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Trans Fatty Acid Intake and its Association with Adenomas and Cancers of the Colon and Rectum

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology, School of Public Health.

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ABSTRACT

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(Under the direction of Robert S. Sandler)

Recently, there has been increasing concern about the health effects of *trans* fatty acid consumption, however, little is known about its role in digestive tract neoplasia. The goal of this dissertation was to investigate this relationship.

The association between *trans* fatty acid consumption and colorectal adenomas (present throughout the entire colon and rectum) was investigated using the Diet and Health Study IV, a cross-sectional study conducted between 2001 and 2002. The highest quartile of consumption was associated with an increased prevalence of colorectal adenomas, with an adjusted prevalence odds ratio comparing the highest to the lowest quartile of consumption of 1.86 (95%CI 1.04, 3.33).

The North Carolina Colon Cancer Study I, a case-control study taking place between 1996 and 2000, was utilized to examine the association for colon cancer (located between the cecum and sigmoid colon). No association was seen between *trans* fatty acid consumption and colon cancer among Whites or African Americans. Those in the highest quartile of consumption had an adjusted odds ratio of 1.01 (95%CI 0.69, 1.49) for Whites and 0.99 (95%CI 0.61, 1.62) for African Americans when compared to participants in the lowest quartile.

The North Carolina Colon Cancer Study II was similar to the above study except cases of distal colorectal cancer (present in the sigmoid colon, rectosigmoid, and rectum) were recruited from 2001-2006. An association was seen between *trans* fatty acid consumption and distal colorectal cancer in Whites, giving an adjusted odds ratio of 1.34 (95%CI 0.99, 1.83) for the comparison of the highest quartile of consumption to the lowest. For African Americans this adjusted odds ratio was 0.54 (95%CI 0.28, 1.02).

In sum, the research presented in this dissertation demonstrated that high *trans* fatty acid consumption was positively associated with colorectal adenomas and cancers of the sigmoid colon, rectosigmoid, and rectum (in Whites). No association was present between consumption and cancers of the colon (cecum through sigmoid colon). Although further research needs to be done investigating the relationship for distal colorectal cancer in African Americans, as *trans* fatty acid consumption declines in the United States, rates of colorectal cancer may fall as well.

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LIST OF ABBREVIATIONS

BMI: Body mass index

CI: Confidence interval

DHS IV: Diet and Health Study IV

DHQ: Diet History Questionnaire

DMV: Department of Motor Vehicles

FFQ: Food frequency questionnaire

IQR: Interquartile range

MET: Metabolic equivalents

NCCCS I: North Carolina Colon Cancer Study I

NCCCS II: North Carolina Colon Cancer Study II

NCI: National Cancer Institute

NSAID: Non-steroidal anti-inflammatory drug

OR: Odds ratio

POR: Prevalence odds ratio

WHO: World Health Organization

1. REVIEW OF THE LITERATURE

1.1 SUMMARY

Colorectal cancer is one of the most common cancers in the United States. Diet, a key component of the environment, is a risk factor for colorectal cancer. Total dietary fatty acid has not been demonstrated to be associated with colorectal cancer. It is possible, however, that a specific type of dietary fatty acid is associated with colorectal cancer. In this dissertation I hypothesize that *trans* fatty acid is positively associated with colon and rectal neoplasia. This chapter begins with a review of colorectal cancer. It continues with a discussion of fatty acids and *trans* fatty acids, including postulated biologic mechanisms for the *trans* fatty acid and colorectal cancer/adenoma relationship. This chapter concludes with a review of the current literature examining the association between *trans* fatty acids and colorectal cancer/adenomas and their limitations.

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1.2 BACKGROUND AND SIGNIFICANCE

1.2.1 COLORECTAL CANCER

A. DESCRIPTIVE EPIDEMIOLOGY

Colorectal cancer (hereafter defined as cancer present throughout the entire colon and rectum, unless otherwise specified) is the third most common cancer in the United States. It has the third highest mortality rate, accounting for approximately 10% of all cancer deaths. An estimated 112,340 people were diagnosed with colon cancer and 41,420 people were diagnosed with rectal cancer in the United States in 2007. An estimated 52,180 deaths resulted from colorectal cancer this year (1). Colorectal cancer is diagnosed later in life, with approximately 67% of the diagnoses occurring after age 64. SEER, the Surveillance Epidemiology and End Results Program of the National Cancer Institute, reports an overall 5-year relative survival rate of 64.1% (2).

There is a disparity in both the incidence and mortality rates for colorectal cancer between Whites and African Americans. The colorectal cancer incidence rate for African American men is 70.2/100,000 compared with 63.7/100,000 for White men. The rates for women are 53.5/100,000 and 45.9/100,000, respectively. Among men, the disparity is greater for mortality (33.6 compared to 23.7/100,000) (1).

B. ADENOMA-CARCINOMA SEQUENCE

Colorectal cancer arises from a series of easily recognizable pathological precursor stages, the adenoma-carcinoma sequence. In 1990, Fearon and Vogelstein proposed a

genetic model for colorectal neoplasia (Figure 1.1) (3). They described a series of genetic alterations and postulated how these alterations affected the process of carcinogenesis, starting with the normal epithelium and ending with metastasis. While they proposed this model as the most common order of mutations and tumor development, they noted that it may be the accumulation of changes, and not the order, that is important (3).

Adenomas, the precursor lesions to the majority of colon cancers, are common. Studies done postmortem have found that by age 70, approximately 25-50% of people have at least one colorectal adenoma. About 50% of the people who had an adenoma detected will have a recurrent adenoma in less than 8 years (4). The development of an adenoma is thought to arise after a mutation in the *APC* gene, a tumor suppressor gene found on chromosome 5*q*, which allows for disorderly cell replication, adhesion, and migration (5, 6). This leads to an accumulation of cells creating a small growth that eventually protrudes from the mucosa and is recognizable grossly as a polyp (6).

In order for the adenoma to progress into cancer, there are several additional steps that must occur. Typically, the DNA of the cells must acquire about half a dozen mutations before the tumor becomes cancerous (3, 7). Some of the most significant of these mutations are the activation of oncogenes, like *ras*, and the inactivation of tumor suppressor genes, like *p53* (3, 7, 8). When oncogenes become activated uncontrolled cell growth and replication occur (7). *ras* gene mutations have been found in approximately 50% of colorectal carcinomas and adenomas larger than 1 cm. This same mutation is present in less than 10% of adenomas less than 1 cm in size (3). Tumor suppressor genes have multiple functions including activating DNA repair genes, controlling cellular adhesion, and regulating the cell cycle. In other words, the purpose of the tumor suppressor genes is to slow cell growth, but

since these genes lose their function, they cannot stop replication of the tumor cells (7). When *p53* is working properly, it stops tumor growth; however, it has been found that tumors have a selective growth advantage even when a wild-type *p53* allele is present if the there is a point mutation present in the other *p53* allele. Moreover, loss of this wild-type allele is often associated with the progression from adenoma to cancer (3).

C. SYMPTOMS

In its early stages colorectal cancer causes no symptoms, which is why screening for this cancer is imperative. Once disease progresses, the symptoms will vary depending on the size and location of the tumor. At later stages, common symptoms include: changes in bowel habits, blood in the stool, persistent abdominal discomfort/pain, weight loss, fatigue, and anemia (9, 10).

D. RISK FACTORS FOR COLON AND RECTAL CANCER

Although the majority of studies combine cancers of the colon and rectum, these may be two distinct cancers with different sets of risk factors. For example, a recent publication by researchers working on the European Prospective Investigation Into Cancer and Nutrition study (EPIC) found that waist circumference and waist-hip ratio were associated with the risk of colon cancer but were not associated with the risk of rectal cancer (11). Similarly, researchers of the EPIC study also reported that increased physical activity decreased the risk of colon cancer but had no effect on the risk of rectal cancer (12). The

same trend was reported in a review of physical activity and cancers of the colon and rectum (13). More research differentiating the risk factors for colon and rectal cancer needs to be done.

When searching for risk factors for both colon and rectal cancer combined, much research has been done examining environmental factors. One reason for this is that studies have reported that the rate of disease in individuals who migrate becomes similar to those of their adopted country with increasing duration of residence (14, 15), implying that there is something about the environment of their adopted country that increases their risk of developing disease. Diet is a key part of an individual's environment and has been widely studied in the examination of risk factors for colon and rectal cancer. In addition to the information from migrant studies, examining diet as a risk factor also makes sense, as what we eat affects what is in contact with the mucosal lining of the colon and rectum. Studies of fruits and vegetables consumption have produced inconsistent results in terms of the association with colorectal cancer (5, 10). Alcohol consumption was shown to increase the risk of colorectal cancer but this may be due to its intermediary role in reducing the concentration of folate, as folate has been found to decrease the risk of colorectal cancer in some studies (5, 10). Increased calcium intake is believed to decrease the risk of colorectal cancer (10). Red meat consumption is often thought to be associated with an increased risk of colorectal cancer though it is unclear whether this is due to the consumption of the meat itself or the intake of molecules associated with certain methods employed in cooking the meat (5, 10).

1.2.2 FATTY ACIDS

A. BIOLOGY OF FATTY ACID DIGESTION

Fatty acids include unsaturated fatty acids (which can be in either a *cis*- or *trans*-formation) and saturated fatty acids. While lipases from the tongue begin the digestion process, most digestion and absorption of fat occurs in the small intestine (7, 16). In the small intestine, pancreatic lipases and bile acids (steroid acids produced in the liver and excreted by the gall bladder) begin breaking fatty acids into triglycerides (7, 16). These triglycerides are combined with cholesterol, phospholipids, and other molecules. They are then absorbed from the small intestine and enter into the blood stream (7, 16).

Most of the bile acids used to break down the fatty acids are recycled. They are re-absorbed in the distal small bowel and travel back to the liver in the portal circulation. It is estimated that between one and five percent of bile acids are unabsorbed and enter the colon (16). The colon works to absorb salt and water remaining from the digested food (7, 16, 17). Bacteria present in the colon transform the bile acids into secondary and tertiary bile acids that are mostly excreted in the feces (18-21).

B. EPIDEMIOLOGIC STUDIES OF FATTY ACIDS AND COLORECTAL CANCER

It was thought for some time that dietary fatty acids might increase the risk of colorectal cancer. However, many published studies have shown that there is no clear association between colorectal cancer and dietary fatty acid consumption. In 1997, Howe et al combined the data from thirteen case-control studies of colorectal cancer. They found no

increase in risk of colorectal cancer with increased consumption of total fat intake (22). Another review published in 2002, looked at the case-control studies utilized in Howe et al.'s study as well as another large case-control study that had been published since then. There was again no association between total fat intake and colorectal cancer. In addition, five prospective cohorts examining this association were identified. Only one out of the five studies reported an increase in the risk of colorectal cancer with the increased consumption of total fat. Yet, this increase was attributed to consumption of animal fat (23). Other studies and reviews also confirmed that there was no association between total dietary fat consumption and the risk of colorectal cancer (18, 19, 24-27).

1.2.3 *TRANS* FATTY ACIDS

A. A SPECIFIC FATTY ACID VERSUS TOTAL FAT INTAKE

While fatty acids are not associated with colorectal cancer, it is still possible that a specific type of fatty acid plays a role in increasing the risk of colon and/or rectal adenomas and/or cancer (24). In one study mentioned above, although the researchers found no increased risk of colon cancer with high consumption of overall dietary fat, they did find that women at least 67 years of age had an increased risk in colon cancer if they were in the two highest quintiles for consumption of fat used in food preparation (i.e. the amount of fat used to prepare foods that they ate). This measure of fat from the food preparation may be acting as a proxy for *trans* fatty acid because fats used in frying foods are often high in *trans* fatty acids (27).

B. PRODUCTION OF TRANS FATTY ACIDS

Trans fatty acids occur naturally in small quantities of some foods. The majority of *trans* fatty acids are the result of partial hydrogenation (28). This process began in the early 1900s. The commonly occurring form of unsaturated fatty acids is the *cis*- structure (Figure 1.2). Hydrogenation uses heat and a catalyst to convert the *cis* fatty acid into a *trans* fatty acid (29). This process converts liquids to solids at room temperature. The fatty acid goes from a kinked shape to a more linear one, similar to that of a saturated fatty acid (30). The goal of hydrogenation is to make storage and transportation of oils easier and to increase the shelf-life of foods (28, 29, 31). *Trans* fatty acids are commonly found in shortenings and margarines. They are present in cookies, crackers, fried foods, baked goods, and other processed foods (32).

During the past few decades, research has emerged with findings that *trans* fatty acid consumption may be detrimental to one's health. Studies show that consumption of *trans* fatty acids increases the risk of coronary heart disease (33). It may also increase the risk of type 2 diabetes (34) and has been shown to increase inflammation in women (35).

In response to the public health problem, the Danish government ruled that no oils or fats with greater than 2% industrial produced *trans* fatty acids were allowed to be sold after January 1, 2004 (31). In the United States, activist groups have also taken up the campaign against *trans* fatty acid by suing companies such as Kraft and McDonalds (36). Labeling of *trans* fatty acid content on food items became mandatory as of January 1, 2006 in the United States (37). Yet, this labeling effort may not have had the desired effect on consumers. A study found that the labeling did not affect consumers' views on *trans* fatty acid consumption and disease risk. They state that consumer education is just as important as the

labeling (36). Additional action has been taken in certain localities, such as New York City, where *trans* fatty acids have been banned from use in commercial food outlets (38, 39).

C. POSSIBLE BIOLOGIC MECAHNISMS

There are several plausible mechanisms by which *trans* fatty acids could affect colorectal carcinogenesis:

1) Fat Absorption, Inflammation, and Oxidative Stress

A study done in male rats found that the fat excretion:intake ratio was two times higher for rats given *trans* fatty acids than rats fed only *cis* fatty acids (40). Studies performed in rats have also reported that the type of dietary fat consumed influenced fecal diacylglyercol composition (41) and colonic phospholipid composition (42).

Therefore, it is plausible that the consumption of *trans* fatty acids results in a different concentration and amount of fatty acids than are normally present in the colon. This may cause irritation of the colon and rectum, which results in inflammation and oxidative stress (43). Oxidative stress produces free radicals which can damage DNA and result in mutations like those seen in the adenoma-carcinoma sequence. A higher amount of an oxidative stress marker (urinary 8-iso-PGF(2alpha)) was found in people who consumed *trans* fatty acids when compared to those without *trans* fatty acids in their diet (44). In addition, the Nurses Health Study showed that *trans* fatty acids were associated with systemic inflammation (35). There is some evidence that systemic inflammation, as measured by circulating cytokines, is associated with colorectal cancer (45-47), although the literature is inconsistent.

2) Insulin Resistance

In a study of *trans* fatty acid and insulin sensitivity, rats fed *trans* fatty acid had decreased insulin sensitivity in their adipocytes. In fact, *trans* fatty acids had a greater effect than saturated fatty acids on insulin resistance (48). Little research has been done in humans and inconsistencies are present (34). A few studies found that *trans* fatty acid consumption did not affect insulin resistance in healthy subjects, but insulin resistance was affected by intake of *trans* fatty acid in people with diabetes or insulin resistance (49).

Two studies looking at metabolic syndrome, which includes dyslipidemia, glucose intolerance, insulin resistance, obesity, and hypertension, found that having metabolic syndrome increased the risk of colorectal mortality in men (50). A review of the potential mechanisms for the development of colorectal cancer suggests that increased insulin stimulates cell signaling pathways to increase proliferation, which will favor cells that are defective (such as those with activated oncogenes) (51, 52).

In sum, *trans* fatty acid may increase the risk of colorectal neoplasia by increasing insulin resistance, which can lead to heightened cell proliferation. When oncogenes are activated, cell growth is already upregulated and increased cellular proliferation can further stimulate these mutated cells to replicate resulting in a cancerous growth.

3) Bile Acids, Inflammation, and Oxidative Stress

It is also possible that consumption of *trans* fatty acids leads to an alteration of the composition of bile acids different from what is normally found in the colon. Secondary and tertiary bile acids are known to irritate to the colonic mucosa (18, 19). In addition, some studies have shown that bile acids in the colon are metabolized by bacteria (21, 53),

producing carcinogenic compounds and increasing cellular proliferation. As stated above, colonic irritation and cellular proliferation may increase the risk of colorectal neoplasia.

D. EPIDEMIOLOGIC STUDIES

An ecologic study performed in Europe found a positive correlation between *trans* fatty acid and colon cancer. Unfortunately, because this was an ecologic study, the researchers could not rule out the possibility that *trans* fatty acid was simply acting as a proxy for another factor (54).

After a recent review of the literature, six studies were identified that examined the association between *trans* fatty acid intake and colorectal cancer or adenomas. These are listed in Table 1.1.

Only one study looked solely at colon cancer (28). The researchers divided *trans* fatty acid consumption into quintiles based on the levels of intake in men and women controls. They reported no increase in relative risk for colon cancer in men. There was an increase in the relative risk of colon cancer for women following high consumption of *trans* fatty acid. In addition, the findings were stronger in people at least 67 years of age. As well as examining the risk of colon cancer by sex, the researchers stratified by use of non-steroidal anti-inflammatory drugs (NSAIDs) and by estrogen positivity (which they defined as being either pre-menopausal or on some sort of hormone replacement therapy). They found no association between *trans* fatty acid consumption and colon cancer for individuals taking NSAIDs. Among participants who were not taking NSAIDs, there was a positive association between colon cancer and *trans* fatty acid consumption. Postmenopausal

women who did not take any hormone replacement therapy drugs and were in the highest quartile of *trans* fatty acid consumption had the greatest relative risk among other estrogen negative and all estrogen positive women (28).

Three studies looked at the association between *trans* fatty acids and colorectal cancer (25, 55, 56). One case-control study demonstrated a positive association between *trans* fatty acid consumption and colorectal cancer among women, but no association was detected for men (56). Neither of the other two studies found compelling evidence to show that *trans* fatty acid intake was associated with colorectal cancer (25, 55).

