association between iron exposure and risk for colorectal neoplasia, which was the main research question of the current review. A number of studies were excluded because they did not address relevant exposures [45-50] or because they evaluated levels of iron exposure in relation to outcomes other than colorectal neoplasia [51, 52]. In addition, several studies did not meet the eligibility criteria because they only included participants from specific subpopulations, such as frequent blood donors[53], patients with hereditary hemochromatosis or FAP [54], abnormally low ferritin levels [55, 56], or anemia [57].

Qualitative review of included studies

In the Mobile Health Clinic of Social Insurance Institution cohort, Knekt et al. recruited 41,276 Finnish men and women aged 20 to 74 years [58]. The relevant exposure assessed in that study was transferrin saturation at baseline. The outcome of interest, CRC, was ascertained by linking the data to the Finnish Cancer Registry over an average follow-up of 14 years. Analyses were conducted separately for men and women, and for cancers of the colon and rectum. The relative risk (RR) of colon cancer in people with the highest quartile compared to the lowest quartile of transferrin saturation was 1.73 (p=0.35) in men and 0.97 (p=0.82) in women. For rectal cancer, the RRs were 1.04 (p=0.71) for men and 0.92 (p=0.66) for women. When using the cutoff of >60% to define high transferrin saturation the RR was 3.98 (95% CI: 2.13-7.41).

Herrinton et al. examined the data pertaining to the Kaiser Permanente Medical Care Program cohort that included 52,150 persons aged 20-84 years who resided in the San Francisco Bay area [59]. The study period began in 1969 and ended in 1990, with an average follow-up period of approximately 18 years. Members were followed prospectively, and transferrin saturation and incidence of cancer was measured. For those with missing information, data were imputed based on mean estimates and Pearson correlation coefficients. The RR of colon cancer in people in the highest quartile of transferrin saturation compared to those in the lowest quartile was 0.98 (0.68-1.4) in women and 0.62 (0.35-1.1) in men. For rectal cancer, the relative risks were 0.88 (0.47-1.7) in women and 0.30 (0.08-1.1) in men. The authors suggested that the inconsistencies

of results in men and women were due to measurement error because transferrin saturation was estimated for 6,380 women and 177 men.

The Iowa Women's Health Study is a cohort of postmenopausal women, aged 55 to 69 years at baseline, and followed for incident colon cancer for an average of 15 years. At the end of follow up 438 proximal cancer cases and 303 distal cancer cases were recorded [60]. Lee et al. examined cases of proximal and distal colon cancer separately. The adjusted RR of proximal colon cancer in women in the highest quintile of heme iron compared to women in the lowest quintile of heme iron was 1.41 (0.90-2.21). The RR of distal colon cancer comparing women in the highest to the lowest quintiles of heme iron was 0.65 (0.38-1.11).

In the Nurses' Health Study and the Health Professionals Follow-up Study, Zhang et al. analyzed the relation between heme iron intake and colorectal cancer risk among 51,529 men and 121,700 women in 11 US states [61]. A total of 2,114 incident CRC cases were diagnosed during follow up, which extended from 1986 through 2000. The relative risk of colorectal cancer in the highest heme iron quintile compared to the lowest was 1.21 (0.96-1.52) in women and 0.98 (0.77-1.26) in men.

The Netherlands Cohort Study on Diet and Cancer began with administration of mailed questionnaires to 58,279 men and 62,573 women ages 55 to 69 years old [62]. Balder et al. used a sample of 5,000 randomly selected cohort members and compared them to 1,535 cases of CRC using a case-cohort design. The association of heme intake with risk

of CRC was tested over an average follow-up of 9.3 years. The adjusted RR of incident colorectal cancer in the highest quintile compared to the lowest quintile of heme iron was 1.32 (0.96-1.80) for men and 1.20 (0.86-1.69) for women.

Bird et al. analyzed a cohort from two Southern California Kaiser Permanente medical centers [63]. A total of 965 eligible men and women were 50 to 75 years old and were prospectively followed for incidence of colorectal polyps until the end of 1993. Plasma ferritin was measured from a blood sample and iron intake measured by FFQ. There were 465 incident cases of colorectal polyps recorded, and matched to polyp-free controls using a 1:1 ratio. The odds ratios for colorectal polyps comparing the highest compared to lowest quartile of plasma ferritin were 1.1 (0.5-2.3) for women and 1.3 (0.8-2.0) for men.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) study is a large, randomized, controlled trial designed to test the efficacy of cancer screening and to investigate early markers and etiology of cancer in 10 U.S. centers [64]. Cross et al. investigated the relationship between iron intake and the incidence of colorectal neoplasia in a case-control study nested within the PLCO cohort. Starting in 1993, 37,203 men and women aged 55 to 74 years completed a baseline questionnaire. Five years after the baseline questionnaire, 356 incident colorectal adenoma cases were reported and matched to 396 controls on age, gender, ethnicity, study center, season of blood draw, and date of sigmoidoscopy. Individuals in the highest compared with the lowest quartile of heme iron had an increased, yet non-significant odds ratio of 1.46 (0.94-2.29). For individuals in the

