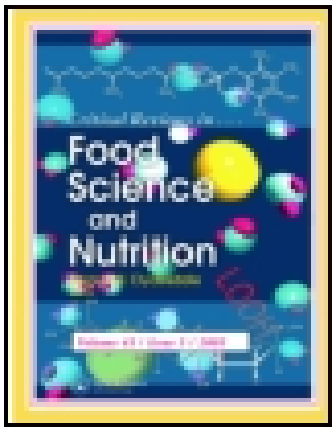

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Abstract:

Iron is an essential micronutrient that is involved in many redox processes and serves as an integral component in various physiological functions. However, excess iron can cause tissue damage through its pro-oxidative effects, potentiating the development of many diseases such as cancer through the generation of reactive oxidative species. The two major forms of iron in the diet are heme and nonheme iron, both of which are found in several different foods. In addition to natural food sources, intake of nonheme iron may also come from fortified foods or in supplement form. This review summarizes the results of human population studies that have examined the role of dietary iron (heme and nonheme), heme iron alone, and iron from supplements in colorectal carcinogenesis.

Introduction:

Iron is an essential mineral in mammals that transports oxygen throughout the body as part of the heme complex, supports growth, plays a key role in the generation of ATP in the electron transport chain, helps maintain immune competence, and is a part of many redox processes (Huang, 2003). While iron has many beneficial effects, it can also cause tissue damage and disrupt many other vital cell processes and components if excess iron is present.

There are two major types of dietary iron: nonheme iron found in plants, meat, and supplements and heme iron which is only found in meat. Nonheme iron can be divided into two different categories: small iron salts or complexes and the iron mineral ferritin (FTN) (Theil, 2011). Because of iron's possible toxic effects, iron absorption is tightly regulated. Uptake of nonheme iron in its reduced form occurs via the divalent metal transporter-1(DMT-1) on the apical membrane of enterocytes. Nonheme FTN is absorbed by a receptor-mediated endocytotic process (Oates et al., 2006). The exact mechanism of heme iron absorption is less well known, but a heme transporter, heme carrier protein 1 (HCP1), has been characterized in rats (Shayeghi et al., 2005).

The percentage of iron absorbed from the diet can vary from less than one percent to greater than 50% (Hallberg, 1981). The amount of iron stored in the body is the main factor controlling iron absorption. Little nonheme iron is absorbed from the diet; on average, adult men and women absorb 6% and 13% of dietary iron, respectively (Hallberg, 1981). The unabsorbed iron travels through the alimentary tract and collects in the colorectum before it is expelled in the feces. Once heme iron is absorbed, the heme protein is catabolized within the enterocyte and

released into the bloodstream along with nonheme iron and primarily utilized for erythropoiesis with excessive iron stored in the liver (Oates et al., 2006; Chua et al., 2007).

Body iron stores accumulate with age in all individuals with adequate intake (Cook et al., 1976; Zacharski et al., 2000), and to a much higher degree in individuals who have hereditary hemochromatosis (HH)(McDonnell et al., 1999). The prevalence rate of HH is approximately one case per 200 persons and often presents with hepatic cirrhosis, hepatocellular carcinoma, and severe fibrosis (Allen et al., 2008). The primary cause of HH is a substitution of a cysteine with a tyrosine amino acid at position 282 in the HFE protein (C282Y) (Feder et al., 1996). HFE is an iron regulatory protein that functions to regulate iron absorption. A second mutation in HFE results in a substitution of aspartic acid for histidine at position 63 (H63D) (Allen et al., 2008). The H63D mutation is more prevalent than the C282Y mutation in U.S. (13.5% vs. 5.4%, respectively) (Steinberg et al., 2001). Both the C282Y and H63D mutations lead to increased iron absorption, but iron overload is most commonly related to the C282Y mutation. Iron overload is defined as transferrin saturation greater than 50% in premenopausal women, or greater than 55% in postmenopausal women and men, and serum ferritin concentration greater than 200μg/L in women, or greater than 300 μg/L in men (Heath et al., 2003). This overload is a problem because there are no direct mechanisms of eliminating excess iron. However, indirect losses occur via sloughing of senescent gastrointestinal cells in feces, menses, parturition following pregnancy, blood loss, and sloughing of skin.