The two studies done to examine the relationship of *trans* fatty acids and colorectal adenomas were performed by McKelvey et al. Though in both papers the researchers found a slight association between colorectal adenomas and high consumption of sweetened baked goods, they concluded that overall there was no association between colorectal adenomas and consumption of *trans* fatty acid (29, 57). Only one of these studies (29) went further to investigate the gram amounts of *trans* fatty acid consumed, but no association was seen.

1.3 LIMITATIONS OF STUDIES CURRENTLY IN THE LITERATURE

While these studies are starting points in the research of the association between *trans* fatty acid and colorectal cancer, there are several points that need to be clarified in future research.

First, in the studies of colorectal adenomas, *trans* fatty acid intake is categorized based on consumption of foods in specific categories. Only one of the studies went further to examine the overall amount of *trans* fatty acid consumed. In that study, because cases and controls were classified based on sigmoidoscopy results, it is possible that cases with adenomas in the proximal colon were misclassified as controls. In addition, if *trans* fatty acids differentially affect the proximal and distal sections of the colon, then results of the studies based on sigmoidoscopy will differ from those investigating adenomas of the entire colon.

Another issue is the control of confounding factors. All six of these studies controlled for potential confounding factors such as age and body mass index (BMI) but control of other potential confounders was more variable (Table 1.1). Also, one study found effect measure modification by sex, use of NSAIDs, and by hormonal status in women (28). While some of the other studies examined if the association between colorectal cancer/adenomas and *trans* fatty acid varied by sex, others did not. None of the other five studies examined NSAID use as a possible effect measure modifier or confounder.

In the United States, there is a disparity in the rates of colorectal cancer between Whites and African Americans. If *trans* fatty acids affect the risk of colorectal cancer and there is differential consumption between Whites and African Americans, part of the

disparity in colorectal cancer rates may be explained. However, none of the studies have included a large population of African Americans about which consumption and risk can be compared with that of Whites.

Finally, as mentioned above, there have been differential effects of risk factors on the occurrence colon and rectal cancers. It may be that *trans* fatty acids affect the colonic mucosa differently than they affect the rectal mucosa. If this is the case, then risk needs to be examined separately for colon and rectal cancers. Only one study examined the risk of colon cancer alone. No studies have been done to look at the risk of rectal cancer and *trans* fatty acid consumption.

1.4 FIGURES AND TABLES

FIGURE 1.1. Fearon and Vogelstein's proposed model for colorectal carcinogenesis (3)

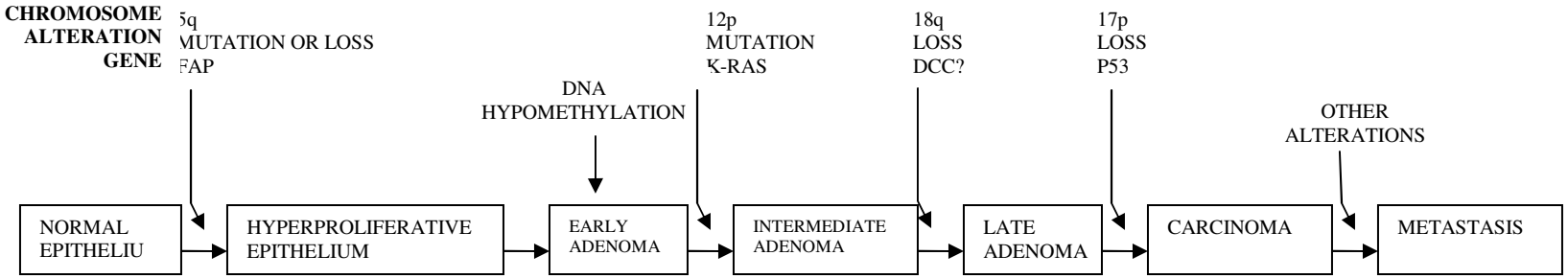

FIGURE 1.2. Chemical bonds structures for fatty acids

Saturated Fatty Acid	Unsaturated Fatty Acid (*cis* formation)	Unsaturated Fatty Acid (*trans* formation)
H H | | ···C--C··· | | H H	H H | | ···C==C···	H | ···C==C··· | H

TABLE 1.1. Literature review of *trans* fatty acid consumption and colon/colorectal cancer and adenoma

Author (Year)	Study Design	Study Population	Exclusions	Exposure	Outcome	Adjusted Covariates	OR (95%CI)	Comments
COLON CANCER								
Slattery (2001)	Case-control	African-Americans, Whites, or Hispanics from Kaiser Permanente Medical Care Programs (CA, UT, MN), aged 30-79, mentally competent to complete the interview N=4403	• Rectal cancer • Familial adenomatous polyposis • Ulcerative colitis • Chron's Disease	Total *trans* fatty acid categorized into quintiles for men and women controls	First primary diagnosis of colon cancer	• Age • BMI • Physical activity • Energy • Dietary fiber • Calcium intake • Estrogen status (women only)	Men: 1.00 1.3(1.0,1.8) 1.3(0.9,1.5) 1.1(0.9,1.5) 1.2(0.9,1.7) p-trend: 0.34 Women: 1.00 1.0(0.7,1.3) 1.1(0.8,1.5) 1.2(0.9,1.6) 1.5(1.1,2.0) p-trend: 0.04	Also looked at OR and trend for *cis* fatty acids Conducted a separate analysis for interaction with NSAIDs and HRT
COLORECTAL CANCER								
Nkondjock (2003)	Case-control	French-Canadians living in a specific region, aged 35-79 (cases were identified from five major teaching hospitals in the area; controls were identified by random digit dialing) N=1070	•No other primary cancer	2-year period before the disease: calorie-adjusted fatty acid was divided into quartiles for men and women controls	Histological diagnosis of colorectal cancer	• Age • Total energy intake • BMI 1 yr prior to diagnosis • History of colorectal cancer in first degree relatives • Marital status • Physical activity since adulthood	Men: 1.00 1.49(0.88,2.55) 0.66(0.36,1.21) 0.88(0.50,1.56) p-trend: 0.336 Women: 1.00 0.68(0.40,1.35) 0.81(0.49,1.35) 1.00(0.61,1.65) p-trend: 0.767	Found sex-specific differences in colorectal cancer risk (most associations found only in women)

Lin (2004)	RCT	Women's Health Study: women health professionals assigned to treatment of either low-dose aspirin or Vitamin E; age>=45 N=37,547	• History of heart disease and/or cancer	Categorized into quintiles based on overall distribution of nutrient intakes in ALL women	Self-report diagnosis of colorectal cancer (verified by medical files)	• Age • Treatment • BMI • Family history of colorectal cancer • History of colorectal polyps • Physical activity • Smoking • Alcohol • HRT • Total energy intake	1.00 0.92(0.59,1.44) 1.08(0.72, 1.69) 0.86(0.55,1.40) 1.30(0.89,2.05) p-trend=0.18	When adjusting for cholesterol and other types of fat, RR of highest quintile became 1.59(0.94,2.70) and p-trend was 0.06; *Trans* fatty acid consumption was not associated with a specific side of the colon (i.e. proximal or distal colon cancer)
Theodoratou (2007)	Case-control	Residents of Scotland aged 16-79 (cases were recruited from patients at surgical units in Scottish Hospitals with adenocarcinmoas; controls were identified from a population-based register)	• Death prior to ascertainment • Too ill to participate •Not able to provide informed consent • Previous diagnosis of colorectal cancer	Diet during the 1-year period before the disease: energy-adjusted fatty acid was divided into quartiles based on the distribution in cases and controls	First diagnosis of colorectal cancer	• Age • Sex • Area of residence • Total energy intake • Family history of colorectal cancer • Total fiber intake • Total alcohol intake • NSAID use	Overall: 1.00 1.28(1.01,1.63) 1.18(0.93,1.50) 1.05(0.82,1.35) p-trend: 0.856 Men: 1.00 1.14(0.84,1.55) 0.99(0.73,1.35) 0.95(0.69,1.32) p-trend: 0.572	Also looked at *trans* mono-fatty acids (results were approximately the same as those for total *trans* fatty acids)

		N=2910				• Smoking status • BMI • Physical activity	Women: 1.00 1.53(1.04,2.25) 1.58(1.06,2.35) 1.28(0.85,1.91) p-trend: 0.230	
COLORECTAL POLYP								
McKelvey (1999)	cross-sectional	English-speaking people aged 50-74 living in Los Angeles area N=1072	•Prior polyps, history of bowel surgery, IBD, cancer, familial polyposis	Foods were grouped based on ingredients since amounts of *trans* fatty acids could not be identified. These groups were: sweetened baked goods; candy bars; oils and condiments; and french fries and chips; Also, used this info and number of servings to estimate a person's *trans* fatty acid intake	Histological diagnosis of colorectal adenomatous polyp through sigmoidoscopy	• Age • Sex • Smoking • BMI • Physical activity • Total energy • Red meat •Vegetables • (Sweetened baked goods - in some analyses)	Overall *trans* fatty acid intake: < 2 grams 1.00 2 to <4 grams 1.0(0.71,1.4) 4 to <6 grams 1.5(0.91-2.5) 6+ grams 1.6(0.82,3.2) Sweetened baked goods: 0-50 calories 1.0 50-100 calories 1.3(0.83-1.9) …300-350 calories 1.9(0.89,3.9) 350+ calories 2.1 (1.3,3.5)	Positive association between sweetened baked goods and adenomas; also positive assoc between total *trans* fatty acid consumption and adenomas

McKelvey (2000)	cross-sectional	People referred to UNC Hospitals for colonoscopy, aged 30-89 N=641	•History of polyposis, colitis, previous bowel surgery, previous adenoma, previous colon cancer, unsatisfactory prep, incomplete exam	Same as above (also, calculated PHVO in frying process by subtracting amount of fat in broiled chicken or fish from the amount of fat in fried chicken or fish)	Diagnosis of at least one adenomatous polyp	• Age • Sex • Smoking • Weight • Height • Physical activity • Total energy • Red meat • Vegetables • Alcohol • Family history	Sweetened baked goods: 0-100 calories 1.0 100-200 calories 1.2(0.70-1.9) 200-300 calories 2.3(1.2,4.6) 300-400 calories 1.3(0.73,2.9) 400+ calories 1.9 (0.95,3.8) Oils and condiments: 0-100 calories 1.0 100-200 calories 1.2(0.77-1.8) 200+ calories 2.4 (1.3,4.2)	

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2. SPECIFIC AIMS AND STUDY HYPOTHESES

Dietary factors play a large role in the risk of colorectal cancer. Although no association has been found between colorectal cancer and total dietary fat, *trans* fatty acid, a particular type of dietary fat, may increase the risk of colorectal cancer. If *trans* fatty acid consumption is a risk factor for colon cancer, rectal cancer, or colorectal adenomas, it would be important to know this for a few reasons. First, advocacy groups working to have *trans* fatty acids removed from foods could utilize this information. Second, consumers could use this information to make educated choices about what they want to eat.

Thus far, very few studies have looked at the risk of colorectal cancer/adenomas and consumption of *trans* fatty acids and most of these studies had limitations. The research performed in this dissertation addressed and accounted for the limitations present in the other studies. It also examined the association for both location of the tumor (colon versus distal colon/rectum) and stage in the carcinogenesis process (adenoma versus cancer). In addition, no prior studies had investigated the consumption patterns and their influence on risk of colon and distal colorectal cancer in a study population with a large number of African Americans.

I hypothesized that increasing consumption of *trans* fatty acids would increase the risk of colon/rectal cancer/adenomas. This study had three specific aims:

1) To determine whether increasing consumption of *trans* fatty acid is associated with increased prevalence of colorectal adenomas (defined as

adenomas present throughout the entire colon and rectum). To accomplish this aim, I utilized the Diet and Health Study IV dataset *(results summarized in Chapter 4)*

2) To determine whether increasing consumption of *trans* fatty acid is associated with colon cancer (defined as cancer present from the cecum through sigmoid colon). To accomplish this aim, I utilized the North Carolina Colon Cancer Study I dataset*(results summarized in Chapter 5).*
3) To determine whether increasing consumption of *trans* fatty acid is associated with distal colorectal cancer (defined as cancers of the sigmoid colon, rectosigmoid, or rectum). To accomplish this aim, I utilized the North Carolina Colon Cancer Study II dataset *(results summarized in Chapter 6).*

3. RESEARCH DESIGN AND METHODS

3.1 OVERVIEW

In order to investigate the above hypotheses, I used the data from three studies. The first aim, examining the relationship between colorectal adenomas and *trans* fatty acid consumption, utilized the data from the Diet and Health Study IV (DHS IV).The second aim, examining the association between colon cancer and *trans* fatty acid intake, was assessed using the North Carolina Colon Cancer Study I (NCCCS I). Finally, the third aim, looking at the relationship between distal colorectal cancer and *trans* fatty acid consumption, was investigated using the North Carolina Colon Cancer Study II (NCCCS II). The study population, data collection, and variable measurement for each of these are described in more detail in the following sections. The analysis of this previously collected data met the guidelines for exclusion from IRB approval (See Appendix).

3.2 STUDY POPULATION

Diet and Health Study IV (DHS IV)

DHS IV recruited consecutive patients undergoing an outpatient colonoscopy at the University of North Carolina Hospitals in Chapel Hill, North Carolina from November 2001 to December 2002. In this study, cases were defined as people who had a colorectal adenoma detected during complete colonoscopy. Eligibility requirements were as follows: aged 30-80 years old, ability to give informed consent, a satisfactory prep for colonoscopy and a complete exam, no previous colonoscopies, not an inpatient, and no history of familial polyposis, colitis, previous colonic resection, or previous colon cancer or polyps. Controls were defined as those patients that had a colonoscopy during this time period but had no adenomas present.

North Carolina Colon Cancer Study (NCCCS)

NCCCS I was a population-based case-control study taking place in central North Carolina. It enrolled subjects from 33 counties, representing urban, suburban, and rural areas of the state.

Cases were identified using the rapid case ascertainment system of the North Carolina Central Cancer Registry. Those patients with a first diagnosis of histologically confirmed invasive adenocarcinoma between October 1996 and September 2000 were classified as potential cases. Additional eligibility requirements were as follows: aged 40-80 years, residence in one of the 33 counties, able to give informed consent, able to complete an interview, had a North Carolina driver's license or identification card issued by the North

Carolina Department of Motor Vehicles (if under the age of 65) , and had no objections from the primary physician in regards to contacting the individual. White cases were under-sampled in order to increase the proportion of non-White cases in the study population.

Controls were selected from two sources. For those under the age of 65, potential controls were identified using the North Carolina Department of Motor Vehicles records. For those 65 years and older, records from the Center for Medicare and Medicaid Services (previously the Health Care Financing Administration) were used to ascertain a control group. Potential controls were contacted in a manner similar to that of the cases. Controls were matched to cases using randomized recruitment strategies (1). This method of matching works well for many reasons, including the concurrent recruitment of cases and controls into the study (1). In the NCCCS I, recruitment probabilities, and therefore probability matching, were done using strata of 5-year age, sex, and race groups.

North Carolina Rectal Cancer Study II (NCCCS II)

NCCCS II was a study almost identical to the NCCCS I except that the cases included only patients with cancer of the sigmoid colon, rectosigmoid, and rectum. Cases and controls in this study were recruited between November 2001 and August 2006.

3.3 DATA COLLECTION

Diet and Health Study IV (DHS IV)

Within twelve weeks of their colonoscopy, patients who consented to the study were followed up with by a phone call from a trained interviewer. The interviewer was blinded as to whether the participant was a case or a control. Information on diet, physical activity, demographics, and other such factors were obtained at this time (see Section 3.6 for more details on the measurement of physical activity). Height and weight were measured at the time of colonoscopy. No incentive was given other than to supply individuals with the results of their personal dietary assessment.

During the study period, there were 3182 colonoscopies performed at the UNC Hospitals. The majority of these individuals (2155) were deemed ineligible and not recruited for the study. Of the remaining 1027 individuals, 91 individuals were not asked to participate because the research assistant was not available and 123 individuals did not consent to participation in the study. One hundred seven individuals were classified as ineligible after the procedure was completed. The study was completed by 701 individuals (196 cases and 505 controls). The response rate for completion of the study was 76% (interview/eligible).

North Carolina Colon Cancer Studies I and II (NCCCSs I and II)

Potential participants received a call from a race-matched enrollment specialist who explained the study. After consent for participation was obtained, an in-person interview was scheduled. Trained nurse interviewers collected data at the individual's house or

another convenient location. The interviews took place within approximately five months of a case's diagnosis. Participants were asked questions pertaining to demographic information, lifestyle factors, diet, and medical history. Information on physical activity, height, and weight was also collected (see section 3.6 for more detail on the measurement of physical activity and BMI). Both cases and controls were offered a $25 incentive for participation in the study.

NCCCS I

Among those who were eligible, reasons for not being interviewed were as follows: refusal (14% cases; 36% controls), untraceable (1% cases, 1% controls), not reachable by phone (6% cases, 1% controls), and physician denial (7% cases). Completed interviews were obtained for 1691 people (643 cases, 1048 controls). The rate of study cooperation (interviewed/(interviewed+refused)) was 84% for cases and 63% for controls. The response rates (interview/eligible) for cases and controls were 72% and 61% respectively.

NCCCS II

Among those who were eligible to participate in the study, the following reasons were given for why no interview was done: refusal (17% cases; 26% controls) and untraceable/not reached (8% cases, 18% controls). A total of 3106 people completed interviews (1045 cases and 1019 controls), giving study cooperation rates (interviewed/(interviewed+refused)) as 81% and 68% and response rates (interview/eligible) of 74% and 56% for cases and controls, respectively.