highest compared with the lowest quartile of serum ferritin, the odds ratio was 0.86 (0.53-1.38), and for transferrin saturation, the odds ratio was 1.28 (0.83-1.98).

The New York University Women's Health Study consists of 15,785 women aged 34 to 65 years recruited from centers in New York City or Florida [65]. Kato et al. investigated the relationship between body iron stores and colorectal cancer risk, using ferritin and transferrin saturation. Between study initiation in 1985 and completion of follow up in 1994, 105 incident CRC cases were reported and matched to 523 controls on age, menopausal status at enrollment, date of enrollment and dates of subsequent blood donations. The adjusted odds ratio of an individual in the highest compared to the lowest quartile of transferrin saturation was 0.63 (0.3-1.2) and for serum ferritin the corresponding odds ratio was 0.40 (0.2-0.8). According to Kato, the most plausible explanation for the inverse association is bleeding from preclinical cancers, which occurred before blood samples were obtained.

The Alpha-Tocopherol and Beta-Carotene (ATBC) cancer prevention study was a randomized, double-blinded, placebo-controlled, 2x2 factorial design, trial testing the efficacy of α-tocopherol and/or β-carotene supplements among 29,133 Finnish male smokers, aged 50 to 69 years. Cross et al. used a 1:2 nested case-control design based on 130 incident colorectal cancer cases diagnosed among ATBC participants. Controls were matched to cases by age, study area, intervention group and month of baseline blood draw. The median length of follow-up was 14.2 years. The odds ratio for colorectal cancer among men in the highest compared to the lowest quartile of serum ferritin was

0.4 (0.2-0.9) and the same comparison for serum transferrin saturation yielded an odds ratio of 0.6 (0.3-1.3). With the long induction period of CRC, the inverse association was likely explained by lower iron indices among preclinical cases [66].

The Antioxidant Polyp Prevention Study was a multicenter clinical trial of antioxidant supplementation to prevent recurrence of colorectal adenoma [67]. Tseng et al. assessed whether serum ferritin concentration was associated with adenoma recurrence among 733 individuals with a history of recently removed polyps who were adenoma-free at enrollment and were followed for 4 years. The risk of colorectal adenoma in the highest compared with the lowest quartile of serum ferritin was 2.42 (0.97-6.02) in women and 1.23 (0.80-1.89) in men.

The Canadian National Breast Screening Study was a randomized controlled trial of mammography in 89,835 women aged 40 to 59 years old [68]. Kabat et al. analyzed a total of 617 incident colorectal cancer cases that were reported after an average of 16.4 years of follow-up. After adjusting for potential confounding variables, quintiles of heme iron intake showed no association with colorectal cancer, the hazard ratio of risk for women in the highest compared with the lowest quintile of heme iron intake was 1.06 (0.80-1.42).

The Japan Public Health Center-based Prospective Study includes 85,097 individuals aged 40 to 69 years[69]. Using data from this cohort, Hara et al. investigated the association between heme iron intake and CRC risk significant association. In individuals

with the highest compared with the lowest quintile of heme iron intake, the colorectal cancer risk ratio was 1.06 (0.79-1.42) for men and 0.88 (0.61-1.29) for women.

Stevens et al. used follow-up data from the first National Health and Nutrition Examination Survey (NHANES I) to investigate the association between body iron stores and the risk of cancer. In total, 8,722 men and women were included in the analysis, and after exclusion of preclinical cases, 445 incident cancers were identified. Only 12 incident colon cancers were reported, all among men [17]. Patients with cancers of the esophagus, bladder, and colon tended to have very low total iron-binding capacity and very high transferrin saturation. Because of the small sample size, the effect estimate was imprecise. For men in the highest compared to the lowest quartile of transferrin saturation, the relative risk of colon cancer was 4.69 (0.45-48.7).