One area that has been widely studied with respect to dietary iron intake is colorectal cancer (cancer of the colon or rectum). Although incidence rates of colorectal cancers have been on the decline for the past 25 years, they still rank third in newly diagnosed cancers and third in

cancer deaths (WCRF/AICR, 2007). In 2011, there were approximately 140,000 new cases of colorectal cancer in the United States (U.S.) with men having a higher incidence rate than women (57.1 vs. 42.4 per 100,000, respectively)(Siegel et al., 2011). The mechanisms through which iron may promote colorectal carcinogenesis are varied. Unabsorbed iron from the diet travels through the alimentary tract, eventually ending up in the colon and rectum before it is lost in the feces. Iron in the lumen of the colorectum may interact with other unabsorbed food components, waste, and the cellular membrane of the colon itself. The role of iron in colorectal carcinogenesis has been summarized elsewhere (Nelson, 2001; Bastide et al., 2011). The pro-oxidative effects of iron can catalyze reactive oxidative species formation that can damage DNA (Glei et al., 2002). Several rodent studies have shown that dietary iron increases colonic crypt cell proliferation (Lund et al., 1998) and enhances colorectal tumor growth (Siegers et al., 1988; Siegers et al., 1992). Dietary meat has also been shown to promote colorectal carcinogenesis with an increased effect directly related to heme iron concentration (Pierre et al., 2004). Heme iron increases the formation of lipid peroxyl radicals (Sawa et al., 1998) such as malondialdehyde and 4-hydroxynonenal which are potent carcinogens in humans (Marnett, 2000; Kanner, 2007).

Epidemiologic studies examining the associations between HFE mutation carrier status and colorectal cancer have found mixed results. A recent international study of over 28,000 individuals found that homozygotes for the C282Y mutation had over twice the risk of colorectal cancer compared to those with no mutation (Osborne et al., 2010). Individuals with only one mutation (C282Y or H63D) were not at increased risk for colorectal cancer in this study (Osborne et al., 2010). Two previous studies found positive associations among subjects with

any mutation in the HFE gene (Nelson et al., 1995; Altes et al., 1999). Studies only assessing the C282Y mutation found no association with colorectal cancer (Macdonald et al., 1999; van der et al., 2003).

Herein, we analyzed the epidemiological studies that have examined the role of dietary iron (heme and nonheme), heme iron alone, and iron from supplements in colorectal carcinogenesis. This review is an analysis of human population-based studies relating dietary iron intake and colorectal cancer risk with a focus on luminal iron exposure. It is meant to be an update to the previous review of case-control studies assessing dietary iron and colorectal cancer (Nelson, 2001) as well as a supplement to the recent meta-analysis of cohort studies assessing heme iron and colorectal cancer risk (Bastide et al., 2011).

Methods:

Articles were initially located by conducting a literary search on PubMed. Key words in various combinations included the following: “colon, rectum, colorectum, HFE, cancer, adenoma, dietary iron, red meat, and heme.” Reference lists of articles were also scanned for relevant articles. Further criteria limited the search to articles in English from the last 15 years (1996-2012) that measured dietary nonheme or heme iron with respect to adenoma, polyp, or colorectal cancer outcomes. Studies were eliminated from consideration if they did not have dietary intakes of nonheme iron or heme iron (e.g. included only meat intake or HFE status). Twenty studies were included in this review from Europe (Levi et al., 2000; Almendingen et al., 2001; Senesse et al., 2004; Larsson et al., 2005; Balder et al., 2006; Cross et al., 2006), North America (Bird et al., 1996; Wurzelmann et al., 1996; Tseng et al., 1997; Kato et al., 1999;

Shaheen et al., 2003; Lee et al., 2004; Chan et al., 2005; Kabat et al., 2007; Ferrucci et al., 2009; Cross et al., 2010; Cross et al., 2011; Zhang et al., 2011), Uruguay (Deneo-Pellegrini et al., 1999), and Australia (van Lee et al., 2011).