3.4 MEASUREMENT OF EXPOSURE

Diet and Health Study IV(DHS IV) and North Carolina Colon Cancer Study II (NCCCS II)

The DHS IV and the NCCCS II used the Diet History Questionnaire (DHQ), a validated food frequency questionnaire developed by the National Cancer Institute (NCI) (2, 3). The DHQ contained 124 food items and was not modified in any way. The time period referenced in the study was one year prior (DHS IV: one year prior to the interview date; NCCCS II: one year prior to diagnosis for cases and one year prior to the interview date for controls), which allowed us to capture seasonal variations in diet. People were asked to report both their typical portion size and frequency of consumption, which varied in range for each food item. This questionnaire also asked questions about how foods were generally cooked and what sorts of fats were used in the cooking process.

The corresponding diet calculator (Diet*Calc) was downloaded from the NCI's website. This program was run for all study participants to determine their total intake of various nutrients and components of diet.

North Carolina Colon Cancer Study I (NCCCS I)

In this study, diet was collected using a modified version of the 100-item semiquantitiative Block Food Frequency Questionnaire (FFQ) (4). The modification that took place was the addition of twenty-nine foods commonly consumed in North Carolina, such as hush puppies and greens.

Each food item had three choices for portion size (given as "small," "medium," and "large") and nine choices for frequency (ranging from "never or less than once per month"

to "2+ times per day"). When estimating frequency and portion size, study participants were asked to use the reference period of one year (one year prior to diagnosis for cases and one year prior to the interview date for controls). Participants were asked to estimate their usual consumption over the period of a year in order to capture the seasonal variation present in consumption of some foods. Additional questions were asked about the following: types of foods used in cooking and preparation techniques, fortified beverages consumed, low-fat foods consumed, and restaurant eating.

Unfortunately, determining the amounts of *trans* fatty acids present in an individual's diet was much more difficult for this study. There were no values for *trans* fatty acids in the nutrient database associated with the Block FFQ. With the help of the Clinical Nutrition Research Center at the University of North Carolina, we paired each food listed in the Block FFQ with food(s) listed in the NCI's DHQ. We assigned the amount of *trans* fatty acid listed for each food in the DHQ to the corresponding food in the Block FFQ (per 100 grams of food). If more than one DHQ food matched, we applied the mean amount of *trans* fatty acids for those foods to the corresponding Block FFQ food. For example, one of the foods in the Block FFQ is "cookies, cake." In the DHQ there are three foods that matched: "cookies, brownies," "cakes," and "cheesecake." The amount of *trans* fatty acids assigned to each of these was averaged to determine the amount of *trans* fatty acids that would be assigned to "cookies, cake" in the Block FFQ. Of the 201 Block FFQ foods, 176 (87.6%) were matched in this manner to foods in the DHQ. For the remaining foods, we searched for *trans* fatty acid values in the USDA National Nutrient Database for Standard Reference (Release 19). Eight more foods were given values (4.0%). We were unable to determine the amount of *trans* fatty acid in 17 foods (8.5%), which were assigned values of

0 grams of *trans* fatty acid. The majority of these foods (12 foods) were vegetables, fruits, or fruit juices so it is unlikely that assigning them a value of 0 will have an affect on the results.

We employed the same methods to derive the energy intake variable. One hundred percent of the Block FFQ foods were matched and assigned caloric values. This was done primarily using the same Block FFQ-DHQ pairings that we used for *trans* fatty acids. For the remaining foods, we used values from the USDA National Nutrient Database. The original values for caloric intake present in the Block FFQ and the values determined using the DHQ and USDA databases were highly correlated (correlation was greater than 0.99).

3.5 MEASUREMENT OF OUTCOME

As described above, cases are those patients identified as having either a colorectal adenoma (DHS IV), colon cancer (NCCCS I), or distal colorectal cancer (NCCCS II). In the DHS IV, the study pathologist reviewed every slide. In addition, a 10% random sample of all biopsies collected were resubmitted for review. This was done to assess the reliability of the case-control classification. Ninety-nine percent of classifications were concordant. In the NCCCSs I and II, all of the diagnoses were confirmed by the study pathologist using pathology reports. In addition, over 95% of the diagnoses were confirmed using the pathology slides.

3.6 MEASUREMENT OF OTHER KEY VARIABLES

Information on all covariates of interest was collected during the interviews or prior to colonoscopy. For all three studies, physical activity was measured for occupational, non-occupational, and non-work/weekend activities using a modified version of a validated seven-day physical activity recall (5-7). Frequency, intensity, and duration was estimated and converted into a variable giving MET minutes per day. Body mass index (BMI) was calculated using the height and weight of each participant. Participants of the DHS IV had their height and weight measured at the time of their colonoscopy. Participants of the NCCCSs I and II had their height and weight measured at the time of interview. They also reported their weight one year prior in order to capture weight prior to any changes that occurred as a result of disease or treatment in the cases. Dietary variables to be used as covariates in the study were obtained from each study's food frequency questionnaire (discussed above). Information on family history of colorectal cancer, smoking status, and NSAID use were gathered during the interview.

3.7 DATA ANALYSIS

The statistical analyses conducted in this study were performed using STATA version 8.2 (8). We excluded participants with extreme values for energy intake as we felt that their responses may not be valid. Men reporting total calories per day less than 800 kcal or greater than 5000 kcal were removed from further analysis. The corresponding values for women were 600 and 4000 kcal. In addition, because we were interested, *a priori*, in stratifying analyses of the NCCCSs I and II by race, we excluded participants of these studies who gave a self-report race as "other," in order to keep only individuals that self-identified as White or African American in the dataset.

Trans fatty acid intake was used as a energy-adjusted variable. Besides potentially confounding the association, total energy intake can add variation and weaken the association present between *trans* fatty acid intake and the outcome (9). As stated by Dr. Willett and Dr. Stampfer in their paper on total energy intake:

> …Before attributing causality to a *specific* nutrient, the burden is upon the epidemiologist to demonstrate that the effect of this nutrient is independent of caloric intake (10).

They suggest that the best method for doing this is through the employment of residuals from a regression model where the independent and dependent variables are total caloric intake and nutrient intake, respectively (10). While the residual method of calorie adjustment is most often used for continuous values of nutrient intake, it is also appropriate to use when categorizing nutrient intake variables (11). Therefore, we energy-adjusted the variable of *trans* fatty acid using the residuals method. The exposure variable, residuals of

trans fatty acids consumption, was then converted from a continuous variable to a categorical one. Quartiles were created based on the distribution in the control population.

Unconditional logistic regression modeling was used to explore the relationship postulated in each of the specific aims. In order to generate unbiased effect estimates, offset terms were included in the models for the NCCCSs I and II to correct for the randomized recruitment sampling fractions, as discussed above (1, 12). Effect measure modification was assessed using a test of homogeneity and a likelihood ratio test with a p-value cut-off of 0.15. *A priori*, the variables chosen to be assessed for effect measure modification in the DHS IV analysis were sex and NSAID use. For the NCCCSs I and II these were sex, NSAID use, and highest level of education attained. Confounding was assessed for multiple variables. First, a directed acyclic graph depicting the relationship occurring between *trans* fatty acid intake, colon/rectal cancer/adenoma, and the possible confounding factors was drawn to get a better understanding of which variables might qualify as confounders (Figure 3.1). From this figure and knowledge of what prior studies of the *trans* fatty acid-colorectal cancer relationship have identified as potential confounders, the following variables were identified and examined as possible confounding factors: age, sex, race, family history of colorectal cancer, BMI, physical activity, NSAID use, smoking status, highest level of education achieved, vegetable consumption, red meat consumption, calcium intake, and alcohol consumption. Once working with the actual data, the criteria for confounding proposed by Drs Rothman and Greenland were used to identify variables that met the definition of a confounder. Based on this criteria, a confounder must: a) be a risk factor for the disease among the unexposed; b) be associated with the exposure in the source population from which the study population was drawn; c) be unaffected by the exposure or

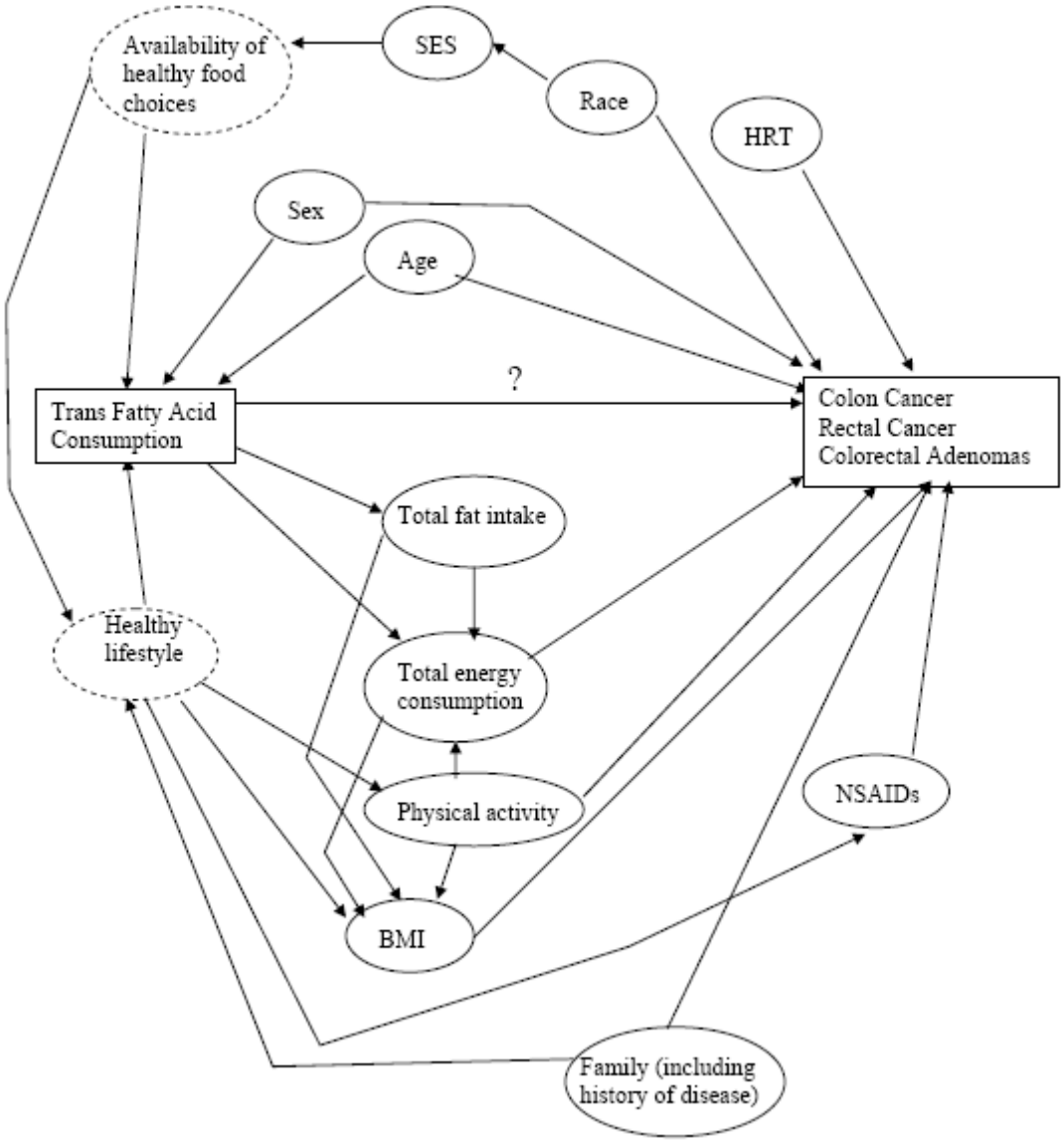
the disease (i.e. not on the causal pathway) (13). These variables were then checked to see if they met the assumption of linearity. If the assumption was not met, the variable was dealt with by creating indicator variables to use in the final model. Once the full model was determined (a model including the exposure, interaction terms for effect measure modifiers, all possible confounding variables, and offset terms, where applicable) backwards elimination with a 10 percent change-in-estimate criterion was used to refine the model.

Additional analyses were conducted in each of the three studies using multinomial logistic regression. In the DHS IV study, adenoma characteristics were analyzed to see if any of these was associated more strongly with *trans* fatty acid consumption. Location (proximal or distal), size (none, less than one centimeter, or one centimeter or greater based on the size of the largest adenoma), and number (none, one adenoma, more than one adenoma) were studied, with controls serving as the referent outcome for all analyses. Location was classified as proximal if an adenoma was detected in the cecum, ascending colon, hepatic flexure, or transverse colon and as distal if an adenoma was present in the splenic flexure, descending colon, sigmoid colon, or rectum. Participants with adenomas in both the proximal and distal colon were excluded. In addition to these analyses on the prevalence of colorectal adenomas, we investigated the association between *trans* fatty acid consumption and the type of polyps identified during colonoscopy. Participants with polyps were categorized as having either hyperplastic or adenomatous polyps and were categorized as controls if they had neither hyperplastic polyps nor adenomatous polyps detected. If a participants had both hyperplastic and adenomatous polyps, they were excluded. Location of the cancer was further investigated in the NCCCSs I and II. For the NCCCS I, cancer was classified as being located in the proximal or distal colon, using the same definition as

used for the DHSIV. For the NCCCS II, cancers were identified as being located in either the sigmoid colon, rectosigmoid, or rectum. The associations for specific types of *trans* fatty acids were also evaluated in the NCCCS II. In each of these additional analyses, confounding factors were re-evaluated to be sure that the final model being presented was not biased as a result of lack of control for confounders.

3.8 FIGURE

FIGURE 3.1. Directed acyclic graph of the relationship between *trans* fatty acid consumption and colon cancer, rectal cancer, and colorectal adenomas*



*Even though some risk factors are known to affect colon cancer and not rectal cancer, for simplicity, all of the outcomes were combined in this figure.

3.9 REFERENCES

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4. RESULTS PAPER 1: Consumption of *Trans* Fatty Acid and its Association with Colorectal Adenomas

4.1 ABSTRACT

Trans fatty acid consumption is known to have detrimental effects on cardiovascular health, but little is known about its role in digestive tract neoplasia. In order to investigate the association between colorectal adenomas and *trans* fatty acid consumption, data from a cross-sectional study of 622 individuals who underwent complete colonoscopy between 2001 and 2002 at the University of North Carolina Hospitals were utilized. Participants were interviewed about demographic, lifestyle, and dietary factors thought to be related to colorectal cancer. Energy intake-adjusted *trans* fatty acid consumption was categorized into quartiles based on its distribution in controls. Compared to participants in the lowest quartile of *trans* fatty acid consumption, those in the highest quartile had an increased prevalence of colorectal adenomas, with an adjusted prevalence odds ratio of 1.86 (95% confidence interval: 1.04, 3.33). We further investigated the relationship between *trans* fatty acid consumption and colorectal neoplasia by examining the adenoma characteristics, with the adjusted prevalence odds ratios showing little or no difference by adenoma location, size, or number. These results suggest that consumption of high amounts of *trans* fatty acid may increase the risk of colorectal neoplasia and provide additional support to recommendations to limit *trans* fatty acid consumption.

4.2 INTRODUCTION

Colorectal cancer is a major health concern in the United States, with over 150,000 diagnoses and 52,180 deaths expected in the year 2007 (1). It is widely accepted that the majority of colorectal cancers develop from precursor lesions, colorectal adenomatous polyps. Recent colonoscopy based studies have shown that adenomas are very common. Rex et al (2) reported that 66 percent of a study population aged 50 and over had at least one adenoma, a higher percentage than most previous reports. The rate of adenoma detection in participants who were undergoing screening colonoscopy for the first time was 55 percent (2). An earlier study also detected adenomas in 55 percent of study participants undergoing screening colonoscopies at a Veterans Affairs Hospital. Patients with adenomas are more likely to develop additional adenomas in the future, with a reported recurrence rate of 37 percent within 5 years (3). The concern about adenomas stems from the fact that they can progress to cancer; therefore preventing adenomas from developing by modifying diet or lifestyle could decrease the incidence of colorectal cancer.

Currently, there is increasing concern that consumption of *trans* fatty acids may contribute to disease risk. This is especially true for heart disease (4) but higher intakes have also been found to be detrimentally associated with other health outcomes, such as type II diabetes (5). Consequently, all nutritional labels in the United States were required to include information on *trans* fat content by January 1, 2006 (6). In addition, some localities, including New York City, have banned *trans* fatty acids from commercial food outlets (7, 8).

There is little published information on *trans* fatty acid consumption and colorectal neoplasia, but there are several mechanisms by which *trans* fatty acids could influence the risk of colorectal neoplasia. For example, *trans* fatty acid consumption may lead to elevated risk of developing colorectal adenomas by altering the concentration of bile normally found in the colon, resulting in irritation of the colonic mucosa (9-13), increasing oxidative stress (14), or increasing insulin resistance (12, 15-17).

We used data from a cross-sectional study of subjects attending UNC Hospitals for a colonoscopy to investigate the association between colorectal adenomas and *trans* fatty acid consumption. We also examined the relationship between *trans* fatty acid consumption and the location, number, and size of adenomas. In contrast to prior publications, the present study reports the relationship between energy-adjusted *trans* fatty acid consumption and colorectal adenomas among participants who had their entire colon examined by complete colonoscopy.

4.3 MATERIALS AND METHODS

4.3.1 STUDY POPULATION

The Diet and Health Study IV (DHS IV) recruited consecutive patients undergoing an outpatient colonoscopy at the University of North Carolina Hospitals in Chapel Hill, North Carolina from November 2001 to December 2002. The study received Human Subjects Approval from the School of Medicine IRB and research assistants obtained written informed consent from individuals prior to their colonoscopy. Eligibility requirements were as follows: age 30-80 years, proficient in English, ability to give informed consent, a satisfactory prep for colonoscopy and a complete exam to the cecum, no previous colonoscopies, not an inpatient, and no history of familial polyposis, colitis, previous colonic resection, or previous colon cancer or polyps. For this study, cases were defined as subjects who had a colorectal adenoma (a polyp with tubular, villoglandular, or villous histology) detected during complete colonoscopy. Controls were defined as those subjects with no adenomas present. A single study pathologist examined all tissue samples collected from participants and reported the diameter, location, and histologic type of each polyp detected. In addition, a 10 percent random sample of all biopsies collected from the study participants was blindly resubmitted for pathology review to determine the reliability of the case-control classification; 99 percent of classifications were concordant.

