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Associations of Dietary Fats with Incident Colorectal Cancer in the Iowa Women's Health Study

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ABSTRACT

Associations of Dietary Fats with Incident Colorectal Cancer in the Iowa Women's Health Study

By, Muhammad Thuneibat

The associations of dietary fats with incident colorectal cancer (CRC) across previous studies have been inconsistent. Certain types of dietary fats are proposed to increase CRC risk through pro-inflammatory mechanisms and stimulating the secretion of bile acids, while others are proposed to decrease risk. To address the inconsistency, we investigated associations of intakes of total fats, animal fats, vegetable fats, saturated fats, polyunsaturated fats, monounsaturated fats, and trans-fats with incident CRC in the prospective Iowa Women's Health Study. Of the 35,221, 55-69-year-old women who were cancer-free at baseline in 1986, 1,731 developed incident CRC during follow-up through 2012. Diet was assessed using a Willett semi-quantitative food frequency questionnaire. Fat intakes were adjusted for energy intakes using the residual method. Fat intake residuals were categorized into quintiles, and associations estimated using multivariable Cox proportional hazards regression models. For those in the highest relative to the lowest total fat quintiles, the adjusted hazard ratios and 95% confidence intervals for overall, proximal, and distal CRC were 0.95 (0.77 – 1.10; P_{trend} = 0.35), 0.86 (0.67 – 1.09; P_{trend} = 0.22), and 1.06 (0.81 – 1.39; P_{trend} = 0.92), respectively. The estimated associations of the various fat subtypes with CRC were similarly close to null. Our findings suggest that dietary fats may not be associated with risk for incident colorectal cancer among older Iowa women.

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CHAPTER I

LITERATURE REVIEW

BACKGROUND

Colorectal cancer is the third most common type of cancer diagnosed among both men and women in the United States. In 2019, it is estimated that 101,420 incident cases of colon cancer and 44,180 incident cases of rectal cancer will occur. The lifetime risk for men for developing CRC is 1 in 22, and 1 in 24 for women. It is estimated that 51,020 colorectal cancer-related deaths will occur in 2019. Colorectal cancer is the third leading cause of cancer-related death in men and in women individually, and second most common when combining sexes.[1]

Colorectal cancer begins in the colon or the rectum region of the body. The similarities in characteristics between the two regions is why they are generally grouped together regarding cancer.[2] Colorectal cancer begins as a noncancerous growth on the inner lining of the colon or rectum known as a polyp[3,4] Most colorectal cancers develop from adenomatous polyps, which, develop over a period of 10-20 years into colorectal cancer.[5,6] The pathogenesis process begins when cancer takes form in a polyp, it then grows into the innermost layer (mucosa) of the colon or rectum before spreading outwards into the other layers. As the cancer cells are in the wall of the colon or rectum, they can then spread to the rest of the body by blood vessels or lymph nodes.[7]

The gold standard for screening for colorectal cancer is a colonoscopy, which is normally recommended every ten years after an initial negative result.[8] However, only 2 in 3 people in the United States get tested for colorectal cancer. It is possible that the reason may be due to cost and health insurance coverage issues.[2]

RISK FACTORS

Many migrant and temporal trend studies suggest that colorectal cancer can be largely determined by environmental and nutritional habits.[9] There are multiple preventable risk factors and causes of colorectal cancer. Physical activity, normal body mass index score (BMI), nutrients such as whole grains and foods containing fiber and calcium are inversely associated with colorectal cancer. However, a high BMI, a history of smoking and drinking, as well as foods containing processed or red meats are associated with higher risk for colorectal cancer. [10]

DIETARY FATS and SUBTYPES

Dietary fats are an essential part of our diet. They are found in most food groups and are the most energy-dense macronutrients.[11] There are many different types of dietary fats, each from a different combination of dietary sources, from meats to plant-oils.[12] The major types of dietary fats and their differences are addressed below.

Saturated fats are primarily found in animal sources, such as processed and red meats. They can also be found in dairy products, such as butter. Saturated fats are dietary fats that do not contain a double bond (thus saturated) between any two of its carbon molecules; instead, they are saturated with hydrogen atoms.[13]

Saturated fats are associated with higher risk for cardiovascular disease, strokes,[13] and other diseases by elevating low density lipoprotein (LDL) cholesterol levels.[13]

Poly-unsaturated fats contain more than one unsaturated carbon bond (double-bonds). [14] The major types of poly-unsaturated fats are omega-6 and omega-3. Omega-6 poly-unsaturated fats contain their first double bond between the sixth and seventh carbon atoms from the terminal methyl group. Omega-3 poly-unsaturated fats have their first double bond between the third and fourth carbon atoms.[11]

Mono-unsaturated fats contain a single unsaturated carbon bond (double-bond).[11] Mono-unsaturated fats are primarily found in plant-based oils, and are known to reduce LDL concentrations in the blood, which contributes to lower risk of certain diseases.[15]

A type of unsaturated fat that is overwhelmingly industrially produced, trans-fatty acids are created via a process known as partial hydrogenation. This process uses hydrogen to reduce the concentration of poly-unsaturated fats while forming positional and geometric fatty acid isomers,[16] that differ from the normal cis position that most unsaturated fats are positioned in.[17] Increased trans-fatty acid consumption has been linked to a variety of diseases, Including heart disease and type II diabetes.[18]

BIOLOGICAL MECHANISMS

The proposed mechanism by which most dietary fats increase the risk of colorectal cancer is by stimulating the secretion of bile acids.[19–22] Primary bile acids are synthesized from cholesterol in the liver hepatocytes, and eventually enter the colon where the bile acids undergo a biotransformation that can lead them to develop into secondary bile

acids.[23,24] The secondary bile acids can then damage the colonic mucosa, stimulating the regeneration of the epithelium, and increasing the risk of an endogenous mutation.[19–22] Additionally, it has been proposed that dietary fats may influence the risk of colorectal cancer by involvement in insulin resistance, as well as changing the fatty acid composition of membranes, and altering immunologic responses.[25] Several studies in humans found trans-fat intake to be associated with markers of oxidative stress[26] and systematic inflammation.[27] The mechanism by which this occurs is that trans-fatty acids consumption may lead to elevated risk of developing colorectal adenomas by altering the concentration of fatty acids or bile acids normally found in the colon.[25,28–30] This mechanism results in irritation of the colonic mucosa, increasing oxidative stress[26] and inflammation.[27]

Yet, some dietary fats have been proposed to decrease the risk of colorectal cancer. Marine omega-3 poly-unsaturated fats such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and docosapenaenoic acid (DPA), are suggested to suppress tumor growth and angiogenesis. This may possibly be through modulation of prostaglandin-endoperoxide synthase activity (PTGS), as well as through the alteration of cell surface receptor functions, and regulation of gene expression.[31]

LITERATURE FINDINGS

Out of 21 studies in our literature review, nine[32–40] investigated the association of dietary fats with incident colorectal cancer in Asia, Europe, and the Middle-East. Eight[33,39,41–46] studies were population-based prospective cohort studies. Twelve

studies[32,34–38,40,47–51] were case-control studied, and one[52] was a cross-sectional study. Additionally, four studies[39,42–44] investigated the association of dietary fats with colorectal cancer in women, and three studies[35,40,45] investigated the association of dietary fats with colorectal cancer stratified by sex.

