2020

The Impact of Dietary Intake on Mortality Risk in Colorectal Cancer Survivors

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This is to certify that the doctoral dissertation by

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Walden University
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Abstract

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by

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MS, Purdue University, 2004

BS, University of Washington, 2000

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health - Epidemiology

Walden University

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Abstract

The colorectal cancer (CRC) survivor population is increasing in the United States. The lack of effective dietary recommendations in recurrence prevention undermines the health-related quality of life of survivors. Grounded in the socioecological model, dietary behavior is a personal-level risk factor that individuals may control. This study investigated the CRC-specific mortality risk as predicted by diet quality, dietary fiber intake, and dietary fat intake in hope of contributing to future dietary recommendations. A secondary analysis using data from 1,166 CRC survivors in the Multiethnic Cohort Study was analyzed via Cox proportional hazard regression models to estimate mortality risk. Results from the regression models found that postdiagnosis diet quality, as measure by the Healthy Eating Index-2010, was not associated with CRC-specific mortality risk. However, a change in scores from below-median to above-median from prediagnosis was associated with an increased risk (HR = 2.00, 95% CI [1.02, 3.99], $p = 0.044$). Meanwhile, dietary fiber intake of moderate and high levels was associated with 58% and 52% risk reduction ($p = 0.011$ and 0.041, respectively). Finally, neither total dietary fat intake nor fat from fish and shellfish was associated with CRC-specific mortality risk. The findings suggested a need to identify an effective tool to evaluate diet quality post-CRC. Additionally, while dietary fiber intake was favorable in improving long-term outcomes, dietary fat and fish consumption may not directly contribute to CRC-specific mortality risk reduction during long-term survivorship. This study provided new evidence on the dietary needs of minority CRC survivors and may shape public health education.

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Dedication

This project is dedicated to the millions of cancer survivors who persevere through daily challenges to live healthier and productive lives, and to the registered dietitians who work tirelessly to support and motivate their patients.

Acknowledgments

A heartfelt thank you to my committee Chair, Dr. James Rohrer, member, Dr. Patrick Dunn, and University Research Reviewer, Dr. Robin Carlson for their guidance; Dr. Carol Boushey at the University of Hawaii for her liaison with the Multiethnic Cohort Study group.

My sincere gratitude goes to my son, Cillian, for his infectious laughter and inspiration to always apply myself fully; to my parents Benson and Helen Chow, for their unwavering support, and to my partner, Kris Carley, for his exceptional patience, uplifting spirit, and care for my well-being. Special recognition to my professional friends and colleagues, Dr. Jimin Yang and Dr. Ruslan Nikitin, for their time and input during manuscripts revisions.

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Part 1: Overview

Introduction

Colorectal cancer (CRC) ranks third in incidence among newly diagnosed malignancies in the United States. In 2020, the expected colon cancer cases will reach 104,610 and rectal cancer will exceed 43,000 cases (Siegel et al., 2020). However, early detection and treatment advancements have led to improved survival rates, contributing to a growing population of over one million CRC survivors in America in 2016 (American Cancer Society [ACS], 2020). Unfortunately, the disease burden is distributed unequally across demographics. In the United States men experience a 30% higher incidence rate and 40% higher mortality rate compared to women (ACS, 2017). From 2000 to 2013, CRC incidence increased by 22% and mortality rate by 13% in those who were under 50 years of age (Siegel et al., 2017). Across racial groups, African Americans carry the highest disease burden in both incidence and mortality rate, far exceeding that of other races.

A host of risk factors have been linked to the development of cancer, in which an estimated 20% of all cancers diagnosed in the United States were associated with lifestyle choices such as alcohol consumption, physical inactivity, poor nutrition, excess body fat, and smoking (World Cancer Research Fund [WCRF], 2018a). Epidemiological and clinical data demonstrated a remarkable link between diet, cancer development, and mortality risk (Wiseman, 2019). However, their relationship with cancer recurrence risk

is less clear. As a result, the challenges faced by CRC survivors in setting evidence-based dietary goals bear growing relevance in both clinical and public health settings.

Problem Statement

To date, the association between habitual diet patterns and CRC incidence and mortality risk is well-established in the literature (WCRF, 2018b). Researchers observed a lifetime incident risk reduction from consuming a healthy diet, a pattern high in plant foods and low in red and processed meat and moderate in fat and alcohol, regardless of genetic risk (Carr et al., 2018).

Although a healthy diet is encouraged, CRC patients may encounter multiple barriers to achieving it. For example, in patients undergoing chemotherapy or radiation therapy, side effects often include dry mouth, mouth sores, altered taste reception, nausea, vomiting, and diarrhea (ACS, 2020), limiting their ability to eat. While the majority of the side effects diminish upon treatment completion, some of them could result in long-term smell and taste disorders, causing food aversions (Cohen, Wakefield, & Laing, 2016). Furthermore, depending on the stage and location of the tumors, surgical resection of the colon or rectum may necessitate reduced fiber intake to manage gastrointestinal (GI) symptoms (Cha et al., 2012). Additionally, CRC survivors reported physical, psychosocial, environmental, and economic challenges (Drury, Payne, & Brady, 2017; Santin et al., 2015) that may have long-term negative effects on dietary choices.

Compared to incident-CRC prevention, the evidence regarding diet and recurrent-CRC prevention is inconclusive. While some researchers reported a null association

between postdiagnosis diets and recurrence (Kohler et al., 2018), others have found positive associations between postdiagnosis diet quality and cancer-free survival (Guinter, McCullough, Gapstur, & Campbell, 2018; Schwedhelm, Boeing, Hoffmann, Aleksandrova, & Schwingshackl, 2016). Consequently, there remains a sizable gap in the existing literature as to whether dietary choices could be an effective deterrent to CRC recurrence.

Purpose of the Study

My aim for this study was narrow the knowledge gap pertaining to the relationship between dietary intake and mortality risk during CRC survivorship. The manuscripts follow a central theme surrounding the relationship between postdiagnosis dietary choices and CRC-specific mortality risk in survivors: (a) Diet quality and its change, (b) Dietary fiber intake and its change, and (c) Dietary fat intake and its change from pre-diagnosis level. The analyses will provide insights on how these components influence CRC survivorship and whether changes from pre-diagnosis levels are associated with mortality risk.

Framework

The socioecological model (SEM) by Bronfenbrenner (1977) theorizes that an individual's development results from multilevel influences. These influences begin with the most direct and strongest impact from the micro- and mesosystems surrounding personal characteristics and relationships. The next levels involve the exo- and macrosystems that relate to institutional, societal, and policy components in a person's

development (Bronfenbrenner, 1989). In the context of health outcomes, the SEM's personal, interpersonal, organizational, community, and societal levels are an applicable epidemiological framework (Sallis, Owen, & Fisher, 2008). For example, the Centers for Disease Control and Prevention's colorectal cancer control program demonstrated an uptick in screening among hard-to-reach populations in a cost-effective manner through an SEM-based approach (Kemper et al., 2018).

In cancer survivorship, each level in the SEM may affect either the recurrent or mortality risk, or both (Figure 1). At the personal level, lifestyle choices contribute to both CRC recurrence and mortality risk (Moore, Buchanan, Fairley, & Lee Smith, 2015; Paul et al., 2016). At the interpersonal level, social support and relationship with healthcare providers are significant drivers in postcancer self-care (Burg et al., 2015). From the organizational perspective, workplace reintegration and medical cost were reported as significant stressors in survivorship (Guy et al., 2015). Upstream are the community and societal levels, such as food security, CRC surveillance guidelines, health insurance status, and more (Ryerson, Eheman, Styles, Rycroft, & Snyder, 2015).

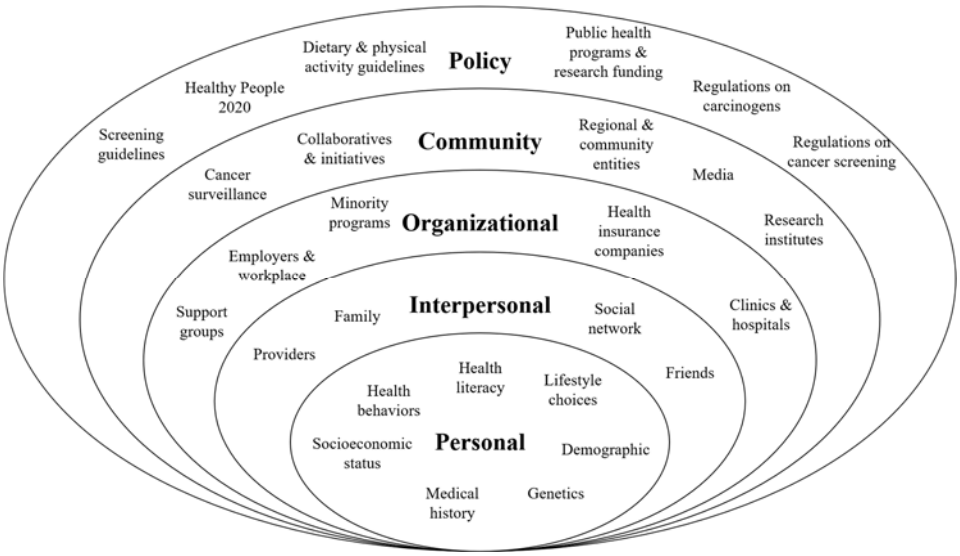

Figure 1. CRC survivorship in the socioecological model.

The Multiethnic Cohort Study (MEC) investigates the relationship between individual attributes and chronic diseases (University of Hawaii, 2020). The demographic characteristics of participants were collected at baseline and follow-up surveys. For participants diagnosed with CRC, information on the diagnoses and deaths were extracted from state-level cancer registries. In the secondary data analysis, dietary choices were examined for their association with CRC-specific mortality in survivors, controlling for potential confounders such as body weight, physical activities, smoking status, and education level. Given that such factors are often interconnected with social support and environmental resources, the SEM was a suitable framework in guiding the study and its future applications (Figure 2).

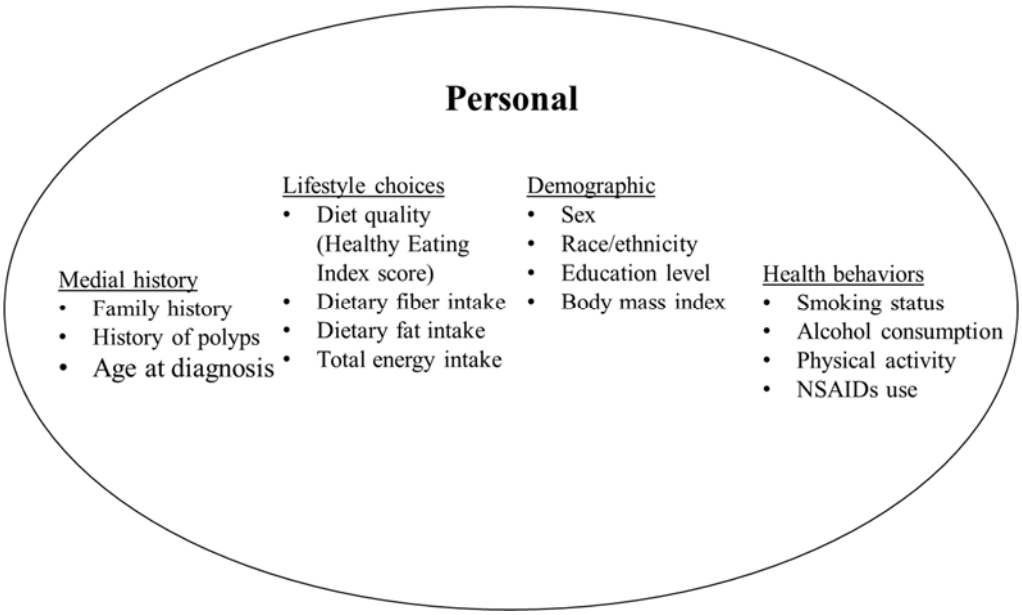

Figure 2. Study variables at the personal level in the SEM construct.

Social Impact

Social cohesiveness relies on functional social units across all socioecological levels. As cancer survivors account for 5% of the United States population (ACS, 2020), they exert significant societal impact. Hence, effective strategies to reduce recurrent and mortality risks can strengthen the survivor community and their extended spheres. Furthermore, a lower CRC-specific mortality rate may also reduce healthcare expenditure (El-Shami et al., 2015) by survivors.

The study on postdiagnosis dietary intake aligns with the personal level influences on CRC-specific mortality risk in survivors. Data generated from this study may lead to the identification of opportunities in improving survivorship care planning. Additionally, the findings may guide public health campaigns in countering personal level barriers with interpersonal, organizational, community, and policy level support.

Background

Multiple risk factors contribute to the recurrence and mortality risks during CRC survivorship. While genetics is a nonmodifiable risk factor, lifestyle choices such as diet, physical activity, and smoking are modifiable and thus, critical components in risk reduction investigation. In particular, diets high in fruits, vegetables, and whole grains and low in fat, red and processed meat, alcohol, and added-sugar consumption were correlated with reduced cancer recurrence, comorbidities, and mortality risk (Meyerhardt et al., 2007; Zhu et al., 2013).

Previous qualitative research revealed CRC survivors' attitudes toward dietary changes (Hardcastle et al., 2017). Common themes that emerged included the desire to return to the precancer lifestyle, uncertainty about the benefit of dietary changes, skepticism of nutrition guidelines, lack of motivation, and personal health beliefs (Hardcastle et al., 2017). Simultaneously, dietary advice has been indicated as a priority by CRC survivors (Tan et al., 2019). To explore the impact of postdiagnostic dietary changes, it was imperative to review the disease's epidemiology, prevention, and the role of diet.

Epidemiology

CRC is one of the most commonly diagnosed malignancies worldwide (WCRF, 2018a). In 2020, colon cancer will surpass 104,000 cases and rectal cancer to exceed 43,000 cases (Siegel et al., 2020). In 2016, nearly one and a half million Americans were living with active or a history of CRC (ACS, 2017). Such incident rates equate to one in

22 men and one in 24 women diagnosed with CRC (Siegel, Miller, & Jemal, 2016). The survival rate is 65% at 5 years and 58% at 10 years postdiagnosis (NCI, 2016). In persons diagnosed with localized adenocarcinoma, the 5-year survival rate was 90% (ACS, 2020). Such gains in survival are attributed mainly to increased and earlier screening as well as therapeutic advances (ACS, 2020).