4.3.2 DATA COLLECTION

Within twelve weeks of their colonoscopy, consenting subjects were followed up with a phone call from a trained interviewer who was blinded to case-control status.

Interviewers collected information on participants' age, sex, educational background, race, smoking history, non-steroidal anti-inflammatory drug (NSAID) use, and physical activity. Physical activity was measured for occupational, non-occupational, and non-work/weekend activities using a modified version of a validated seven-day physical activity recall (18-20). Height and weight were measured at the time of colonoscopy.

4.3.3 DIETARY ASSESSMENT

Dietary information was collected during the interview using the validated Diet History Questionnaire (DHQ) developed at the National Cancer Institute (21-23). Participants were asked to use a reference period of one year prior to their colonoscopy, allowing us to capture usual diet across seasons. The DHQ included questions on portion size and frequency of consumption for each food. The DHQ also accounted for cooking methods individuals employed.

4.3.4 DATA ANALYSIS

Trans fatty acid consumption, was energy-adjusted using the residuals method from a regression model where the independent and dependent variables were energy intake and *trans* fatty acid intake, respectively (24). This method results in *trans* fatty acid values that are independent of an individual's overall amount of energy consumed. While the residual method of energy adjustment is most often used for continuous values of nutrient intake, it is also appropriate when categorizing nutrient intake (25). The residuals of *trans* fatty acid consumption were categorized into quartiles based on consumption in the adenoma-free (i.e. control) population.

We used logistic regression modeling to explore the associations between colorectal adenomas and energy-adjusted *trans* fatty acid consumption. Sex and NSAID use were assessed as potential prevalence odds ratio modifiers using tests of homogeneity and likelihood ratio tests with a p-value cut-off of 0.15. These two variables were selected because a study of colon cancer and *trans* fatty acid consumption demonstrated differences within stratum of similar variables (26) and because NSAIDs have been shown an inverse association with adenoma prevalence and recurrence (27-29) and could alter the effects of *trans* fatty acids if they create inflammation. Adenomas are more common in men, older individuals, and African Americans and *trans* fatty acid consumption was associated with age, sex, and race among the controls; therefore we adjusted for these variables *a priori*. In addition, we evaluated family history of colorectal cancer, body mass index (BMI), physical activity, NSAID use, smoking status, alcohol consumption, calcium consumption, red meat consumption, and total vegetable serving consumption as potential confounders according to a 10 percent change-in-estimate criterion.

We also investigated associations between *trans* fatty acid consumption and adenomas classified according to their location (proximal or distal), size (none, less than one centimeter, or one centimeter or greater based on the size of the largest adenoma), and number (none, one adenoma, more than one adenoma), with controls serving as the referent outcome for all analyses. Location was classified as proximal if an adenoma was detected in the cecum, ascending colon, hepatic flexure, or transverse colon and as distal if an adenoma was present in the splenic flexure, descending colon, sigmoid colon, or rectum. If a participant had an adenoma in both the proximal and distal colon, they were excluded from this analysis (n=30). We estimated these associations using multinomial logistic regression.

In addition, we investigated the association between *trans* fatty acid consumption and two types of polyps. For these analyses, participants with polyps were categorized as having either hyperplastic or adenomatous polyps. Participants were categorized as controls if they had neither hyperplastic polyps nor adenomatous polyps detected during colonoscopy. Participants with both hyperplastic and adenomatous polyps were excluded from this analysis (n=50). The exposure, consumption of *trans* fatty acids, retained the same categorization despite the change in the control group. If cut-points had been reformatted based on the distribution of consumption in the specific control group used in these analyses, 99 percent of individuals would have remained in the same exposure category. Multinomial logistic regression was employed and confounding was reassessed using the 10 percent change-in-estimate criteria.

4.4 RESULTS

Between November 2001 and December 2002, 1,027 eligible individuals had a colonoscopy performed at the UNC Hospitals. Of these individuals, 91 were not asked to participate because the research assistant was not available, and 123 did not provide consent for participation in the study. One hundred seven were classified as ineligible after the colonoscopy was completed for reasons such as an unsatisfactory prep or an incomplete exam. The study was completed by 701 individuals, with a response rate (number interviewed/number eligible) of 76 percent.

Complete information on colorectal adenomas and *trans* fatty acid consumption was available for 622 participants (173 cases and 449 controls). Characteristics of the study participants by case and control status are given in Table 4.1. Mean age at time of interview was similar for the cases and controls (57 and 56 years, respectively). There were more women than men in the study population, but more men had colorectal adenomas detected. Over 75 percent of study participants were white and more than half had at least a college degree. As expected, a higher proportion of cases than controls were classified as obese (BMI $\geq$30 kg/m^2; 31 versus 24 percent, respectively). Cases also had a higher mean consumption of alcohol and a slightly higher energy intake than controls.

Cases reported higher unadjusted *trans* fatty acid consumption than controls, with a mean of 4.97grams (SD 3.20 grams) and median of 4.12 grams compared with 4.42 grams (SD 3.16 grams) and 3.61grams, respectively, in controls (t-test *p* of 0.054). The crude (unadjusted) prevalence odds ratio comparing the highest quartile of *trans* fatty acid consumption to the lowest quartile was 1.55 (95% confidence interval (CI): 0.95, 2.54).

Prevalence odds ratios were homogeneous across strata of sex and NSAID use (likelihood ratio test $p>0.15$), therefore multiplicative interaction terms between these covariates and the exposure were not retained. The following variables were entered into the final model as confounders: age (continuous), sex, race (categorized as white, non-white), physical activity (continuous), BMI (continuous), and alcohol consumption (continuous). In addition to adjusting the exposure, *trans* fatty acid consumption, for energy intake, a continuous variable for energy intake was included in the final model. For the multinomial model comparing subjects with hyperplastic polyps and adenomatous polyps to controls, smoking status (categorized as never, former, current smoker), consumption of red meat (continuous), and total number of vegetable servings consumed (continuous), were also found to be confounders based on a 10 percent change in estimate criterion and were added to the model in addition to the covariates above.

The fully adjusted prevalence odds ratio comparing those in the lowest quartile of *trans* fatty acid consumption to those in the highest quartile was 1.86 (95% CI: 1.04, 3.33) in the fully adjusted model (Table 4.2). Consumption of *trans* fatty acid was not associated with the prevalence of colorectal adenomas for those in the second or third quartiles of consumption. Estimates from the minimally adjusted models were similar (Table 4.2).

Other categorizations were undertaken to further examine the association present in the extreme quartile of *trans* fatty acid consumption (data not shown). Although it was difficult to draw definitive conclusions regarding a specific threshold of *trans* fatty acid consumption due to small numbers, similar trends were seen. In models of the various categorizations the highest 20-25 percent of energy-adjusted *trans* fatty acid consumption had similar point estimates to those seen in the highest quartile of consumption from our

original model. These results confirm the appearance of a threshold affect; the prevalence of adenomas was increased only among those with the highest levels of *trans* fatty acid consumption in our study population.

The results of the minimally and fully adjusted models for the investigation of adenoma location, size, and number were very similar and therefore only the results of the fully adjusted model are presented (Table 4.3). As seen in the models examining only the presence/absence of colorectal adenomas, the fourth quartile of consumption was associated with the largest increase in prevalence among all categories of location, number, and size of adenomas. Adenomas in the proximal colon were more strongly associated with high consumption of *trans* fatty acids (POR: 2.80; 95% CI: 1.14, 6.87) than adenomas of the distal colon (POR: 1.51; 95% CI: 0.68, 3.35); however, for the fourth quartiles the *p*-value for the difference between the two adenoma locations was 0.28. Also, there does not appear to be a difference in the prevalence of multiple or large adenomas versus single or small adenomas with increasing consumption of *trans* fatty acid.

Minimally adjusted prevalence odds ratios comparing the highest to lowest consumption of *trans* fatty acid were 1.60 (95% CIs 0.75, 3.44) for hyperplastic polyps and 1.74 (95% CIs 0.98, 3.06) for adenomatous polyps. The estimates from the fully adjusted model were less precise but otherwise similar to the minimally adjusted estimates (Table 4.4).

4.5 DISCUSSION

Using data from a large cross-sectional study, we found that the prevalence of colorectal adenomas was positively associated with high *trans* fatty acid consumption. This association was not evident with lower levels of consumption, suggesting a possible threshold effect. We also identified a stronger association between high *trans* fatty acid consumption and prevalence of proximal versus distal adenomas when these case subtypes were compared with controls though a difference between associations with adenomas classified by location could not be firmly established given the precision of our estimates. Associations between *trans* fatty acid consumption and location, size, and number of adenomas were imprecise, but were consistently elevated for the highest versus lowest quartiles of consumption. This supports the conclusion that the association is limited to the highest versus lowest quartiles of consumption without clear differences in the relationship by location, size, or number.

It is well established that adenomatous polyps are precursor lesions for colorectal cancer. However, recent evidence suggests that hyperplastic polyps may also have malignant potential (30). In addition, some studies have found that the risk factors for adenomatous polyps and hyperplastic polyps are similar. Smoking (31-33), fiber consumption (33, 34), alcohol intake (33, 34), and hormone replacement therapy use (31) have all been shown to increase the risk of both hyperplastic and adenomatous polyps. To explore the possibility that high *trans* fatty acid consumption is associated with both types of polyps, we estimated associations with adenomas and hyperplastic polyps separately. The number of subjects within each quartile of consumption for this analysis was small, but point

estimates were elevated for the fourth quartile of consumption, without clear differences between histologic subtypes. Further work with larger sample sizes need to be performed before a definitive conclusion can be drawn.

Previous studies have generally not reported an association between total fat consumption and adenoma development. Randomized trials of a low-fat, high-fiber diet found no association between recurrent colorectal adenomas and total fat intake using intent-to-treat analyses (35, 36). Two earlier observational studies found associations between colorectal adenomas and higher total fat consumption (37, 38), but other observational studies have not confirmed this association. Using data from one of the above randomized trials (36), Cantwell et al estimated the association between what people actually reported consuming and the risk of recurrent adenomas using the food records collected during the intervention (39). There was no increase in the risk of recurrent colorectal adenomas with increasing consumption of total or saturated fats (39). Another study performed a similar analysis and also found no association between total fat intake and recurrent colorectal adenomas (40).

We hypothesized that specific types of fatty acids, rather than the overall amount, may be important in determining disease risk, and therefore, investigated the relationship between *trans* fatty acid intake and colorectal adenomas. Two prior studies also examined the relationship between *trans* fatty acids and colorectal adenomas (41, 42). In these studies investigators looked at the association between risk of colorectal adenomas and groups of foods that contain partially hydrogenated vegetable oils. Both studies reported a weak association between colorectal adenomas and high consumption of sweetened baked goods, but the authors concluded that there was no overall association between colorectal adenomas

and consumption of partially hydrogenated vegetable oils. Only one of these studies went further and investigated the association between colorectal adenomas and amount of *trans* fatty acid (categorized in intervals of two grams per day); there was no association after adjustment for confounding (41). However, in that study, because cases and controls were classified based on sigmoidoscopy results, it is possible that cases with adenomas in the proximal colon were misclassified as controls. In addition, if *trans* fatty acids differentially affect the proximal and distal sections of the colon, then results of the studies based on sigmoidoscopy will differ from those investigating adenomas of the entire colon.

This study has important strengths. First, every participant underwent complete colonoscopy to the cecum, increasing the likelihood that all visible adenomas were enumerated and there was no misclassification of case-control status. The study had a high response rate. Dietary data were collected using a validated FFQ. In addition, all colorectal adenoma pathology slides were reviewed by a single experienced GI pathologist, and reliability was evaluated and found to be good.

There are some limitations to the present study. First, results may not be generalizable to other populations since individuals going to UNC Hospitals for screening colonoscopies are not representative of the general population. However, previous reports using data from similar populations have identified associations that are supported by other studies. For example, in the Diet and Health Study III population NSAID use was inversely associated colorectal adenomas (29), which is consistent with two randomized control trials that reported associations between recurrent colorectal adenomas and aspirin use (27, 28). Other limitations are the relatively small size of the study population and the possibility that the people who participated in the study are different than those who refused. Also, DHQ-

based estimates of *trans* fatty acid consumption have not been validated. Finally, *trans* fatty acid consumption may not be directly related to colorectal adenoma risk, but may instead be acting as a proxy for unhealthy behaviors. We attempted to decrease this bias by controlling for other characteristics that are associated with unhealthy behaviors (energy intake, physical activity, and alcohol consumption).

In conclusion, we found that the highest quartile of *trans* fatty acid consumption in our study population was positively associated with colorectal adenoma prevalence. These results provide further support for recommendations to limit consumption of *trans* fatty acids.

4.6 TABLES

TABLE 4.1. Characteristics of the Diet and Health Study IV population by case status, NC, November 2001-December 2002 (N=622)

Participant Characteristics	Colorectal Adenoma (n=173)	No Colorectal Adenoma (n=449)
Age (%)*		
30-49 years	28 (16.38)	98 (21.88)
50-59 years	82 (47.95)	193 (43.08)
60-69 years	39 (22.81)	116 (25.89)
70-80 years	22 (12.87)	41 (9.15)
Mean years (SD)	56.96 (9.60)	55.95 (9.86)
Sex (%)		
Men	98 (56.65)	172 (38.31)
Women	75 (43.35)	277 (61.69)
Race (%)*		
White	133 (77.78)	349 (78.25)
Non-White	38 (22.22)	97 (21.75)
Highest level of education (%)*		
Some high school	24 (14.04)	40 (8.93)
High School	27 (15.79)	72 (16.07)
Some college	30 (17.54)	95 (21.21)
College degree or above	90 (52.63)	241 (53.80)
Body Mass Index 1 year prior to enrollment (%)*		
Normal (18-24.9 kg/m2)	53 (32.92)	174 (42.03)
Overweight (25-29.9 kg/m2)	58 (36.02)	140 (33.82)
Obese (≥30 kg/m2)	50 (31.06)	100 (24.15)
Mean kg/m^2 (SD)	28.15 (5.82)	27.00 (5.54)
Current Physical Activity (MET-minutes/day) *		
1^{st} quartile	41 (26.11)	106 (24.65)
2^{nd} quartile	37 (23.57)	110 (25.58)
3^{rd} quartile	34 (21.66)	113 (26.28)
4^{th} quartile	45 (28.66)	101 (23.49)
Mean MET-minutes/day (SD)	2670.47 (845.85)	2591.08 (754.79)
Smoking status (%)*		
Never	80 (47.06)	229 (51.12)
Former	63 (37.06)	171 (38.17)
Current	27 (15.88)	48 (10.71)

Family History (%)		
Yes	27 (15.61)	59 (13.14)
No	146 (84.39)	390 (86.86)
NSAID use over the past 5 years (%)*		
Regular User†	50 (29.76)	124 (28.51)
Non-regular User†	118 (70.24)	311 (71.49)
Trans Fat Consumption		
Mean grams/day (SD)	4.97 (3.20)	4.42 (3.16)
Total Energy Intake		
Mean kcal/day (SD)	2084.74 (1037.18)	1958.67 (917.30)
Calcium Consumption		
Mean milligrams/day (SD)	796.42 (442.11)	820.72 (467.44)
Alcohol Consumption*		
Mean grams/day (SD)	12.49 (20.98)	8.03 (14.23)
Red Meat Consumption		
Mean ounces/day (SD)	1.88 (1.57)	1.57 (1.44)
Vegetable Consumption		
Mean number vegetable servings/day (SD)	4.34 (2.40)	4.32 (2.46)

*Data were missing for: age (n=3), race (n=5), education (n=3), BMI (n=47), physical activity (n=35), smoking (n=4), NSAID use (n=19), and alcohol consumption (n=1)

†Regular user is defined as using NSAIDS at least 15 times/month

TABLE 4.2. Adjusted prevalence odds ratios (95% confidence intervals) of quartiles of *trans* fatty acid intake with colorectal adenoma prevalence, Diet and Health Study IV, November 2001-December 2002

Quartiles of *trans* fatty acid consumption	Minimally Adjusted Model (N=614)†				Fully Adjusted Model (N=546)‡			
	Controls N	Cases N	POR*	95%CI*	Controls N	Cases N	POR*	95%CI*
1	111	40	1.00		99	35	1.00	
2	111	36	1.01	0.58, 1,75	101	31	0.98	0.53, 1.79
3	111	32	0.95	0.54, 1.67	98	29	1.07	0.57, 2.00
4	112	61	1.74	1.06, 2.86	103	50	1.86	1.04, 3.33

*POR: prevalence odds ratio; 95%CI: 95% confidence interval from logistic regression models
†Adjusted for age, sex, race, and caloric intake
‡Adjusted for caloric intake, alcohol consumption, physical activity, race, age, sex, and BMI

TABLE 4.3. Adjusted prevalence odds ratios (95% confidence intervals)† for location, number, and size of adenomas for quartiles of *trans* fatty acid consumption, Diet and Health Study IV, November 2001-December 2002

Location of Adenomas[‡]

Quartiles of consumption	Controls N	Proximal Adenomas			Distal Adenomas		
		N	POR*	95%CI*	N	POR*	95%CI*
1	99	11	1.00		15	1.00	
2	101	14	1.23	0.50, 3.07	14	1.13	0.49, 2.61
3	98	9	0.94	0.34, 2.59	13	1.16	0.49, 2.75
4	103	21	2.80	1.14, 6.87	21	1.51	0.68, 3.35