Meta-analysis of ferritin studies

The meta-analysis for ferritin included five studies that represented 2,889 participants with 1,132 incident cases. The mean age of participants was 59 years, and ranged from 34 to 75 years. The cohort size ranged from 390 to 965 individuals across all included studies. The studies covered the period between 1985 and 2001, and included data from France, Finland, and the United States. Study follow-up period ranged from 3 to 7.5 years. Tseng et al. used cutoff values determined from previous literature—all other studies used internally-generated quartile values. Kato and Cross (2006) used CRC as the primary outcome; Tseng et al. used colorectal adenoma; Bird et al used colorectal polyps;

and Cross (2011) designated any colorectal neoplasia as the main study endpoint. Table 1 is the summary table of studies included in the ferritin analysis.

The summary OR of all included studies was 0.97 (95% CI: 0.78-1.21) with high degree of heterogeneity (p=0.004; I^2=71%). The odds ratio using a random effects model is 0.90 (0.58-1.39). In analysis of the funnel plot for included studies, NYU Women's Health Study and the ATBC study were considered outliers. However, these studies were balanced by the female arm of the Antioxidant Polyp Prevention Study, suggesting that no publication bias was present. Figures 2 and 3 include the forest and funnel plots for the ferritin analysis.

Meta-analysis of transferrin saturation studies

This analysis includes six studies representing 1,893 men and women between the ages of 20 and 84 years (mean = 52 years). The studies covered the period between 1969 and 2001. All studies, except one (ATBC), were conducted in the United States. A total of 909 incident colorectal cancer cases were reported and included in this analysis. One case-control study was nested within the PLCO trial and all others were prospective cohorts. The average follow-up of included studies was 8.9 years, with a range of 1.6 to 17.7 years across all studies that reported this information. All studies compared the highest to lowest quartile of transferrin saturation. One analysis (The Mobile Health Clinic and Social Insurance Institution study) also used 60% transferrin saturation as the cutoff for high exposure level. Table 2 is the summary table of studies included in the transferrin saturation analysis.

The summary odds ratio of all included studies was 0.94 with a 95% confidence interval from 0.80 to 1.12. When the colon cancer result in one study was replaced with the corresponding result for the cancer of the rectum, the meta-estimate did not change appreciably (data not shown). The test for heterogeneity p-value was 0.20 and the I^2 was 28%, justifying the use of a fixed effects model. The funnel plot demonstrated that the distribution of studies across the center was balanced, indicating no evidence of publication bias. Figures 4 and 5 include the forest and funnel plots for the transferrin saturation analysis.

Meta-analysis of heme iron studies

This analysis included six different studies that examined eight independent groups, representing 190,953 men and women, with 3,765 incidence colorectal cancer cases reported during follow up. The average age of all participants was 58 years with a range of 30 to 69 years. The included studies were conducted in Canada, the United States, the Netherlands and Japan, and conducted over a period between 1982 and 2006. All studies were prospective, and each obtained the effect estimate by comparing the extreme quartiles or quintiles of FFQ-derived heme iron intake. The endpoint of interest in these studies included CRC, colon cancer, or a specific region of the colon affected by cancer. The mean follow-up period was 13 years. Table 3 is the summary table of included studies in the heme iron analysis.

The summary odds ratio of all included studies was 1.13 with a 95% confidence interval from 1.02 to 1.25. The weak positive association between heme iron and colorectal cancer is statistically significant. There was no evidence of heterogeneity

across results with a Cochrane test p-value of 0.67, and an I^2 value of 0%. The funnel plot indicated no evidence of publication bias. Figures 6 and 7 include the forest and funnel plots for the heme iron analysis.

DISCUSSION

Summary of evidence

The association between nutrients and cancer is complex. The evidence linking red or processed meat to CRC is reasonably consistent, but it is still unclear which specific nutrients may be responsible for this association [70]. It is important to point out that red meat contains large amounts of iron [69]; however, data on the association between iron intake and CRC are conflicting [70]. One of the possible explanations for this lack of consistency across studies is the variability of study designs and methods of exposure assessment [30].

In the current meta-analysis we examined the hypothesis that iron intake increases the risk of CRC by including only prospective studies, and by grouping all effect estimates according to the three most commonly advocated methods of measuring iron intake. We found no appreciable departure from the null for serum ferritin and transferrin saturation; however, the results for heme iron did show a statistically significant, albeit weak association.

The literature on the risk factors for CRC includes several previous relevant reviews that can be compared to our study. In 2001, Nelson et al. suggested in a qualitative review of 33 studies that approximately three-quarters of reports supported a positive association of iron with colorectal neoplasia risk. However, iron exposure in that review was defined rather broadly, and there was no attempt at a quantitative synthesis of the evidence.