Findings from the above-cited literature have been largely inconclusive in determining associations of dietary fats with incident colorectal cancer. The findings are inconclusive regarding the association of total dietary fats with colorectal cancer. Nine[32–34,41–43,47–49] case-control and prospective cohort studies, found total dietary fats to be associated with higher risk of colorectal cancer; however, the findings from only three[35,41,47] these were statistically significant. Four[36,37,44,48] studies found total dietary fats to be inversely associated with risk for colorectal cancer.

Associations of saturated fats with incident colorectal cancer have also been investigated. Four studies[36,38,42,43] found an inverse association of saturated fats intakes with incident colorectal cancer. Three studies[32,33,38] found saturated fats to be associated with higher risk for incident colorectal cancer; the findings from two[32,38] of these were statistically significant, of which one investigated plasma levels of fat.[38]

Eight[33,38,39,42,43,45,49,50] studies found poly-unsaturated fats to be associated with higher risk of incident colorectal cancer, of which the findings from two[45,49] were statistically significant. Four[36,44,45,50] studies found poly-unsaturated fats to be inversely associated with incident colorectal cancer. However, marine omega-3 poly-unsaturated fats were found to be inversely associated with risk for colorectal cancer. [45,46]

The literature has been inconsistent with whether mono-unsaturated fats are associated with colorectal cancer. Two studies[36,38] found inverse associations, and three studies[33,38,42] found direct associations.

Three studies investigated an association of trans-fats with colorectal adenoma[52] and cancer.[42,51] Two[51,52] found statistically significant direct associations with colorectal adenoma and cancer, and one study found an inverse association with colorectal cancer.[42]

STUDY PURPOSE

To help clarify whether dietary fat intakes may be associated with incident colorectal cancer risk, we conducted a comprehensive analysis of associations of total dietary fat and of fat sub-types with incident colorectal cancer, overall and by colorectal sub-sites, in the Iowa Women's Health Study, a large prospective cohort of older, white women.

CHAPTER II

MANUSCRIPT

ABSTRACT

Associations of Dietary Fats with Incident Colorectal Cancer in the Iowa Women's Health Study
By, Muhammad Thuneibat

The associations of dietary fats with incident colorectal cancer (CRC) across previous studies have been inconsistent. Certain types of dietary fats are proposed to increase CRC risk through pro-inflammatory mechanisms and stimulating the secretion of bile acids, while others are proposed to decrease risk. To address the inconsistency, we investigated associations of intakes of total fats, animal fats, vegetable fats, saturated fats, polyunsaturated fats, monounsaturated fats, and trans-fats with incident CRC in the prospective Iowa Women's Health Study. Of the 35,221, 55-69-year-old women who were cancer-free at baseline in 1986, 1,731 developed incident CRC during follow-up through 2012. Diet was assessed using a Willett semi-quantitative food frequency questionnaire. Fat intakes were adjusted for energy intakes using the residual method. Fat intake residuals were categorized into quintiles, and associations estimated using multivariable Cox proportional hazards regression models. For those in the highest relative to the lowest total fat quintiles, the adjusted hazard ratios and 95% confidence intervals for overall, proximal, and distal CRC were 0.95 (0.77 – 1.10; P_{trend} = 0.35), 0.86 (0.67 – 1.09; P_{trend} = 0.22), and 1.06 (0.81 – 1.39; P_{trend} = 0.92), respectively. The estimated associations of the various fat subtypes with CRC were similarly close to null. Our findings suggest that dietary fats may not be associated with risk for incident colorectal cancer among older Iowa women.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States and the third most common type of cancer diagnosed in men and women in the country. In 2019, it is estimated that 101,420 incident cases of colon cancer, and 44,180 incident cases of rectal cancer occurred.[1] Additionally, only 2 in 3 individuals in the United States undergo CRC screening,[2] reinforcing the vital importance of primary prevention.

Migration and temporal trend studies suggest that CRC can be largely determined by lifestyle and dietary habits.[53] Dietary fats are hypothesized to increase CRC risk by stimulating the secretion of bile acids. Bile acids can damage the colonic mucosa, DNA structure, and stimulate the regeneration of the epithelium, leading to an increased risk of an endogenous mutation.[19–22] Moreover, dietary fats can influence risk for CRC through involvement in changes in the fatty acid composition of membranes, altered immunologic response, and insulin resistance.[25]

Previous animal and ecological studies suggested a strong positive association of dietary fat intake with incident colorectal cancer risk.[54–58] However, the findings across previous epidemiological studies have been inconsistent. Two meta-analyses that evaluated 31 prospective cohort studies found no association of dietary fat intake with colorectal cancer risk.[59,60]

Among thirteen[16–27] epidemiologic studies that investigated a total dietary fat-incident CRC association, nine[32–34,41–43,47–49] observed a weak positive association, and four[36,37,44,48] found inverse associations. A positive association of saturated fat intake with

risk of colorectal cancer was observed in three studies,[32,33,38] whereas four studies[36,38,42,43] observed inverse associations. Of eight studies,[33,38,39,42,43,45,49,50] two[45,49] observed statistically significant direct associations of polyunsaturated fat intake with incident CRC. Four other studies[36,44,45,50] observed an inverse association. Of five studies[19,22,25,28] that investigated an association of monounsaturated fat intake with incident CRC, three[33,38,42] found a weak positive association, and two[36,38] inverse associations. One study[32] found strong evidence for a positive association of trans fat intake with incident colorectal cancer, while two other studies[42,61] observed null to weak inverse associations.

To help clarify whether dietary fat intakes may be associated with incident colorectal cancer risk, we conducted a comprehensive analysis of associations of total dietary fat and of fat sub-types with incident colorectal cancer, overall and by sub-sites, in a large prospective cohort of older, white women in the Iowa Women's Health Study.

MATERIALS AND METHODS

Study Population and Design

The Iowa Women's Health Study (IWHS), was established in 1986, as a population-based prospective cohort study. As described previously[62], the 1985 Iowa Driver's License List was used to identify women from Iowa aged 55-69 years old. A total of 98,030 women was randomly approached and selected, of those selected, 41,837 were eligible, gave consent, and were enrolled in the study. The original study was approved by the University of Minnesota Institutional Review Board (IRB), and the Emory University's IRB

also approved the present analysis. Participants completed a survey at baseline to provide information on demographics, family history of cancer, medical history, lifestyle, and dietary data. Five follow-up surveys were conducted in the years 1987, 1989, 1992, 1997, and 2004[63].

Dietary Assessment

Diet and nutritional supplement intakes were assessed using a self-administered, 127-item modified semi-quantitative Willett food frequency questionnaire (FFQ). The validity and reliability of the questionnaire in the study population was previously reported.[64] A commonly used portion size was specified for each food item, and nine possible frequency-of-consumption responses ranged from "never or less than once per month" to "6+ per day". Diet was reassessed in 2004, however, only 68.3% of the participants remained alive.