Number of Adenomas

Quartiles of consumption	Controls N	1 Adenoma			> 1 Adenoma		
		N	POR*	95%CI*	N	POR*	95%CI*
1	99	22	1.00		13	1.00	
2	101	23	1.09	0.55, 2.19	8	0.74	0.28, 1.97
3	98	20	1.08	0.52, 2.23	9	1.04	0.39, 2.77
4	103	34	1.79	0.91, 3.53	16	2.01	0.83, 4.87

Size of Adenomas[§]

Quartiles of consumption	Controls N	Adenomas <1 cm			Adenomas ≥1 cm		
		N	POR	95%CI*	N	POR	95%CI*
1	99	27	1.00		7	1.00	
2	101	26	1.08	0.56, 2.07	5	0.69	0.20, 2.36
3	98	24	1.16	0.58, 2.28	5	0.79	0.22, 2.80
4	103	37	1.81	0.96, 3.44	13	2.01	0.69, 5.81

*POR: prevalence odds ratio; 95%CI: 95% confidence interval; cm: centimeter
† Adjusted for caloric intake, alcohol consumption, physical activity, race, age, sex, and BMI
‡ Adenomas were classified as proximal if they were detected in the cecum, ascending colon, hepatic flexure, or transverse colon and distal if present in the splenic flexure, descending colon, sigmoid colon, or rectum. Participants with adenomas in both the proximal and distal colon were excluded from this analysis (n=30).
§ Size of adenoma was classified based on the size of the largest adenoma detected

TABLE 4.4. Adjusted prevalence odds ratios (95% confidence intervals) for quartiles of *trans* fatty acid intake in association with hyperplastic and adenomatous polyp† prevalence, Diet and Health Study IV, November 2001-December 2002

	Minimally Adjusted‡							Fully Adjusted§						
	Controls	Hyperplastic Polyps			Adenomatous Polyps			Controls	Hyperplastic Polyps			Adenomatous Polyps		
Quartiles of consumption	N	N	POR*	95%CI*	N	POR*	95%CI*	N	N	POR*	95%CI*	N	POR*	95%CI*
1	97	14	1.00		30	1.00		88	11	1.00		26	1.00	
2	91	20	1.49	0.69, 3.22	28	1.05	0.57, 1.95	84	17	1.46	0.60, 3.57	24	1.00	0.49, 2.04
3	93	18	1.37	0.62, 3.03	20	0.79	0.40, 1.53	83	15	1.43	0.55, 3.71	18	0.80	0.36, 1.75
4	92	20	1.60	0.75, 3.44	44	1.74	0.98, 3.06	83	20	1.93	0.77, 4.85	35	1.66	0.80, 3.43

*POR: prevalence odds ratio; 95%CI: 95% confidence interval

†Cases were categorized as having either hyperplastic or adenomatous polyps. Participants with both were excluded from this analysis (n=50)

‡Adjusted for age, sex, race, and caloric intake

§Adjusted for caloric intake, age, sex, race, alcohol consumption, physical activity, BMI, smoking status, red meat intake, vegetable intake

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5. RESULTS PAPER 2: Associations between *Trans* Fatty Acid Consumption and Colon Cancer among Whites and African Americans in the North Carolina Colon Cancer Study I

5.1 ABSTRACT

Background: Colon cancer is one of the most common cancers in the United States. Disparities in both incidence and mortality rates exist between Whites and African Americans. Prior studies have examined the association between *trans* fatty acid consumption and colorectal cancer, but none have looked at this relationship within a large study population of African Americans and Whites. Methods: Using data from a population-based case-control study in North Carolina, we investigated the association between *trans* fatty acid consumption and colon cancer, with attention to possible racial differences in the relationship. Cases and matched controls were queried on demographic characteristics, lifestyle factors, medical history, and diet (using the Block Food Frequency Questionnaire). Results: Cases reported a higher daily consumption of *trans* fatty acids intake per day than controls [mean (standard deviation) and median: cases 5.9 (2.9) and 5.5 grams/day; controls 5.2 (2.4) and 4.7 grams/day, respectively]. Energy-adjusted *trans* fatty acid consumption was not associated with colon cancer; compared to participants in the lowest quartile of *trans* fatty acid consumption, those in the highest quartile had an adjusted odds ratio of 1.01 (95% confidence interval 0.69, 1.49) for Whites and 0.99 (95% confidence interval 0.61, 1.62) for African Americans. We further investigated tumor location and found no

association with increased consumption of *trans* fatty acid in either the proximal or distal colon. We conclude that *trans* fatty acid consumption is not associated with colon cancer.

5.2 INTRODUCTION

Colorectal cancer is one of the most common cancers in the United States. Rates of both incidence and mortality vary by race. In the United States the age-adjusted incidence rate for colorectal cancer is 70.2/100,000 for African American men compared to 63.7/100,000 for White men. The disparity is seen in women too, with African American women having an age-adjusted incidence rate of 53.5/100,000 compared to 45.9/100,000 in White women (1).

The etiology of colorectal cancer is thought to be due largely to environmental factors, including diet. Migrant studies have shown that, with increasing duration of residence, migrants have rates of colorectal cancer similar to those of their adopted country (2, 3). Diet is thought to be one of the strongest environmental risk factors for colorectal cancer (4, 5). In a recent report from the World Cancer Research Fund and American Institute for Cancer Research, a panel concluded that consumption of red and processed meats and alcohol are likely to increase the risk of colorectal cancer (6).

Although socioeconomic factors and differential screening rates between African Americans and Whites may partly explain the disparity in colorectal cancer incidence, diet may play a role as well. Previous research using the North Carolina Colon Cancer Study I found that African Americans and Whites have different consumption patterns for various groups of foods (7). One of the components of diet that differed between these races was "fats, oils, and snacks," with African Americans having a higher mean daily intake than Whites. This category included unsaturated, saturated, and *trans* fatty acids. Other reports

from this study showed similar mean daily intakes of total fat and saturated fatty acids for Whites and African Americans (8).

Total dietary fat has previously been postulated to affect the risk of developing colorectal cancer but the majority of studies have shown no association (9, 10). It is possible, however, that it is not overall fat consumption but perhaps specific fat subtypes that may be relevant to the etiology of colon cancer. Recently there has been concern over the health effects of *trans* fatty acid consumption. *Trans* fatty acids have been linked to increased risk of heart disease (11) and potentially type II diabetes (12). Although a few studies examined the risk of colorectal cancer associated with *trans* fatty acid consumption (13-16), none has looked at this relationship within a large population of African Americans and Whites. If *trans* fatty acid consumption does play a role in increasing the risk of colorectal cancer, it is possible that differential consumption patterns between Whites and African Americans may account for some of the disparity in colorectal cancer incidence rates.

The objectives of this study were to examine the associations of *trans* fatty acid consumption and colon cancer both overall and by location. This study contributes to the existing body of knowledge by exploring possible differences in the association by race.

5.3 MATERIALS AND METHODS

The North Carolina Colon Cancer Study I (NCCCS I) was a large population-based case-control study conducted in central North Carolina. It enrolled subjects from 33 counties, representing urban, suburban, and rural areas of the state. The study was approved by the Institutional Review Board at the University of North Carolina School of Medicine.

5.3.1 STUDY POPULATION

Cases were identified using the rapid case ascertainment system of the North Carolina Central Cancer Registry. Those patients with a first diagnosis of histologically confirmed invasive adenocarcinoma of the colon between October 1996 and September 2000 were classified as potential cases. Additional eligibility requirements were as follows: aged 40-80 years, residence in one of the 33 study counties, able to give informed consent, able to complete an interview, had a North Carolina driver's license or identification card (if under the age of 65) , and have received no denials from their primary physician for us to contact them.

Potential cases received a call from a race-matched enrollment specialist, who explained the study and scheduled an in-person interview with the patient once consent had been obtained. On average, interviews took place within five months of the participant's diagnosis. White cases were under-sampled for recruitment in order to increase the proportion of non-White cases in the study population.

Controls were selected from two sources: the North Carolina Department of Motor Vehicles records (for participants under the age of 65) and the Center for Medicare and

Medicaid Services (previously the Health Care Financing Administration) records (for those 65 years and older). Potential controls were contacted in a manner similar to that of the cases. Controls were matched to cases using randomized recruitment strategies (17) with recruitment probabilities defined according to strata of 5-year age, sex, and race groups.

5.3.2 DATA COLLECTION

Interviews were conducted by trained nurse interviewers at the participant's residence or another convenient location. Participants were asked questions about demographic information, lifestyle factors, medical history, and diet. Physical activity was measured for occupational, non-occupational, and non-work/weekend activities using a modified version of a seven-day physical activity recall (18-20). Frequency, intensity, and duration was estimated and converted into a variable estimating MET minutes per day. Interviewers also measured the height and weight of each participant. They recorded the participant's self-reported weight for one year prior in order to capture weight prior to illness or cancer therapy for cases. Both cases and controls were offered a $25 incentive for participation in the study.

5.3.3 DIETARY INFORMATION

Dietary information was collected using a modified version of the 100-item semiquantitiative Block Food Frequency Questionnaire (21). Twenty-nine foods commonly consumed in North Carolina were added to the questionnaire to offer local cuisine choices to participants. Each food item had three choices for portion size (given as "small," "medium," and "large") and nine choices for frequency (ranging from "never or less than once per

month" to "2+ times per day"). When estimating frequency and portion size, study participants were asked to use a reference period of the year prior to diagnosis (for cases) or interview (for controls) so that seasonal variations in diet could be captured. Additional questions were asked about the following: types of foods/oils used in cooking and preparation techniques, fats used in cooking, fortified beverage consumption, low-fat food consumption, and restaurant eating.

The version of the Block food frequency questionnaire that we used did not contain nutritional information on *trans* fatty acids for any of the foods it included. Therefore, with the help of the Clinical Nutrition Research Center at the University of North Carolina, we paired each food listed in the Block FFQ with foods listed in the National Cancer Institute's Diet History Questionnaire (DHQ). We assigned the amount of *trans* fatty acid listed for each food in the DHQ to the corresponding food in the Block FFQ (per 100 grams of food). If more than one DHQ food matched, we applied the mean amount of *trans* fatty acids for those foods to the corresponding Block FFQ food. Of the 201 Block FFQ foods, 176 (87.6%) were matched to foods in the DHQ. For the remaining foods, we searched for *trans* fatty acid values in the USDA National Nutrient Database for Standard Reference (Release 19) and eight more foods were assigned values (4.0% of all foods). We were unable to determine the amount of *trans* fatty acid in 17 foods (8.5%), which were assigned values of 0 grams of *trans* fatty acid. We employed the same methods to estimate energy intake. One hundred percent of the Block FFQ foods were matched and assigned caloric values. The original values for caloric intake present in the Block FFQ and the values determined using the DHQ and USDA databases were highly correlated (correlation was greater than 0.99).

5.3.4 DATA ANALYSIS

We excluded participants with extreme or implausible values for energy intake [men: total kcal/day <800 or >5000 (n=10); women: total kcal/day <600 or >4000 (n=21)]. In addition, participants that self-reported their race as "other" were removed from further analyses (n=11).

We energy-adjusted the variable of *trans* fatty acid using the residual method with energy intake as the independent variable and *trans* fatty acid intake as the dependent variable (22, 23). This allowed us to investigate the association between *trans* fatty acid consumption and colon cancer independent of the amount of energy consumed. In addition, energy adjustment removes potential variation contributed to the association by total energy intake (22). This method is often used for continuous nutrient values but is also an acceptable method of energy adjustment when the nutrient values are categorized (23). Residuals of *trans* fatty acid consumption were then divided into quartiles based on the distribution of consumption in the control population.

Unconditional logistic regression models were used to examine the relationship between colorectal cancer and *trans* fatty acid consumption. In all models, we included an offset term to account for the randomized recruitment sampling fractions (17). Highest educational level achieved (dichotomized as high school or less, more than high school), sex, and non-steroidal anti-inflammatory drug (NSAID) use (dichotomized as never/rare use, frequent use) were assessed as potential effect measure modifiers using tests of homogeneity and likelihood ratio tests with an *a priori* p-value cut-off of 0.15. Similar studies found that the relationship between *trans* fatty acid consumption and colon/colorectal cancer varied by sex (15, 16) and NSAID use (15). Previous research has

shown NSAID use to be inversely associated with colon cancer (24). NSAIDs could affect the association between *trans* fatty acid consumption and colon cancer if inflammation resulting from *trans* fatty acid consumption (25) affects the development of colon cancer. Highest level of education achieved was used as a proxy for socioeconomic status, as individuals with low socioeconomic status may have less access fresh foods (resulting in higher consumption of *trans* fatty acids). None of these were found to be odds ratio modifiers and interaction terms were not retained in the final models. Using the 10% change-in-estimate criterion with backwards elimination, we assessed the following variables, which have previously been found to be associated with colorectal cancer and which may be associated with trans fatty acid consumption, as potential confounding variables: family history of colorectal cancer (yes, no), body mass index (BMI) one year prior (normal, overweight, obese according to the World Health Organization cut-points), physical activity (quartiles based on the control group), NSAID use (never, occasional, or regular), smoking status (never, former, current), highest level of education achieved (high school degree or less, some college, college degree or higher), alcohol consumption (none, one or fewer drinks/day, more than 1 drink/day), and calcium consumption, red meat consumption, and total vegetable serving consumption (quartiles based on the control groups). All models also included a term for the matching factors (five-year age and sex stratum) as well as total energy intake. We found that the only confounder of the energy-adjusted model was calcium intake; therefore, it was included with total energy intake, the matching factors, and the offset term in the final model.

We further explored the relationship between *trans* fatty acid consumption and colorectal cancer by examining risk by location of the cancer. Cases were categorized as

having proximal tumors if the cancer was present in the cecum, ascending colon, hepatic flexure, or transverse colon. Cancers were considered distal tumors if they were present in the splenic flexure, descending colon, or sigmoid colon. Cases with unspecified tumor locations or overlapping lesions were excluded from this analysis (n=59). We estimated these associations using multinomial logistic regression and reevaluated potential odds ratio modifiers and confounders using the aforementioned criteria. Due to the limitations of multinomial logistic regression, we were not able to include an offset term with theses models. Alcohol consumption and calcium intake were confounders of the energy-adjusted model based on our change-in-estimate criterion and were included in the energy-adjusted model with the matching factors and energy intake.

5.4 RESULTS

Among those who were eligible, reasons for not being interviewed were as follows: refusal (14% cases; 36% controls), untraceable (1% cases, 1% controls), not reachable by phone (6% cases, 1% controls), and physician denial (7% cases). Completed interviews were obtained for 1691 participants (643 cases, 1048 controls). The rate of study cooperation (interviewed/(interviewed+refused)) was 84% for cases and 63% for controls. Response rates (interview/eligible) for cases and controls were 72% and 61%, respectively. Excluding the aforementioned participants with implausible dietary values or self-reported "other" race, our final study population included 623 cases (341 Whites and 282 African Americans) and 1020 controls (606 Whites and 414 African Americans).

Characteristics of the study population are given in Table 5.1. The majority of the study population was over 60 years old with less than a college degree. The proportion in both cases and controls of participants with a high school degree or less was greater among African Americans than Whites (cases: 72.3% versus 57.1%; controls: 69.1% versus 48.8%). Overall, cases had a higher mean BMI than controls [29.4 (standard deviation: 6.1) versus 28.4 (standard deviation: 5.8), respectively]. The proportion of African American cases and controls classified as overweight or obese (BMI of 25 kg/m^2 or higher) one year prior to diagnosis/interview was greater than the proportion of White cases and controls, respectively. Cases of both races were more likely to have a family history of colorectal cancer. Both Whites and African American cases reported higher total energy intake than their respective controls, and total energy intake was found to be associated with colon cancer among both races. This was demonstrated using a t-test as well as a logistic

regression model controlled for other potential covariates [p-values<0.01 for tests among both Whites and African Americans; logistic regression results for 100 kcal units of total energy intake: Whites 1.05 (95% CI 1.02, 1.08), African Americans 1.05 (95%CI 1.02, 1.07)]. Also, *trans* fatty acid consumption and total energy intake were correlated (correlation>0.80 overall and among Whites and African Americans).

Cases also had a higher mean daily intake of *trans* fatty acid than controls. White cases reported a mean (standard deviation) and median (interquartile range) *trans* fatty acid consumption of 5.9 (2.7) and 5.5 (3.9, 7.3) grams per day compared with 5.2 (2.4) and 4.8 (3.5, 6.4) grams per day for White controls (p-values: t-test <0.01; Wilcoxon rank-sum test <0.01). The mean (standard deviation) and median (interquartile range) for African Americans was 6.1 (3.2) and 5.4 (3.7, 7.5) grams per day among cases and 5.2 (2.6) and 4.7 (3.5, 6.4) grams per day among controls, respectively (p-values: t-test <0.01; Wilcoxon rank-sum test <0.01). Although African American cases had a higher mean daily intake of *trans* fatty acids compared to White cases, statistically these values were not different (p-value 0.34).

Prior to adjustment for energy intake, colon cancer was positively associated with high *trans* fatty acid consumption. Odds ratios adjusted for confounding factors other than energy intake comparing the fourth quartile with the first quartile of *trans* fatty acid consumption were 2.01 (95% CI: 1.22, 3.30) for Whites and 2.50 (95% CI: 1.40, 4.47) for African Americans (Table 5.2). This relationship did not persist in energy-adjusted analyses. The adjusted odds ratios for the fourth quartiles of consumption compared with the lowest quartiles were 1.01 (95% CI: 0.69, 1.49) and 0.99 (95% CI: 0.61, 1.62) for Whites and African Americans, respectively (Table 5.2).