Several meta-analyses have been conducted on meat consumption and CRC [20, 48, 71], all concluding that red meat intake was positively associated with risk of colorectal cancer. The results of meta-analyses on red meat intake cannot be directly compared to ours. Certain cooking practices (e.g. frying or grilling) result in the production of heterocyclic amines in meat, and these compounds have been shown to have high mutagenic activity independently of iron [72]. Additionally, there is evidence that the type of fat most strongly associated with colorectal cancer is fat from red meat sources [73]. Thus, the weak association that we observed for heme iron may likely be explained by red meat-related exposures other than iron intake.

STRENGTHS AND WEAKNESSES

To our knowledge, this is the first review to quantitatively assess the relationship between three different indicators of iron exposure and CRC risk. In conducting this meta-analysis, we made an effort to follow all current recommendations for systematic reviews [34]. This entails a formal assessment of heterogeneity and publication bias. Additionally, the quantitative analysis was based on prospective studies, which are better suited for assessing causal hypotheses.

The limitations of this study fall into two categories: those related to the weaknesses of the available literature and those pertaining to our analysis.

Our meta-analysis made some key assumptions that should be viewed as limitations. In combining the effect estimates, the most extreme exposure categories were used. These introduced considerable heterogeneity because different studies used different approaches for categorizing exposures. In addition, several effect estimates came from non-overlapping populations, but were obtained from the same study by the same authors. For this reason, it is possible that some studies in the meta-analysis were more influential than others because they did not reflect entirely independent observations.

Thirteen studies including 14 different cohorts represent a heterogeneous body of literature with relatively few studies available in each of the exposure categories assessed in the current review. Additionally, the follow-up period for each of the studies varied greatly, ranging from three to 22 years. Thus, most of the available studies were not

designed to take into consideration the long induction period for colorectal cancer. We considered a separate analysis by duration of follow up by because of the small number of studies included in each subcategory, such analysis could not be justified [74].

CONCLUSION

Summary

In summary, the current literature does not support the hypothesis that iron intake is causally related to the risk for colorectal cancer, regardless of the methods used to assess exposure. This analysis did not find a significant association for serum ferritin and transferrin saturation, and a weak association for heme iron. Although the evidence supporting the positive relationship between meat consumption and CRC is convincing, we cannot conclude that the effect of meat is attributable to iron.

Future Directions

The logical next step for future research would be to conduct studies with sufficient latency period. As transformation of normal colon mucosa to cancer takes several decades, the follow-up period should be at least 10 years.