Eighteen of the 20 studies included in this review calculated dietary iron intake which is comprised of both nonheme and heme iron (Bird et al., 1996; Wurzelmann et al., 1996; Tseng et al., 1997; Deneo-Pellegrini et al., 1999; Kato et al., 1999; Levi et al., 2000; Almendingen et al., 2001; Shaheen et al., 2003; Senesse et al., 2004; Chan et al., 2005; Balder et al., 2006; Cross et al., 2006; Kabat et al., 2007; Ferrucci et al., 2009; Cross et al., 2010; Cross et al., 2011; van Lee et al., 2011; Zhang et al., 2011). Nine studies calculated dietary intakes of heme iron (Lee et al., 2004; Chan et al., 2005; Larsson et al., 2005; Balder et al., 2006; Kabat et al., 2007; Ferrucci et al., 2009; Cross et al., 2010; Cross et al., 2011; Zhang et al., 2011).Two studies analyzed the iron regulatory gene HFE in conjunction with dietary iron intake (Shaheen et al., 2003; Chan et al., 2005). The majority of these studies included both men and women. Five studies were female only (Kato et al., 1999; Lee et al., 2004; Chan et al., 2005; Larsson et al., 2005; Kabat et al., 2007; Ferrucci et al., 2009) and one study had all male subjects (Cross et al., 2006). These studies utilized several experimental designs. Eight of the studies were case-control (Bird et al., 1996; Deneo-Pellegrini et al., 1999; Levi et al., 2000; Almendingen et al., 2001; Shaheen et al., 2003; Senesse et al., 2004; Ferrucci et al., 2009; van Lee et al., 2011), five were nested case-control (Tseng et al., 1997; Kato et al., 1999; Chan et al., 2005; Cross et al., 2006; Cross et al., 2011), six were cohort (Lee et al., 2004; Larsson et al., 2005; Balder et al., 2006; Kabat et al., 2007; Cross et al., 2010; Zhang et al., 2011), and one was a follow-up of the NHANES I dataset from the National Health Evaluation Follow-up Study (NHEFS) (Wurzelmann et al., 1996).

Iron Intake Results:

Dietary iron:

The outcomes of the 18 studies that measured dietary iron are mixed (**Tables 1 & 2)**. We included 10 cohort and nested case-control studies in this review (**Table 1**). Of the studies that used cancer incidence as an endpoint, one study (Wurzelmann et al., 1996) found a significant positive association and one study (Cross et al., 2010) found a significant inverse association between dietary iron and colon cancer. In the follow-up from the NHANES I study (Wurzelmann et al., 1996), men and women with the highest iron intake had an increased risk for colon cancer (RR Q_4 vs. Q_1 = 3.35; 95% CI = 1.74-6.46). Conversely, in the study by Cross et al. (Cross et al., 2010), both dietary iron and total iron (dietary iron + supplements) had a significant inverse association in each of the 2^{nd}-5^{th} quintiles of intake in the colon, rectum, and colorectum as well as a significant dose-response relationship. In a subsequent sub-analysis of the NHANES I study (Wurzelmann et al., 1996), men and women with the highest iron intake had an increased risk for proximal colon cancer (RR Q_4 vs. Q_1 = 1.44; 95% CI = 1.23-1.69) , and women alone had an even greater risk (RR Q_4 vs. Q_1 = 1.51; 95% CI = 1.41-1.60). The study by Kato et al. (Kato et al., 1999) found a positive dose-response in the proximal colon of females (P = 0.04). One study found a significant inverse association between high dietary iron and adenoma recurrence(Tseng et al., 1997). The majority of the remaining cohort studies found positive, but non-significant associations between dietary iron intake and colorectal cancer or adenoma incidence.

The results of the 8 case-control studies are listed in **Table 2**. Three of the five studies that used cancer incidence as an endpoint found a significant positive association between

dietary iron and colorectal cancer (Deneo-Pellegrini et al., 1999; Levi et al., 2000; Shaheen et al., 2003; Senesse et al., 2004; van Lee et al., 2011). In the Uruguayan study by Deneo-Pellegrini et al. (Deneo-Pellegrini et al., 1999) rectal cancer was positively associated with dietary iron in both men and women (OR T_3 vs. T_1 = 3.18; 95% CI = 1.92-5.29), but was particularly evident in men (OR T_3 vs. T_1 = 4.01; 95% CI = 2.09-7.69). In contrast, there were no significant associations between dietary iron and incidence of adenoma. These inconsistent results from both cohort and case-control studies indicate that dietary iron may play a role in modifying colorectal cancer risk.

Supplemental iron:

Of the 20 studies included in this review, only 11 measured supplemental iron intake. The methods used to assess the impact of supplemental iron on colorectal cancer risk varied greatly by study. Many of these studies compared dietary iron and total iron intake (dietary iron + supplements) to evaluate the influence of iron supplements on colorectal risk estimates. Three of the reviewed studies had no data or excluded subjects taking iron supplements because so few reported iron supplement use (Chan et al., 2005; Cross et al., 2006; Cross et al., 2011). Two studies only reported risk associated with total iron intake so no conclusions can be made concerning supplements (Kato et al., 1999; Shaheen et al., 2003). The NIH-AARP cohort study, which was also the largest study in this review, reported similar risk estimates for high dietary and total iron intake and colorectal cancer (Cross et al., 2010). Interestingly, a study by Ferrucci et al. (Ferrucci et al., 2009), showed a potential protective effect of supplemental iron intake on adenoma incidence. In this study, dietary iron was positively associated (OR Q_4 vs. Q_1 = 1.11;