Sex. Men experience about 30% higher incidence and a 40% higher mortality rate related to CRC compared to women (ACS, 2020). Although the differences in sexes are not fully understood, they may be partial reflections of lifestyle and biological factors such as alcohol consumption, cigarette smoking, and sex hormones (Murphy et al., 2011).

Age. The median age at diagnosis is 68 in men and 72 in women for colon cancer and 63 years old for both men and women for rectal cancer (ACS, 2020). However, there is a rising trend among younger Americans. Between 2000 and 2013, Americans over 50 years old reported a decline of 32% in incidence (Siegel et al., 2017). Whereas, diagnosis in adults under 50 years old had risen by 22% in the same period (Patel & Ahnen, 2018). Mortality rates between 2005 and 2014 showed a similar pattern.

Race. Racial disparity exists in association with biological, social, and environmental determinants (Augustus & Ellis, 2018). In 2013, the incidence rate among African Americans was 51.1 per 100,000 population—a marked difference of 20% higher incidence than non-Hispanic Whites and 50% higher than Asian Pacific Islanders (ACS, 2020). The mortality rates were 40% and 100% higher than that of non-Hispanic Whites and Asian Pacific Islanders, respectively (ACS, 2020). Nationally, the incidence rates for

Hispanics and Asians are 35.5 and 32.2 per 100,000, with mortality rates at 11.7 and 10.3, respectively. Since the mid-2000s, mortality rates have gradually declined at roughly 2% per year for non-Hispanic Whites, Hispanics, and Asians, and by 3% per year in African Americans (ACS, 2020). The slightly greater decline in mortality rate among African Americans over a decade has narrowed the gap between races.

Preventive Efforts

The goal of CRC screening is early detection and removal of polyps to reduce cancer incidence and mortality rates. Multiple professional organizations and public health authorities including the U.S. Preventive Services Task Force (2016), the ACS (Wolf et al., 2018), the American College of Gastroenterologists (Rex et al., 2017), the American College of Physicians (Qaseem, Crandall, Mustafa, Hicks, & Wilt, 2019), and the National Cancer Care Network (Provenzale et al., 2018) have released guidelines on CRC screening. These guidelines are similar in their recommendations on the age of initial screen, methods, and follow-up frequencies.

Screening guidelines. The ACS recommends an initial screening at 45 years of age (Wolf et al., 2018). The frequency for screening is based on the chosen method, with stool-based tests to be repeated every 1 to 3 years and structural examinations by colonoscopy and sigmoidoscopy repeated every 5 to 10 years (Wolf et al., 2018). Both the U.S. Preventive Services Task Force (2016) and ACS strongly recommend regular screening through 75 years of age (Wolf et al., 2018). For individuals 76 to 85 years old,

clinicians should base screening decisions on the individual's risk level. The guidelines do not recommend routine screening for those who are over 85 years old.

For individuals with increased risk, the American College of Gastroenterologists 2017 guideline addresses their screening needs (Rex et al., 2017). Those with a first-degree relative documented for early-onset CRC or advanced adenomas, colonoscopy screening may begin as early as 40 years old and repeated every 5 years. The guideline also recommends that African Americans begin screening at 45 years old.

The Role of Diet

There is strong evidence that diet is associated with the initiation and progression in and protection against CRC (Wiseman, 2019). Based on epidemiological and mechanistic data, diet is estimated to contribute an estimated 47% of the modifiable risks in CRC pathogenesis (Vieira et al., 2017). In CRC, dietary components directly interact with colonic and rectal tissues during digestion and absorption (Song, Garrett, & Chan, 2015), heightening both the potentially harmful and protective properties of the diet. Many dietary elements had been studied extensively over the past 3 decades in which several types of food (whole grains, dairy), as well as nutrients (antioxidants, vitamin D, calcium, fiber), had emerged as anticarcinogenic (Wiseman, 2019).

However, while many studies examined the association between habitual diet and incident-CRC incidence and mortality risks, less is known regarding the dietary choices of CRC survivors and their relationships with recurrence and long-term survival. This

analysis investigated the role of diets among CRC survivors from the perspective of diet quality, dietary fiber, and dietary fat intake.

Diet quality and dietary indices. Historically, nutrition research focused on single-nutrients and their relationships with diseases, for example, vitamin C and scurvy, iron and anemia, or protein and malnutrition. Over time, there was an increasing recognition of nutrient interactions and the synergistic effect of whole foods and long-term dietary habits. The subsequent interest in quantifying diet patterns and quality led to the development of dietary indices. To evaluate an individual's diet quality, food intake is often assessed by dietary recalls or food frequency questionnaires (FFQs), then calculated into a score according to an index's scoring system.

The Healthy Eating Index (HEI) is a frequently used evaluation tool to measure compliance with the Dietary Guideline for Americans (DGA). The U.S. Department of Agriculture (USDA) debuted the HEI in 1995 for diet quality assessment, which has since been incorporated in many epidemiological studies (Kennedy, Ohls, Carlson, & Fleming, 1995). The HEI is updated every 5 years to reflect changes to the DGA. The 2010 version, HEI-2010, was a collaborative update by the USDA and the U.S. Department of Health and Human Services (Guenther, Casavale et al., 2013,). It contains 12 components and emphasizes food group the higher the conformity to the 2010 DGA (Guenther, Kirkpatrick et al., 2013).

Dietary patterns that scored high on the HEI have shown promising results in incident-CRC risk reduction. Schwingshackl, Bogensberger, and Hoffmann (2018)

conducted a large-scale meta-analysis of cohort studies, investigating diet quality and multiple health outcomes. The pooled analysis of 68 cohorts totaling 1.67 million participants showed a 16% reduction in cancer incidence. Specific to CRC, there was a 23% reduction in combined incidence and mortality risk (Relative Risk [RR] = 0.77; 95% CI [0.73, 0.81]). Nevertheless, no such association was found in survivors. Reedy et al. (2008) compared HEI-2005 scores from participants in the National Health Institute-American Association of Retired Persons (NIH-AARP) Diet and Health Study (N = 567,169) reported a 20% and 28% lower incidence risk in women and men, respectively. Similarly, Vargas et al. (2016) found a 27% lower incidence risk in postmenopausal women measured by the HEI-2010 from the Women's Health Initiative (N = 161,808). Meanwhile, in a case-control study (431 cases, 726 controls), Miller et al. (2010) reported a 56% reduced incidence risk in women and 44% in men associated with high-quality diets measured by the HEI-2005.

Despite the large sample size of many cohorts, data on racial minorities are scarce. As a result, the MEC was initiated to address questions regarding nutrition and cancer (Kolonel et al., 2000). The study enrolled over 215,000 participants from the state of Hawaii and Los Angeles County, California. Since 1993, participants were surveyed every 4 to 6 years (University of Hawaii, 2019). Park, Boushey, Wilkens, Haiman, and Le Marchand (2017) examined baseline diet quality and incidence CRC risk in 190,949 participants (49,443 Japanese Americans, 26,719 African Americans, 35,991 Latinos, 12,338 Native Hawaiians, and 43,318 non-Hispanic Whites); extreme quintiles

comparison showed a 21% reduction in incidence risk in Japanese Americans, Latinos, and non-Hispanic Whites who scored in the top quintiles on the HEI-2010.

The observed reduction in incidence-CRC and mortality risks associated with the HEI score was consistent across several cohorts. As such, it is reasonable to extend the HEI's application in recurrent-CRC mortality risk assessment investigation.

Dietary fiber. Dietary fiber is indigestible complex carbohydrates that are fermented by bacteria in the GI tract. The relationship between dietary fiber and CRC incidence and mortality risks is mediated by the physical properties of fiber and its influence on the gut microbiota. Fiber is known to increase stool consistency and colonic motility, thus reducing carcinogens' exposure to colonocytes (Perry & Ying, 2016). In the colon, diet residuals including a small amount of protein, fatty acids, primary bile acids, and undigested carbohydrates undergo bacterial fermentation. During this process, fiber fermentation produces short-chain acids, including butyrate, yielding vital metabolites that strengthen the immune functions of the GI tract. Butyrate has anti-inflammatory and antineoplastic properties and is the preferred energy source in colonocytes in the luminal mucosa. Bacterial fermentation supports homeostasis, modulates immune responses, and regulates epigenetic expression in the microbiota (O'Keefe, 2016). In contrast, a low fiber, high protein diet increases protein fermentation and bile acids deconjugation in the colon, which promotes a proinflammatory and proneoplastic environment, increasing the risk for CRC development (O'Keefe, 2016).

The human GI tract harbors over 100 trillion microbial that span over 1,000 species (Ursell et al., 2014). Gut microbiome diversity and balance vary vastly by an individual's genetics, physiology, age, and diet (Hollister, Gao, & Versalovic, 2014). In the past decade, the microbiome has been linked to multiple chronic diseases, including GI disorders and cancers (Perry & Ying, 2016). In interventional studies, changes to the diet led to changes in the microbiome in as little as 4 to 6 weeks. These shifts in the microbiome, however, were reverted when subjects resumed their habitual diets (Xu & Knight, 2015). Such observations suggest that the gut microbiota is dynamic in its response to their environment.

Experimental models and clinical observations demonstrated the relationship between fiber intake and CRC incidence via the microbiome. In experimental studies, butyrate can induce apoptosis in colonocytes, regulate gene expression, and activate gluconeogenesis (Bultman, 2013). These activities support the protective role of fiber against CRC development. One of the first documentation of the potential link between fiber and CRC risk stemmed from the observation of high fiber consumption in native Africans and the low rate of CRC incidence (Burkitt, 1971). Conversely, interventional studies that manipulated fiber and fat contents of the diet in native Africans and African Americans reported increased secondary bile acids production and colonocytes proliferation (David et al., 2014; O'Keefe et al., 2015). Subsequent studies reported reduced risk when comparing high and low fiber intake. In one of the largest studies on nutrition and cancer, over 428,000 participants across 10 European countries enrolled in

the European Prospective Investigation into Cancer and Nutrition (EPIC) study. From this cohort, Bingham et al. (2003) reported 25% reduced incidence risk in participants with the highest fiber intake (95% CI [0.59, 0.95]; $p < .001$). Later, Murphy et al. (2012) reported from an 11-year follow-up of the EPIC cohort and found a dose-response-like effect by fiber intake, a 13% incidence risk reduction per 10 grams (g) average daily consumption (Hazard Ratio [HR] = 0.87; 95% CI [0.79, 0.96]). Similarly, Aune et al. (2011) reported from a meta-analysis of 25 prospective studies that every 10 grams per day (g/d) of fiber intake was associated with approximately 10% decrease in CRC incidence.

However, there was also reporting that fiber intake was inconsequential in CRC development (Lin et al., 2005; Park et al., 2005; Schatzkin et al., 2007). This inconsistency may be due to the various lengths of follow-up, heterogeneity in methodologies, as well as uncaptured confounding factors. For example, in a prospective case-control study, data on fiber intake collected via food diaries, rather than FFQs, reached statistical significance (Dahm et al., 2010). Meanwhile, in a meta-analysis of 20 studies, case-control studies but not cohort studies showed an inverse association between fiber intake and incident-CRC risk reduction (Ben et al., 2014).

As the population of CRC survivors grows in number and age, the role of dietary fiber in secondary prevention demands further examination. Song et al. (2018) analyzed data between 1980 to 2010 from the Nurses' Health Study (Colditz, Manson, & Hankinson, 1997) and the Health Professionals Follow Up Study (Rimm et al., 1991) to

address fiber intake and mortality in CRC survivors. Self-administered FFQs from the 1,575 cohort participants with stages I, II, and III CRC provided pre- and postdiagnosis fiber intake. For every five grams of daily fiber intake, they observed a 22% decrease risk of CRC-specific mortality risk (HR = 0.78; 95% CI [0.65, 0.93]; p = .006). When looking at the change in fiber intake postdiagnosis, every five-gram of incremental increase from prediagnosis intake level was associated with an 18% reduction in CRC-specific mortality risk (95% CI [0.72, 0.93]; p = .002). In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial, high fruits and vegetable intake was linked to a 25% risk reduction of baseline adenomas detection. However, a similar intake in CRC survivors did not lower recurrent adenomas detection (Kunzmann et al., 2015).

Based on current literature, the role of fiber in CRC risk reduction appears to be two-fold: the absolute intake and the change in intake postdiagnosis. When examined alone, neither factor demonstrated strong and consistent outcomes. This is likely because the amount of fiber intake necessary to exert a definitive anticarcinogenic effect is above 40 g/d (Burkitt, 1971), far exceeds the current recommendation of 25 g/d by the DGA for general health maintenance, and the 16 g/d of average intake in the United States (Hoy & Goldman, 2014). For individuals with low fiber intake prediagnosis, increasing intake may produce detectable health benefits. This study examined both the absolute and the change in fiber intake in the MEC cohort in the hope of determining if these two factors are associated with CRC-specific mortality in survivors.

Dietary fat. The term *total dietary fat* describes the types of fatty acids collectively including saturated fatty acids (SFA), trans fatty acids, monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). Perhaps due to its heterogeneity, total dietary fat intake has not been consistent in its association with CRC incidence and mortality risk.

In a retrospective case-control study of over 4,000 Canadians, total fat intake was not associated with CRC incidence risk and neither was SFA (Odds Ratio [OR] = 1.00; 95% CI [0.79, 1.26]), MUFA (OR = 0.99; 95% CI [0.78, 1.26]), or PUFA (OR = 0.98; 95% CI [0.77, 1.23]); Sun et al., 2012). In a meta-analysis of 18 studies, no association was found between fat consumption and incident-CRC risk: Total fat intake, RR = 1.00 (95% CI [0.90, 1.12]); SFA intake, RR = 0.97 (95% CI [0.86, 1.10]); MUFA intake, RR = 1.08 (95% CI [0.92, 1.26]); and PUFA intake, RR = 0.99 (95% CI [0.93, 1.04]). These findings highlight the effect of fats, if any, is modified by additional dietary, lifestyle, and environmental factors.