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TABLES & FIGURES

Figure 1. Flow diagram of study selection

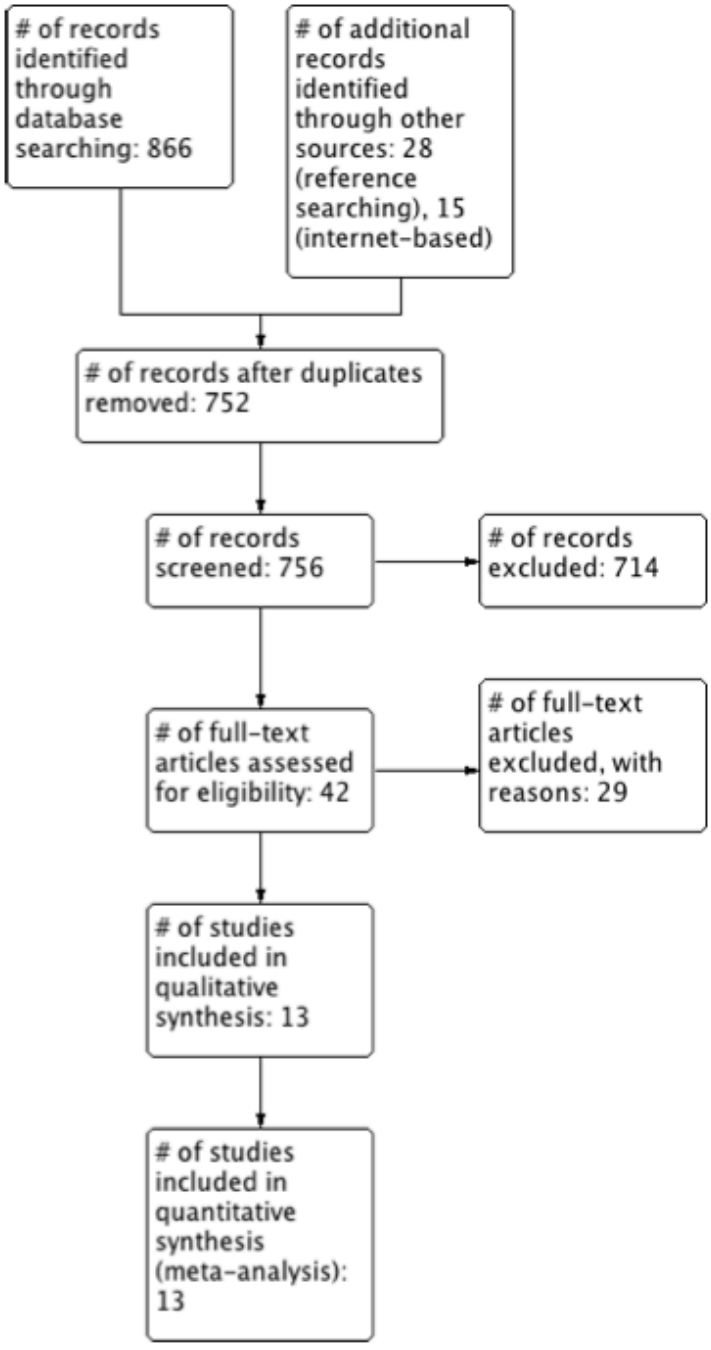


Table 1. Summary characteristics of studies included in ferritin analysis

Date	Author	Study Population	Study Design	Population[1]	Comparison[2]	Outcome	Effect Estimate[3]	Study period[4]
1996	Bird	Kaiser Centers	case-control	965 50-75	<73ug/L vs. >289ug/L	colorectal polyps	1.2 (0.8-1.8)	1991-1993
1999	Kato	NYU Women's Health Study	prospective cohort	628 F 34-65	Q4 vs. Q1	CRC	0.4 (0.2-0.8)	1985-1991 (4.7)
2000	Tseng	Antioxidant Polyp Prevention Study	prospective cohort	733 one previously removed adenoma	>70ug/L vs. <70ug/L	colorectal adenoma	1.36 (0.78-2.38)	1984-1988 (4)
2006	Cross	ATBC	prospective cohort	390 M smokers 50-69	Q4 vs. Q1	CRC	0.4 (0.2-0.9)	1985-1993
2011	Cross	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	case-control	752 55-74	Q4 vs. Q1	colorectal neoplasia	0.86 (0.53-1.38)	1993-2001 (3-5)

1. Cohort size and eligible age range; F=female; M=male; when not indicated, population included both men and women
2. Q4 = fourth quartile; Q1 = first quartile
3. Effect estimate (95% confidence interval)
4. Study period in years (average follow-up period, if reported)

Table 2. Summary characteristics of studies included in transferrin saturation analysis

Date	Author	Study Population	Study Design	Population[1]	Comparison[2]	Outcome	Effect Estimate[3]	Study period[4]
1988	Stevens	NHANES	prospective cohort	M 25-74	Q4 vs. Q1	colon cancer	4.69 (0.45-48.7)	1971-1984
1994	Knekt	Mobile Health Clinic and Social Insurance Institution	prospective cohort	41276 20-74	Q4 vs. Q1	CRC	3.04 (2.13-7.41)	1966-1984 (14)
1995	Herrinton	Kaiser Medical Plan	prospective cohort	259 F 81 M 20-84	Q4 vs. Q1	colon carcinoma	.98 (.68-1.4) & 0.62 (0.35-1.1)	1969-1971 (17.7)
1999	Kato	NYU Women's Health Study	prospective cohort	628 F 34-65	Q4 vs. Q1	CRC	0.63 (0.3-1.2)	1985-1991 (4.7)
2006	Cross	ATBC	prospective cohort	390 M smokers 50-69	Q4 vs. Q1	CRC	0.6 (0.3-1.3)	1985-1993
2011	Cross	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	case-control	752 55-74	Q4 vs. Q1	colorectal neoplasia	1.28 (0.83-1.98)	1993-2001 (3-5)

1. Cohort size and eligible age range; F=female; M=male; when not indicated, population included both men and women
2. Q4 = fourth quartile; Q1 = first quartile
3. Effect estimate (95% confidence interval)
4. Study period in years (average follow-up period, if reported)