95% CI = 0.57-2.16), total iron intake was inversely associated with adenoma incidence (OR Q_4 vs. Q_1 = 0.91; 95% CI = 0.52-1.59), and supplemental iron had a mild protective effect on adenoma incidence (OR T_3 vs. T_1 = 0.82; 95% CI = 0.54-1.25). While none of these results were significant, overall they suggest a potential benefit on colorectal adenomas from supplemental iron.

In contrast, four studies showed a potential positive association for supplemental iron intake and colorectal cancer or adenoma incidence when comparing dietary iron and total iron intake (Bird et al., 1996; Tseng et al., 1997; Almendingen et al., 2001; Zhang et al., 2011). In one study conducted by Zhang et al. (Zhang et al., 2011), female subjects consuming high levels of iron from supplements (≥ 25 mg/day) were at an increased risk for rectal cancer compared with women who consumed no supplements (RR = 2.54; 95% CI = 1.43-4.50), but no significant associations were observed among men. The results of these studies assessing supplemental iron intake and colorectal cancer or adenoma are too varied to draw any definitive conclusions; further research needs to be conducted in order to elucidate supplemental iron's impact on colorectal cancer risk.

Heme iron:

The results of the nine studies assessing heme iron intake are presented in **Table 3**. There were significant positive associations with cancer risk in three of the studies with risk estimates ranging from 1.13 to 2.18 (Lee et al., 2004; Larsson et al., 2005; Cross et al., 2010) for high compared to low heme iron intakes. Five of the remaining six studies reported positive, but non-significant associations between heme iron intake and colorectal cancer (Chan et al., 2005;

Balder et al., 2006; Ferrucci et al., 2009; Cross et al., 2011; Zhang et al., 2011). The positive associations observed from the studies assessing heme iron intake strengthen the previous findings that red and processed meats increase colorectal cancer risk. The cohort studies assessing the effect of both dietary iron and heme iron on colorectal cancer risk suggest that heme iron may play a greater role than iron from non-meat sources on cancer risk.

Mutations in HFE:

Two studies assessed effects of HFE gene status and iron intake on cancer and adenoma incidence. A study conducted by Chan et al. (Chan et al., 2005)found that women in the highest quartile of dietary iron intake with one or more mutations in the HFE gene (C282Y or H63D) had an OR of 1.14 (95% CI = 0.64-2.03) for adenoma incidence. Similar results were found among women with any HFE mutation with the highest intake of heme iron (OR Q_4 vs. Q_1 = 1.11; 95% CI = 0.64-1.93). The study by Shaheen et al. (Shaheen et al., 2003)found that subjects having any mutation in HFE had an OR of 1.40 (95% CI = 1.07-1.87) for colorectal cancer incidence. Among subjects with any mutation in HFE, those with the highest total iron intake had a significant positive association with colorectal cancer (OR Q_4 vs. Q_1 = 1.86; 95% CI = 1.09-3.18). These two studies indicate that HFE mutations have the potential to increase colorectal risk but further studies need to be done to elucidate gene-nutrient interactions, especially large studies that are powered to assess the risk associated with the homozygous C282Y mutation in conjunction with dietary intake.

Discussion:

Over the past 15 years a total of 20 human population-based studies have evaluated the associations between dietary iron or heme iron and colorectal cancer or adenoma. Fifteen studies reviewed used cancer as an endpoint while the remaining five used a surrogate for cancer, adenoma or adenoma recurrence, as an endpoint (**Tables 1-3**). Studies that use adenoma or adenoma recurrence as an endpoint are better assessments of early stage colorectal carcinogenesis because adenomas precede cancer, while studies that use cancer as an endpoint typically measure later stages of carcinogenesis. Previous radiologic evidence has found that 8% of adenomas undergo unrestricted cell division and became carcinomas over 10 years and 24% of adenomas become carcinomas at 20 years (Stryker et al., 1987). This information may help explain the mixed results between adenoma and cancer studies.