In addition, we investigated cancer in the proximal and distal colon separately to determine if the relationship between *trans* fatty acid consumption and cancer differed by location (Table 5.3). There was no association present for proximal or distal colon cancer in relation to increased *trans* fatty acid consumption. Among Whites, the adjusted odds ratio (95% confidence interval) for the highest quartile compared to the lowest quartile of intake were 1.05 (95% CI: 0.60, 1.83) and 0.92 (95% CI: 0.55, 1.56) for the proximal and distal colon, respectively. These results were 1.35 (95% CI: 0.71, 2.55) and 0.69 (95% CI: 0.36, 1.31), respectively, among African Americans.

5.5 DISCUSSION

In this population-based case-control study of colon cancer in North Carolina, *trans* fatty acid consumption was not associated with colon cancer in either Whites or African Americans. In addition, the association did not differ between proximal or distal cancer locations. The point estimate for the highest quartile of *trans* fatty acid was greater for the proximal colon compared with the distal colon among African Americans, but due to a lack of precision we were unable to establish whether high *trans* fatty acid consumption was truly related to cancer in this section of the colon.

The greater consumption of "fats, oils, and snacks" by African Americans in comparison to the consumption by Whites previously illustrated in our research (7) is not likely to be due to *trans* fatty acid consumption. Whites and African Americans in this study had similar daily intakes of *trans* fatty acids. Moreover, the absence of an association between *trans* fatty acid consumption and colon cancer, combined with the similarity in *trans* fatty acid consumption between the races, makes it unlikely that *trans* fatty acid consumption contributes to the disparity in colon cancer rates observed between Whites and African Americans.

Thus far, results of studies examining the association between colorectal cancer and *trans* fatty acid consumption have been mixed. Three previous case-control studies investigated the association between *trans* fatty acid consumption and colon (15) and colorectal cancer (14, 16). One demonstrated that higher consumption was positively associated with colon cancer for post-menopausal women not on hormone replacement therapy (15) and another found an elevated relative risk among women, in general (16).

There was no association among men in either study (15, 16). The other case-control study also showed no association between colorectal cancer and *trans* fatty acid consumption (14). A cohort study, the Women's Health Study, also examined *trans* fatty acid consumption but found no association (13). No previous studies to which we could compare our results have examined the relationship between *trans* fatty acid consumption and colon cancer in a large population of African Americans.

We have previously shown that high consumption of *trans* fatty acid is associated with higher prevalence of colorectal adenomas (unpublished). Other studies of adenomas have found no association (26, 27). *Trans* fatty acids may work to increase the risk of colorectal adenomas by altering the concentration of fat and bile normally found in the colon (28),thereby irritating the colonic mucosa and resulting in increased oxidative stress (29) and inflammation (25). In addition, some studies have shown that colonic bacteria metabolize bile acids to form compounds that are carcinogenic and increase cellular proliferation (9, 30-32). *Trans* fatty acids may also affect insulin resistance (12, 33, 34), which could lead to increased cellular proliferation (35, 36). It is plausible that these mechanisms bring about changes in the mucosa that result in the formation of adenomas but that *trans* fatty acid consumption does not affect the transition from adenoma to cancer in the colon. Other studies have also found certain exposures to be associated with colorectal adenomas but not with cancer. Despite the lack of association between *trans* fatty acid consumption and colon cancer in our study, if *trans* fatty acids have a moderate affect on developing colorectal adenomas, we expect that the current reductions in the amount of *trans* fatty acids in the food supply, via voluntary removal from food products and bans in the commercial food outlets of certain localities, will favorably affect the rates of colon cancer.

The present study has many strengths, one of which is that we performed in-depth in-person interviews. In addition, we had a large number of African Americans in the study population, a group that has not been examined with respect to *trans* fatty acid consumption and colon cancer. There are limitations to the study as well. We did not have *trans* fatty acid values for all of the foods options present in the Block Food Frequency questionnaire. For example, fried chicken can be classified as homemade or restaurant-made. These may have different amounts of *trans* fatty acid but we assigned them the same value. This is unlikely to have greatly affected our results as it was a small number of foods contributing to only a minor part of participant's reported diets. The mean grams per day of *trans* fatty acid reported in our study is similar to that seen in similar studies, thereby validating our assignment of *trans* fatty acid values.

In conclusion, using data from a large case-control study, we found no association of *trans* fatty acid consumption with colon cancer in either Whites or African Americans. Based on these results, it is unlikely that *trans* fatty acid intake contributes to racial disparities in colon cancer incidence.

5.6 TABLES

TABLE 5.1. Characteristics of the North Carolina Colon Cancer Study I (NCCCS I) population by case status and race, NC, 1996-2000

Participant Characteristics	Whites (n=947)		African-Americans (n=696)	
	Cases (n=341)	Controls (n=606)	Cases (n=282)	Controls (n=414)
Age (%)				
<50	27 (7.92)	34 (5.61)	37 (13.12)	25 (6.04)
50-59	66 (19.35)	108 (17.82)	73 (25.89)	81 (19.57)
60-69	117 (34.31)	206 (33.99)	92 (32.62)	129 (31.16)
>70 years	131 (38.42)	258 (42.57)	80 (28.37)	179 (43.24)
Mean years (SD)	65.06 (9.70)	66.16 (9.30)	62.04 (10.32)	65.94 (9.63)
Sex (%)				
Men	190 (55.72)	328 (54.13)	135 (47.87)	181 (43.72)
Women	151 (44.28)	278 (45.87)	147 (52.13)	233 (56.28)
Education (%)				
≤ High School	194 (57.06)	296 (48.84)	204 (72.34)	286 (69.08)
Some college	69 (20.29)	148 (24.42)	50 (17.73)	73 (17.63)
College graduate/advanced degree	77 (22.65)	162 (26.73)	28 (9.93)	55 (13.29)
Body Mass Index 1 year prior to enrollment (%)*				
Normal (18-24.9 kg/m2)	95 (28.53)	190 (31.99)	44 (15.94)	81 (20.72)
Overweight (25-29.9 kg/m2)	139 (41.74)	250 (42.09)	113 (40.94)	145 (37.08)
Obese (>=30 kg/m2)	99 (29.73)	154 (25.93)	119 (43.12)	165 (42.20)
Mean kg/m^2 (SD)	28.37 (5.62)	27.57 (5.15)	30.07 (6.52)	29.73 (6.50)
Physical Activity (MET-minutes/day) (mean, %)*				
1st quartile	64 (18.93)	121 (20.17)	73 (27.24)	131 (32.11)
2nd quartile	87 (25.74)	151 (25.17)	62 (23.13)	102 (25.00)
3rd quartile	95 (28.11)	175 (29.17)	59 (22.01)	76 (18.63)
4th quartile	92 (27.22)	153 (25.50)	74 (27.61)	99 (24.26)
Mean MET-minutes/day (SD)	2261.46 (565.66)	2199.71 (450.66)	2229.19 (566.56)	2154.99 (533.56)
Smoking status (%)				
Never	115 (33.92)	243 (40.10)	133 (47.50)	188 (45.41)
Former	180 (53.10)	267 (44.06)	91 (32.50)	143 (34.54)
Current	44 (12.98)	96 (15.84)	56 (20.00)	83 (20.05)
Family History (%)				
Yes	74 (21.83)	57 (9.48)	47 (16.67)	43 (10.41)
No	265 (78.17)	544 (90.52)	235 (83.33)	370 (89.59)
NSAID use over the past 5 years (%)†				
Never	38 (11.18)	43 (7.10)	32 (11.35)	31 (7.49)
Occasionally	128 (37.65)	173 (28.55)	123 (43.62)	133 (32.13)
Regularly	174 (51.18)	390 (64.36)	127 (45.04)	250 (60.39)

Trans Fat Consumption				
Mean grams (SD)	5.85 (2.69)	5.17 (2.35)	6.07 (3.15)	5.20 (2.56)
Total Energy Intake				
Mean grams (SD)	1951.58 (689.12)	1784.01 (599.53)	1940.41 (832.11)	1697.62 (652.52)
Calcium Consumption				
Mean grams (SD)	721.10 (340.21)	755.93 (349.77)	615.97 (342.40)	577.03 (280.37)
Alcohol Consumption				
0 drinks/day	209 (61.29)	361 (59.57)	220 (78.01)	334 (80.68)
>0 and ≤1 drink/day	81 (23.75)	182 (30.03)	38 (13.48)	67 (16.18)
>1 drink/day	51 (14.96)	63 (10.40)	24 (8.41)	13 (3.14)
Red Meat Consumption				
Mean ounces (SD)	139.00 (94.96)	118.33 (80.06)	122.77 (85.56)	104.14 (77.85)
Vegetable Consumption				
Mean servings (SD)	231.99 (107.13)	251.94 (123.00)	188.92 (117.43)	191.40 (105.37)

*Data were missing for: Education (n=1), BMI (n=49), physical activity (n=29), smoking status (n=4) and family history (n=8), NSAID use (n=1)

† Non-steroidal anti-inflammatory drug (NSAID) use is defined as Never for subjects who reported no use, Occasional for subjects who reported some use but use less than 15 times/month, and Frequent for subjects who reported use at least 15 times/month

TABLE 5.2. Odds ratios (95% confidence intervals)* of quartiles of non-energy adjusted and energy adjusted *trans* fatty acid intake with colon cancer risk by race, NCCCS I, 1996-2000

NON-ENERGY ADJUSTED†

		WHITES				AFRICAN AMERICANS			
Quartiles of *trans* fatty acid consumption	Median grams trans fatty acid/day (IQR)	N cases	N controls	OR	95% CI	N cases	N controls	OR	95% CI
1	2.70 (2.22, 3.11)	62	140	1.00		57	96	1.00	
2	4.07 (3.76, 4.41)	66	136	1.02	0.65, 1.60	52	104	0.87	0.52, 1.45
3	5.50 (5.11, 5.91)	77	154	1.10	0.69, 1.77	57	85	1.36	0.79, 2.33
4	8.04 (7.20, 9.79)	122	144	2.01	1.22, 3.30	105	96	2.50	1.40, 4.47

ENERGY ADJUSTED‡

		WHITES				AFRICAN AMERICANS			
Quartiles of *trans* fatty acid consumption	Median grams energy-adjusted trans fatty acid/day (IQR)	N cases	N controls	OR	95% CI	N cases	N controls	OR	95% CI
1	4.26 (3.66, 4.59)	92	173	1.00		53	70	1.00	
2	5.24 (5.07, 5.44)	79	138	1.10	0.74, 1.63	57	108	0.80	0.47, 1.34
3	5.99 (5.81, 6.19)	69	137	0.87	0.58, 1.32	75	111	1.02	0.62, 1.68
4	7.12 (6.71, 7.84)	94	138	1.01	0.69, 1.49	91	114	0.99	0.61, 1.62

*Odds ratio: OR; 95% confidence interval (95%CI); Interquartile Range: IQR

†Adjusted for age, sex, vegetable consumption, meat consumption, calcium intake, and BMI

‡Adjusted for age, sex, energy intake, and calcium intake

TABLE 5.3. Odds ratios (95% confidence intervals)* of quartiles of non-energy adjusted and energy adjusted *trans* fatty acid intake with colon cancer risk by location and race, NCCCS I, 1996-2000

Quartiles of trans fatty acid consump-tion§	WHITES								AFRICAN AMERICANS							
	Non-Energy Adjusted†				Energy Adjusted‡				Non-Energy Adjusted†				Energy Adjusted‡			
	N cases	N controls	OR	95% CI	N cases	N controls	OR	95% CI	N cases	N controls	OR	95% CI	N cases	N controls	OR	95% CI
	PROXIMAL COLON															
1	26	140	1.00		42	173	1.00		23	96	1.00		22	70	1.00	
2	34	134	1.15	0.62, 2.15	40	138	1.40	0.83, 2.37	25	104	1.08	0.55, 2.14	29	108	0.97	0.49, 1.90
3	33	153	1.22	0.63, 2.35	23	137	0.73	0.40, 1.35	26	84	1.72	0.84, 3.55	24	111	0.77	0.39, 1.55
4	44	144	1.96	0.98, 3.96	35	138	1.05	0.60, 1.83	46	96	3.10	1.45, 6.63	48	114	1.35	0.71, 2.55
	DISTAL COLON															
1	32	140	1.00		43	173	1.00		31	96	1.00		31	70	1.00	
2	28	134	0.79	0.43, 1.46	35	138	0.96	0.56, 1.63	24	104	0.69	0.36, 1.33	26	108	0.77	0.39, 1.50
3	37	153	0.96	0.51, 1.80	35	137	0.90	0.52, 1.56	25	84	0.93	0.46, 1.85	38	111	1.26	0.68, 2.33
4	58	144	1.55	0.81, 2.99	46	138	0.92	0.55, 1.56	49	96	1.72	0.82, 3.59	28	114	0.69	0.36, 1.31

*Odds ratio: OR; 95% confidence interval (95%CI)

†Adjusted for age, sex, calcium intake, meat consumption, alcohol consumption, BMI one year prior, and family history of colorectal cancer

‡Adjusted for age, sex, energy intake, calcium intake, and alcohol intake

§ Median grams trans fatty acid/day (IQR): Non-energy adjusted quartiles: Q1) 2.70 (2.22, 3.11); Q2) 4.07 (3.76, 4.41); Q3) 5.50 (5.11, 5.91); Q4) 8.04 (7.20, 9.79); Energy adjusted quartiles: Q1) 4.26 (3.66, 4.59); Q2) 5.24 (5.07, 5.44); Q3) 5.99 (5.81, 6.19); Q4) 7.12 (6.71, 7.84)

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6. RESULTS PAPER 3: *Trans* Fatty Acid Consumption and its Association with Distal Colorectal Cancer in the North Carolina Colon Cancer Study II

6.1 ABSTRACT

Background: Recently, there has been much concern about the effect of *trans* fatty acid consumption on health. A few studies have looked at the risk of colorectal cancer with increased consumption of *trans* fatty acid, but to our knowledge, none have investigated the risk of rectal cancer, which may have different risk factors than colon cancer.

Methods: We used a large case-control study of Whites (n=1516) and African Americans (n=392) in central and eastern North Carolina. Incident cases of histologically confirmed distal colorectal (sigmoid, rectosigmoid, and rectal) cancer (n=950) and controls matched by sex, race, and 5-year age groups (n=958) were interviewed about demographic information, lifestyle factors, and diet (using the Diet History Questionnaire).

Results: White cases reported a higher mean consumption of *trans* fatty acid compared to controls (6.1 versus 5.4 grams/day). The mean consumption of *trans* fatty acid was similar for African American cases and controls (6.3 grams/day). Relative to the lowest quartile, the highest quartiles of energy-adjusted *trans* fatty acid consumption were positively associated with distal colorectal cancer for Whites [adjusted odds ratios for the third and fourth quartiles, respectively: 1.45 (95% confidence interval: 1.06, 1.97) and 1.34 (95% confidence interval: 0.99, 1.83)]. *Trans* fatty acid consumption was inversely associated

with distal colorectal cancer in African Americans [adjusted odds ratio for the fourth quartile compared to the lowest quartile of consumption of 0.54 (95% confidence interval 0.28, 1.02)]. These associations persisted in the analyses of different types of *trans* fatty acids. *Trans* fatty acid consumption was not differentially associated with cancer of the sigmoid colon, rectosigmoid, or rectum.

Conclusion: High consumption of *trans* fatty acids is positively associated with cancer in the sigmoid colon, rectosigmoid, and rectum among Whites.

6.2 INTRODUCTION

In the United States, colorectal cancer is the third leading cause of cancer death among both men and women, accounting for approximately 10% of all cancer deaths each year. It is estimated that in 2007, 112,340 people were diagnosed with colon cancer and 41,420 people were diagnosed with rectal cancer in the United States (1). Diet is thought to play a large role in the development of colorectal cancer (2). Total dietary fat has been studied as a potential risk factor for colorectal cancer, but no overall association has been found (3-9). It is possible, however, that a specific type of dietary fat may be associated with colorectal cancer. For example, the majority of studies agree that saturated fatty acids do not affect the risk of colorectal cancer (6, 8, 10, 11). Other fatty acids, such as, n-3 and n-6 polyunsaturated fatty acids have been studied but the results are inconsistent (8, 10, 11).

Trans fatty acid consumption has been linked to a variety of diseases, including heart disease and type II diabetes (12, 13). Ecologic studies have demonstrated a relationship between *trans* fatty acids and the rates of prostate, breast, and colon cancer in Europe (14). Therefore, we hypothesized that *trans* fatty acid might be involved in increasing the risk of developing cancers of the colon and rectum.

Although the majority of etiologic studies combine cancers of the colon and rectum, the risk factors for these cancers may be distinct. In the EPIC study cohort waist circumference, waist-hip ratio, and physical activity were positively associated with colon cancer but not rectal cancer (15, 16). These findings were also supported by a review of physical activity and cancers of the colon and rectum (17). Thus far, to our knowledge, no studies of *trans* fatty acid consumption and colorectal cancer have examined associations

with cancers of the colon and rectum separately. Therefore, we used data from the North Carolina Colon Cancer Study II to investigate the potential association between consumption of *trans* fatty acids and cancer of the distal colon and rectum. In addition, we investigated whether these associations differed by race.

6.3 MATERIALS AND METHODS

6.3.1 STUDY POPULATION

The North Carolina Colon Cancer Study II (NCCCS II) is a population-based case-control study conducted in central and eastern North Carolina. Subjects were enrolled from 33 counties, representing urban, suburban, and rural areas of the state.

Cases were identified using the rapid case ascertainment system of the North Carolina Central Cancer Registry. Those individuals with a first diagnosis of histologically confirmed sigmoid colon, rectosigmoid, or rectal adenocarcinoma between November 2001 and August 2006 were classified as potential cases. To be eligible for the study, subjects had to be between the ages of 40 and 80, reside in one of the 33 counties included in the study, be able to give informed consent, be able to complete an interview, had a North Carolina driver's license or identification card (if under the age of 65), and had no denial by the primary physician for us to contact them.