Table 3. Summary characteristics of studies included in heme iron analysis

Date	Author	Study Population	Study Design	Population[1]	Comparison[2]	Outcome	Effect Estimate[3]	Study period[4]
2004	Lee	Iowa's Women Health Study	prospective cohort	34708 F 55-69 postmenopausal	Q5 vs. Q1	proximal colon cancer	1.41 (0.90-2.21)	1986-2000 (15)
2006	Balder	Netherlands Cohort Study	case-cohort	2156 M, 2215 F, 55-69	Q5 vs. Q1	colon cancer	1.32 (0.96-1.80) & 1.20 (0.86-1.69)	1986-2006 (9.3)
2007	Kabat	Canadian National Breast Screening Study	prospective cohort	48666 F 40-59	Q4 vs. Q1	CRC	1.06 (0.80-1.42)	1982-2002 (16.4)
2011	Zhang	Nurses' Health Study	prospective cohort	1,079 F 30-55	Q5 vs. Q1	CRC	1.21 (0.96-1.52)	1976-2006 (22)
2011	Zhang	Health Professionals' Follow-up Study	prospective cohort	1,035 M 40-75	Q5 vs. Q1	CRC	0.98 (0.77-1.26)	1976-2006 (22)
2012	Hara	Japan Public Health Center-based Prospective Study	prospective cohort	9930 M, 11344 F, 40-69	Q4 vs. Q1	CRC	1.06 (0.79-1.42) & 0.88 (0.61-1.29)	1995-2006 (5)

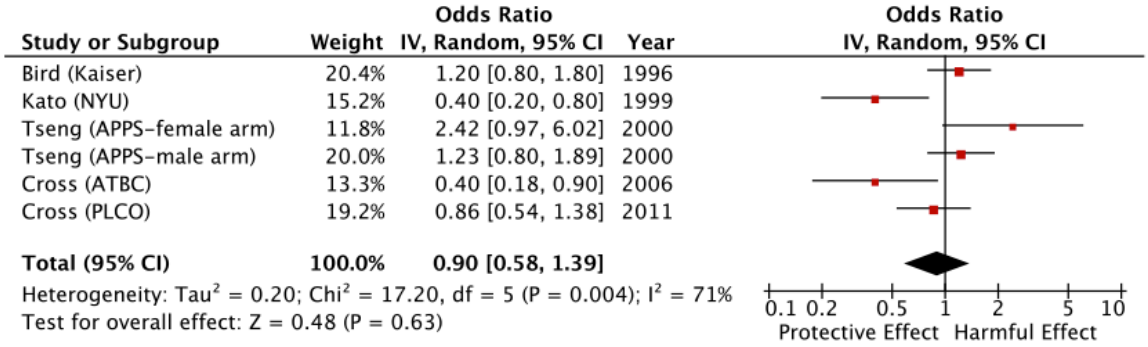
1. Cohort size and eligible age range; F=female; M=male; when not indicated, population included both men and women
2. Q5/Q1 = fifth quintile/first quintile; Q4/Q1 = fourth quartile/first quartile
3. Effect estimate (95% confidence interval)
4. Study period in years (average follow-up period, if reported)

Table 4. Summary of study quality indicators

Year	Study	Exclusion of preclinical cases[1]	Participation rate[2]	Stratification by gender[3]	Adjustments
1999	Kato	No	CACO (94%)	NA	Age, menopausal status at enrollment, date of enrollment, dates of blood donations, fat intake, demographic variables, ethnicity and religion, vitamin/mineral supplement use, family history of colorectal cancer, alcohol intake, cigarette smoking, history of occult blood testing, baseline total caloric intake, intake of calorie-adjusted micronutrients and dietary fiber, intake of total vitamins, height, BMI, physical activity
2011	Cross	No	CACO	No	Age, gender, ethnicity, study center, season of blood draw, date of sigmoidoscopy
1995	Herrinton	Yes (5)	Not reported	Yes	Age, race, cigarette smoking, alcohol intake
2006	Cross	Yes (5)	CACO	NA	Age, study area, intervention group, month of baseline blood draw, education, BMI, smoking status, physical activity, total caloric intake, alcohol, aspirin use, serum CRP level
1994	Knekt	Yes (5)	82.50%	Yes	Age, smoking status
1996	Bird	No	CACO	Yes	History of colorectal polyps, sex, age, date of sigmoidoscopy, and Kaiser center
2000	Tseng	Yes (1)	87%	Yes	Age, sex, center, intake of energy, alcohol, total dietary fiber, folate, fat, number of months between colonoscopies, smoking status, and aspirin use
2007	Kabat	Yes (3)	Not reported	NA	Age, BMI, menopausal status, oral contraceptive use, hormone replacement use, dietary intake of fat, fiber, folic acid, total calories, smoking, alcohol intake, and education
2012	Hara	Yes	84.22%	Yes	Age, health center, BMI, smoking status, alcohol consumption, physical activity, history of diabetes, screening for colorectal cancer, menopausal status, female hormones, energy-adjusted intake of calcium, magnesium, vitamin B-6, vitamin B-12, vitamin D and n-3 PUFAs, fiber
2011	Zhang	No	>90%	Yes	Age, smoking, family hx of cancer, hx of endoscopy, aspirin use, BMI, physical activity, alcohol consumption, folate, vitamin D, calcium, postmenopausal hormone use (women only), zinc
2008	Lee	Not reported	Not reported	NA	Age, total caloric intake, BMI, physical activity score, cigarette smoking, alcohol consumption, hx of diabetes, hormone replacement therapy, intake of multivitamins, saturated fat, soluble fiber, insoluble fiber, calcium, vitamin E, folate
2006	Balder	Yes (2)	Not reported	Yes	Age, education, cigarette smoking, nonoccupational physical activity, body mass index, intake of energy, alcohol, folate, fiber, total vegetable consumption, family history of colorectal cancer
1988	Stevens	Yes	CACO	Yes	Age, smoking status