Outcome Assessment

By 2012, 1,731 incident CRC cases (International Classification of Diseases for Oncology codes (ICD-O-3) 18.0 – 18.9, 19.9 and 20.9) were identified via linkage to the State Health Registry of Iowa. The registry is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program[65]. Deaths were ascertained via the State Health Registry of Iowa and the National Death Index.[63]

Statistical Analysis

For analysis, we excluded participants with self-reported history of cancer, expect non-melanoma skin cancer, at baseline. We also excluded from analysis participants who did not answer ≥ 30 of their FFQ questions and/or if they reported an implausible total energy intakes (< 600 or > 5000 kcal/day). The final analysis sample size was 35,221.

Due to the high correlation between total energy and total dietary fat intakes (Pearson r = 0.90), we adjusted fat intakes for energy using the residual method[66]. Briefly, we used the residuals from linear regression models of total dietary fat (dependent variable) with total energy intake (independent variable) to represent total fat intake. This process yielded zero correlation of the residuals with total energy intake. The residuals were then categorized into quintiles. The process was repeated for individual types of dietary fat (animal fats, vegetable fats, saturated fats, polyunsaturated fats, monounsaturated fats, and trans fats).

Follow-up time was calculated for colorectal cancer cases as the time from the date of completion of the baseline questionnaire until the date of diagnosis. For non-cases the time was calculated from the date of completion of the baseline questionnaire until 1) date of death occurring in Iowa, 2) date when the participant moved out of Iowa if known, 3) the midpoint date between the last contact in Iowa and the first known date of residence outside of Iowa, 4) the midpoint date between the last contact in Iowa and the end of follow-up if the study participant moved from Iowa at an unknown date, 5) the midpoint between the last contact in Iowa and the death date if the death occurred

outside Iowa, or 6) the end of study follow-up (December 31st, 2012), whichever was earliest.

The characteristics of the participants at baseline were compared using chi-square tests for categorical variables and general linear models for continuous variables (transformed when indicated to meet normality assumptions). Cox proportional hazards regression models were used to calculate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) to estimate the associations of dietary fats with incident colorectal cancer. Trend tests were conducted using the median values of each fat residual quintile.

Potential confounders were selected based on biological plausibility and previous literature. Variables considered as potential confounders were: age (years; continuous), family history of colorectal cancer in a first-degree relative (yes/no), education (1-8 years/ 9-12 years/ high school graduate/ vocational education/ some college/ college graduate/ graduate school), body mass index ([weight in kg] / [height in meters]^2, continuous), physical activity (low/medium/high), smoking status (never/past/current), alcohol intake (gm/day, continuous), diabetes status (yes/no/not sure), hormone replacement (never/past/current), total energy intake (kcal/day, continuous), total calcium intake (mg/day, continuous), total vitamin D intake (IU/day, continuous), total tocopherol intake (mg/day, continuous), processed meat intake (servings/week, continuous), red meat intake (servings/week, continuous), total folate intake (mg/day, continuous), dietary fiber intake (gm/day), total fruit intake (servings/week, continuous), and total vegetable intake (servings/week, continuous). For models to investigate fat sub-types, we also

considered the following variables as potential confounders: animal fats (% energy, continuous) for vegetable fat models, vegetable fats (% energy, continuous) for animal fat models, and saturated fats (% energy, continuous), polyunsaturated fats (% energy, continuous), monounsaturated fats (% energy, continuous), and trans-fats (% energy, continuous) for all other fat sub-type models. The covariates for each final model are shown in the Tables' footnotes.

Potential effect modification was assessed by conducting analyses stratified by age (median age: < 61/≥ 61 yrs.), BMI (< 25/ ≥ 25 kg/m^2), family history of colorectal cancer in a first-degree relative (yes/no), post-menopausal hormone therapy (never/ever), education (high school graduate or less vs. more), and smoking status (ever/never), as well as the following dietary intakes dichotomized based on the median intakes in the analytic population at baseline: total energy, total calcium, total fruit, and total vegetables.

We also assessed associations of the exposure variables with cancer at colorectal sub-sites, including proximal colon (cecum through the transverse colon; ICD-O-3 codes 18.0 – 18.4), distal colon cancer (splenic flexure through sigmoid colon; ICD-O-3 codes 18.5 – 18.7), colon cancer, recto-sigmoid junction/rectal cancer (ICD-O-3 codes 19.9 and 20.9), and distal colon cancer/rectal cancer.

To assess for the potential influence of pre-morbid health conditions, we conducted sensitivity analyses in which we excluded CRC cases or deaths that occurred within 1, 2, and 6 years of follow up.

All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, North Carolina). A two-sided *P* value ≤ 0.05 or a 95% CI that did not include 1.0 were considered statistically significant.

RESULTS

Selected baseline characteristics of the study population are summarized in Table 1. At baseline, the average age was 62 years, 99% were white, and 3% reported a history of colorectal cancer in a first-degree relative. Participants in the higher quintiles relative to those in the lower quintiles of the residuals of total dietary fat intake, on average, had a higher BMI, were less likely to be physically active, were more likely to smoke, and consumed less alcohol. They also, on average, consumed more dietary fats as a percentage of total energy intake, more processed and red meats, and less fruits and vegetables.

The estimated associations of total sub-types of fats with incident colorectal cancer are presented in Table 2. All estimate associations were close to null and not statistically significant. The findings furthest from the null were those for animal and polyunsaturated fats. For those in the highest relative to the lowest energy-adjusted quintiles of animal fat and polyunsaturated fat intakes, the HRs were 0.88 (95% CI, 0.72 – 1.08; P_{trend} 0.69) the and 0.89 (95% CI, 0.72 – 1.10; P_{trend} 0.83), respectively.

The estimated adjusted associations of total fat with colorectal cancer according to selected participant characteristics are presented in Table 3. We observed no clear differences in the total fat-CRC association across categories of age, family history of

colorectal cancer in a first degree relative, education, smoking status, BMI, post-menopausal hormone therapy use, total energy intake, total calcium intake, total fruit intake, and total vegetable intake.

The estimated associations of energy-adjusted total fat and fat sub-types with proximal colon cancer and distal colon cancer are shown in Table 4. We found no substantial or consistent patterns for differences in fat-CRC associations by colorectal sub-site.

In sensitivity analyses, exclusion of participants who died or were diagnosed with CRC within 1, 2 or 6 years after enrollment (Supplement Table 1), made no material differences in our findings.

DISCUSSION

Our results suggest that intakes of total dietary fat, fat from different sources (vegetables, animals), nor fat sub-types (saturated, monounsaturated, polyunsaturated, and trans-fats) may not be associated with risk for incident colorectal cancer, overall or for different colorectal sub-sites, among older Iowa women.

Although animal and ecological studies support that dietary fat may increase risk for incident colorectal cancer,[54–58] our results are consistent with those from previous prospective cohort studies[41–44] that suggested that total dietary fat intake is not associated with risk of incident colorectal cancer. Two meta-analyses[59,60] that evaluated 31 prospective cohort studies, found null association of total dietary fat intake with incident colorectal cancer. It is hypothesized that dietary fats increase the CRC risk by

stimulating bile acid secretion. Bile acids can damage the colonic mucosa, DNA structure, and stimulate the regeneration of the epithelium, leading to an increased risk of an endogenous mutation.[19–22] Additionally, dietary fats are thought to influence risk for CRC involvement via changes in the fatty acid composition of membranes, altered immunologic response, and insulin resistance.[25] Dietary fats also increase the level of energy intake, which is thought to increase CRC risk.[67] However, despite the strong plausibility, as noted above, the collective results from prospective cohort studies do not support an association of fats with CRC that is detectable using current dietary measurement methods.