However, data on intake of PUFA subtypes, primarily ω-3 PUFA such as α-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA), supports the hypothesis that ω-3 PUFA may be protective against incident-CRC development (Kato, Majumdar, Land, Barnholtz-Sloan, & Severson, 2010; Norat et al., 2005; Song et al., 2018). Norat et al. (2005) reported from the EPIC study that, during a 5-year follow-up period, fish consumption of approximately

2.82 ounces per day reduced incident-CRC risk by 31% (HR = 0.69; 95% CI [0.54, 0.88]) compared to less than 0.35 ounce average daily consumption.

On the contrary, an analysis combining data from the Nurses' Health Study and Health Professionals Follow Up Study cohorts by Song et al. (2014) examined marine ω-3 intake from over 123,000 American adults for 24 to 26 years reported neither marine ω-3 nor ω-6 intake was associated with overall CRC risk. Rather, marine ω-3 intake was associated with an increased risk in distal colon cancer in women (HR = 1.36; 95% CI [1.03, 1.80]) and men (HR = 1.50; 95% CI [1.06, 2.12]). This finding was in line with the observation that bacterial concentration is highest in the proximal colon, resulting in stronger cellular protection from SCFA derived short-chain acids from fiber fermentation, creating a gradient of diminishing defense in the distal colon (Yoshimoto et al., 2013). In fact, despite the health benefits of fish and marine ω-3 consumption, several species are prone to accumulate toxins such as mercury, dioxins, and polychlorinated biphenyls (PCBs) that may contribute to cancer risk (Domingo, 2016; Paliwoda, Newbigging, Wang, & Le, 2016). This theory is consistent with data from a Japanese study that reported a U-curve associated with marine ω-3 intake and rectal cancer (Sasazuki et al., 2011) as well as a study in Chinese women that found no association between salt-water fish, fresh-water fish, and shellfish intake and incident-CRC risk but increased risk from consuming seafood raised in industrial areas (Lee et al., 2009).

To date, few studies investigated, prospectively, the accumulative and the change in marine ω-3 intake in CRC survivors (Song et al., 2017). CRC survivors from the

Nurses' Health Study and Health Professionals Follow Up Study were followed for a median of 10.4 years. The highest postdiagnosis intake demonstrated a trend in CRC-specific mortality risk reduction (HR = 0.59; 95% CI [0.35, 1.01]; *p* for trend 0.03). Survivors with the highest increase, > 0.15 g/d, experienced a 70% CRC-specific mortality risk reduction, HR = 0.30 (95% CI [0.14, 0.64]) compared to minimal or no change. In a smaller prospective study, 1,011 stage III CRC survivors were followed for a median of 7 years (Van Blarigan et al., 2018). The highest quartile of marine ω-3 intake was associated with a 32% risk reduction in recurrence (HR = 0.68, 95% CI [0.50, 0.94]). In survivors whose tumors expressed high level of prostaglandin-endoperoxide synthase 2 (PTGS2), indicative of higher inflammation burden compared to those without, recurrence-free survival by marine ω-3 intake was improved by 68% (HR = 0.32; 95% CI [0.11, 0.95]). Data from these studies suggest that the effect of ω-3 PUFA intake may differ in pre- and postdiagnosis. Furthermore, survivors with previously low ω-3 PUFA intake or with late-stage and high inflammation CRC pathology may potentially receive significant benefits in secondary prevention. Unfortunately, the insufficient amount of evidence on CRC-specific mortality risk during survivorship leaves a notable void in dietary recommendations for survivors.

Overview of the Manuscripts

The SEM describes the individual and environmental factors that influence health outcomes. The following analyses address dietary intake and its implications on CRC-specific mortality risk in a racially diverse cohort. As reviewed, emerging evidence

suggests that improved diet quality, increased fiber intake, and increased marine ω-3 fatty acids may reduce mortality risks in survivors. As a result, the topic is examined from three aspects: the predictiveness of postdiagnosis status of diet quality, dietary fiber intake, dietary fat intake, and the change from prediagnosis levels on CRC-specific mortality risk. The findings could provide future directions in interventional research and public health education.

Manuscript 1

The health disparity between whites and non-white persons in the United States encompasses a myriad of economic, psychosocial, and genetic factors. Among modifiable risk factors, diet quality is inversely correlated with CRC incidence and mortality rates. However, it is unclear whether a change in dietary quality following CRC diagnosis could produce a similar health impact. This analysis examined the potential association between diet quality and the likelihood of CRC-specific mortality risk in a racially diverse cohort.

Research question.

Do postdiagnosis HEI-2010 score and its change from prediagnosis predict CRC-specific mortality in CRC survivors in the MEC?

My hypothesis is that increased HEI-2010 postdiagnosis is associated with a reduction in CRC-specific mortality risk in survivors when compared to a decrease or no change in score from prediagnosis level.

Nature of the study.

This quantitative study is a secondary data analysis of prospectively collected dietary data from the MEC to examine the relationship between diet, cancers, and chronic diseases (University of Hawaii, 2019). The FFQ used in dietary data collection was culturally tailored and validated for use with African Americans, Japanese Americans, Latinos, Native Hawaiians, and non-Hispanic whites. CRC cases and deaths in the cohort were identified via established linkage between the MEC database and state-level cancer registries and death records. Dietary intake of CRC survivors at baseline and follow-up was calculated into HEI-2010 scores and then quartiles. The first part of the study will estimate CRC-specific mortality risk by comparing postdiagnosis score quartile. The second part of the study will pair participants' pre and postdiagnosis quartiles to reflect change in diet quality. The 1st and 2nd quartiles are defined as low quality whereas the 3rd and 4th quartiles are defined as high quality, thus creating four categories for diet quality change: low/low (referent), low/high, high/low, and high/high. The quartiles are then entered into a Cox proportional hazard regression model to compare the different levels of change and compute hazard ratios (HRs) and 95% confidence intervals (CIs) corresponding to the mortality risk associated with each level of change in diet quality.

Study procedures.

The MEC's questionnaire development, sampling method, and data collection have been previously published (Kolonel et al., 2000). Consent to participate in the MEC surveys were collected at the time of cohort entry by the University of Hawaii (UH) and the University of Southern California (USC). The analysis will utilize readily available

data with no supplemental questionnaires, biological samples, or personal contact with the participant. Upon approval from Walden University's Institutional Review Board (IRB), UH will create a limited data set for download via password-protected remote access. Statistical analysis and results will be stored as encrypted files on the author's Laureate Education cloud-based OneDrive server for the duration of this study. The analysis will be performed at the author's secured home office in Seattle, Washington.

This study utilizes the established linkage between the MEC's database and the Surveillance, Epidemiology, and End Results Program tumor (SEER) registries in California and Hawaii for CRC case ascertainment. For CRC-specific mortality, the MEC cohort database is linked to the States' death certificate records and the National Death Index. All personal identifiable information (PII) is masked by the UH following data cleaning and linkage to cancer registries and death records. The main exclusion criterion for this study is the history or presence of CRC at enrollment, as identified from responses in the baseline questionnaire or the tumor registries. Furthermore, participants who identified outside of the major racial groups of African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic white are excluded. Finally, participants who reported implausible dietary intakes would be excluded.

Variables.

The dependent variable is CRC-death. Predictor in Cox regression (dietary exposure) is the postdiagnosis HEI-2010 score and the change in scores from (prediagnosis level, calculated into quartiles.

Descriptive statistics: (a) Age at cohort entry, continuous variable; (b) Age at diagnosis, continuous variable; (c) Race (non-Hispanic white, African American, Native Hawaiian, Japanese American, Latino), categorical variable; (d) Sex, categorical variable; (e) Body mass index, continuous variable; (f) Family history of CRC; categorical variable; (g) History of intestinal polyps; categorical variable; (h) NSAIDs use, categorical variable; (i) Physical activity (hours/day), continuous variable; (j) Smoking status, categorical variable; (k) Alcohol intake (grams ethanol/day), continuous variable; (l) Total energy intake (calories/day), continuous variable; (m) Education level, interval variable.

Sources of data.

The study utilizes data from the MEC in conjunction with established linkage to publicly available administrative data from the SEER registries, the death certificate files from the states of California and Hawaii, and the National Death Index. CRC case ascertainment will be based on the following *International Statistical Classification of Oncology,* (3rd ed.; ICD-O-3) codes (National Cancer Institute [NCI], 2016) to identify cohort participants with CRC diagnosis:

a. Malignant neoplasm of the cecum (C18.0)
b. Malignant neoplasm of the appendix (C18.1)
c. Malignant neoplasm of the ascending colon; right colon (C18.2)
d. Malignant neoplasm of the hepatic flexure of the colon (C18.3)
e. Malignant neoplasm of the transverse colon (C18.4)

f. Malignant neoplasm of the splenic flexure of the colon (C18.5)

g. Malignant neoplasm of descending colon; left colon (C18.6)

h. Malignant neoplasm of the sigmoid colon (C18.7)

i. Malignant neoplasm of overlapping lesion of the colon (C18.8)

j. Malignant neoplasm of the colon, NOS (C18.9)

k. Malignant neoplasm of the rectosigmoid junction (C19.9)

l. Malignant neoplasm of the rectum, NOS (C20.9)

Power analysis.

The MEC reported 6,451 cases of invasive CRC between baseline and December 31, 2014. Of this, 1,166 participants provided postdiagnosis dietary data. Power analysis by the Statistical Package for the Social Sciences (SPSS) version 25 for Cox proportional hazard regression using a two-tailed alpha of 0.05, 0.25 effect size, and 55% survival rate yielded 0.8844.

Manuscript 2

Dietary fiber intake has been inversely associated with decreased incidence and mortality rates in CRC. However, it is less conclusive if dietary fiber intake postdiagnosis is associated with long-term survival outcomes. Meanwhile, postdiagnosis dietary fiber intake can be influenced by cultural food preferences as well as GI tolerance. This analysis examines the relationship between dietary fiber intake postdiagnosis and CRC-specific mortality in a culturally diverse cohort.

Research question.

Does dietary fiber intake postdiagnosis, and its change from prediagnostic level predict CRC-specific mortality risk in survivors in the MEC?

I hypothesized that an increase in dietary fiber intake postdiagnosis is associated with reductions in the risk of CRC-specific mortality compared to a decrease or no change in intake.

Nature of the study.

This quantitative study was a secondary data analysis of prospectively collected dietary data from the MEC to examine the relationship between diet, cancers, and chronic diseases (University of Hawaii, 2019). The FFQ used in dietary data collection was culturally tailored and validated for use with African Americans, Japanese Americans, Latinos, Native Hawaiians, and non-Hispanic whites. CRC cases and deaths in the cohort were identified via established linkage between the MEC database and state-level cancer registries and death records. Postdiagnosis fiber intake is calculated from FFQ responses in the follow-up survey. The change in intake will be calculated by subtracting prediagnosis intake from postdiagnosis intake and grouped as followed: ≥ 5 g/d decrease, < 5 g/d decrease, < 5 g/d increase, and ≥ 5 g/d increase. Cox regression will be used to estimate the corresponding mortality risk, using the least increase group, ≥ 5 g/day decrease, as the referent. The model computes the hazard ratios (HRs) and 95% confidence intervals (CIs)for each level of change, indicating their associated CRC-specific mortality risk.

Study procedures.

The MEC's questionnaire development, sampling method, and data collection have been previously published (Kolonel et al., 2000). Consent to participate in the MEC surveys were collected at the time of cohort entry by the University of Hawaii (UH) and the University of Southern California (USC). The analysis will utilize readily available data with no supplemental questionnaires, biological samples, or personal contact with the participant. Upon approval from Walden University's IRB, UH will create a limited data set for download via password-protected remote access. Statistical analysis and results will be stored as encrypted files on the author's Laureate Education cloud-based OneDrive server for the duration of this study. The analysis will be performed at the author's secured home office in Seattle, Washington.

This study utilizes the established linkage between the MEC's database and the SEER registries in California and Hawaii for CRC case ascertainment. For CRC-specific mortality, the MEC cohort database is linked to the States' death certificate records and the National Death Index. All personal identifiable information (PII) is masked by the UH following data cleaning and linkage to cancer registries and death records. The main exclusion criterion for this study is the history or presence of CRC at enrollment, as identified from responses in the baseline questionnaire or the tumor registries. Furthermore, participants who identified outside of the major racial groups of African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic white are excluded. Finally, participants with implausible responses regarding dietary intakes are excluded.

Variables.

The dependent variable is CRC-death. Predictors for CRC-specific mortality in Cox regression model: (a) Dietary fiber (g/d), continuous variable; and (b) Change in dietary fiber intake (g/d), interval variable. Change in intake is calculated by subtracting the participant's prediagnosis intake from postdiagnosis intake.

Descriptive statistics: (a) Age at cohort entry, continuous variable; (b) Age at diagnosis, continuous variable; (c) Race (non-Hispanic white, African American, Native Hawaiian, Japanese American, Latino), categorical variable; (d) Sex, categorical variable; (e) Body mass index, continuous variable; (f) Family history of CRC; categorical variable; (g) History of intestinal polyps; categorical variable; (h) NSAIDs use, categorical variable; (i) Physical activity (hours/day), continuous variable; (j) Smoking status, categorical variable; (k) Alcohol intake (grams ethanol/day), continuous variable; (l) Total energy intake (calories/day), continuous variable; (m) Education level, interval variable.

Sources of data.