Potential cases were sent a letter describing the study, which was followed up with a call from a race-matched enrollment specialist. The specialist explained the study and answered any questions that the patient had about participating. If the patient consented, then the enrollment specialist scheduled an in-person interview. On average, interviews took place within five months of diagnosis. White cases were under-sampled for recruitment in order to increase the proportion of African American cases in the study population.

Controls were selected from two sources: North Carolina Department of Motor Vehicles records (for controls under the age of 65) and Center for Medicare and Medicaid

Services records (for controls age 65 and older). Randomized recruitment (18) was used to sample controls according to the expected age (within 5-year strata), sex, and race distribution of the cases. Potential controls were contacted in a manner similar to that of the cases. The same eligibility requirements (with the exception of physician contact) were applied to the control population.

6.3.2 DATA COLLECTION

Data were collected by trained nurse interviewers at the person's house or another convenient location. Individuals were offered a $25 incentive for participation in the study. All participants were asked questions pertaining to demographic information, lifestyle factors, and medical history. Information on physical activity was ascertained using a seven-day recall previously validated in a group of men and women aged 20-59 (19-21). Height and weight were measured at the interview, and participants were also asked about their weight one year prior to diagnosis (for cases) or interview (for controls).

Dietary information was collected using the validated Diet and Health Questionnaire (DHQ) developed at the National Cancer Institute (22-24). This food frequency questionnaire allows participants to choose both the portion size and frequency of foods that they consume and also accounts for differences in cooking methods. In order to capture usual diet across seasons, we asked participants to use a reference period of the year prior to cancer diagnosis (for cases) or interview (for controls). Diet*Calc, a program developed by the NCI to accompany the DHQ, was used to determine average daily nutrient intakes, including *trans* fatty acids, for each subject.

6.3.3 DATA ANALYSIS

Participants who self-identified their race as "other" or were missing information on self-identified race were removed from the analysis (n=61). Participants with extreme or implausible dietary values [< 800 or >5000 kcal/day for men (n=74) and <600 or >4000 kcal/day for women (n=34)] were also excluded from the analysis.

We utilized the residual method to measure *trans* fatty acid consumption adjusted for energy intake. Specifically, the values of each participant's energy-adjusted intakes were estimated based on a regression model in which energy intake was the independent variable and *trans* fatty acid intake was the dependent variable (25). This allowed us to focus on *trans* fatty acid consumption estimates that were not correlated with energy intake. *Trans* fatty acid consumption was then categorized into quartiles based on consumption in the control group.

We used unconditional logistic regression to investigate the relationship between *trans* fatty acid consumption and distal colorectal cancer. An offset term was included in all models to correct for the randomized recruitment sampling fractions (18). Non-steroidal anti-inflammatory drug (NSAID) use and sex were assessed as potential effect measure modifiers, using tests of homogeneity and likelihood ratio tests comparing models with and without interaction terms (with an a priori p-value cut-off for retention in the final model of less than 0.15). These variables were chosen because similar studies found that the association between *trans* fatty acid consumption differed within strata of these variables (11, 26). In addition, NSAID use has previously been inversely associated with colon cancer (27) and could play a biologic role if *trans* fatty acid consumption does promote inflammation (28). Likelihood ratio tests examining NSAID use as an effect measure

modifier had *p*-values of 0.36 in Whites and 0.90 in African Americans. P-values for the likelihood ratio tests examining sex as an effect measure modifier were 0.26 in Whites and 0.42 in African Americans. The following variables, which have been previously associated with colorectal cancer and may be associated with *trans* fatty acid consumption, were assessed as potential confounders using a 10% change-in-estimate criterion: body mass index (BMI) one year prior to diagnosis/interview (normal, overweight, and obese according to the World Health Organization cut-points), physical activity (quartiles based on the control group), at least one first degree family member with a diagnosis of colorectal cancer (yes, no), NSAID use (never, rare, and frequent), smoking status (never, former, and current smoker), and daily consumption of calcium (dietary and supplemental), alcohol, vegetables, and red meat (quartiles based on the control group). Although the actual number of missing observations was small, multiple imputation was performed to impute data for potential confounding variables with more than 0.5% percent missing data (physical activity: 5.2% missing, BMI one year prior: 3.7% missing, family history: 2.3% missing, smoking status: 0.9% missing, and NSAID use: 0.6% missing). Characteristics that met our change-in-estimate criterion in one or both racial groups [highest level of education completed (in both groups), BMI one year prior to interview (in Whites), and family history of colorectal cancer (in African Americans)] were included in the final models for both races. In addition, the final model included a term for total energy intake, a term for stratum of matching variable (sex and five-year categories of age), and an offset term to account for sampling probabilities.

In addition, we investigated the relationship between the location of the tumor (sigmoid colon, rectosigmoid, or rectum) and *trans* fatty acid consumption. Cases without a

specified location were excluded from this analysis (n=12). This analysis was performed using multinomial logistic regression, without imputing data for missing covariates, as this was not possible with the model we used. Another limitation of this model is that we were not able to include offset terms. Potential confounders were reassessed for this model using a 10% change-in-estimate criterion.

6.4 RESULTS

Among those who were eligible to participate in the study, 17% of cases and 26% of controls refused and 8% of cases and 18% of controls were untraceable or not reached. A total of 2076 people completed interviews (1057 cases and 1019 controls), yielding study cooperation rates (interviewed/(interviewed+refused)) for cases and controls of 81% and 68% and response rates (interview/eligible) of 74% and 56%, respectively.

Characteristics of the study population are shown according to case-control status and race in Table 6.1. Most of the study participants were at least 60 years old. A larger percentage of White and African American cases had a high school degree or less compared with controls (19.4 and 35.2% compared with 12.1 and 26.4%, respectively). Both White and African American cases were more likely to be obese compared to controls (36.7 and 49.5% versus 28.3 and 41.3%, respectively). Cases had a higher total energy intake compared to controls [mean (standard deviation) kcal/day of 2280.5 (855.8) versus 2158.0 (813.6)]. Within each group of cases and controls, African Americans reported higher total energy intake than Whites. Both t-tests (Whites: p-value 0.02; African Americans: p-value 0.06) and a logistic regression model using 100 kcal units of total energy intake and controlling for possible covariates [Whites: 1.02 (95% CI 1.01, 1.04) p-value 0.01; African Americans: 1.03 (95% CI 1.00, 1.06) p-value 0.04] showed total energy intake to be associated with distal colorectal cancer. This association, combined with the determination that energy intake was correlated with *trans* fatty acid consumption (correlation was 0.77 for Whites and 0.81 for African Americans) support our use of energy adjustment.

White cases had a higher mean intake of unadjusted *trans* fatty acid than controls [mean (standard deviation) grams/day of 6.1 (3.0) and 5.4 (2.9), respectively] (t-test p-value <0.01). The median grams/day (interquartile range) for intake among Whites were 5.6 (3.8, 7.7) for cases and 4.9 (3.2, 7.0) for controls (Wilcoxon rank-sum test p-value <0.01). Intakes were similar among African American cases and controls: a mean of 6.33 for both cases and controls (standard deviation of 3.3 and 3.5, respectively) (t-test p-value 0.97). The similarity was also seen for the medians of *trans* fatty acid consumption (5.7 grams/day; Wilcoxon rank-sum test 0.84). We modeled the association between total *trans* fatty acid intake, prior to energy adjustment and distal colorectal cancer, controlling for variables found to be confounders of the non-energy adjusted model (physical activity, education, calcium intake, and meat consumption), sex, age, and offset terms. There was a positive relationship between increasing *trans* fatty acid consumption and distal colorectal cancer for Whites. Odds ratios comparing the second, third, and fourth quartiles to the lowest quartile of consumption were 1.66 (95% CI 1.20, 2.31), 1.74 (95% CI 1.22, 2.48) and 2.44 (95% CI 1.64, 3.65), respectively. For African Americans the odds ratios were 1.22 (0.59, 2.52), 1.52 (95% CI 0.68, 3.39) and 0.69 (95% CI 0.30, 1.60), respectively.

High consumption of *trans* fatty acids was positively associated with distal colorectal cancer for Whites (Table 6.2). The odds ratios for the energy-adjusted models were slightly decreased from those seen in the non-energy adjusted models. Both the third and fourth quartiles of *trans* fatty acid consumption remained positively associated with distal colorectal cancer [third quartile: odds ratio 1.45 (95%CI: 1.06, 1.97); fourth quartile: odds ratio 1.34 (95% CI: 0.99, 1.83)]. A similar association was not seen for African Americans (Table 6.2) with the odds ratios comparing the third and fourth quartiles to the lowest

quartile being 0.72 (95% CI: 0.36, 1.43) and 0.54 (95% CI: 0.28, 1.02), respectively. *A priori*, we decided to present both combined and race-stratified results. Therefore, although we noted differences in the estimated association by race, the combined results are also given in Table 6.2. The results for the overall study population are 1.31 (95% CI: 0.99, 1.74) for the third quartile and 1.14 (95%CI: 0.87, 1.51) for the fourth quartile compared with the lowest quartile of consumption. We further examined the relationship looking at specific types of *trans* fatty acid: 16:1 *trans*-hexadecenoic acid. 18:1*trans*-octadecenoic acid, and 18:2*trans*-octadecadienoic acid. The same relationships seen in total *trans* fatty acid consumption were present for each of these in both Whites and African Americans (Table 6.2).

Finally, we explored the relationships between consumption of *trans* fatty acids and tumor location (sigmoid colon, rectosigmoid, or rectum). Though the results were more imprecise due to smaller numbers in each of the categories, a positive association was seen for all three locations with moderate/high consumption of *trans* fatty acid in Whites. There was a positive but imprecise association between high *trans* fatty acid consumption (fourth quartile) and cancer of the rectosigmoid among African Americans, but only twenty-four African Americans had cancer present in this location. The other tumor sites showed inverse associations consistent with those of the combined analysis (Table 6.3). Overall, associations with *trans* fatty acid consumption did not clearly differ in either racial group based on the location of the cancer.

6.5 DISCUSSION

In this study, we found distal colorectal cancer was positively associated with consumption of *trans* fatty acids for Whites. The two highest quartiles of *trans* fatty acid consumption had the largest increase in relative risk of colorectal cancer. This was true for all types of *trans* fatty acid (16:1 *trans* hexadecenoic acid, 18:1 *trans* octadecenoic acid , and, 18:2 *trans* octadecadienoic acid). In addition there was no difference in relative risk for cancer of the sigmoid colon, rectosigmoid, or rectum. In Whites, increased consumption of *trans* fatty acids was positively associated with cancer for each of these locations.

The results of the combined analysis showed a positive association between distal colorectal cancer and the third quartile of *trans* fatty acid consumption compared with the lowest quartile, but no association was present in the comparison of the highest to lowest quartiles. In African Americans the association between distal colorectal cancer and increased consumption of *trans* fatty acid was the opposite of what we saw for Whites; higher consumption appeared protective. This was true among all types of *trans* fatty acid. We cannot explain why increased consumption of *trans* fatty acid is inversely associated with distal colorectal cancer in African Americans. It could be the result of sampling error among the control population, inaccurate dietary reporting among the controls, or confounding by an unknown factor. It is also possibly a chance finding. Further work should be done examining the association in a large sample of African Americans.

Previous studies examined colon or colorectal cancer in association with *trans* fatty acid consumption (8, 10, 11, 26) and have reported mixed results. However, our study is different from these previous works in that we concentrate on the sigmoid colon and rectum.

It is possible that the proximal areas of the colon are not affected by *trans* fatty acid consumption whereas the more distal sections are. Potentially, prior studies that combined cancers of colon and rectum into one outcome group would not have seen a positive association between colorectal cancer and *trans* fatty acid consumption if the majority of cases in their study were comprised of individuals with cancers of the proximal colon. The incidence of rectal cancer is much lower than that of colon cancer so it is possible that relatively few distal colorectal cancers were included in previous studies.

There are several potential mechanisms by which *trans* fatty acid consumption could affect the risk of distal colorectal cancer. First, *trans* fatty acids themselves could irritate the colonic mucosa. A study in male rats found that the fat excretion:intake ratio was two times higher for rats fed *trans* fatty acid compared to rats fed *cis*- fatty acids (29). Though to our knowledge no similar studies have been performed in humans, it is possible that *trans* fatty acids present in fecal matter irritate the distal colon and rectum, resulting in increased proliferation, inflammation and, oxidative stress. A higher amount of an oxidative stress marker (urinary 8-iso-PGF(2alpha)) was found in participants of a small randomized trial who consumed 6.0 grams of *trans* fatty acid per day for six weeks when compared with those given a diet free of *trans* fatty acids over the same time period (30). In addition, systemic inflammatory markers [soluble tumor necrosis factor α receptor 1 and 2 (sTNF-R1 and –R2)] have been positively associated with *trans* fatty acid intake in women from the Nurses' Health Study cohort (28). Bile acids resulting from the digestion of *trans* fatty acids may also play a role. Some studies have shown that bile acids in the colon are metabolized by bacteria, producing carcinogenic compounds and increasing cellular proliferation (31, 32). Another mechanism explaining the roles of *trans* fatty acids in the development of

distal colorectal cancer could be that of insulin resistance. Studies have found that *trans* fatty acid intake increased insulin resistance in subjects with diabetes or insulin resistance, though this effect was not seen in healthy subjects (33). Increased insulin stimulates cell signaling pathways to increase proliferation, which will favor cells that are defective (such as those with activated oncogenes) (34). Cellular proliferation has been positively associated with the incidence of colorectal cancer in animals (35).

Currently, there is a campaign to have *trans* fatty acids removed from foods. Certain localities, including New York City, have banned *trans* fatty acids from commercial food outlets (36, 37). As of January 1, 2006, all food products sold in the United States were required to list the amount of *trans* fatty acids in the nutritional information on packaging (38). Though we did not stop enrollment until August of 2006, we do not believe that the removal and labeling of foods affected our results. First, it is not consumption immediately prior to the development of cancer that is likely to be the most important, so diet during this period of eight months is not likely to have resulted in immediate cancer. Also, the Diet*Calc system uses *trans* fatty acid values for foods prior to January 2006 (when many companies began removing them from their foods) so the amount of *trans* fatty acids in the food supply matches that of the amount we assigned to each food participants reported consuming.

This study has certain strengths. The study was large, population-based, and used dietary instruments previously validated in other populations (23). The interviews were conducted in-person and captured information on various potential colorectal cancer risk factors. There are some limitations as well. First, although there were a large number of White participants the number of African Americans in our study population was small. As

in all case-control study designs, there is the potential for selection and recall bias. Also, our food frequency questionnaire grouped all foods of a certain type together. The amount of *trans* fatty acids vary within each type of food based on the brand, preparation, etc. Thus, we were unable to discern if people eating certain foods had more or less *trans* fatty acids in their diet than people eating different brands of a similar food.

In conclusion, we have demonstrated that increased consumption of *trans* fatty acid is associated with an increased risk of cancers in the sigmoid colon, rectosigmoid, and rectum in Whites. The results for African Americans are inconclusive but in our study population distal colorectal cancer appeared to be inversely associated with *trans* fatty acid consumption. This research contributes to the growing literature supporting negative health effects of *trans* fatty acid. Reductions in consumption of *trans* fatty acids and their removal from foods should be advocated.