We observed no substantial or statistically significant association of animal fats with CRC, although there was a pattern consistent with a very modest inverse association. Fats from animals raised using commercial methods tends to be high in saturated fats, Animal fats have been investigated only a few times in epidemiological studies as a unique analytic variable.[68] Findings from two meta-analyses[60,68] containing 31 large-scale prospective cohort studies found null associations of animal fats with incident colorectal cancer overall and by colorectal sub-sites. This is consistent with four other prospective studies,[25,42,43,69] which found similar null results. However, the Nurses' Health Study found a nearly two-fold higher risk for colon cancer (Q5:Q1 RR 1.89; 95% CI 1.13 – 3.15; P_{trend} = 0.01) among women in the highest relative to the lowest intake quintile. However, the Nurses' Health Study participants[69] were younger (aged 34 – 59 years) than those in most cohort studies, including our own (mean age of 62 years), which raises the possibility that the age of the participants may have modified the association. This is important as a

previous meta-analysis[70] found that age modified the association in women, such that there was higher risk for incident colorectal cancer with higher animal fat intakes among women younger than 50 years of age, but not in those 50 years or older. However, we found no evidence for differential fat-CRC associations by age.

Vegetable fats primarily consist of polyunsaturated and monounsaturated fats. Our results for vegetable fats were similar to those from other prospective cohort studies. Lin et al.[42] found a null vegetable fats-CRC association in the US-based Women's Health Study (n = 37,547).

We also found null associations of saturated fats with incident colorectal cancer overall and with its sub-sites. Our findings are consistent with those from three prospective cohort and one case-cohort study,[33,36,42,43] which observed null to weak associations. However, in a case-cohort study[38] in an Australian population (n = 4,205 participants in the Melbourne Collaborative Cohort Study), a null association for saturated fats was found when using data from a food frequency questionnaire (Q5:Q1 HR 0.93; 95% CI 0.66 – 1.32; P_{trend} = 0.81), but statistically significant positive association was found when using data obtained via measurements of plasma-phospholipid fatty acids (PPL) (Q5:Q1 HR 1.53; 95% CI 1.05 -2.22; P_{trend} = 0.005). A possible explanation for the difference in findings may be that PPL measurements avoid certain problems inherent in food frequency questionnaires. However, the interpretation of the results using PPL are complicated by endogenous production of various fatty acids in biological materials that may not be correlated with dietary fat intake.[71]

Our results suggested the possibility of a weak inverse association of polyunsaturated fat intake with risk of incident colorectal cancer overall (Q5:Q1 HR 0.89; 95% CI 0.72 – 1.10; P_{trend} = 0.83). This is inconsistent with eight case-control and prospective cohort epidemiological studies[33,38,39,42,43,45,49,50] that observed positive associations of polyunsaturated fats with incident colorectal cancer. However, four other epidemiological studies[36,44,45,50] observed an inverse association. Many of these studies were either small-scale retrospective case-control studies or investigated the associations of polyunsaturated fats as omega-3 and omega-6 fatty acids separately. Polyunsaturated fats are composed mainly of omega-3 and omega-6 fatty acids. These fatty acids have different effects on tumorigenesis, related to enzymatic competition.[72,73] Omega-3 fatty acids are thought to decrease the risk of colorectal cancer by suppressing tumor growth and angiogenesis through modulating prostaglandin-endoperoxide synthase activity (PTGS), and through altering cell surface receptor functions and regulating of gene expression[31]. Omega-6 fatty acids have been hypothesized to increase risk of incident colorectal cancer.[74] In our study, considering total polyunsaturated fats, rather than omega-3 and omega-6 fatty acids separately, may have yielded an association close to null.

Our results also suggested a null association of monounsaturated fats with incident colorectal cancer, overall and with colorectal sub-sites. This is consistent with the findings from four previous prospective cohort and case-cohort large-scale studies[33,36,38,42] in the United States, United Kingdom, Australia, and Finland.

Trans-fats are a type of unsaturated fats that are artificially produced by partial hydrogenation. The proposed mechanism by which trans-fat consumption may increase risk for colorectal adenomas is via altering the concentration of bile acids normally found in the colon.[25,28–30] increasing the amount of secondary bile acids, which can result in increased irritation of the colonic mucosa, increasing oxidative stress[26] and inflammation.[27] In our study, we found null associations of trans-fats with incident colorectal cancer overall and with colorectal cancer sub-sites. This is consistent with results found in large-scale prospective cohort studies.[42,61] Limburg et al.[61] investigated the association of trans-fats with incident colorectal cancer in the Iowa Women's Health study (n = 35,216) in 2008, finding a null association (Q4:Q1 RR 1.12; 95% CI 0.96 – 1.32; P_{trend} = 0.40). However, two small-scale case-control studies[51,75] found statistically significant positive associations of trans-fats with incident colon cancer and distal colon cancer. Vinikoor et al.[51] investigated an association of trans-fat intake with incident distal colon cancer among Caucasian and African-American North Carolina residents (n = 1,908) and found a statistically significant direct association among the Caucasians (Q4:Q1 OR 1.45; 95% CI 1.04 – 2.03; P_{trend} = 0.008). Slattery et al.[75], in a population from Utah, Northern California, and Minnesota (n = 4,403), investigated an association of trans-fats with colon cancer, adjusted for aspirin and nonsteroidal anti-inflammatory drug (NSAID) use, and found a statistically significant positive association among women (Q5:Q1 OR 1.50; 95% CI 1.10 – 2.00; P_{trend} = 0.04), and null association among men (Q5:Q1 OR 1.20; 95% CI 0.90 – 1.70; P_{trend} = 0.34). Aspirin and other NSAIDs are thought to decrease risk of colorectal cancer by acting as cyclooxygenase 1 and 2 (COX1 and COX2) inhibitors.

COX1 and COX2 inhibitors typically convert trans-fats into prostaglandins.[76] Prostaglandins can decrease colonic motility while increasing cell proliferation.[77,78] In our study, data on the use of aspirin and NSAIDs were not collected until the 1992 follow-up. Our analysis included only baseline data from 1986. It is possible that not being able to adjust for NSAID use may have contributed to our null results.

Our study had several strengths, including prospective study design, large sample size, and the large number and complete ascertainment of colorectal cancer cases, long follow-up duration, and the collection and assessment of many potential effect modifying/confounding risk factors. Our study also provides needed data on associations of fat intakes with cancers of different colorectal sub-sites.

Limitations included that diet was assessed only at baseline and the general limitations of food frequency questionnaires (e.g., recall error, limited food choices), both of which could have attenuated our results. Also, we had no information on colorectal cancer screening, which also could have attenuated our results. This is because if a participant undergoes CRC screening and has a colorectal adenoma removed, they are unlikely to get CRC, which can result in misclassifying the participant. Finally, our population was essentially all older mid-western white women. This had two possible limitations. First, our populations' exposures may have been relatively homogeneous, which would have attenuated associations. Second, the generalizability of our results to men and other races may be limited.

In conclusion, our results taken together with previous literature, suggest that dietary fat alone may not be substantially associated with risk for colorectal cancer, but

do not rule out that fat intakes may contribute modestly to risk as part of larger dietary patterns.