The study utilizes data from the MEC study in conjunction with established linkage to publicly available administrative data from the SEER registries, the death certificate files from the states of California and Hawaii, and the National Death Index. CRC case ascertainment will be based on the following ICD-O-3 codes to identify cohort participants with CRC diagnosis:

a. Malignant neoplasm of the cecum (C18.0)

b. Malignant neoplasm of the appendix (C18.1)
c. Malignant neoplasm of the ascending colon; right colon (C18.2)
d. Malignant neoplasm of the hepatic flexure of the colon (C18.3)
e. Malignant neoplasm of the transverse colon (C18.4)
f. Malignant neoplasm of the splenic flexure of the colon (C18.5)
g. Malignant neoplasm of descending colon; left colon (C18.6)
h. Malignant neoplasm of the sigmoid colon (C18.7)
i. Malignant neoplasm of overlapping lesion of the colon (C18.8)
j. Malignant neoplasm of the colon, NOS (C18.9)
k. Malignant neoplasm of the rectosigmoid junction (C19.9)
l. Malignant neoplasm of the rectum, NOS (C20.9)

Power analysis.

The MEC reported 6,451 cases of invasive CRC between baseline and December 31, 2014. Of this, 1,166 participants provided postdiagnosis dietary data. Power analysis by the Statistical Package for the Social Sciences (SPSS) version 25 for Cox proportional hazard regression using a two-tailed alpha of 0.05, 0.25 effect size, and 55% survival rate yielded 0.8844.

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The Western diet— a diet pattern high in fat, sugar, and processed food—has been linked to varying degrees of risk in CRC development. However, dietary fat subtypes were observed to differ in their health impacts. To date, little is known if altering one's dietary fat intake postdiagnosis could be beneficial during CRC survivorship. This analysis examines whether postdiagnosis intake of dietary fat, fat from fish and shellfish, and their changes from prediagnosis levels are associated with CRC-specific mortality.

Research question.

Do changes in intake of dietary fat from fish and shellfish postdiagnosis predict CRC-specific mortality in African American, Japanese American, Latino, and non-Hispanic white CRC survivors in the MEC?

I hypothesized that an increase in total dietary fat intake would increase mortality risk, whereas an increase in fat from fish and shellfish would reduce mortality risk in CRC survivors compared to a decrease or no change postdiagnosis.

Nature of the study.

This quantitative study was a secondary data analysis of prospectively collected dietary data from the MEC to examine the relationship between diet, cancers, and chronic diseases (University of Hawaii, 2019). The FFQ used in dietary data collection was culturally tailored and validated for use with African Americans, Japanese Americans, Latinos, Native Hawaiians, and non-Hispanic whites. CRC cases and deaths in the cohort

were identified via established linkage between the MEC database and state-level cancer registries and death records. The level of total fat as percent of energy and fat from fish and shellfish intake were assessed from participants' follow-up FFQ responses. The change in intake will be calculated by subtracting prediagnosis intake from postdiagnosis level and grouped into quartiles: ≥ 5% decrease, < 5% decrease, < 5% increase, and ≥ 5% increase for total fat and ≥ 0.25 g decrease, < 0.25 g decrease, < 0.25 g increase, and ≥ 0.25 g increase for fat from fish and shellfish. Cox regression models will be used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the mortality risk by intake quartiles.

Study procedures.

The MEC's questionnaire development, sampling method, and data collection have been previously published (Kolonel et al., 2000). Consent to participate in the MEC surveys were collected at the time of cohort entry by the University of Hawaii (UH) and the University of Southern California (USC). The analysis will utilize readily available data with no supplemental questionnaires, biological samples, or personal contact with the participant. Upon approval from Walden University's IRB, UH will create a limited data set for download via password-protected remote access. Statistical analysis and results will be stored as encrypted files on the author's Laureate Education cloud-based OneDrive server for the duration of this study. The analysis will be performed at the author's secured home office in Seattle, Washington.

This study utilizes the established linkage between the MEC's database and the SEER registries in California and Hawaii for CRC case ascertainment. For CRC-specific mortality, the MEC cohort database is linked to the States' death certificate records and the National Death Index. All personal identifiable information (PII) is masked by the UH following data cleaning and linkage to cancer registries and death records. The main exclusion criterion for this study is the history or presence of CRC at enrollment, as identified from responses in the baseline questionnaire or the tumor registries. Furthermore, participants who identified outside of the major racial groups of African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic white are excluded. Finally, participants who reported implausible dietary intakes are excluded.

Variables.

The dependent variable is CRC-death. Predictors for CRC development in Cox regression model, continuous variables: (a) Total dietary fat, as a percentage of total energy intake; (b) fat from fish and shellfish; (c) change in total dietary fat intake; (d) change in fat intake from fish and shellfish (subtracting prediagnosis level from postdiagnosis level).

Descriptive statistics: (a) Age at cohort entry, continuous variable; (b) Age at diagnosis, continuous variable; (c) Race (non-Hispanic white, African American, Native Hawaiian, Japanese American, Latino), categorical variable; (d) Sex, categorical variable; (e) Body mass index, continuous variable; (f) Family history of CRC; categorical variable; (g) History of intestinal polyps; categorical variable; (h) NSAIDs use,

categorical variable; (i) Physical activity (hours/day), continuous variable; (j) Smoking status, categorical variable; (k) Alcohol intake (grams ethanol/day), continuous variable; (l) Total energy intake (calories/day), continuous variable; (m) Education level, interval variable.

Sources of data.

The study utilizes data from the MEC study in conjunction with established linkage to publicly available administrative data from the SEER registries, the death certificate files from the states of California and Hawaii, and the National Death Index. CRC case ascertainment will be based on the following ICD-O-3 codes to identify cohort participants with CRC diagnosis:

a. Malignant neoplasm of the cecum (C18.0)
b. Malignant neoplasm of the appendix (C18.1)
c. Malignant neoplasm of the ascending colon; right colon (C18.2)
d. Malignant neoplasm of the hepatic flexure of the colon (C18.3)
e. Malignant neoplasm of the transverse colon (C18.4)
f. Malignant neoplasm of the splenic flexure of the colon (C18.5)
g. Malignant neoplasm of descending colon; left colon (C18.6)
h. Malignant neoplasm of the sigmoid colon (C18.7)
i. Malignant neoplasm of overlapping lesion of the colon (C18.8)
j. Malignant neoplasm of the colon, NOS (C18.9)
k. Malignant neoplasm of the rectosigmoid junction (C19.9)

l. Malignant neoplasm of the rectum, NOS (C20.9)

Power analysis.

The MEC reported 6,451 cases of invasive CRC between baseline and December 31, 2014. Of this, 1,166 participants provided postdiagnosis dietary data. Power analysis by the Statistical Package for the Social Sciences (SPSS) version 25 for Cox proportional hazard regression using a two-tailed alpha of 0.05, 0.25 effect size, and 55% survival rate yielded 0.8844.

Significance

The number of CRC survivors is increasing due to younger onset, earlier detection, and improved treatment. However, the volume of evidence in recurrent-CRC and mortality is limited. Additionally, much of the data on nutrition and CRC recurrence was extrapolated from cohorts with high participation by non-Hispanic Whites, which does not reflect the demographics of CRC patients in the United States. The lack of evidence in secondary prevention results in dietary recommendations that are essentially identical for cancer-free individuals and survivors, failing to harness the interdisciplinary experience in established risk factors. This disconnect is amplified as survivor care needs reach public health magnitude. Meanwhile this data gap creates an opportunity for epidemiologists to explore if and how diets may influence long-term health outcomes. The proposed study initiates some of the first steps in identifying dietary factors that may enhance CRC survivorship, thus an innovation toward social change.

Summary

CRC is among the top five malignancies domestically and globally. As survivorship grows in length, concerns for recurrence are common. This study examines the relationship between diet quality, fiber, and fat consumption and CRC-specific mortality risk in survivors in the MEC. The research questions surround a central theme of pre- and postdiagnosis changes in dietary intakes and their association with recurrence-associated mortality. The analyses aim to extend existing knowledge on the role of diet in secondary prevention. As such, the findings may contribute to the understanding of the dietary choices of survivors and generate evidence toward meaningful survivorships.

Part 2: Manuscripts

The Impact of Diet Quality on Mortality Risks in Colorectal Cancer Survivors

Ellen Chow, MS, RD

Walden University

Outlet for Manuscript

The intended first choice of manuscript submission is Cancer Epidemiology as an original research article. The journal is dedicated to the understanding, prevention, and control of cancer causes. This study's examination of secondary prevention in a growing survivor population aligns with the journal's mission.

The journal's homepage can be accessed at: https://www.journals.elsevier.com/cancer-epidemiology

The author's guide: https://www.elsevier.com/journals/cancer-epidemiology/1877-7821/guide-for-authors

Abstract

Strong evidence exists on the relationship between diet and colorectal cancer (CRC) concerning primary prevention. As the number of CRC survivors grows, there is an emerging gap in nutrition knowledge focused on the secondary prevention of CRC. The objective of this study was to examine the risk of CRC-specific mortality based on post-CRC diet quality as measured by the Healthy Eating Index-2010 (HEI-2010. The Multiethnic Cohort Study (MEC) is a prospective cohort established to explore the relationship between diet and chronic diseases in a diverse population. Dietary intakes were assessed via a culturally validated Food Frequency Questionnaire (FFQ). Nine hundred eighty-nine CRC survivors were included in this post-hoc analysis. Cox proportional hazard regression was used to estimate CRC-specific mortality risk associated with postdiagnosis HEI-2010 scores and the change in scores from baseline. Median follow up was 18.4 years, with an average of 5.6 years between CRC diagnosis and postdiagnosis FFQ. Survival analysis of postdiagnosis HEI-2010 scores showed no impact on CRC-specific mortality risk (4th versus 1st quartile HR = 0.72, 95% CI [0.36, 1.75], p = .572). However, participants who increased their scores from prediagnosis level experienced an increased CRC-specific mortality risk (low/high versus low/low HR = 2.00, 95% CI [1.02, 3.92], p = .044). In this sample, the HEI-2010, which was designed to assess diet quality in the general population, may not be aligned with the dietary needs to reduce CRC-specific mortality risk in survivors. Consequently, CRC survivors may

require tailored instruments or study designs to generate applicable dietary recommendations.

Background

Colorectal cancer (CRC) is the third leading cancer for men and women, and the second most common cause of cancer deaths in the United States (American Cancer Society [ACS], 2020a). In 2020, the expected number of incident colon cancer will reach 104,610 cases while rectal cancer will reach 43,340 (Siegel et al., 2020). In recent years, screening efforts and treatment advancements have led to improved survival. When combining all stages of CRC at diagnosis, the 5-year survival rates of colon and rectal cancers are 64% and 67%, respectively (ACS, 2020a). As a result, CRC survivors are a growing population of over one million Americans. However, compared to primary prevention, less is understood about secondary prevention in CRC. Moreover, most studies to date investigated non-Hispanic White cohort participants. Considering that African Americans and Japanese Americans experience increased incidence risks (ACS, 2020a; Jin, Pinheiro, Xu, & Amei, 2016), research in a racially diverse population is needed.

Diet has consistently demonstrated an association with incidence and mortality risks in first-time CRC patients. It is a personal level factor in the socioecological model of health and frequently one of the first line targets in cancer survivorship. However, its relationship with recurrence-free survival is inconclusive (Fung et al., 2014; Meyerhardt, Niedzwiecki, & Hollis, 2007; Ratjen et al., 2017; Vrieling & Kampman, 2010). Historically, nutrition research focuses on single-nutrients and their relationships with diseases. In the past decade, there is increasing recognition of the synergistic effect of

foods, leading to the development of dietary indices as a tool to quantify dietary patterns and quality. In practice, an individual's food intake is quantified into a score corresponding to the index's scoring system (Kant, 2004).

The U.S. Department of Agriculture (USDA) debuted the Healthy Eating Index (HEI) in 1995 to measure adherence to the Dietary Guideline for Americans (DGA) (Kennedy, Ohls, Carlson, & Fleming 1995). It is a priori index based on scientific evidence and updated every 5 years along with new DGA releases. The HEI-2010 was a collaborative update by the USDA and the U.S. Department of Health and Human Services (Guinther et al., 2013). It contains 12 components that emphasize nutritional adequacy and moderation (National Cancer Institute [NCI], 2018). The HEI-2010 includes nine adequacy categories (total vegetables, total fruits, whole fruits, greens and beans, whole grains, dairy, total protein, seafood and plant protein, and fatty acids) and three moderation components (sodium, refined grains, and empty calories; NCI, 2019). The higher the index score, the higher the conformance to the DGA (Guinther, 2014).

High-quality diets have shown promising results in incident-CRC risk reduction. Schwingshackl, Bogensberger, and Hoffmann (2018) conducted a large-scale meta-analysis in which the pooled analysis of 6 cohorts showed a 23% relative risk reduction in combined incidence and mortality risk associated with high HEI scores. In the National Health Institute-American Association of Retired Persons (NIH-AARP) cohort, Reedy et al. (2008) found a 20% and 28% lower incidence risk in women and men, respectively, associated with high HEI scores. Meanwhile, Park, Boushey, Wilkens, Haiman, &

Marchand (2017) reported that high HEI-2010 scores at baseline were inversely linked to CRC incidence risk in the MEC. Men and women who scored in the top quintile experienced 31% and 28% reduced incidences, respectively.

Similar dietary effects may be at play among cancer survivors. Karavasiloglou et al. (2019) detected a 42% recurrence risk reduction among 522 cancer survivors who scored in the top 40% of the HEI-2010. Specific to CRC, Meyerhardt et al. (2007) reported a 185% increase in recurrent cancer risk among 1,009 CRC survivors who scored in the highest quintile of a Western dietary pattern. Additionally, in a meta-analysis by Schwedhelm et al. (2017), a prudent dietary pattern postdiagnosis showed a 23% reduction, while a Western dietary pattern was associated with a 51% increase in recurrent-CRC risk. However, the volume of evidence specific to CRC survivors remains low and may or may not be extrapolated from analyses that combined multiple cancer types.

The objective of this analysis is whether changes in diet quality, as assessed by the HEI-2010, affect the CRC-specific mortality risk in survivors in the Multiethnic Cohort Study. (MEC) It is hypothesized that improvement in diet quality postdiagnosis is associated with a reduction in CRC-specific mortality risk.