6.6 TABLES

TABLE 6.1. Characteristics of the North Carolina Colon Cancer Study II (NCCCS II) population by case status and race, NC, 2001-2006

Participant Characteristics	Whites (n=1516)		African-Americans (n=392)	
	Cases (n=717)	Controls (n=799)	Cases (n=233)	Controls (n=159)
Age (%)				
<50	87 (12.13)	74 (9.26)	32 (13.73)	17 (10.69)
50-59	193 (26.92)	183 (22.90)	68 (29.18)	41 (25.79)
60-69	211 (29.43)	253 (31.66)	79 (33.91)	54 (33.96)
>70 years	226 (31.52)	289 (36.17)	54 (23.18)	47 (29.56)
Mean years (SD)	62.7 (10.1)	64.1 (9.8)	61.3 (9.9)	63.2 (9.6)
Sex (%)				
Men	410 (57.18)	483 (60.45)	118 (50.64)	84 (52.83)
Women	307 (42.82)	316 (39.55)	115 (49.36)	75 (47.17)
Education (%)				
≤ High School	139 (19.39)	97 (12.14)	82 (35.19)	42 (26.42)
Some college	369 (51.46)	372 (46.56)	100 (42.92)	81 (50.94)
College graduate/advanced degree	209 (29.15)	330 (41.30)	51 (21.89)	36 (22.64)
Body Mass Index 1 year prior to enrollment (%)*				
Normal (18-24.9 kg/m2)	171 (24.68)	246 (31.62)	41 (18.98)	33 (22.00)
Overweight (25-29.9 kg/m2)	268 (38.67)	312 (40.10)	68 (31.48)	55 (36.67)
Obese (>=30 kg/m2)	254 (36.65)	220 (28.28)	107 (49.54)	62 (41.33)
Mean kg/m^2 (SD)	29.1 (6.3)	28.0 (5.5)	31.6 (7.8)	29.8 (6.5)
Physical Activity (MET-minutes/day) (mean, %)*				
1^{st} quartile	176 (25.69)	186 (24.35)	66 (30.84)	42 (28.77)
2^{nd} quartile	168 (24.53)	183 (23.95)	54 (25.23)	44 (30.14)
3^{rd} quartile	138 (20.15)	201 (26.31)	36 (16.82)	27 (18.49)
4^{th} quartile	203 (29.64)	194 (25.39)	58 (27.10)	33 (22.60)
Mean MET-minutes/day (SD)	2249.7 (664.3)	2152.6 (475.0)	2172.5 (540.0)	2148.9 (495.0)
Smoking status (%)				
Never	264 (36.87)	301 (37.96)	87 (38.50)	62 (40.00)
Former	342 (47.77)	386 (48.68)	87 (38.50)	67 (43.23)
Current	110 (15.36)	106 (13.37)	52 (23.01)	26 (16.77)
Family History (%)				
Yes	92 (13.16)	89 (11.37)	27 (11.84)	8 (5.16)
No	607 (86.84)	694 (88.63)	201 (88.16)	147 (94.84)
NSAID use over the past 5 years (%)*†				
Never	160 (22.32)	120 (15.02)	65 (28.76)	39 (25.32)
Occasionally	307 (42.82)	315 (39.42)	105 (46.46)	79 (51.30)
Regularly	250 (34.87)	364 (45.56)	56 (24.78)	36 (23.38)

Trans Fat Consumption				
Mean grams (SD)	6.05 (3.03)	5.41 (2.88)	6.32 (3.31)	6.34 (3.53)
Total Energy Intake				
Mean kcal (SD)	2248.1 (822.4)	2147.5 (793.9)	2389.5 (944.6)	2210.5 (907.4)
Calcium Consumption				
Mean grams (SD)	816.9 (359.1)	859.4 (393.3)	779.7 (350.7)	725.5 (359.6)
Alcohol Consumption				
0 drinks/day	366 (51.05)	320 (40.04)	156 (66.95)	97 (61.01)
>0 and <1 drink/day	219 (30.54)	315 (39.42)	45 (19.31)	45 (28.30)
≥1 drink/day	132 (18.41)	164 (20.53)	32 (13.73)	17 (10.69)
Red Meat Consumption				
Mean ounces (SD)	1.9 (1.4)	1.8 (1.4)	1.8 (1.5)	1.8 (1.6)
Vegetable Consumption				
Mean servings (SD)	4.1 (2.0)	4.3 (2.1)	4.1 (2.3)	3.8 (2.3)

*Data were missing for: BMI (n=71), physical activity (n=99), smoking status (n=18), family history (n=43) and NSAID use (n=12)

† NSAID use is defined as Never for subjects who reported no use, Occasional for subjects who reported some use but use<15 times/month, and Frequent for subjects who reported use of NSAIDs at least 15 times/month

TABLE 6.2. Odds ratios (95% confidence intervals)*† of quartiles of *trans* fatty acid intake with distal colorectal cancer by race (n=1908), NCCCS II, 2001-2006

Quartiles of intake	Total Study Population (n=1908)‡					Whites (n=1516)				African-Americans (n=392)			
TOTAL TRANS FATTY ACID CONSUMPTION													
	Median grams of trans fatty acid /day (IQR)	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1	4.40 (3.70, 4.84)	199	240	1.00		146	216	1.00		53	24	1.00	
Q2	5.66 (5.41, 5.92)	214	239	1.10	0.83, 1.46	154	203	1.12	0.81, 1.54	60	36	0.89	0.44, 1.77
Q3	6.65 (6.39, 6.91)	267	240	1.31	0.99, 1.74	213	198	1.45	1.06, 1.97	54	42	0.72	0.36, 1.43
Q4	8.30 (7.73, 9.29)	270	239	1.14	0.87, 1.51	204	182	1.34	0.99, 1.83	66	57	0.54	0.28, 1.02
16:1 TRANS HEXADECENOIC FATTY ACID CONSUMPTION													
	Median grams of trans fatty acid /day (IQR)	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1	0.05 (0.04, 0.06)	234	240	1.00		167	211	1.00		67	29	1.00	
Q2	0.07 (0.07, 0.08)	210	239	1.01	0.77, 1.33	162	203	1.05	0.78, 1.43	48	36	0.80	0.41, 1.58
Q3	0.09 (0.08, 0.10)	222	240	1.03	0.78, 1.37	169	202	1.10	0.80, 1.50	53	38	0.72	0.37, 1.41
Q4	0.13 (0.11, 0.16)	284	239	1.20	0.92, 1.56	219	183	1.45	1.08, 1.94	65	56	0.57	0.31, 1.04
18:1 TRANS OCTADECENOIC FATTY ACID CONSUMPTION													
	Median grams of trans fatty acid /day (IQR)	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1	3.77 (3.20, 4.16)	208	240	1.00		153	215	1.00		55	25	1.00	
Q2	4.99 (4.65, 5.10)	206	239	0.99	0.75, 1.32	149	204	1.00	0.73, 1.37	57	35	0.84	0.42, 1.68
Q3	5.77 (5.55, 6.03)	264	240	1.22	0.93, 1.61	210	200	1.31	0.96, 1.78	54	40	0.75	0.38, 1.48
Q4	7.28 (6.76, 8.21)	272	239	1.08	0.82, 1.42	205	180	1.27	0.93, 1.73	67	59	0.51	0.27, 0.95
18:2 TRANS OCTADECADIENOIC FATTY ACID CONSUMPTION													
	Median grams of trans fatty acid /day (IQR)	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1	0.52 (0.44, 0.56)	207	240	1.00		143	210	1.00		64	30	1.00	
Q2	0.64 (0.62, 0.66)	206	239	1.08	0.81, 1.43	150	201	1.11	0.81, 1.53	56	38	0.91	0.48, 1.74
Q3	0.74 (0.71, 0.77)	257	240	1.21	0.92, 1.60	202	197	1.35	0.99, 1.85	55	43	0.72	0.38, 1.38
Q4	0.89 (0.84, 0.97)	280	239	1.18	0.90, 1.55	222	191	1.38	1.02, 1.88	58	48	0.60	0.32, 1.11

*OR: odds ratio; 95%CI: 95% Confidence Interval, IQR: Interquartile range

† Adjusted for energy intake, age, sex, BMI 1 year prior, highest level of education attained, family history of colorectal cancer, and race (in the combined estimates)

‡Likelihood ratio tests of odds ratio modification by race gave the following results: Total *trans* fatty acid intake 0.02; 16:1 *Trans* fatty acid intake 0.08; 18:1 *Trans* fatty acid intake 0.02; 18:2 *Trans* fatty acid intake 0.03

TABLE 6.3. Adjusted odds ratios (95% confidence intervals)*† of quartiles of *trans* fatty acid intake with cancer risk by race and location, NCCCS II, 2001-2006

	Whites				African-Americans			
RECTUM								
Quartiles of intake	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1‡	48	191	1.00		13	21	1.00	
Q2‡	52	194	1.15	0.72, 1.86	25	34	2.09	0.76, 5.75
Q3‡	71	175	1.56	0.98, 2.25	11	36	0.77	0.26, 2.30
Q4‡	68	164	1.32	0.82, 2.11	18	47	0.68	0.25, 1.81
SIGMOID								
Quartiles of intake	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1‡	52	191	1.00		26	21	1.00	
Q2‡	63	194	1.04	0.66, 1.63	23	34	0.59	0.24, 1.46
Q3‡	84	175	1.35	0.87, 2.11	30	36	0.96	0.40, 2.33
Q4‡	80	164	1.25	0.80, 1.97	27	47	0.51	0.22, 1.18
RECTOSIGMOID								
Quartiles of intake	No. of cases	No. of controls	OR	95% CI	No. of cases	No. of controls	OR	95% CI
Q1‡	25	191	1.00		4	21	1.00	
Q2‡	23	194	1.01	0.52, 1.95	3	34	0.53	0.09, 3.11
Q3‡	34	175	1.63	0.87, 3.07	6	36	1.17	0.26, 5.35
Q4‡	34	164	1.31	0.70, 2.43	11	47	1.17	0.29, 4.72

*OR: odds ratio; 95%CI: 95% Confidence Interval

†Adjusted for energy intake, age, sex, BMI 1 year prior, highest level of education attained, family history of colorectal cancer, smoking status, meat consumption, calcium intake, and physical activity

‡Median *trans* fatty acid intake grams/day (IQR): Q1) 4.40 (3.70, 4.84); Q2) 5.66 (5.41, 5.92); Q3) 6.65 (6.39, 6.91); Q4) 8.30 (7.73, 9.29)

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7. CONCLUSIONS

7.1 RECAPITULATION OF STUDY AIMS AND FINDINGS

The goal of this dissertation was to explore the relationship between *trans* fatty acid consumption and digestive tract neoplasia. Through the use of three large studies, each of the proposed aims was investigated. These aims were: to determine whether increasing consumption of *trans* fatty acids is associated with 1) colorectal adenomas (adenomas present throughout the entire colon and rectum); 2) colon cancer (cancers from the cecum through the sigmoid colon); and 3) distal colorectal cancer (cancers of the sigmoid colon, rectosigmoid, and rectum). No relationship was present between colon cancer and *trans* fatty acid consumption, but a positive association was detected with increasing consumption for colorectal adenomas and distal colorectal cancer (in Whites). The findings regarding each of the three aims are further summarized below.

7.1.1 *TRANS* FATTY ACID CONSUMPTION AND COLORECTAL ADENOMAS

Using the Diet and Health Study IV, the relationship between *trans* fatty acid consumption and the prevalence of colorectal adenomas (adenomas present throughout the entire colon and rectum) was examined. High consumption was associated with colorectal adenomas, but lower levels of consumption did not show an association. Associations between *trans* fatty acid consumption and location, size, and number of adenomas were

imprecise, but were consistently elevated for the highest versus lowest quartiles of consumption. A strong association was present in the proximal versus distal colon; however, a difference in the association by location could not be firmly established due to the precision of the estimates. There was no difference in the relationship between colorectal adenomas and *trans* fatty acid consumption by size or number of adenomas.

7.1.2 *TRANS* FATTY ACID CONSUMPTION AND COLON CANCER

The second aim of this dissertation was to explore the relationship between *trans* fatty acid consumption and colon cancer (cancers present throughout the colon from the cecum through the sigmoid colon). In this study, *trans* fatty acid consumption was not associated with the risk of colon cancer among Whites or African Americans. Furthermore, the association did not vary by cancer location.

This study went further than proposed by examining the association by race, with the possibility that differential consumption of *trans* fatty acids might explain some of the disparity in colon cancer rates between Whites and African Americans. Based on the similar consumption patterns and the lack of association seen in this study, it is unlikely that *trans* fatty acid consumption is contributing to the disparity in colon cancer rates between Whites and African Americans.

7.1.3 *TRANS* FATTY ACID CONSUMPTION AND DISTAL COLORECTAL CANCER

The third aim looked at the relationship between *trans* fatty acid consumption and colorectal cancer but this time concentrated on distal colorectal cancer (cancer of the sigmoid colon, rectosigmoid, or rectum). Increasing consumption of *trans* fatty acids was positively associated with distal colorectal cancer in Whites. This relationship was the opposite for African Americans, with increased consumption resulting in an inverse association.

Recent studies have shown that cancers of the colon and rectum may have different risk factors (1-3). The results of this aim combined with that of the previous aim support the conclusion that *trans* fatty acid consumption may be another risk factor that is different for the colon and the rectum. High consumption of *trans* fatty acids may be a risk factor for cancers of the sigmoid colon, rectosigmoid, and rectum but not a risk factor for colon cancer.

7.2 STRENGTHS

One of the key strengths of this research was the opportunity to utilize data on three different aspects of colorectal neoplasia. The association between *trans* fatty acid consumption and colorectal neoplasia was examined for different stages in the carcinogenesis process (adenoma and cancer), as well as varying locations of cancer (colon versus distal colon/rectum). Moreover, previous studies have not examined the association within a large sample of African Americans as was possible in the NCCCS I.

All of the studies utilized included a large number of participants and had good response rates. In addition, data was collected by trained interviewers in all three studies. The interviews were in-depth and covered a wide range of information on potential risk factors. The food frequency questionnaires that were utilized have been previously validated in other study populations (4-6).

Finally, effort was taken to reduce the misclassification of cases as controls. In the DHS IV study, a study pathologist reviewed every slide and a random sample of all biopsies collected was resubmitted for review, which found there to be high concordance among the classifications. For the NCCCSs I and II, all of the diagnoses were confirmed by the study pathologist using pathology reports and over 95% of the diagnoses were confirmed using the pathology slides.

7.3 LIMITATIONS

As is the case for all case-control studies as well as some cross-sectional studies, our studies are subject to selection and recall biases. Selection bias occurs when individuals who choose to participate in the study are different than the individuals who refuse to be a part of the study. In other words, the cases and controls that were recruited for the NCCCSs I and II and DHS IV may be different from the actual participants of the studies. However, high response rates among both cases and controls minimized the amount of selection bias present in the studies. Selection bias could also occur if subjects are recruited for the study in a nonrandomized fashion. The NCCCSs I and II both used randomized recruitment strategies as explained in the Methods section (Chapter 3). In the DHS IV, almost every eligible individual undergoing a colonoscopy during the study period was recruited. The recruitment methods used in all three of these studies greatly reduced the possibility of selection bias resulting from nonrandomized participant selection. Recall bias is a type of information bias that occurs when cases and controls remember their exposure differently due to their knowledge of case-control status. For example, cases may have believed that poor dietary habits resulted in their development of adenomas/cancer. Therefore, they recalled consumption of unhealthy foods, such as those containing *trans* fatty acids, more readily than would controls who are not searching for an explanation to a health problem. However, due to the lack of previous research, it is unlikely that cases believed their cancers to be caused specifically by *trans* fatty acid consumption. Consequently, it is not expected that cases would disproportionately recall foods with high amounts of *trans* fatty acids.

In addition, because the NCCCSs I and II are case-control studies and we inquire about diet only one year prior to diagnosis, we cannot establish temporality between *trans* fatty acid consumption and distal colorectal cancer; we can only detect the presence of an association. This issue of temporality is also present in the DHS IV. Only an association can be determined between *trans* fatty acid consumption and colorectal adenomas.

None of the food frequency questionnaires that we utilized in these studies have been validated for *trans* fatty acid intake. Also, we had to assign the values for *trans* fatty acid to each food present in the Block Food Frequency Questionnaire. As discussed in the Results section (Chapter 5), this was a problem for certain options, such as "restaurant fried chicken" versus "homemade fried chicken" since we did not have values that differed in regards to where the food was eaten. Most likely, this did not affect the results as it was a small number of foods contributing to only a minor portion of participants' reported diets. One problem that was present in all of the studies was that the food frequency questionnaires did not ask participants about the brands of food that they consumed. Different brands contain varying amounts of *trans* fatty acids and we were unable to distinguish between participants that consumed brands with high amounts of *trans* fatty acids from participants eating similar foods with lower amounts of *trans* fatty acids. Finally, *trans* fatty acid consumption could be acting as a proxy for other unhealthy behaviors. We attempted to control for this by including covariates that would also be indicative of unhealthy behaviors, such as alcohol consumption, physical activity, and BMI, when determining what confounders should remain in the final models of each study.

7.4 PUBLIC HEALTH SIGNIFICANCE

Colorectal cancer is the third leading cause of cancer death among men and women in the United States. It is also the third most commonly diagnosed cancer in the United States (7). Various aspects of diet are known to be associated with colorectal cancer (8, 9, 10). Diet is a modifiable risk factor, which allows individuals and policies to change in order to reduce the rates of colorectal cancer.

Thus far, few studies have examined the association between colorectal neoplasia and *trans* fatty acid consumption. However, due to the strong association found between *trans* fatty acid consumption and cardiovascular disease, there is already a strong push to have them removed from the food supply. Certain localities, including New York City, have banned *trans* fatty acids from commercial food outlets (11, 12), and as of January 1, 2006, all food products sold in the United States were required to list the amount of *trans* fatty acids in the nutritional information on packaging (13). Activist groups in the United States have also taken action by suing corporations such as McDonald's and Kraft to have them remove the *trans* fatty acids from their foods (14).

High *trans* fatty acid consumption was associated with colorectal adenomas in our study population. Through one or more of the biologic mechanisms proposed in Chapter 1.2.3 (Background Section on *Trans* Fatty Acids) high consumption of *trans* fatty acids increased the relative risk for colorectal adenoma. Though adenomas are the precursors to cancer, increased consumption of *trans* fatty acids was not associated with cancer in all areas of the colon. The association between *trans* fatty acid consumption and colorectal cancer was limited to cancers of the sigmoid colon, rectosigmoid, and rectum. In these

distal areas, high *trans* fatty acid consumption increased the relative risk of cancer among Whites in our study population. An inverse association was detected for *trans* fatty acid consumption and cancer in these distal areas of the colon for African Americans in our study population, but further research needs to be done with a large sample of African Americans to elucidate if this association exists in other populations of African Americans or if it is the result of bias present in our study.

The results of this dissertation provide further support to campaigns whose goal is to limit the amount of *trans* fatty acids present in the food supply and to recommendations for individuals to reduce their intake of *trans* fatty acids. As consumption of *trans* fatty acids continues to decline in the United States, it is expected that rates of colorectal adenomas and cancer may fall as well.

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APPENDIX – IRB NOTIFICATION

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097

TO: Lisa Vinikoor
Carolina Population Center
CB:7555

FROM: Public Health-Nursing IRB

DATE: 6/06/2007

RE: Determination that Research or Research-Like Activity does not require IRB Approval
Study #: 07-0848

Study Title: Trans Fatty Acid Consumption and the Risk of Colon Cancer, Rectal Cancer, and Colorectal Adomas

This submission was reviewed by the above-referenced IRB. The IRB has determined that this submission does not constitute human subjects research as defined under federal regulations (45 CFR 46.102 [d or f] and OHRP guidance) and does not require IRB approval.

No further review of this research is required unless your study changes in such a way that this determination would no longer apply, at which time resubmission to the IRB should be undertaken. Call the IRB at 966-3113 if you have any questions. You can now access IRB status information at https://my.research.unc.edu/.

Study Description:
This project will examine the potential association between trans fatty acid consumption and colon cancer, tectal cancer, and colorectal adenomas. To perform this research, data from three large research studies will be used: the North Carolina Colon Cancer Study, the North Carolina Rectal Cancer Study, and the Diet and Health Study IV. A data use agreement is on file for access to these data.

CC:
Robert Sandler, Medicine, CB:7555, Faculty Advisor