1. If study reported the cutoff value for cases considered preclinical, in years
2. CACO = case-control. Participants selected from those that completed study
3. NA = not applicable. Study population was one gender

Figure 2. Forest plot of studies included in ferritin analysis



* Results for random-effects model shown

Figure 3. Funnel plot of studies included in ferritin analysis

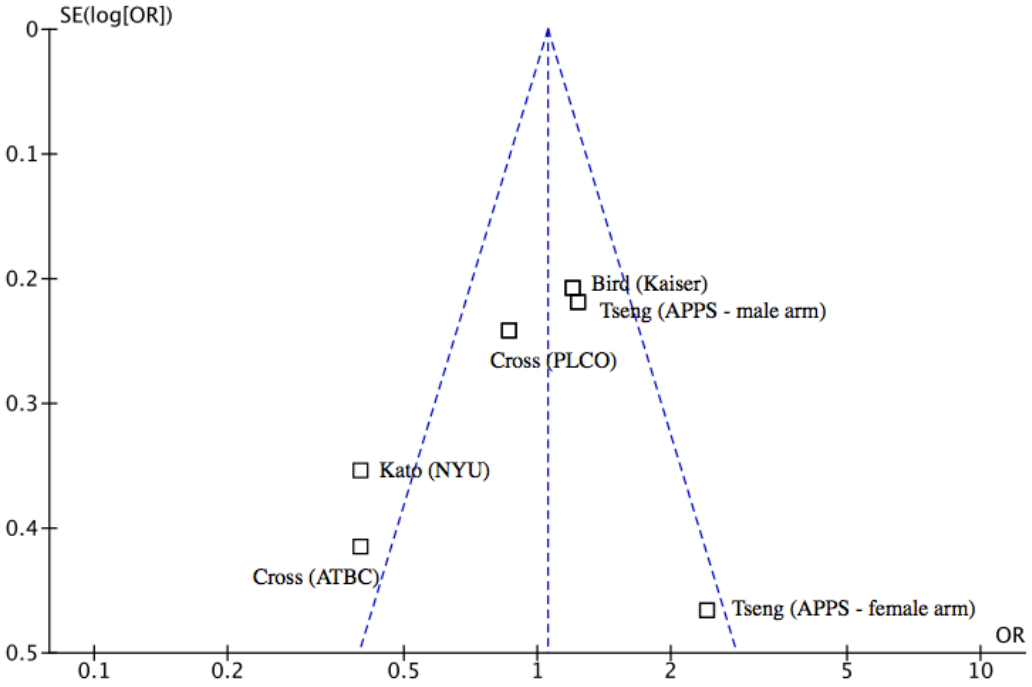