Methodology

Study Population

The MEC is a prospective cohort study established to investigate the association of lifestyle and genetic factors in the development of cancer and chronic diseases

(Kolonel et al., 2000). The sampling frames utilized publicly available information from driver's license files, voter registration records, and Medicare enrollment to achieve a racially and socioeconomically diverse participant pool in Los Angeles County and the state of Hawaii from 1993 to 1996. The study's design and data collection method have been previously published (Kolonel et al., 2000). Surveys were mailed to eligible individuals with up to three attempts. MEC participation was initiated when residents completed a self-administered questionnaire that included baseline demographic information, medical history, and a detailed dietary assessment. Over 215,000 participants were enrolled, who self-identified primarily with the following race/ethnicities: African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic White. The institutional review boards of the University of Hawaii and the University of Southern California approved the MEC study protocol, and all participants provided written informed consent. In addition, this analysis was approved by Walden University's institutional review board (01-08-20-0641131).

Healthy Eating Index Score Assessment and Calculation

The MEC's questionnaire development, sampling method, and data collection have been previously published (Kolonel et al., 2000; Stram et al., 2000). Upon entry to the cohort, participants completed a 26-page baseline questionnaire. As part of the survey, a culturally tailored quantitative Food Frequency Questionnaire (FFQ) with more than 180 items was included (Stram et al., 2000). The FFQ was validated and calibrated in ethnic-sex matched groups through three repeated 24-hour diet recalls. The

questionnaire assessed habitual intake over the previous 12 months. Detailed instructions in English and Spanish were provided along with images of portion sizes referenced in the multiple-choice responses. Prediagnosis diet quality was based on baseline FFQ, while the follow-up FFQ assessed postdiagnosis diet quality. Average daily nutrient intakes were calculated using the food composition tables developed and maintained at the University of Hawaii Cancer Center specifically for the use in the MEC (Murphy, 2002). The HEI score was calculated using MEC participants' FFQ responses (Liese et al., 2015).

Case Ascertainment

This study utilizes the established linkage between the MEC study dataset and the Surveillance, Epidemiology, and End Results Program (SEER) tumor registries in California and Hawaii for the identification of CRC cases (Kolonel et al., 2000). The main exclusion is the history or prevalence CRC at baseline, as identified from responses in the baseline questionnaire or the tumor registries. Cases in this study only included invasive colonic, rectal, or mixed adenocarcinomas. Classification of anatomic sites was based on the International Classification of Disease for Oncology, third edition (ICD-O-3) codes under colon excluding rectum and rectum and rectosigmoid junction: C180-C189, C199, C209, and C260. For CRC-specific death ascertainment, public records from the States' death certificate records and the National Death Index were accessed through December 31, 2014. Furthermore, participants who identified outside of the major race/ethnicity groups of African American, Native Hawaiian, Japanese American,

Latino, and non-Hispanic White are excluded. Finally, participants with implausible responses regarding dietary intakes are also excluded.

Statistical Analysis

Between baseline and December 31, 2014, there were 6,451 cases of invasive CRC reported in the cohort in which postdiagnosis dietary data was available for 1,166 of them. After eliminating implausible dietary intakes— energy over 5,000 kcal/d and dietary fiber over 100 g/d for (N = 25) and excluding participants who returned their follow-up questionnaire within 12 months of incident-CRC diagnosis (n = 152), the final sample size was 989. Missing data were handled with median replacement. Post-hoc power analysis for Cox proportional hazard regression used a two-tailed alpha of 0.05, 0.25 effect size, and a 55% 10-year survival rate, which yielded a statistical power of 0.8285. For prediagnosis diet quality, person-time was calculated from the date of cohort entry to the index date. For postdiagnosis diet quality, the date of CRC diagnosis to the first instance of death, censoring, or end of study was used to calculate the person-time.

Descriptive statistics were used to demonstrate baseline characteristics. Cox proportional hazards regression modeling was used to examine CRC-specific mortality risks for both postdiagnosis HEI-2010 scores and the change in scores from prediagnosis intake. Hazard ratios and 95% confidence intervals (CI) estimations were calculated. Univariate analysis was performed to assess model fit before adjustments with covariates, which included demographic characteristics (sex, race, and education level), clinicopathological factors (age at diagnosis, history of polyps, and family history of

CRC), lifestyle factors (body mass index (BMI), physical activity, smoking status, and the use of non-steroid anti-inflammatory drug (NSAID) at follow-up), and dietary factors (total energy and alcohol consumption at follow-up). The participant's affirmative response defined the history of intestinal polyps. Family history of CRC was defined by participants' baseline response of the disease in mother, father, or siblings. BMI was calculated from self-reported height and weight at follow-up. Physical activity was coded as none, up to 150 min/day, or more than 150 min/day of moderate to vigorous activities. Cigarette smoking statuses were never smoked, past smoker, and current smoker. Education levels were grouped as less than high school, high school, some college and college, and post-graduate. Finally, NSAIDs use was based on self-reported use at follow-up as never used, past, or current usage of at least twice a week for longer than one month. Missing data were replaced with median values. To analyze the change in HEI-2010 score and mortality risk, the prediagnosis and postdiagnosis scores were calculated into quartiles where the 1st and 2nd quartiles were classified as *low* and 3rd and 4th quartiles were classified as *high*. The quartiles were then paired as low/low, low/high, high/low, and high/high to reflect the participant's change in score. Likelihood ratio test confirmed model fit. Regression analysis was applied to test for interactions and collinearity. All analyses were performed in SPSS version 25.

Results

The sample was composed of 55.4% male. The racial/ethnic distribution was as followed: 42.6% Japanese Americans, 22.0% non-Hispanic whites, 14.5% Latinos,

13.5% African Americans, and 7.4% Native Hawaiians. Among the 989 CRC survivors, 718 cases were colon cancer, 263 cases were rectal cancer, and 8 cases were mixed cancer. The mean follow-up was 18.6 years. Table 1 presents the participants' characteristics at baseline and follow-up by HEI-2010 quartiles. The average age at cohort entry was 62.5 years old (*SD* = 8.0), the age at incident-CRC diagnosis was 68.4 years old (*SD* = 8.2), and the age at death was 81.9 years old (*SD* = 7.5). On average, there were 5.6 years (*SD* = 3.0) between diagnosis and follow-up FFQ. By the end of the study period, there were 261 deaths with 49 cases attributed to CRC (18.8%) (Table 2). The CRC-specific mortality rate was 22.1% for HEI scores below the median and 16.1% for scores above the median.

The median baseline HEI-2010 score was 68 (*SD* = 11). Quartile medians were 53, 64, 71, and 80. Postdiagnosis, there was a small increase of HEI scores across all quartiles. The median score was 70 (*SD* = 11), with interquartile medians 57, 67, 73, and 82. Compared to baseline, participants exhibited a change in score from a reduction of 34 points to an increase of 43 points. The quartile medians for change in score were -10, -1, 6, and 15 (data not shown). Participants with the most increase in scores tend to be younger at diagnosis compared to those who decreased in scores (66.7 versus 71.0 years old).

The impact of the postdiagnosis score and the change in score on CRC-mortality were examined in univariate regression models, in which neither model produced statistical significance (data not shown). In the adjusted models, the postdiagnosis score

was not statistically significant. However, a change in score was statistically significant. Table 3 shows the low/high pairing was a significant predictor, HR = 2.00 (95% CI [1.02, 3.92], p = .044), suggesting that participants whose scores increased from below to above the median experienced a higher odds of CRC-specific mortality in comparison to those whose scores remained below the median. The high/high pairing was not entered into the regression model due to linear dependencies with the low/high and high/low groupings. For covariates, older age at diagnosis was associated with higher odds of mortality (HR = 1.05, 95% CI [1.02, 1.09], p = .004). Participants who reported a history of intestinal polyps showed lower odds of mortality (HR = 0.50, 95% CI [0.30, 0.81], p = .005). Their significance is consistent with chi-square and point-biserial correlation tests (data not shown).

Discussion

This study examined the impact of the HEI-2010 score postdiagnosis in the context of CRC secondary prevention. Although the rate of CRC-specific mortality trends down in the upper quartiles, the hazard ratio did not differ statistically across quartile. Interestingly, participants who increased their scores from the lower to upper quartiles experienced increased odds in CRC-specific mortality risk. The finding suggests that an effort to improve diet quality, as measured by the HEI-2010 may not reap the health benefits that are typically expected.

Previous studies have shown that diets high in whole grains, fruits, and vegetables, low in fat and added sugar were associated with lower mortality risk among

CRC survivors. Guinter et al. (2018) reported from the Cancer Prevention Study-II Nutrition Cohort that postdiagnosis increase in the DASH and prudent dietary pattern scores were associated with lower CRC-specific mortality. In another study, Karavasiloglou et al. (2019) analyzed self-reported lifestyle data from cancer survivors in NHANES III. They found that HEI-2010 scores above 69.3 were associated with reduced all-cause mortality by 42%. Meanwhile, Meyerhardt et al. (2007) reported that postdiagnosis scores on a Western dietary pattern scale in stage III CRC survivors were positively associated with recurrence. In comparison, the prudent dietary pattern scale correlated with neither recurrence nor all-cause mortality. Such findings point to the possible benefits of healthful diets in lowering CRC recurrence and mortality during survivorship.

In contrast, our findings revealed a potential risk in CRC-specific mortality associated with an increase that crossed the sample's median HEI-2010 score, 70. It is worth noting that our survival analysis did not allude to any causational direction. As seen in the socioecological model of health, behavioral factors at the personal level are more controllable than that of organizational and societal levels. A possible explanation is that survivors who perceived higher mortality risk made a more considerable effort to improve their diets. Also, the observed trend of greater score increase among younger age at diagnosis could have implications on the long length of the follow-up period. As the HEI score is calculated from multiple dietary components, it is difficult to speculate the drivers in our results without analyzing each of the components. For example, an

individual may receive one less point for five components or 0 points for a single component and arrives at the same total score. However, each component's health effects may not be equal, especially post CRC, where the physiology, immune functions, and microbiome of the GI tract may be altered.

Additionally, the cohort populations in previous studies were composed of mainly Caucasians, up to 97%. This factor might influence incident-CRC risk, and mortality rates since the MEC participants' racial background may entail health determinants that could be challenging to quantify in epidemiological settings. Also, differences in study designs such as geographical regions and available clinical covariates may contribute to differences in findings. Finally, CRC treatment often results in critical disturbances to the GI system. Thus, survivors are a highly heterogeneous group with varying dietary tolerance. The ACS recommends a high protein and low fiber during treatment recovery to accommodate common symptoms like cramps, bloating, flatulence, diarrhea, and more (ACS, 2020-b). As such, it contradicts that of a conventional healthy diet. In cases where surgical resection necessitates, the remaining ileum or colon can take up to 5 years to adapt and compensate for lost functions. It is not clear when and how CRC survivors' diet transitions from the recovery phase to long-term health maintenance, which is likely individually tailored.

Strengths and Limitations

This study has several limitations. First, the cohort was established in Los Angeles County and the State of Hawaii. Therefore, the socio-environmental factors may

have both direct and indirect influences on health outcomes that cannot be generalized nationally. Second, clinical data lacked length and regimen of CRC treatment, which could have implications on the recovery and dietary needs. Third, demographic data such as social support and dietary acculturation levels were not available, both of which have been known to affect dietary behaviors. The strengths of this study included the large cohort sample size, the diversity of the participants, the use of a culturally validated FFQ, and the length of the follow-up period. To the best of our knowledge, this is the first study on this topic in a racially diverse prospective cohort.

Conclusion

In summary, the dietary transition from CRC recovery to long-term survivorship is full of unique challenges. In this sample of diverse survivors, an improvement in diet quality as measured by the HEI-2010, specifically from below to above the median score of 70 points, was associated with increased odds of CRC-specific mortality compared to remaining below the median score. Considering that the HEI was validated in generally healthy Americans, it may or may not be the ideal index to evaluate diet quality in CRC survivors. Alternately, the ACS dietary score, DASH score, and prudent dietary pattern scale have shown an inverse relationship with CRC recurrence and mortality risk. In practice, clinicians and public health educators supporting CRC survivors may consider additional health determinants relevant to the individual when devising a holistic lifestyle plan toward disease-free living. Future cohort studies may recruit participants from multiple geographies representative of national regions. Furthermore, data collection,

including both the selection of instruments and questionnaires that are validated in the CRC survivor population may be of interest.

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Tables and Figures

Table 1

Baseline and Follow-up Characteristics of Colorectal Cancer Survivors in the Multiethnic Cohort Study by Quartiles of the Healthy Eating Index-2010 Score

		Baseline (prediagnosis)					Follow-up (postdiagnosis)			
Quartile median	N	Q1	Q2	Q3	Q4	N	Q1	Q2	Q3	Q4
Score, median	989	53	64	71	80	989	57	67	73	82
Cases	989	285	272	299	285	989	284	256	315	286
Men %	548	67.4	62.1	52.2	36.8	548	66.9	59.8	52.7	39.5
Women %	441	32.6	37.9	47.8	63.2	441	33.1	40.2	47.3	60.5
Ethnicity %										
White	218	17.5	21.0	20.4	27.4	218	21.8	20.3	19.0	25.2
African American	134	11.9	11.4	15.7	18.2	134	15.5	12.5	14.6	14.7
Native Hawaiian	73	11.6	7.7	4.0	5.3	73	8.8	6.3	8.9	4.2
Japanese American	421	40.4	42.3	47.5	39.9	421	34.5	43.4	45.4	46.2
Latino	143	18.6	17.6	12.4	9.8	143	19.4	17.6	12.0	9.8
BMI[a], kg/m^2 (SD)	989	27.3	26.8	26.7	25.8	989	26.6	26.4	26.6	25.4
		(5.0)	(5.1)	(5.2)	(4.3)		(5.1)	(4.9)	(5.0)	(4.4)
Calories, kcal/d (SD)	989	2228	2182	2167	1933	989	1821	1758	1858	1743
		(938)	(861)	(841)	(732)		(828)	(772)	(691)	(641)
Alcohol, g ethanol/d	989	18.3	11.7	7.19	5.5	989	6.8	5.2	4.9	4.7
(SD)		(38.7)	(23.0)	(15.5)	(11.4)		(16.0)	(12.1)	(11.1)	(10.3)
Smoking, %										
Never	360	26.6	31.1	44.4	47.5	348	27.5	32.8	37.8	45.1
Past	491	51.8	56.3	46.1	44.0	603	62.7	62.9	60.3	53.5
Current	126	21.6	12.6	9.5	8.5	38	9.9	4.3	1.9	1.4

(Table continues)

		Baseline (prediagnosis)					Follow-up (postdiagnosis)			
Quartile median	N	Q1	Q2	Q3	Q4	N	Q1	Q2	Q3	Q4
Physical activity[b], %										
None	18	4.0	3.0	1.0	0.4	52	9.1	4.0	5.2	3.6
<150 min/d	831	85.6	83.3	84.5	84.2	818	84.8	81.8	79.7	82.1
>150 min/d	129	10.4	13.7	14.5	15.5	119	6.2	14.2	15.1	14.3
Education, %										
>High school	128	16.5	14.7	12.7	7.7	128	18.0	12.9	11.4	9.4
High school	289	34.4	27.9	26.1	27.4	289	35.2	26.2	30.8	23.1
Some college, college	446	40.4	46.3	47.5	49.8	446	40.8	48.0	44.8	50.7
Post-graduate	126	8.8	11.0	13.7	15.1	126	6.0	12.9	13.0	16.8
Family history[c], yes %	108	11.2	12.1	8.4	11.2	220	23.2	22.3	20.6	23.8
History of polyps, yes %	66	7.0	5.1	7.7	7.0	553	53.9	59.0	52.7	54.5
NSAIDs use[d], current %	291	27.8	32.4	33.1	27.3	457	35.	39.6	47.9	40.7

Note.(N = 989). Kcal, kilocalories; SD, standard deviation; NSAIDs, non-steroid anti-inflammatory drugs.