Dietary Iron:

Dietary iron is a measure of total heme and nonheme iron from all food sources. The primary sources of dietary iron are red meat, poultry, beans, leafy vegetables, fruit juice, and fortified breads and cereals. Although these studies are from different populations, many studies found the highest intakes of dietary iron to be 18-20 mg/day with men having slightly higher intakes than women. The results from studies assessing dietary iron intake and colorectal cancer risk were mixed. Two cohort studies that assessed dietary iron intake deserve special mention. In one study of non-institutionalized men and women between 24-74 years of age in the U.S. (Wurzelmann et al., 1996), dietary iron was found to be positively associated with colorectal cancer. This study is particularly important because it is nationally representative and was specifically designed to account for the heterogeneity of the U.S. population and provide a

variety of nutritional and health measures. In contrast, a study conducted by Cross et al. (Cross et al., 2010) found an inverse association between dietary iron and colorectal cancer. This analysis is from the largest study of diet and health ever conducted – the NIH-AARP cohort (also known as the Diet & Health Study) and is comprised men and women age 50-71 years from six states and two major metropolitan areas. The authors of this study point out that many sources of dietary iron are generally healthy (eg. fruit juice, fortified cereals, bread) and highlighted the importance of distinguishing between heme and nonheme iron (Cross et al., 2010).

These discrepancies between studies are likely due to the complex interaction between foods within the digestive tract as well as the varied sources of iron within the diet. For example, Tseng et al. (Tseng et al., 1997) found that adenoma recurrence was inversely associated with dietary iron intake. Subjects from this study were part of a clinical trial to assess effects of antioxidant supplementation on adenoma prevention and thus these individuals may have altered their dietary habits during the study. The authors noted that there was very low meat intake in this population and iron intake was highly correlated with dietary fiber (Pearson's $r = 0.70$) which may explain the inverse association (Tseng et al., 1997). This study is important because it shows that dietary iron may be beneficial if it is derived from fruit and vegetable sources as opposed to meat. Future studies assessing dietary iron need to account for the source of iron to clarify the relation between dietary iron intake and colorectal cancer.

The preponderance of case-control studies found a positive association between dietary iron and colorectal cancer. These associations were strongest in studies that used cancer as an endpoint (**Table 2**). The strongest association between dietary iron and cancer incidence was observed in the rectal cancer study conducted by Deneo-Pellegrini et al. (Deneo-Pellegrini et al.,

1999); however, the small sample size and large 95% confidence interval (CI) make it necessary to interpret these findings cautiously. Increased rectal cancer risk was not observed with higher iron consumption in any other case-control study. All but one (van Lee et al., 2011) of these case-control studies asked subjects to provide dietary intake information for the year or two years prior to diagnosis which may have led to recall bias (Willett, 1998). Also, because colorectal cancer takes many years to develop, it is possible that earlier dietary habits are of greater etiological interest than the reference diet. The study by van Lee et al. (van Lee et al., 2011) asked subjects to provide dietary information for the 10 years prior to filling out the food frequency questionnaire (FFQ) to decrease recall bias and assess a longer exposure period. As a result of the potential recall bias and smaller sample size in many of the case-control studies, more emphasis should be placed on the large cohort studies.

Heme Iron:

A recent consensus report conducted by the World Cancer Research Fund and American Institute for Cancer Research concluded that there was “convincing” evidence that red and processed meat increases the risk for colorectal cancer and individuals should limit their intake of red meat while avoiding processed meat (WCRF/AICR, 2007). Red meat has approximately ten-fold the amount of iron as white meat, which may explain the increased risk associated with red meat intake (Carpenter et al., 1992). Heme iron is known to be more bio-available than non-heme iron, but its absorption is still tightly regulated. Unabsorbed heme and nonheme iron from red meat pass through the digestive tract and end up in the lumen of the colon and rectum.

The large cohort study by Cross et al. (Cross et al., 2010) is especially pertinent because they found a significant inverse association between dietary and total iron intake and colorectal cancer risk but a significant positive association between heme iron intake and colorectal cancer risk. These findings highlight the importance of identifying the source of iron. The number of null associations observed in this review as well as the small risk estimates may be due to the imprecise methods used to assess heme iron content as well as the relatively small range of intakes observed in many studies.

In several studies, the amount of heme iron from meat was estimated using a standard percentage (40%) of total iron from all meat sources (Lee et al., 2004; Larsson et al., 2005). Other studies have applied a percentage according to the animal from which the meat was derived, for example, beef (65%), pork (39%), chicken/fish (26%), or liver (21%) (Balder et al., 2006; Kabat et al., 2007). Studies using this second method have not found an overall association between heme iron intake and colorectal cancer risk. Recently, a heme iron database has been developed to more accurately quantify the amount of heme iron as well as other possible carcinogenic compounds found in unprocessed and processed meats (Sinha et al., 2005). Three studies (Ferrucci et al., 2009; Cross et al., 2010; Cross et al., 2011)included in this review used information from the heme database, and two found a significant positive association between heme iron and risk for colorectal cancer (Cross et al., 2010; Cross et al., 2011).