TABLES

Table 1. Selected baseline characteristics of the participants according to quintiles of energy-adjusted total dietary fat in the Iowa Women's Health Study (n = 35,221), 1986 – 2012

Characteristics[a]	Total fat[b] quintiles 1 (n = 7,044)	2 (n = 7,044)	3 (n = 7,045)	4 (n = 7,044)	5 (n = 7,044)	P[c]
Demographics						
Age, years	61.9 (4.3)	61.6 (4.2)	61.6 (4.2)	61.3 (4.2)	61.1 (4.1)	< 0.0001
White, %	98.6	99.1	99.5	99.4	99.4	< 0.0001
First degree relative with colorectal cancer, %	2.7	3.1	3.2	3.0	3.5	0.19
College graduate or higher, %	15.1	13.8	13.6	12.3	9.9	< 0.0001
Lifestyle factors						
Body mass index, kg/m^2	26.4 (4.8)	26.8 (5.0)	26.9 (5.0)	27.1 (5.1)	27.4 (5.4)	< 0.0001
Height, meters	1.60 (0.06)	1.60 (0.06)	1.60 (0.06)	1.60 (0.06)	1.60 (0.06)	0.04
Physical activity, %	-	-	-	-	-	<0.0001
Moderate	27.2	29.0	28.6	27.9	25.0	
High	32.0	28.0	24.7	21.5	18.8	
Current smokers, %	14.2	12.7	13.6	15.00	19.2	< 0.0001
Alcohol, gm/day	5.5 (12.6)	4.3 (9.4)	3.6 (7.9)	3.0 (6.7)	2.3 (5.5)	< 0.0001
Current or previous PHT, %	39.6	39.7	39.0	37.9	37.7	0.10
Diabetes, %	5.5	5.4	5.5	5.7	7.4	< 0.0001
Dietary intakes						
Total energy, kcal/day	1,762 (884)	1,799 (627)	1,819 (536)	1,820 (466)	1,793 (400)	< 0.0001
Total carbohydrates, % total energy	56.2 (7.7)	51.7 (5.7)	48.9 (5.0)	46.1 (4.6)	40.9 (5.5)	< 0.0001
Total proteins, % total energy	17.6 (3.8)	18.0 (3.2)	18.1 (3.1)	18.2 (2.9)	18.6 (3.1)	< 0.0001
Total fat, % total energy	26.8 (4.3)	31.2 (2.7)	33.9 (2.2)	36.6 (2.0)	41.4 (3.2)	< 0.0001
Animal fats, % total energy	15.3 (4.1)	18.0 (4.0)	19.8 (4.2)	21.7 (4.5)	25.1 (5.9)	< 0.0001
Vegetable fats, % total energy	11.5 (3.6)	13.2 (3.7)	14.1 (4.0)	15.0 (4.3)	16.3 (5.4)	< 0.0001
Saturated fats, % total energy	9.3 (1.9)	10.8 (1.6)	11.8 (1.6)	12.8 (1.7)	14.7 (2.3)	< 0.0001
Mono-unsaturated fats, % total energy	9.9 (1.9)	11.7 (1.3)	12.9 (1.1)	14.0 (1.1)	16.0 (1.6)	< 0.0001
Poly-unsaturated fats, % total energy	5.1 (1.3)	5.7 (1.3)	6.1 (1.3)	6.4 (1.5)	7.0 (1.9)	< 0.0001
Trans fats, % total energy	1.3 (0.5)	1.5 (0.5)	1.7 (0.5)	1.8 (0.5)	2.1 (0.6)	< 0.0001
Cholesterol, mg/day	229 (171)	258 (125)	275 (113)	292 (113)	312 (120)	< 0.0001
Total meat, servings/week	11.2 (8.4)	12.7 (6.5)	13.6 (5.9)	14.5 (5.8)	15.9 (6.6)	< 0.0001
Processed meats, servings/week	0.4 (1.1)	0.6 (1.2)	0.7 (1.3)	0.9 (1.4)	1.1 (1.8)	< 0.0001
Red meat, servings/week	4.0 (4.0)	5.2 (3.8)	5.9 (3.5)	6.6 (3.5)	7.8 (4.1)	< 0.0001
Total fruit, servings/week	24.2 (16.3)	20.4 (10.3)	18.4 (8.9)	16.3 (7.8)	13.0 (7.0)	< 0.0001
Total vegetables, servings/week	29.1 (21.0)	26.9 (14.2)	26.0 (13.2)	24.5 (11.6)	21.9 (10.8)	< 0.0001
Dietary fiber, gm/day	22.5 (11.5)	21.0 (7.8)	20.0 (6.8)	18.8 (5.8)	16.4 (5.1)	< 0.0001
Total folate, mg/day	485 (287)	457 (250)	432 (235)	406 (224)	362 (219)	< 0.0001
Total calcium, mg/day	1,191 (639)	1,158 (555)	1,120 (537)	1,052 (503)	958 (497)	< 0.0001
Total vitamin D, IU/day	452 (340)	443 (318)	420 (300)	392 (287)	353 (283)	< 0.0001
Total tocopherols, mg/day	88.4 (158.1)	87.1 (158.1)	79.0 (147.0)	75.6 (141.8)	76.3 (142.9)	< 0.0001

Abbreviations: PHT, postmenopausal hormone therapy.

[a]Continuous variables are presented as means (standard deviations); categorical variables are presented as percentages.

[b]Total fat was energy adjusted using the residuals method, and then categorized according to quintiles.

[c]P values from general linear models for continuous variables (transformed by the natural logarithm when needed to improve normality) and the chi-square test for categorical variables.

Table 2. Associations of total dietary fat and its subtypes with incident colorectal cancer among the Iowa Women's Health Study participants (n = 35,221), 1986 – 2012