[a] BMI was calculated from self-reported height and weight at follow-up.

[b] Physical activity level was specified as moderate to vigorous.

[c] Family history of CRC was defined as participants' baseline response of the disease in mother, father, or siblings.

[d] NSAIDs use was based on self-reported use at follow-up as never used, past, or current usage of at least twice a week for longer than one month.

Table 2

Cohort Participants' Ages at Cohort Entry, CRC Diagnosis, Death, and CRC-Specific Mortality by Quartiles of Postdiagnosis HEI score

Quartiles	Q1	Q2	Q3	Q4
Age at entry, year (SD)	61 (8.5)	63 (8.1)	63 (7.5)	62 (8.0)
Age at CRC diagnosis, year (SD)	68 (8.4)	70 (8.4)	69 (8.4)	69 (8.1)
Age at death, year (SD)	81 (8.5)	83 (7.0)	81 (7.5)	82 (7.0)
Years from cohort entry to diagnosis (SD)	6.1 (3.4)	6.2 (3.4)	6.0 (3.4)	6.2 (3.2)
Person-years, prediagnosis	6549			
Years from CRC diagnosis to death or 12/31/2014	12.5 (4.8)	12.4 (4.6)	12.6 (4.5)	12.8 (4.4)
Person-years, postdiagnosis	13,610			
CRC-specific mortality, %	17.8	26.3	15.5	16.7

Note. (N = 989). CRC, colorectal cancer. HEI, Healthy Eating Index.

Table 3

Cox Regression Results on CRC-Specific Mortality Risk by Postdiagnosis HEI-2010 Quartiles and Change.

Quartile[1]	HR	95% CI		*p*
1st quartile, 20-62 (low)	1.00 (ref)			
2nd quartile, 63-69 (low)	1.39	0.687	2.796	0.362
3rd quartile, 70-76 (high)	0.87	0.399	1.887	0.721
4th quartile, 77-97 (high)	0.80	0.363	1.752	0.572
Change in score [a,b]				
Low/low	1.00 (ref)			
Low/high	2.00	1.020	3.992	0.044
High/low	0.59	0.260	1.346	0.211

Note. CRC, colorectal cancer. HEI, Healthy Eating Index.

[a]Adjusted for sex, race, age at diagnosis, education level, postdiagnosis body mass index, postdiagnosis daily energy intake, postdiagnosis alcohol consumption, physical activity, smoking status, family history of CRC, history of intestinal polyps, and NSAIDs use.

[b]HEI change high/high pairing not entered into regression model due to linear dependencies with the low/high and high/low pairings.

The Impact of Dietary Fiber Intake on Mortality Risk in Colorectal Cancer Survivors

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Outlet for Manuscript

The intended outlet for this manuscript is the Nutrition and Health as an original research article. The study's focus on the interactions between nutrition with health outcomes is one of the areas of interest of this journal and falls under its nutrition epidemiology section.

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Manuscript submitted on July 19, 2020.

Abstract

Background: Colorectal cancer (CRC) is the third leading malignancy diagnosed in the United States. While dietary fiber is inversely associated with incident-CRC and mortality risk, there is little evidence if the same benefit applies to CRC-specific mortality risk during survivorship. Objective: This study examined the impact of dietary fiber intake postdiagnosis and the change from prediagnosis level on CRC-specific mortality in survivors from the Multiethnic Cohort Study. (MEC) Methods: Adults ages 45 to 70 were recruited from Los Angeles County and the State of Hawaii between 1993 and 1996. Invasive CRC cases were identified between baseline and December 31, 2014. A survey was administered to collect data on self-reported demographic and medical history. Lifestyle data was collected through a culturally validated Food Frequency Questionnaire. Cox proportional hazard regression was used to estimate CRC-mortality risk based on postdiagnosis dietary fiber intake and change from baseline. Results: One thousand one hundred and forty-one CRC survivors were included in this analysis. The average age of incident-CRC diagnosis was 68.9 years old (*SD* = 8.3). There were 4.9 years (*SD* = 3.3) between diagnosis and follow-up surveys. The median dietary fiber intake was 11.6 grams/day (g/d) per 1,000 kilocalories (kcal) with quartile medians of 7.9, 10.2, 11.8, and 14.5 g/d per 1000 kcal. Postdiagnosis intake in the 3rd and 4th quartiles (25 g/d and 30 g/d, respectively) were associated with 58% and 52% lower CRC-specific mortality risk compared to the 1st quartile (less than 20 g/d). Conclusion:

Dietary fiber intake of at least 25 g/d was associated with the reduction in CRC-specific mortality risk among a racially diverse group of survivors from the MEC.

Introduction

Colorectal cancer (CRC) is the third leading malignancy, and the second most common cause of cancer deaths in the United States (Siegel et al., 2020). In 2020, 104,610 new cases of colon cancer and 43,340 new cases of rectal cancer are expected (Siegel et al., 2020). Despite the staggering incidence rate, the 5-year survival rates of colon and rectal cancers are 64% and 67%, respectively, reducing approximately 1% per year (American Cancer Society [ACS], 2019). With improved screening efforts and treatment, CRC survivors are a growing population of over one million American men and women. However, compared to primary prevention, less is understood about secondary prevention in CRC. Moreover, most studies to date investigated non-Hispanic White cohort participants. Considering that African Americans and Japanese Americans report increased incidence risk (ACS, 2010; Jin, Pinheiro, Xu, & Amei, 2016), research in racially diverse populations is urgently needed.

The relationship between dietary fiber and CRC initiation, recurrence, and mortality risks is an intricate one. Fiber has long been known to increase stool mass and colonic motility, thus shortening stool transit time, promoting regular bowel movements, and reducing potential carcinogenic exposures to colonocytes (Perry & Ying, 2016). Additionally, higher fiber intake results in higher short-chain acids production through bacterial fermentation, yielding vital metabolites that strengthen the immune functions of the gastrointestinal (GI) tract. In recent years, the microbiome has been linked to the risk of multiple chronic diseases' development, including cardiovascular disease, diabetes, GI

disorders, and cancer (Perry & Ying, 2016). The microbiome composition varies vastly between individuals by genetics, host physiology, age, and diet (Hollister, Gao, & Versalovic, 2014).

Diet has a significant influence on the diversity and balance of the microorganism communities. Interventional studies that manipulated fiber and fat contents of the diet reported immediate changes in gut microbiome and metabolites linked to CRC risk (O'Keefe et al., 2015; David et al., 2014). O'Keefe et al. (2015) demonstrated changes in the luminal environment when African Americans were placed on a high-fiber, low-fat diet, and native rural Africans consumed a high-fat, low-fiber diet for two weeks, compared to their baseline intake, respectively (O'Keefe et al., 2014). The high-fiber, low-fat diet increased butyrogenesis, reduced inflammatory markers, and decreased colonocytes proliferation (O'Keefe et al., 2014). In healthy subjects, plant-based and animal-based diets resulted in measurable changes in microbial diversity and gene expression after five days (David et al., 2014), suggesting the anticarcinogenic role of higher fiber intake. Meanwhile, CRC patients' microbiome was perturbed compared to cancer-free subjects (Saus, Iraola-Guzman, Willis, Brunet-Vega, & Gabaldon, 2019). Additional studies also reported reduced relative risk when comparing high and low fiber intakes. From the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Bingham et al. (2003) reported 42% relative risk reduction in CRC incidence, approximately 8% reduction per increased quintile intake of three to five grams/day (g/d). Later, Murphy et al. (2012) reported from an 11-year follow-up of the same cohort and

found a dose-response-like effect by fiber intake— a 13% risk reduction per 10 g/d. A meta-analysis of 25 prospective studies by Aune et al. (2011) reported that every 10 g/d intake was correlated to an approximately 10% decrease in CRC incidence. However, there were also reporting that fiber intake was inconsequential in CRC development (Lin et al., 2005; Park et al., 2005; Schatzkin et al., 2007).

As the population of CRC survivors increase and age, the role of fiber in secondary prevention demands further examination. Song et al. (2018) analyzed data between 1980 to 2010 from the Nurses' Health Study and the Health Professionals Follow Up Study to address this question. Self-administered FFQ from the 1,575 cohort participants with stages I, II, and III CRC provided pre- and postdiagnosis fiber intake. For every five grams of cumulative fiber intake per day at baseline, there was a 22% decrease in the risk of CRC-specific mortality risk. In survivors, per five g/d increase compared to baseline intake was associated with a 12% decrease in CRC-specific mortality (Song et al., 2018). In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial, of the 1,667 cases of incident adenomas, 738 participants developed recurrent adenomas (Kunzmann et al., 2015). Higher grains and cereal fiber intakes were linked to reduced recurrence of rectal adenomas; however, no other fiber sources or bowel areas were associated with intakes (Kunzmann et al., 2015). Given the potentially significant benefits in recurrent risk reduction, it was worthwhile to investigate if changes in postdiagnosis fiber intake may improve CRC-free survival across racial groups.

The present study addressed the gap in the literature by examining whether postdiagnosis fiber intake, as well as changes from prediagnosis intake, are associated with CRC-specific mortality risk in survivors in the Multiethnic Cohort Study (MEC). It is hypothesized that an increase in fiber intake postdiagnosis is associated with a reduction in CRC-specific mortality risk.

Methods

Study Population

The MEC is a prospective cohort study established to investigate the association of lifestyle and genetic factors and with the development of cancer and chronic diseases (Kolonel et al., 2000). The study's design and data collection method have been previously described (Kolonel et al., 2000). Sampling frames were developed using publicly available information from driver's license files, voter registration records, and Medicare enrollment to achieve a racially and socioeconomically diverse participant pool. Over 215,000 adults between the ages of 45- and 75-years old living in the state of Hawaii and Los Angeles County consented to enroll from 1993 to 1996. MEC participation was initiated when eligible individuals completed a self-administered questionnaire that included baseline demographic information, medical history, and detailed dietary assessment. Study participants were primarily of the following race/ethnicities: African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic White. The institutional review boards of the University of Hawaii and the University of Southern California approved the study protocol. Additionally, the Walden

University institutional review board approved the present analysis (approval #01-08-20-0641131).

Dietary Assessment

The MEC's questionnaire development, sampling method, and data collection have been previously published (Kolonel et al., 2000; Stram et al., 2000). Upon entry to the cohort, participants completed a 26-page baseline questionnaire. As part of the survey, a culturally tailored quantitative Food Frequency Questionnaire (FFQ) with more than 180 items was included (Stram et al., 2000). The questionnaire assessed habitual intake over the previous 12 months. Detailed instructions in English and Spanish were provided along with images of portion sizes referenced in the multiple-choice responses. The FFQ was validated and calibrated in ethnic-sex matched groups through repeated 24-hour diet recalls on three separate occasions (Stram et al., 2000). The correlation for dietary fiber densities (grams of intake per 1,000 kilocalories per day) ranged from .68 to .79. Upon data collection, average daily nutrient intakes, including dietary fiber were calculated using the food composition tables developed and maintained at the University of Hawaii Cancer Center specifically for the use in the MEC (Murphy, 2002). Pre- and postdiagnosis intakes of dietary fiber intake were assessed by baseline FFQ and the FFQ following CRC diagnosis.

Case Ascertainment

The primary exclusion criterion was the presence or a history of CRC at baseline, as identified from responses in the baseline questionnaire or the Surveillance,

Epidemiology, and End Results Program (SEER) tumor registries in California and Hawaii. The confirmation of CRC cases and tumor sites were based on the International Classification of Disease for Oncology, third edition (ICD-O-3) codes (World Health Organization [WHO], 2013). Sites included were cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, large intestine not otherwise specified, rectosigmoid junction, and rectum (C180-C189, C199, C209, and C260). This information was then classified as colon, rectal, or mixed cancer. CRC-specific deaths were verified through the State's vital records of California and Hawaii and the National Death Index. Participants who identified outside of the major race/ethnicity groups of non-Hispanic white, African American, Japanese American, Latino, and Native Hawaiian were excluded. Finally, participants who reported implausible dietary intakes were also excluded (average daily energy exceeding 5,000 kcal and dietary fiber exceeding 100 g/d).