The mechanisms by which heme iron may promote colorectal cancer are poorly understood. Several proposed mechanisms of action are the N-nitrosylation of amines which forms N-nitroso compounds (NOC) and lipid peroxidation (Bastide et al., 2011). NOCs are known carcinogens which can cause mutations in DNA resulting in cancer if gone unchecked

(Jacoby et al., 1992; Hebels et al., 2011). Heme iron promotes endogenous NOC formation in humans (Cross et al., 2003). NOCs can also be introduced exogenously by adding nitrates to meat during processing (Cross et al., 2010). In addition, heme iron catalyzes the oxidation of polyunsaturated fats. Free radicals attack membrane lipids producing reactive compounds such as epoxides and aldehydes (Bastide et al., 2011). One major aldehyde product is malondialdehyde which has been indicated in several human diseases, including colorectal cancer (Basu et al., 1983; Kanner, 2007; Allam et al., 2011). Cooking of red meat at high temperatures also introduces heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) which are known gastrointestinal carcinogens in animal models (Ohgaki et al., 1991; Culp et al., 1998). Combined, these data suggest that heme iron may promote carcinogenesis and intake should be limited, especially among individuals who are at increased risk for colorectal cancer.

Supplemental Iron:

Dietary supplement use is increasing in both the U.S. and Europe. Over 40% of U.S. adults used some form of dietary supplement in 1988-1994 and that number grew to over 50% in 2003-2006 (Gahche et al., 2011). Zhang et al. (Zhang et al., 2011) noted an increase in iron supplement use in both men and women from 1990 to 2004 (men: 14% to 20%; women: 20% to 26%) which is consistent with the overall trend in the U.S. Supplement use in Europe is varied, but many countries document that over 30% of their population takes some form of dietary supplement (Skeie et al., 2009). Although large numbers of people are taking supplements, little is known about their impact on colorectal cancer risk, especially iron supplements. Four studies

in this review noted that a large percentage of their study population used iron supplements (Bird et al., 1996; Kato et al., 1999; Ferrucci et al., 2009; Zhang et al., 2011). In the study by Kato et al. (Kato et al., 1999), 69% of the women in the study were taking supplemental iron which amounted to 38% of the total iron intake. However, many authors of the studies included in this review noted that there were an insufficient number of individuals taking iron supplements to calculate the risk independently associated with iron supplement use. With dietary supplement use on the rise, it is important that future studies measure supplement intake to assess their effectiveness and determine if there are any risks associated with their use.

HFE and Colorectal Cancer:

A long-term determinant of iron status is variation in HFE. The two studies that assessed HFE status in conjunction with dietary iron found conflicting results. These results may be explained by the different outcome measures chosen as well as the limited ability to stratify subjects by HFE status. For example, Chan et al. (Chan et al., 2005)utilized adenoma incidence as a surrogate for cancer and found no interaction with genotype whereas Shaheen et al. (Shaheen et al., 2003) assessed cancer incidence as the endpoint and found a significant effect only among those with any HFE mutation. Both studies lacked the power to stratify subjects as either homozygous or heterozygous for the C282Y HFE mutation which is the primary cause of HH. Instead, they were limited to examining subjects having any or no mutations of the HFE gene (C282Y or H63D). Both mutations cause an increase in iron absorption; however, homozygotes of the recessive C282Y allele accumulate iron to a much greater extent than heterozygotes.

A recent report by Allen and colleagues (Allen et al., 2008) has shown that 60-80% of individuals homozygous for the C282Y mutation will develop abnormal iron indices, but only 28% of men and 1% of women will develop significant iron overload as a result. The most common explanation for this discrepancy between sexes is the loss of iron through menstruation. Six of the twenty studies in this review were female-only studies (Kato et al., 1999; Lee et al., 2004; Chan et al., 2005; Larsson et al., 2005; Kabat et al., 2007; Ferrucci et al., 2009). Only one of the six studies was comprised solely of post-menopausal women (Lee et al., 2004) while the rest included both pre- and post-menopausal women. Thus, iron loss from menstruation and pregnancy may help explain the conflicting results seen in these studies and may also help explain some of the differences in overall incidence rates between men and women. These findings indicate that the risk for colorectal cancer associated with HFE mutation carrier status and iron intake are likely higher for men than women, but individuals with HFE mutations should limit heme iron intake and monitor their iron levels closely.