	Quintiles								p for trend[a]
	1 (n = 7,044)	2 (n = 7,044)		3 (n = 7,045)		4 (n = 7,044)		5 (n = 7,044)	
Total Fat									
Person-Years	129,068	132,823		133,550		134,543		132,697	
No. of Cases	346	312		360		361		352	
Unadjusted HR, 95% CI	1.0 (ref)	0.87	(0.75 - 1.02)	1.0	(0.86 - 1.16)	1.0	(0.86 - 1.15)	0.96	(0.85 - 1.14)	0.34
Minimally adjusted HR, 95% CI[b]	1.0 (ref)	0.87	(0.75 - 1.02)	1.03	(0.88 - 1.19)	1.02	(0.88 - 1.19)	1.04	(0.90 - 1.21)	0.16
Adjusted HR, 95% CI[c]	1.0 (ref)	0.85	(0.73 – 1.00)	0.96	(0.82 - 1.13)	0.93	(0.79 - 1.10)	0.92	(0.77 - 1.10)	0.35
Saturated fats									
Person-Years	129,635	131,986		135,211		133,925		131,924	
No. of Cases	335	369		331		348		348	
Unadjusted HR, 95% CI	1.0 (ref)	1.08	(0.93 - 1.25)	0.94	(0.81 - 1.10)	1.0	(0.86 -1.16)	1.02	(0.88 - 1.18)	0.52
Minimally Adjusted HR, 95% CI[b]	1.0 (ref)	1.09	(0.94 - 1.26)	0.97	(0.83 - 1.13)	1.04	(0.89 - 1.20)	1.07	(0.92 - 1.25)	0.54
Adjusted HR, 95% CI[d]	1.0 (ref)	1.04	(0.89 - 1.23)	0.88	(0.74 -1.05)	0.92	(0.76 - 1.12)	0.89	(0.71 - 1.13)	0.28
Poly-unsaturated fats									
Person-Years	130,522	132,712		133,161		133,523		132,762	
No. of Cases	347	350		347		344		343	
Unadjusted HR, 95% CI	1.0 (ref)	0.99	(0.85 - 1.15)	0.98	(0.84 - 1.13)	0.97	(0.83 - 1.12)	0.97	(0.84 - 1.13)	0.99
Minimally Adjusted HR, 95% CI[b]	1.0 (ref)	0.98	(0.85 - 1.14)	0.98	(0.84 - 1.14)	0.96	(0.82 - 1.11)	0.99	(0.85 - 1.15)	0.99
Adjusted HR, 95% CI[d]	1.0 (ref)	0.96	(0.82 -1.12)	0.94	(0.79 - 1.11)	0.91	(0.76 - 1.09)	0.89	(0.72 - 1.10)	0.83
Mono-unsaturated fats									
Person-Years	129,144	132,711		132,722		134,336		133,769	
No. of Cases	337	317		351		366		360	
Unadjusted HR, 95% CI	1.0 (ref)	0.91	(0.78 - 1.06)	1.01	(0.87 - 1.17)	1.04	(0.90 - 1.20)	1.03	(0.89 - 1.19)	0.47
Minimally Adjusted HR, 95% CI[b]	1.0 (ref)	0.91	(0.78 - 1.06)	1.04	(0.89 - 1.21)	1.07	(0.92 - 1.24)	1.08	(0.93 - 1.25)	0.2
Adjusted HR, 95% CI[d]	1.0 (ref)	0.87	(0.74 - 1.04)	0.96	(0.80 - 1.15)	0.93	(0.76 - 1.15)	0.90	(0.70 - 1.16)	0.58
Trans fats									
Person-Years	129,284	131,216		133,168		134,752		134,261	
No. of Cases	324	333		352		369		353	
Unadjusted HR, 95% CI	1.0 (ref)	1.01	(0.87 - 1.18)	1.05	(0.90 - 1.22)	1.09	(0.94 - 1.26)	1.04	(0.90 - 1.21)	0.82
Minimally Adjusted HR, 95% CI[b]	1.0 (ref)	0.98	(0.84 - 1.15)	1.05	(0.90 - 1.22)	1.09	(0.93 - 1.26)	1.04	(0.90 - 1.22)	0.72
Adjusted HR, 95% CI[d]	1.0 (ref)	0.92	(0.78 - 1.08)	0.95	(0.81 - 1.13)	1.01	(0.84 - 1.20)	0.91	(0.74 - 1.12)	0.63
Animal fats									
Person-Years	130,210	132,160		133,960		133,957		132,394	
No. of Cases	348	343		347		344		349	
Unadjusted HR, 95% CI	1.0 (ref)	0.97	(0.83 - 1.12)	0.97	(0.83 - 1.12)	0.96	(0.82 - 1.11)	0.98	(0.85 - 1.14)	0.98
Minimally Adjusted HR, 95% CI[b]	1.0 (ref)	1.0	(0.86 - 1.16)	1.0	(0.86 - 1.16)	1.0	(0.86 - 1.16)	1.05	(0.90 - 1.22)	0.96
Adjusted HR, 95% CI[e]	1.0 (ref)	0.97	(0.83 - 1.13)	0.93	(0.79 - 1.09)	0.89	(0.75 - 1.06)	0.88	(0.72 - 1.08)	0.69

	Quintiles									p for trend[a]
	1 (n = 7,044)	**2 (n = 7,044)**		**3 (n = 7,045)**		**4 (n = 7,044)**		**5 (n = 7,044)**		
Vegetable fats										
Person-Years	130,011	133,365		133,483		132,722		133,100		
No. of Cases	348	351		319		362		351		
Unadjusted HR, 95% CI	1.0 (ref)	0.98	(0.84 - 1.14)	0.89	(0.76 - 1.03)	1.02	(0.88 - 1.18)	0.98	(0.85 - 1.14)	0.45
Minimally Adjusted HR, 95% CI[b]	1.0 (ref)	0.97	(0.84 -1.13)	0.88	(0.75 - 1.02)	1.00	(0.87 - 1.17)	0.98	(0.84 - 1.14)	0.41
Adjusted HR, 95% CI[f]	1.0 (ref)	0.99	(0.84 - 1.15)	0.88	(0.75 - 1.04)	1.01	(0.86 - 1.19)	0.97	(0.81 - 1.15)	0.44

Abbreviations: CI, confidence interval; HR, hazards ratio; PHT, post-menopausal hormone therapy, ref, reference category

[a]P for trend calculated using medians of each quintile.

[b]Fats adjusted for energy using the residual method; model covariates included age, first degree relative with colorectal cancer, total energy intake.

[c] Fats adjusted for energy using the residual method; model covariates included age, first degree relative with colorectal cancer, education, BMI, physical activity, smoking status, alcohol intake, diabetes status, PHT use, total energy intake, dietary fiber intake, total calcium intake, total vitamin D intake, total tocopherols intake, red meat intake, processed meat intake, total folate intake, total fruit intake and total vegetable intake.

[d]Adjusted for variables in footnote c plus % energy from saturated fats, % energy from mono-unsaturated fats, % energy from poly-unsaturated fats, and % energy from trans fats.

[e]Adjusted for variables in footnote c plus % energy from vegetable fats.

[f]Adjusted for variables in footnote c plus % energy from animal fats.

Table 3. Multivariable-adjusted associations of total dietary fat with incident colorectal cancer according to categories of selected participant characteristics; the Iowa Women's Health Study (n = 35,221), 1986 - 2012

	Categories									p for trend[a]
	1	2		3		4		5		
Age										
< 61 Y										
No. of Cases	118	113		128		146		143		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.82	(0.62 - 1.07)	0.89	(0.69 - 1.17)	0.95	(0.73 - 1.24)	0.90	(0.67 - 1.20)	0.63
≥ 61 Y										
No. of Cases	228	199		232		215		209		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.88	(0.72 - 1.08)	1.02	(0.84 - 1.24)	0.92	(0.75 - 1.14)	0.94	(0.75 - 1.19)	0.60
Body mass index										
Normal and underweight										
No. of Cases	128	118		135		116		131		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.95	(0.74 - 1.24)	1.08	(0.83 - 1.40)	0.96	(0.72 - 1.27)	1.11	(0.82 - 1.49)	0.74
Overweight and obese										
No. of Cases	218	194		225		245		221		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.80	(0.65 - 0.97)	0.91	(0.75 - 1.11)	0.91	(0.75 - 1.12)	0.83	(0.67 - 1.04)	0.21
Family History of CRC*										
No History										
No. of Cases	325	289		346		345		331		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.85	(0.72 – 1.00)	0.98	(0.83 - 1.15)	0.94	(0.80 - 1.11)	0.91	(0.76 - 1.09)	0.29
Yes History										
No. of Cases	13	13		10		8		17		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.94	(0.43 – 2.05)	0.69	(0.29 - 1.63)	0.62	(0.24 - 1.58)	1.19	(0.49 - 2.87)	0.54
PHT use										
Never										
No. of Cases	235	206		240		215		234		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.86	(0.71 - 1.04)	0.93	(0.77 - 1.13)	0.82	(0.67 - 1.01)	0.87	(0.70 - 1.10)	0.34
Ever										
No. of Cases	111	104		118		144		118		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.84	(0.64 - 1.12)	1.05	(0.79 - 1.38)	1.20	(0.90 - 1.59)	1.06	(0.77 - 1.44)	0.18
Total energy intake										
Low										
No. of Cases	226	179		157		169		170		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.90	(0.74 - 1.11)	0.85	(0.68 - 1.07)	0.94	(0.74 - 1.19)	0.99	(0.76 - 1.29)	0.56
High										
No. of Cases	120	133		203		192		182		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.87	(0.67 - 1.14)	1.23	(0.95 - 1.59)	1.09	(0.82 - 1.43)	1.05	(0.77 - 1.42)	0.06