Statistical Analysis

Between baseline and follow up, there were 6,451 cases of invasive CRC identified in the cohort. Among them, dietary data pre- and postdiagnosis were available for 1,166 cases. After excluding dietary outliers, 1,141 participants remained in the analysis. Missing data in the covariates were replaced with median value. A post-hoc power analysis used a two-tailed alpha of .05, .25 effect size, and a 55% 10-year survival rate, which yielded a statistical power of .88. For prediagnosis fiber intake, person-time was calculated from the date of cohort entry to the date of incident-CRC diagnosis. For

postdiagnosis fiber intake, the date of CRC diagnosis to the first instance of death, censoring, or end of study was used to calculate the person-time.

Dietary fiber intake was standardized by density per 1,000 kilocalories (kcal). Cox proportional hazard regression modeling was used to estimate CRC-specific mortality risks as hazard ratios (HR) with 95% confidence interval (CI) for postdiagnosis fiber intake and the change between pre- and postdiagnosis. Postdiagnosis intake was calculated into quartiles and entered into the model for comparisons. For the change in intake, daily averages were calculated by subtracting the prediagnosis intake from that of postdiagnosis. The change in intake was grouped as followed: ≥ 5 g/d decrease, ≤ 5 g/d decrease, ≤ 5 g/d increase, and ≥ 5 g/d increase. Using the least increased group as the referent, the model computed the CRC-specific mortality risk for each level of change in intake.

Univariate Cox regression models were used to evaluate model fit and HRs before adjusting for covariates. Potential confounders were included in the subsequent models as covariates: Age at diagnosis, sex, race, education, BMI, physical activities, smoking status, history of intestinal polyps, family history of CRC, alcohol consumption, and total energy. BMI was calculated from self-reported height and weight. Physical activity was categorized as 0, up to 150, and more than 150 minutes per day of moderate to vigorous exercise. Cigarette smoking status was never smoked, past smoker, and current smoker. Education level was grouped as less than high school, high school, some college and college, and graduate education. History of intestinal polyps was defined by participants'

responses if their health care providers have ever informed them. Family history of CRC was defined as participants' affirmation of the disease in at least one biological parent or sibling. Finally, NSAIDs use was based on self-reported use as never used, past use, or current user. Wald statistics and likelihood ratio tests were used to check for interactions and collinearity. Confidence interval (CI) and *p*-values < 0.05 were used to indicate statistically significant results.

Sensitivity analysis was performed to exclude analysis of participants who returned the postdiagnosis FFQ within 12 months of CRC diagnosis to account for the potential influence on the diet from treatment. All analyses were performed in SPSS version 25.

Results

The sample was composed of 622 men and 519 women. The racial distribution is as following: 42.4% Japanese Americans, 26.6% non-Hispanic whites, 14.5% Latinos, 14.4% African Americans, and 7.1% Native Hawaiians. The mean follow-up was 18.7 years. Person-time was 6,975 years prediagnosis and 14,359 postdiagnosis. Table 1 4shows the baseline and follow-up characteristics of the participants by quartiles of dietary fiber. At baseline, the median intake was 10.9 g/d per 1000 kcal (interquartile range 8.3 to 14.1 g). Postdiagnosis, median intake was 11.6 g (interquartile range 9.3 to 14.3 g). Participants with higher fiber intake postdiagnosis tended to be females, were more physically active, and consumed less alcohol.

Table 5 presents the participants' ages at critical events during the study period. Participants averaged 62.3 years old (*SD* = 8.1) at cohort entry while the average age at incident-CRC diagnosis was 68.9 years old (*SD* = 8.3). There were 4.9 years (*SD* = 3.3) between diagnosis and the completion of follow-up FFQ. In this group of survivors, there were approximately three times more colon cancers (73.8%) than rectal cancers (25.4%). Between the two cancer types, a higher proportion of colon cancer survivors reported fiber intake in the upper quartiles (Table 6).

The hazard ratios of postdiagnosis fiber intake and the change in intake on CRC-specific mortality are shown in Table 7. In the univariate models, the postdiagnosis intake and change in intake did not show an association with CRC-specific mortality (results not shown). After adjusting for covariates, postdiagnosis intakes in the 3rd and 4th quartiles were associated with 58% and 52% reduction in CRC-specific mortality risk, respectively (HR = 0.42; 95% CI [0.2, 0.82]; $p = .011$ and HR = 0.48; 95% CI [0.24, 0.97]; $p = .041$, respectively). Based on the average caloric intake, the quartile medians equate to approximately 26.0 g and 29.9 g of dietary fiber daily postdiagnosis. On the contrary, the change in intake did not reach statistical significance in CRC-mortality risk. Sensitivity analysis excluding participants who completed their postdiagnosis survey within the first year was consistent where intake in the 3rd and 4th quartiles were inversely associated with lowered CRC-specific mortality.

Discussion

In the general population, dietary fiber is an integral part of a healthy diet. The results here suggest that intake over approximately 25 g daily was associated with over 50% lower CRC-specific mortality risk in this sample. However, the change in intake level was found to be irrelevant. In other words, regardless of prediagnosis intake level, achieving at least 25 g/d, which coincides with the minimal adequacy in the Dietary Guidelines for Americans (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015), may promote CRC-free living in long term survivorship.

The findings align with some of the existing literature. In a previous study, Song et al. (2018) reported a similar finding from the Nurses' Health Study and the Health Professionals Follow Up Study cohorts. They reported a 52% reduction in CRC-specific mortality associated with intakes in the 3rd quartile and a 46% reduction associated with the 4th quartile. However, the mortality risk observed from the change in intake did not occur in this group of CRC survivors. One potential explanation is the timing of the follow-up survey. Song et al. examined dietary data collected between six months and four years postdiagnosis, whereas the average length of time in this sample was 4.9 years (SD = 3.3) postdiagnosis. This may indicate that increased fiber intake during early survivorship could provide additional health benefits during CRC treatment recovery and intestinal adaptation.

Limitations and Strengths

There are several limitations and strengths in this study. Since surgery is the primary treatment for non-metastasized CRC, the lack of treatment methods— especially the type of surgical resection performed, could have implications on dietary tolerance that affected fiber intake. Second, the MEC cohort is based in Southern California and Hawaii, which may limit the findings' generalizability to CRC patients in other regions. On the other hand, the total follow-up period was 18.7 years, with an average of 12.6 years (*SD* = 4.6) postdiagnosis. This length of follow-up allows for a comprehensive period to capture mortality occurrence. Additionally, this study provided much-needed data about racial minorities, who have a disproportionately higher of incidence of CRC diagnoses in the US (Siegel et al., 2020).

Conclusion

High fiber intake has been linked to lower incident-CRC risk. The present analysis suggested significant benefits in CRC-specific mortality risk during long term survivorship in a racially and socioeconomically diverse sample. Future studies may expand on geography for recruitment, such as the Appalachia, southern, and midwestern regions in the US due to some of the highest incident-CRC rates. Meanwhile, the types and sources of fiber are also of interest as the evidence may be incorporated into dietary education. A potential new area to investigate may be the recurrent and mortality risk with the timing of increasing dietary fiber intake postdiagnosis.

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Tables and Figures

Table 4

Baseline and Follow-up Characteristics of the Incident-CRC Survivors in the MEC by Quartiles of Fiber Iintake.

		Baseline (prediagnosis)					Follow-up (postdiagnosis)			
Quartile median	n	Q1	Q2	Q3	Q4	n	Q1	Q2	Q3	Q4
Total fiber Intake, g/1000 kcal/d	1141	6.9	9.6	12.2	16.9	1141	7.9	10.2	11.8	14.5
Soluble fiber intake, g/d	1141	4.3	6.2	7.9	9.7	1141	4.7	6.2	7.8	9.0
Insoluble fiber intake, g/d	1141	5.9	8.5	10.2	13.4	1141	6.8	8.6	10.3	11.8
Men %	622	75.4	58.1	51.0	33.8	622	74.3	62.8	52.6	36.3
Women %	519	24.6	41.9	49.0	66.2	519	25.7	37.2	47.4	63.7
Ethnicity %										
White	246	18.2	20.4	21.9	25.6	246	21.8	19.6	22.2	22.3
African American	164	9.8	15.1	15.8	16.7	164	12.9	14.0	14.9	15.1
Native Hawaiian	81	12.6	8.7	3.5	3.9	81	13.4	6.8	6.3	4.1
Japanese American	484	51.9	44.5	42.9	30.2	484	43.6	44.8	44.8	36.3
Latino	166	7.4	11.3	15.8	23.5	166	8.4	14.8	11.8	22.3
BMI[a], kg/m^2 (*SD*)	1141	26.8 (4.8)	27.0 (5.4)	26.6 (4.9)	26.2 (4.8)	1141	26.7 (4.7)	26.6 (5.0)	26.8 (4.9)	26.5 (5.3)
Calories, kcal/d (*SD*)	1141	2327 (906)	2178 (857)	2075 (825)	1926 (771)	1141	2168 (875)	2069 (875)	2201 (885)	2062 (768)
Alcohol, g ethanol/d (*SD*)	1141	23.8 (40.0)	9.4 (21.3)	5.6 (11.0)	3.8 (8.5)	1141	16.5 (30.6)	11.7 (28.6)	9.0 (20.4)	5.7 (17.4)

(Table continues)

	Baseline (prediagnosis)					Follow-up (postdiagnosis)				
	n	Q1	Q2	Q3	Q4	n	Q1	Q2	Q3	Q4
Smoking %										
Never	424	24.8	33.2	43.3	48.2	410	24.3	31.2	40.1	42.5
Past	558	53.2	53.8	47.2	43.9	682	63.4	62.8	58.2	56.8
Current	147	22.0	13.0	9.4	7.9	49	12.4	6.0	1.8	0.7
Physical activity[b] %										
No exercise	23	2.5	1.5	2.9	1.1	61	8.4	6.4	4.8	3.1
< 150 min/d	953	84.3	85.9	82.1	85.6	913	81.7	80.8	84.4	81.8
> 150 min/d	153	13.2	12.6	14.9	13.3	139	9.9	12.8	10.8	15.1
Education %										
>High school	147	9.1	12.8	16.8	12.5	147	10.4	13.2	12.6	14.7
High school	330	34.7	26.8	25.8	28.5	330	32.2	31.2	28.0	26.0
4-year college	525	45.3	48.3	45.5	45.2	525	49.0	43.2	46.3	45.9
Post-graduate	139	10.9	12.1	11.9	13.9	139	8.4	12.4	13.1	13.4
Family history[c], yes %	122	12.3	10.9	11.0	8.5	256	26.2	23.2	21.2	20.9
History of polyps, yes %	77	5.3	7.2	7.7	6.8	626	66.3	52.4	51.4	53.8
NSAIDs use[d], current %	332	26.0	30.6	32.3	31.7	509	43.1	48.0	43.8	43.8

Note. CRC, colorectal cancer; MEC, multiethnic cohort study; kcal, kilocalories; SD, standard deviation; NSAIDs, non-steroid anti-inflammatory drugs.

[a] BMI was calculated from self-reported height and weight at follow-up.

[b] Physical activity level was specified as moderate to vigorous.

[c] Family history of CRC was defined as participants' baseline response of the disease in mother, father, or siblings.

[d] NSAIDs use was based on self-reported use at follow-up as never used, past, or current usage of at least twice a week for longer than one month.

Table 5

The Age of Cohort Entry, Diagnosis, and Death in CRC Survivors by Quartiles of Dietary Fiber Intake Postdiagnosis

	Q1	Q2	Q3	Q4
Age at entry, y (SD)	60.7 (8.7)	62.7 (8.3)	62.9 (7.7)	63.2 (7.2)
Age at diagnosis, y (SD)	67.0 (8.8)	69.6 (8.5)	69.4 (8.1)	69.8 (7.5)
Age at death, y (SD)	80.9 (8.7)	81.9 (7.3)	82.1 (7.0)	81.7 (7.2)
Years from cohort entry to CRC diagnosis (SD)	5.9 (3.2)	6.4 (3.4)	6.1 (3.3)	6.1 (3.4)
Years from CRC diagnosis to death or 12/31/2014 (SD)	12.7 (4.7)	12.2 (4.7)	12.5 (4.4)	12.8 (4.5)

Note. CRC, colorectal cancer; SD, standard deviation.

Table 6

Incident-CRC Tumor Site and CRC-Specific Mortality by Quartiles of Dietary Fiber Intake Postdiagnosis

	N	Q1	Q2	Q3	Q4
Tumor site %					
Colon	791	70.6	69.7	77.1	76.0
Rectum	279	28.3	29.9	22.1	23.2
Mixed	8	1.1	0.4	0.7	0.7
CRC-specific mortality (%)	49	25.9	25.5	11.2	18.5

Note. CRC, colorectal cancer.

Table 7

CRC-Specific Mortality Risk by Fiber Intake and Its Change Postdiagnosis in the Multiethnic Cohort

		HR	95% CI	*p*-value
Postdiagnosis fiber intake,	2.9-9.3 (1st)	Ref		
g/d per 1000 kcal (quartile)	9.3-11.6 (2nd)	0.74	0.42-1.30	0.293
	11.6-14.3 (3rd)	0.42	0.21-0.82	0.011
	14.3-33.4 (4th)	0.48	0.24-0.97	0.041
Fiber change postdiagnosis,	> 5 g/d decrease	Ref		
g/d per 1000 kcal	< 5 g/d decrease	1.36	0.56-3.31	0.502
	< 5 g/d increase	1.78	0.73-4.24	0.210
	> 5 g/d increase	2.91	0.98-8.66	0.055

Note.(N = 1,141) [a,b]. CRC, colorectal cancer.

[a]HRs and 95% CIs were obtained by Cox regression.

[b]Adjusted for sex, race, education level, BMI, physical activity level, caloric intake, alcohol consumption, family history of CRC, history of polyps, age at diagnosis, smoking status, and NSAIDs use.

The Impact of Dietary Fat Intake on Mortality Risk in Colorectal Cancer Survivors

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Outlet for Manuscript

The manuscript is intended for the submission to Nutrition and Cancer as an original research article.