Strengths and Weaknesses:

Several strengths and weaknesses of the current available studies must be recognized. Self-reported measures of dietary intake may be biased, particularly in case-control studies, which must be taken into consideration when interpreting results. Over- and under-reporting are common problems that occur when participants feel pressured to report consuming more healthy foods (eg. fruits and vegetables) and less unhealthy foods (eg. fried food, foods high in fat, etc.). In addition, due to the limited number of items that may be included in a FFQ, participants have been shown to underestimate actual energy intake (Willett, 1998; Livingstone et al., 2003).

Using this rationale, subjects are likely to under-report meat intake and over-report intake of foods such as salads and fruits which have an inverse association with colorectal cancer risk. To attempt to overcome some of these issues, an additional meat questionnaire was included in three of the studies (Ferrucci et al., 2009; Cross et al., 2010; Cross et al., 2011)which was aimed at reducing reporting errors and improved calculation of heme iron content of meats using the NCI heme database.

The strengths of this review include the use of both prospective and cross-sectional studies from a variety of different study populations, comparison of different methods for heme iron content across studies, and the use of both cancer and adenoma studies. This is also the first review to date to assess the risk of iron from supplements, but no conclusions could be made due to inconsistent reporting of intake and risk between studies.

Future Directions:

Following our review of the current literature, there are several avenues that require investigation. Further studies need to be conducted to assess the role of iron regulatory genes in conjunction with dietary iron to help elucidate any gene-environmental interactions in iron absorption and cancer formation and progression. A better understanding of the differences between males and females is needed as well as the effect of iron on specific regions of the colon and rectum. Importantly, few studies have investigated the associations between dietary iron intake and colorectal cancer among minorities as well. Studies specifically assessing supplemental iron intake would also add to the current literature where the results are mixed.

Finally, a validated heme iron calculation that can be used consistently between studies is also needed to properly ascertain the role of heme iron in colorectal carcinogenesis.

Conclusion:

While iron is an essential mineral for proper cellular function, it may be detrimental if consumed in excess. Dietary iron has been widely studied in relation to colorectal cancer with mixed results. Many of the mixed results that have resulted from these studies are a result of diverse study populations or lack of power. Results from some of the larger cohort studies suggest that the primary cause of increased risk is heme iron and red meat intake rather than total dietary iron.

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Table 1: Cohort and Nested Case-Control Dietary Iron Studies

(Reference)	Cases	Controls/ Cohort Size	Result[†]	OR/HR/RR[‡] (*P*-trend)	95% CI	Outcome	Measured Supplements
(Wurzelmann et al., 1996)	136	8,876	+	RR=3.35 (*P*<0.001) [Colon]	1.74-6.46	Cancer	N
	65	3,631	+	RR=3.73 (*P*=0.001) [Men]	1.62-8.59		
	72	5,245	+	RR=3.01 (*P*=0.08) [Women]	1.05-8.64		
(Cross et al., 2010)	2,719	300,948	-	HR=0.75 (*P*<0.001)	0.65-0.87	Cancer	Y
(Balder et al., 2006)	869	58,279	NS	RR=1.34 (*P*=0.12) [Men]	0.93-1.93	Cancer	N
	666	62,573	NS	RR=1.08 (*P*=0.90) [Women]	0.72-1.62		
(Cross et al., 2006)	130	260	NS	OR=0.4 (*P*=0.06) [Men]	0.1-1.1	Cancer	Y
(Kabat et al., 2007)	617	49,654	NS	HR=1.07 (*P*=0.94) [Women]	0.75-1.53	Cancer	N
(Kato et al., 1999)	105	523	NS	OR=1.17 (*P*=0.44) [Total Iron; Women]	0.6-2.3	Cancer	Y
(Zhang et al., 2011)	2,114	115,016	NS	RR=1.09 (*P*=0.37)	0.93-1.30	Cancer	Y
	1,035	42,373	NS	RR=1.08 (*P*=0.61) [Men]	0.84-1.38		
	1,079	69,345	NS	RR=1.11 (*P*=0.44) [Women]	0.88-1.41		
(Tseng et al., 1997)	247	419	-	OR=0.37 (*P*=0.005)	0.19-0.73	Adenoma	Y
(Chan et al., 2005)	527	527	NS	RR=1.04 (*P*=0.94) [Women]	0.68-1.57	Adenoma	Y
(Cross et al., 2011)	356	396	NS	OR=0.98 (*P*=0.98)	0.62-1.55	Adenoma	Y