Total calcium intake										
Low										
No. of Cases	168	170		186		201		240		
Adjusted HR, 95% CI[b]	1.0 (ref)	1.03	(0.82 - 1.28)	1.03	(0.82 - 1.29)	0.97	(0.77 - 1.23)	1.01	(0.79 - 1.29)	0.99
High										
No. of Cases	178	142		174		160		112		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.73	(0.58 - 0.92)	0.96	(0.77 - 1.21)	0.96	(0.76 - 1.23)	0.88	(0.67 - 1.17)	0.07
Total fruit intake										
Low										
No. of Cases	116	136		161		202		256		
Adjusted HR, 95% CI[b]	1.0 (ref)	1.07	(0.82 - 1.38)	1.05	(0.82 - 1.35)	1.01	(0.79 - 1.30)	0.99	(0.77 - 1.28)	0.97
High										
No. of Cases	230	176		199		159		96		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.74	(0.60 - 0.91)	0.93	(0.76 - 1.14)	0.89	(0.71 - 1.11)	0.88	(0.67 - 1.15)	0.07
Total vegetable intake										
Low										
No. of Cases	155	155		166		168		214		
Adjusted HR, 95% CI[b]	1.0 (ref)	1.02	(0.81 - 1.29)	1.02	(0.81 - 1.29)	0.89	(0.70 - 1.14)	0.93	(0.72 - 1.20)	0.75
High										
No. of Cases	191	157		194		193		138		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.72	(0.57 - 0.90)	0.90	(0.72 - 1.12)	0.95	(0.75 - 1.19)	0.89	(0.68 - 1.15)	0.04
Education										
High School Graduate and less										
No. of Cases	207	207		213		223		231		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.93	(0.76 - 1.14)	0.91	(0.74 - 1.12)	0.90	(0.73 - 1.11)	0.91	(0.73 - 1.14)	0.88
Beyond High School										
No. of Cases	139	104		147		137		119		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.73	(0.56 - 0.95)	1.05	(0.82 - 1.35)	0.99	(0.76 - 1.28)	0.94	(0.70 - 1.27)	0.06
Smoking status										
Ever										
No. of Cases	114	103		98		116		129		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.96	(0.73 - 1.27)	0.94	(0.71 - 1.25)	0.98	(0.74 - 1.31)	0.99	(0.73 - 1.34)	0.99
Never										
No. of Cases	229	207		252		237		219		
Adjusted HR, 95% CI[b]	1.0 (ref)	0.80	(0.66 - 0.97)	0.97	(0.80 - 1.18)	0.91	(0.74 - 1.11)	0.88	(0.71 - 1.10)	0.19

Abbreviations: CI, confidence interval; HR, hazards ratio; PHT, post-menopausal hormone therapy, ref, reference category

*History of colorectal cancer in first-degree relative.

[a]P for trend calculated using medians of each quintile.

[b] Total fat adjusted for energy using the residual method; model covariates included age, first degree relative with colorectal cancer, education, BMI, physical activity, smoking status, alcohol intake, diabetes status, PHT use, total energy intake, dietary fiber intake, total calcium intake, total vitamin D intake, total tocopherols intake, red meat intake, processed meat intake, total folate intake, total fruit intake and total vegetable intake.

Table 4. Multivariable-adjusted associations of total and subtypes of dietary fat with incident proximal and distal colorectal cancers among Iowa Women's Health Study participants (n = 35,221), 1986 – 2012

	Colon Sites					
	Proximal[a]			Distal[b]		
Total dietary fat[c]	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
1	193	1.00	Referent	142	1.00	Referent
2	160	0.79	(0.64 - 0.98)	144	0.95	(0.75 - 1.21)
3	196	0.95	(0.77 - 1.18)	152	0.99	(0.77 - 1.26)
4	189	0.85	(0.68 - 1.06)	160	1.05	(0.81 - 1.34)
5	186	0.86	(0.67 - 1.09)	162	1.06	(0.81 - 1.39)
p for trend[d]		*0.22*			*0.92*	
Animal fats[e]						
1	188	1.00	Referent	148	1.00	Referent
2	181	0.92	(0.74 - 1.14)	157	1.10	(0.87 - 1.39)
3	175	0.85	(0.69 - 1.07)	165	1.08	(0.85 - 1.39)
4	174	0.81	(0.63 - 1.03)	155	1.00	(0.76 - 1.30)
5	206	0.90	(0.69 - 1.19)	135	0.89	(0.64 - 1.23)
p for trend[d]		*0.45*			*0.56*	
Vegetable fats[f]						
1	194	1.00	Referent	142	1.00	Referent
2	191	0.98	(0.80 - 1.21)	150	1.00	(0.79 - 1.28)
3	169	0.83	(0.67 - 1.04)	138	0.93	(0.73 - 1.20)
4	193	1.00	(0.81 - 1.25)	162	1.05	(0.82 - 1.35)
5	177	0.90	(0.71 - 1.15)	168	1.08	(0.83 - 1.41)
p for trend[d]		*0.39*			*0.79*	
Saturated fats[g]						
1	186	1.00	Referent	140	1.00	Referent
2	203	1.05	(0.84 - 1.30)	159	1.08	(0.84 -1.37)
3	174	0.85	(0.67 - 1.08)	144	0.90	(0.68 - 1.17)
4	165	0.80	(0.61 - 1.05)	177	1.11	(0.83 - 1.47)
5	196	0.95	(0.69 - 1.30)	140	0.81	(0.57 - 1.15)
p for trend[d]		*0.11*			*0.08*	
Poly-unsaturated fats[g]						
1	188	1.00	Referent	146	1.00	Referent
2	194	1.00	(0.81 - 1.24)	149	0.94	(0.74 - 1.20)
3	182	0.94	(0.75 - 1.19)	149	0.91	(0.70 - 1.17)
4	178	0.91	(0.71 - 1.17)	162	0.95	(0.72 - 1.24)
5	182	0.95	(0.71 - 1.27)	154	0.84	(0.62 - 1.16)
p for trend[d]		*0.94*			*0.84*	
Mono-unsaturated fats[g]						
1	188	1.00	Referent	139	1.00	Referent
2	170	0.87	(0.69 - 1.09)	138	0.89	(0.68 - 1.16)
3	184	0.95	(0.74 - 1.22)	155	0.98	(0.74 - 1.30)
4	192	0.88	(0.66 - 1.17)	162	1.00	(0.73 - 1.37)
5	190	0.88	(0.62 - 1.25)	166	0.98	(0.67 - 1.45)
p for trend[d]		*0.77*			*0.88*	
Trans-fats[g]						
1	179	1.00	Referent	135	1.00	Referent
2	187	0.96	(0.77 - 1.19)	135	0.86	(0.67 - 1.11)
3	179	0.88	(0.69 - 1.11)	162	1.04	(0.80 - 1.33)
4	195	1.00	(0.78 - 1.27)	166	1.03	(0.79 - 1.34)
5	184	0.88	(0.66 - 1.28)	162	0.93	(0.68 - 1.26)
p for trend[d]		*0.67*			*0.51*	