Figure 4. Forest plot of studies included in transferrin saturation analysis

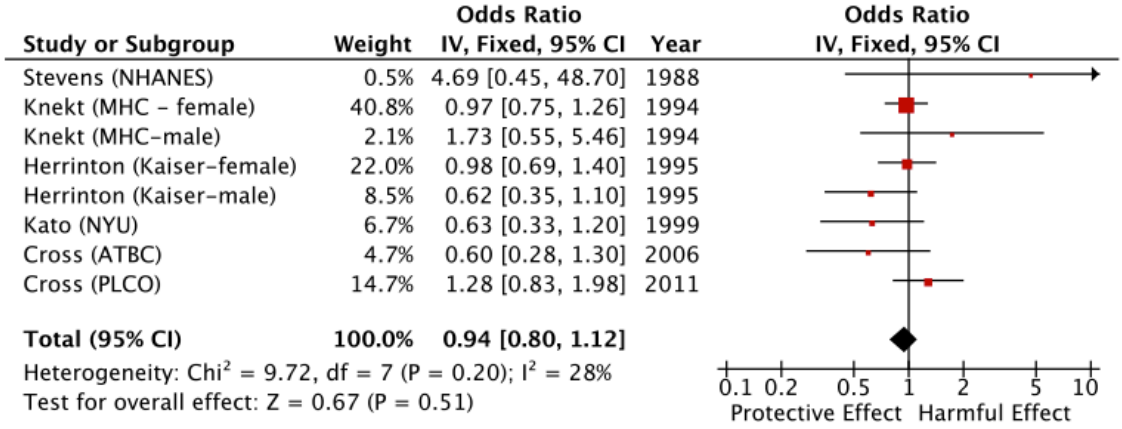


Figure 5. Funnel plot of studies included in transferrin saturation analysis

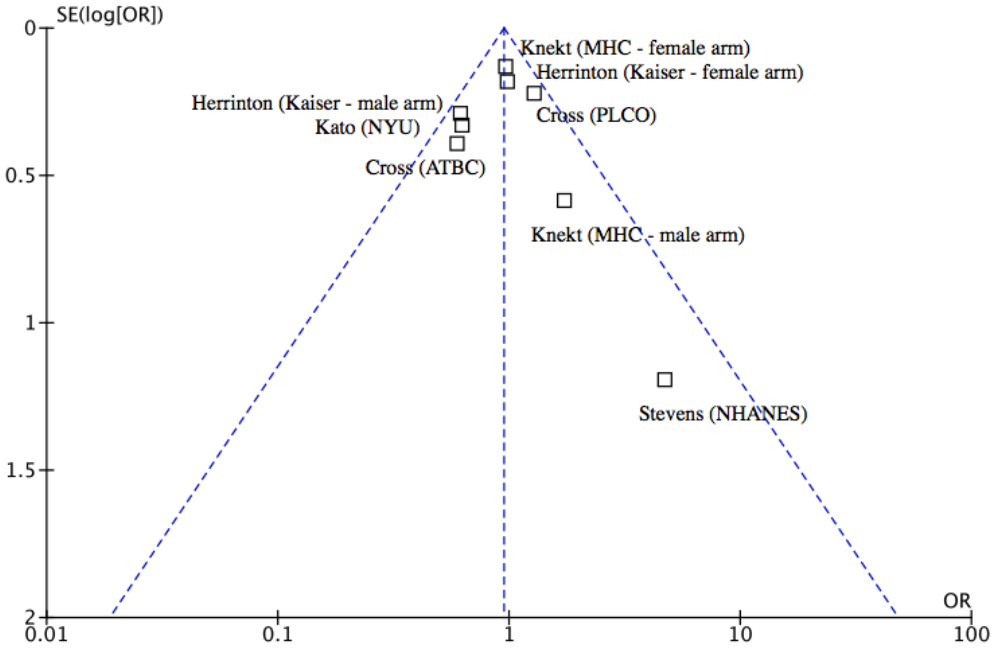


Figure 6. Forest plot of studies included in heme iron analysis

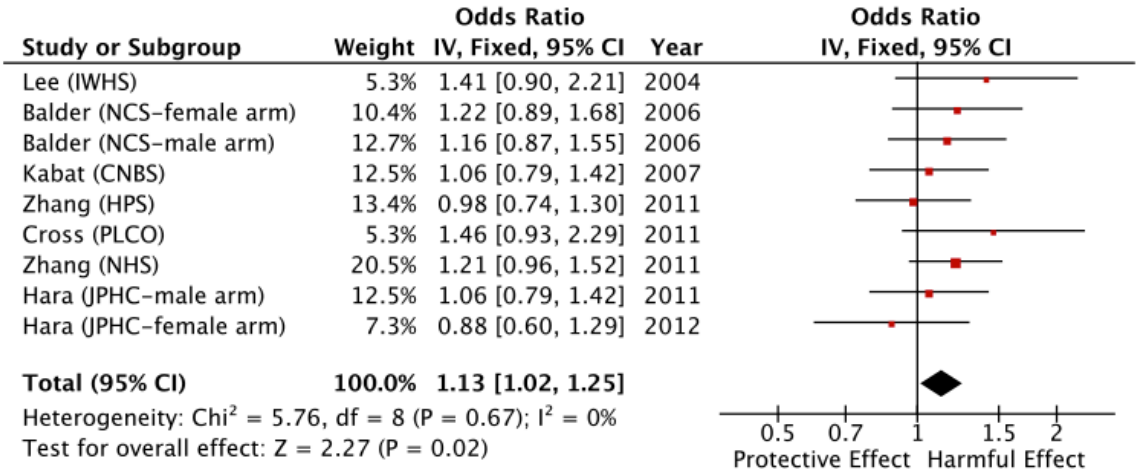


Figure 7. Funnel plot of studies included in heme iron analysis