[†] Highest intake quantile vs. lowest; NS = Not significant (95% CI includes 1.0); + means significant positive association;
- means significant inverse association

[‡] OR = Odds Ratio; HR = Hazard Ratio; RR = Relative risk

Table 2: Case-Control Dietary Iron Studies

(Reference)	Cases	Controls	Result†	Odds Ratios (*P*-trend)	95% CI	Outcome	Measured Supplements
(Deneo-Pellegrini et al., 1999)	216	433	+	OR=3.18 (*P*<0.001) [Rectum]	1.92-5.29	Cancer	N
	141	284	+	OR=4.01 (*P*<0.001) [Men]	2.09-7.69		
	75	149	+	OR=2.61 (*P*=0.02) [Women]	1.12-6.10		
(Levi et al., 2000)	223	491	+	OR=2.43 (*P*<0.05)	1.2-5.1	Cancer	N
(Senesse et al., 2004)	171	309	+	OR=2.3 (*P*=0.02)	1.1-4.7	Cancer	N
(Shaheen et al., 2003)	475	833	NS	OR=1.05 [Total Iron]	0.75-1.49	Cancer	Y
(van Lee et al., 2011)	854	958	NS	OR=0.86 (*P*=0.17)	0.64-1.15	Cancer	N
(Almendingen et al., 2001)	87	35*	NS	OR=0.2 (*P*=0.08)	0.1-2.3	Adenoma	Y
(Bird et al., 1996)	467	498	NS	OR=1.4	0.9-2.0	Adenoma	Y
	300	331	NS	OR=1.6 [Men]	0.9-2.8		
	167	167	NS	OR=1.0 [Women]	0.5-2.0		
(Ferrucci et al., 2009)	158	649	NS	OR=1.11 (*P*=0.77) [Women]	0.57-2.16	Adenoma	Y

† Highest intake quantile vs. lowest; NS = Not significant (95% CI includes 1.0); + means significant positive association;

- means significant inverse association

* ORs for 'Healthy' controls. 'Hospital' controls (n=35): OR=1.3 (0.1-13.8; *P*=0.8)

Table 3: Heme Iron Studies

(Reference)	Cases	Controls/ Cohort Size	Result[†]	OR/HR/RR[‡] (*P*-trend)	95% CI	Outcome	Study Design
(Cross et al., 2010)	2,719	300,948	+	HR=1.13 (*P*=0.022)	0.99-1.29	Cancer	Cohort
(Larsson et al., 2005)	547	61,433	+	RR=1.31 (*P*=0.03) [Women]	0.98-1.75	Cancer	Cohort
(Lee et al., 2004)	741	41,836	+	RR=2.18 (*P*=0.01) [Women; Prox. Colon]	1.24-3.86	Cancer	Cohort
(Balder et al., 2006)	869	58,279	NS	RR=1.16 (*P*=0.27) [Men]	0.87-1.55	Cancer	Cohort
	666	62,573	NS	RR=1.22 (*P*=0.22) [Women]	0.89-1.68		
(Kabat et al., 2007)	617	49,654	NS	HR=0.99 (*P*=0.99) [Women]	0.70-1.40	Cancer	Cohort
(Zhang et al., 2011)	2,114	115,016	NS	RR=1.10 (P=0.51)	0.93-1.30	Cancer	Cohort
	1,035	42,373	NS	RR=0.98 (*P*=0.80) [Men]	0.77-1.26		
	1,079	69,345	NS	RR=1.21 (*P*=0.10) [Women]	0.96-1.52		
(Chan et al., 2005)	527	527	NS	RR=1.13 (*P*=0.23)	0.74-1.72	Adenoma	Nested C-C
(Cross et al., 2011)	356	396	NS	OR=1.46 (*P*=0.08)	0.94-2.29	Adenoma	Nested C-C
(Ferrucci et al., 2009)	158	649	NS	OR=1.50 (*P*=0.32) [Women]	0.83-2.73	Adenoma	Case-Control

[†] Highest intake quantile vs. lowest; NS = Not significant (95% CI includes 1.0); + means significant positive association;

- means significant inverse association

[‡] OR = Odds Ratio; HR = Hazard Ratio; RR = Relative risk