Abbreviations: CI, confidence interval; HR, hazards ratio; PHT, post-menopausal hormone therapy, ref, reference category
[a]Proximal includes cecum, appendix, ascending colon, hepatic flexure and transverse colon.
[b]Distal includes splenic flexure, descending colon, sigmoid colon, rectosigmoid junction and rectum.
[c]Total fat adjusted for energy using the residual method; model covariates included age, first degree relative with colorectal cancer, education, BMI, physical activity, smoking status, alcohol intake, diabetes status, PHT use, total energy intake, dietary fiber intake, total calcium intake, total vitamin D intake, total tocopherols intake, red meat intake, processed meat intake, total folate intake, total fruit intake and total vegetable intake.
[d]P for trend calculated using medians of each quintile.
[e]Animal fat adjusted for energy using the residual method; model covariates included those in footnote c plus % energy vegetable fats.
[f]Vegetable fats adjusted for energy using the residual method; model covariates included those variables in footnote c plus % energy animal fats.
[g]Fats adjusted for energy using the residual method; model covariates included variables in footnote c plus each of the other fat subtypes as % energy.

CHAPTER III

SUMMARY, PUBLIC HEALTH IMPLICATIONS, AND POSSIBLE FUTURE DIRECTIONS

Colorectal cancer is the second cancer-related cause of death in the United States. Our findings combined with those from previous epidemiological studies do not support an association of dietary fats with incident colorectal cancer. However, the biological plausibility for contributions of fats to colorectal carcinogenesis remains strong, and current dietary assessment methods remain somewhat crude. It is possible that the contributions of fats and most other individual dietary constituents to colorectal carcinogenesis are too small to reliably detect using our current dietary assessment methods. A growing trend has been to combine multiple dietary factors into scores (e.g., Mediterranean Diet Score, Evolutionary Concordance Diet Score, Oxidative Balance Score, Dietary Inflammation Index, Health Eating Index, etc.). The findings related to these scores are strong, and suggest that fats contribute to risk as part of overall dietary patterns.

It should also be kept in mind that dietary fats have been associated with other outcomes, such as cardiovascular diseases. Most still regard keeping fat intakes moderate to low intake may be prudent for optimal health.

Given the large international differences in colorectal cancer incidence, and the rapid changes in incidence accompanying migration from low- to high-risk countries, further investigation of associations of dietary fats with incident colorectal cancer is needed among first-generation immigrants and minority populations.

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APPENDIX

Supplement Table 1. Associations of total dietary fat with incident colorectal cancer after excluding participants who died or were diagnosed with colorectal cancer within one, two, and six years of follow-up; the Iowa Women's Health Study, 1986 – 2012

1 Year Validation				**Categories**					**p for trend**
	1 (n = 6,905)	**2 (n = 6,892)**		**3 (n = 6,901)**		**4 (n = 6,928)**		**5 (n = 6,905)**	
Total Fat									
Person-Years	128,968	132,721		133,459		134,470		132,606	
No. of Cases	335	302		344		347		342	
Unadjusted HR, 95% CI	1.0 (ref)	0.87	(0.75 - 1.02)	0.99	(0.85 - 1.15)	0.99	(0.85 - 1.15)	0.99	(0.85 - 1.15)	0.39
Minimally Adjusted HR, 95% CI	1.0 (ref)	0.87	(0.74 - 1.02)	1.00	(0.86 - 1.17)	1.01	(0.86 - 1.17)	1.04	(0.89 - 1.21)	0.20
Adjusted HR, 95% CI	1.0 (ref)	0.85	(0.72 - 1.00)	0.95	(0.81 - 1.11)	0.92	(0.77 - 1.08)	0.92	(0.77 - 1.10)	0.38
2 Year Validation				**Categories**					**p for trend**
	1 (n = 6,800)	**2 (n = 6,790)**		**3 (n = 6,781)**		**4 (n = 6,844)**		**5 (n = 6,810)**	
Total Fat									
Person-Years	128,809	132,561		133,270		134,342		132,460	
No. of Cases	324	290		332		335		327	
Unadjusted HR, 95% CI	1.0 (ref)	0.86	(0.74 - 1.01)	0.98	(0.84 - 1.14)	0.98	(0.84 - 1.15)	0.98	(0.84 - 1.14)	0.37
Minimally Adjusted HR, 95% CI	1.0 (ref)	0.86	(0.74 - 1.01)	1.00	(0.86 - 1.17)	1.01	(0.86 - 1.17)	1.03	(0.88 - 1.20)	0.22
Adjusted HR, 95% CI	1.0 (ref)	0.84	(0.72 - 0.99)	0.94	(0.80 - 1.11)	0.92	(0.77 - 1.09)	0.90	(0.75 - 1.09)	0.36
6 Year Validation				**Categories**					**p for trend**
	1 (n = 6,212)	**2 (n = 6,232)**		**3 (n = 6,259)**		**4 (n = 6,327)**		**5 (n = 6,261)**	
Total Fat									
Person-Years	126,353	130,280		131,070		132,222		130,172	
No. of Cases	260	241		278		285		270	
Unadjusted HR, 95% CI	1.0 (ref)	0.89	(0.74 - 1.06)	1.02	(0.86 - 1.20)	1.03	(0.87 - 1.22)	1.00	(0.84 - 1.18)	0.45
Minimally Adjusted HR, 95% CI	1.0 (ref)	0.90	(0.75 - 1.07)	1.05	(0.88 - 1.24)	1.06	(0.89 - 1.25)	1.05	(0.89 - 1.25)	0.32
Adjusted HR, 95% CI	1.0 (ref)	0.87	(0.72 - 1.04)	0.98	(0.82 - 1.17)	0.96	(0.79 - 1.15)	0.93	(0.76 - 1.14)	0.60

HR, hazard ratio; 95% CI, 95% confidence interval.

[a]P for trend calculated using medians of each quintile.

PHT, post-menopausal hormone therapy

[b]Adjusted for age, first degree relative with colorectal cancer, total energy intake.

[c]Adjusted for age, first degree relative with colorectal cancer, education, BMI, physical activity, smoking status, alcohol intake, diabetes status, PHT use, total energy intake, dietary fiber intake, total calcium intake, total vitamin D intake, total tocopherols intake, red meat intake, processed meat intake, total folate intake, total fruit intake and total vegetable intake.