Journal homepage: https://www.tandfonline.com/toc/hnuc20/current

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Abstract

Background: Dietary fat is a heterogeneous group of nutrients that are essential to healthy living. Fatty acid subtypes have been shown to affect incident cancer risk based on their pro- or anti-inflammatory properties. In colorectal cancer (CRC), fat from meat sources and processed foods was associated with neoplastic initiation while fat from plants and fish was associated with reduced incident and mortality risk. Objective: To examine the role of total fat intake and fat from fish and shellfish postdiagnosis in CRC-specific mortality risk among survivors in the Multiethnic Cohort Study. Method: Adults ages 45 to 75 from Los Angeles County, California, and the State of Hawaii were recruited between 1993-1996. Baseline and subsequent surveys included a culturally validated food frequency questionnaire to collect dietary data from self-reporting intakes. Follow-up surveys were conducted every 4 to 6 years. Results: One thousand one hundred and forty-one participants were included in the final analysis. Total fat and fat from fish and shellfish intake postdiagnosis were not associated with CRC-specific mortality risk (HR = 1.48, 95% CI [.74, 2.95] and HR = 1.24, 95% CI [.58, 2.66], respectively). Furthermore, no statistical significance was observed with changes in intakes postdiagnosis (HR = .56, 95% CI [.28, 1.11] and HR = 1.29, 95% CI [.69, 2.39], respectively). Sensitivity analysis restricting risk estimation from survivors who responded at least 12 months after diagnosis showed consistent results. Conclusion: The findings align with existing literature that total fat intake did not affect secondary CRC

mortality risk whereas the fat from fish and shellfish intake was non-significant when assessing the potential benefits form all fatty acids combined.

Introduction

Colorectal cancer (CRC) is the third leading malignancy diagnosis and the second cause of cancer deaths in the United States (American Cancer Society [ACS], 2019). First-time colon and rectal cancer are expected to reach 104,610 and 43,340 cases in 2020, respectively (Siegel et al., 2020). In 2015, the 5-year survival rates of colon and rectal cancers were 64% and 67%, respectively, declining at approximately 1% per year since the previous decade (ACS, 2019). With improved screening efforts and treatment, CRC survivors are a growing population of over one million American men and women. However, the prevention of CRC recurrence, including using lifestyle strategies, is not well understood. Moreover, most large-scale cohorts to date are composed of primarily non-Hispanic White participants. Because CRC incidence risk has been rising among African and Japanese Americans, research in racially diverse populations was needed (ACS, 2019; Jin, Pinheiro, Xu, & Amei, 2009).

Diet has been demonstrated to correlate with incidence and mortality risks in CRC. One of the mediators between dietary fat and CRC pathogenesis is via increased primary bile acids secretion in response to intake. Although bile acids level alone is not associated with the initiation of CRC, its level was found to correlate with biomarkers of cell proliferation and mucosal inflammation in humans (Boleij & Tjalsma, 2012). Additionally, the mechanism in which saturated fatty acids (SFAs) and trans fatty acids may increase CRC incidence risk due to their proinflammatory properties (Doerner et al., 2016; Viggiano et al., 2016), stem cell regulation disruption (Beyaz et al., 2016), altered

prostanoid metabolism (Wang & DuBois, 2013), and modulation of the gut microbiota (Yoshimoto et al., 2013). However, in a retrospective case-control study of over 4,000 Canadians, total fat intake was not associated with incidence CRC risk, and neither was SFAs, monounsaturated fatty acids (MUFAs), or polyunsaturated fatty acids (PUFAs; Sun et al., 2012). In a meta-analysis of 18 studies, no association was found between CRC risk and total fat, SFAs, MUFAs, and PUFAs intake (Kim & Park, 2018). This finding highlights that additional nutritional and socioenvironmental factors likely modify dietary fat's effect on CRC development.

Among the subtypes of fatty acids, omega-3 (ω-3) PUFAs, particularly those from marine sources, may be protective against CRC development (Norat et al., 2005; Kato, Majumdar, Land, Barnholtz-Sloan, & Severson, 2010; Song et al., 2014). Norat et al. (2005) reported from over 428,000 participants across 10 European countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study that fish consumption of > 80 grams/day (g/d) reduced CRC incidence risk by 31% when compared to < 10 g/d.

On the contrary, neither marine ω-3 nor ω-6 intake was associated with CRC risk reduction in an analysis combining data from the Nurses' Health Study and Health Professional Follow-up Study by Song et al. (2014). Instead, marine ω-3 intake was nonsignificantly associated with an increased risk of distal colon cancer but potentially protective against rectal cancer. This finding was in line with physiological characteristics that the presence of gut bacteria is most concentrated in the proximal

colon, resulting in more robust cellular protection from fiber fermentation, creating a gradient of weakening defense toward the distal colon (Yoshimoto et al., 2013). Second, based on cellular data, rectal tissues are susceptible to inflammation, and oxidative stress-induced carcinogenesis (Yesudhas, Gosu, Anwar, & Choi, 2014), thus marine ω-3's anti-inflammatory property may counter cellular damages associated with CRC development.

To date, few studies investigated, prospectively, the postdiagnostic and the change from pre and postdiagnostic intake of fat from marine sources in CRC survivors. In one of the most comprehensive studies with CRC survivors, 1,659 participants from the Nurses' Health Study and Health Professionals Follow Up Study were followed for a median of 10.4 years. Survivors who increased marine ω-3 intake by > 0.15 g/d experienced a 70% CRC-specific mortality risk reduction compared to unchanged intake (Song et al., 2017). In another prospective study, 1,011 stage III CRC survivors were followed for a median of seven years (Van Blarigan et al., 2018). The highest quartile of ω-3 intake was associated with a 32% risk reduction in recurrence (Van Blarigan et al., 2018).

The growing survivor population demands practical secondary prevention guidelines and strategies. This study examined whether changes in total dietary fat intake postdiagnosis, including fat from fish and shellfish, affect CRC-specific mortality risk in survivors in the Multiethnic Cohort Study. (MEC)

Materials and Methods

Study Population

The MEC is a prospective cohort study initiated to investigate the association of lifestyle and genetic factors and with the development of cancer and chronic diseases (Kolonel et al., 2000). The study's design and data collection method have been previously described (Kolonel et al., 2000). Over 215,000 adults living in Hawaii and Los Angeles County between the ages 45 and 75 years old were enrolled from 1993 to 1996. Publicly available information from driver's license files, voter registration records, and Medicare enrollment was used to develop sampling frames that are racially and ethnically diverse. MEC participation was established when eligible individuals completed a self-administered baseline questionnaire that included demographic information, medical history, and a detailed dietary assessment. Study participants were primarily of the following race/ethnicities: African American, Native Hawaiian, Japanese American, Latino, and non-Hispanic White. The institutional review boards of the University of Hawaii and the University of Southern California approved the study protocol. Additionally, the Walden University institutional review board approved the present analysis (#01-08-20-0641131).

Dietary Assessment

The MEC's questionnaire development, sampling method, and data collection have been previously published (Kolonel et al., 2000; Stram et al., 2002). Upon entry to the cohort, participants completed a 26-page baseline questionnaire. As part of the

survey, a culturally tailored quantitative Food Frequency Questionnaire (FFQ) with more than 180 items was included (Stram et al., 2002). The FFQ was validated and calibrated in ethnic-sex matched groups through 3 repeated 24-hour diet recalls. The questionnaire assessed habitual intake over the previous 12 months. Detailed instructions in English and Spanish were provided along with images of portion sizes referenced in the multiple-choice responses. Average daily nutrient intakes were calculated using the food composition tables developed and maintained at the University of Hawaii Cancer Center, specifically for the use in the MEC (Murphy, 2002).

Case Ascertainment

The MEC dataset is linked to the Surveillance, Epidemiology, and End Results Program tumor (SEER) registries in California and Hawaii for the identification of CRC cases. For CRC-specific death ascertainment, records from the States' death certificate records and the National Death Index were used for confirmation. The main exclusion was a history or presence of CRC at baseline, as identified from responses in the baseline questionnaire or the tumor registries. Furthermore, participants who identified outside of the major race/ethnicity groups of African American, Native Hawaiian, Japanese American, Latino, and white are excluded. Finally, participants with implausible responses regarding dietary intakes are also excluded.

Statistical Analysis

Between baseline and follow up, 6,451 MEC participants were diagnosed with invasive CRC, in which postdiagnosis dietary data were available from 1,166 of them.

After excluding implausible dietary intakes of over 5,000 kcal average daily energy and over 100 grams of daily dietary fiber intakes, 1,141 participants remained in the final sample. Missing data were handled with median replacements. Post-hoc power analysis for Cox proportional hazard regression used a two-tailed alpha of 0.05, 0.25 effect size, and assuming a 55% 10-year survival rate, which yielded a statistical power of 0.8777. For postdiagnosis intake as well as the change in intake, person-time was calculated from the date of CRC diagnosis to the first instance of death, censoring, or end of the study period on December 31, 2014.

Multivariate Cox proportional hazards regression models were used in calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) for CRC-specific deaths. Intakes of total fat were standardized into percent of energy for analysis. For the changes in intakes, prediagnosis intake reported at baseline was subtracted from the postdiagnosis intakes at follow-up. All intake and change levels were calculated into quartiles and used to estimate HRs for mortality risk. Demographic characteristics, clinicopathological, lifestyle, and dietary predictors for CRC outcomes were included as covariates in the models (age at diagnosis, sex, race, education level, physical activities, smoking status, history of intestinal polyps, family history of CRC, BMI, total energy, and alcohol consumption). Education levels were classified as less than high school, some college, and college graduate. A history of intestinal polyps was defined by participants' affirmative response to the detection of the condition. A family history of CRC was determined by participants' baseline reports of CRC in first-degree family members. BMI

was calculated from self-reported height and weight postdiagnosis and entered as a continuous covariate. Physical activity was grouped into less than or more than 150 minutes of daily activities at moderate to vigorous intensity. Self-reported cigarette smoking status was never smoked, past smoker, or current smoker. Finally, energy and alcohol consumption were calculated from FFQ responses. Wald statistics and likelihood ratio tests were used to check for interactions and collinearity.

Sensitivity analysis was performed by excluding participants who returned the postdiagnosis FFQ within 12 months of CRC diagnosis to limit the potential influence on the diet from treatment. All analyses were performed in SPSS version 25.0 (IBM Corporation, Armonk, NY). All statistical tests were two-sided, $p < 0.05$ was considered statistically significant.

Results

Among the 1,141 participants who were diagnosed with invasive CRC, 54.5% of them were men. Table 8 details the participants' characteristics. This cohort of CRC survivors included 42.4% Japanese Americans, 21.6% non-Hispanic Whites, 14.5% Latinos, 14.4% African Americans, and 7.1% Native Hawaiians. Average BMI was 26.3 kg/m^2 (*SD* = 4.9), energy intake was 1,798 kcal (*SD* = 735), and alcohol consumption was 5.4 g ethanol per day (*SD* = 12.5). The majority of the participants reported regular physical activities of moderate to vigorous levels (%). Most of them were either never or past cigarette smokers both before and after incident-CRC diagnosis.

The mean follow-up was 18.7 years. The average age of incident-CRC diagnosis was 68.9 years old (*SD* = 8.3). There was an average of 4.9 years (*SD* = 3.3) between incident-CRC diagnosis and the completion of the postdiagnosis FFQ (Table 9). The CRC-specific mortality rates were 23.1% for the participants in the lowest intake quartile of total fat and 28.3% for the highest intake quartile. For the intake of fat from fish and shellfish, an inverse relationship emerged at 37.5% and 19.8% from the lowest and highest intake quartiles, respectively.

Median total fat intake was 64 g/d pre- and 58 g/d postdiagnosis. Postdiagnosis, median intakes of fatty acid subtypes were 17 g/d for saturated fat, 22 g/d for monounsaturated fat, 13 g/d for polyunsaturated fat, and 1.5 g/d for omega-3 fatty acids— all of which were lower than prediagnosis levels (data not shown). Intake of fat from fish and shellfish decreased from 0.70 g/d prediagnosis to 0.65 g/d postdiagnosis. Table 3 10presents the HRs and 95% CI for CRC-specific mortality risk estimated from both the unadjusted and adjusted models. There was no statistically significant association between either postdiagnosis total fat intake or fat from fish and shellfish and CRC-specific mortality risk (HR = 1.48, 95% CI [.74, 2.95], p = .264 and HR = 1.24, 95% CI [.58, 2.66], p = .585, respectively). Furthermore, the two sources of fat's change in intakes did not reach statistical significance in their association with CRC-specific mortality risk. Compared to at least 5% increase in total fat intake, CRC survivors who reported at least 5% decrease in fat as energy had an HR = .56 (95% CI [.28, 1.11], p = .095). Similarly, those who increased intake of fat from fish and shellfish sources by at

least 0.25 g/d did not experience significant differences in CRC-specific mortality compared to those decreased consumption by at least 0.25 g/d (HR = 1.29, 95% CI [.69, 2.39], p = .423). Sensitivity analysis restricting risk estimation from survivors who responded at least 12 months postdiagnosis did not change the results.

Among covariates in the models, older age at diagnosis was associated with slightly increased risk with CRC-specific mortality (HR = 1.045, 95% CI [1.015, 1.077], p = 0.003). Being a current smoker postdiagnosis significantly increased risk (HR = 3.61, 95% CI [1.658, 7.870], p = 0.001). Meanwhile, participants who reported having been informed of the presence of intestinal polyps experienced a 48% reduced mortality risk (95% CI [0.339, 0.801], p = 0.003).

Discussion

My results did not link the total fat intake level and that from fish and shellfish to CRC-specific mortality risk among invasive CRC survivors. In addition, the change in intake levels postdiagnosis, including a decrease in fat as a percent of total energy or an increase in fish and shellfish sources, did not statistically significantly affect CRC-specific mortality risk in long-term survivorship.

The lack of association between total fat intake and CRC-specific mortality risk aligns with a previous study in which fat intake during survivorship did not impact CRC-recurrence, or all-cause mortality risks in 1,011 stage III CRC survivors (Van Blarigan et al., 2018). In that cohort, quartile median intakes were 57, 68, 76, and 87 g/d. In the MEC cohort, participants reported lower quartile medians of 40, 60, 64, and 78 g/d. Our result

supports that total fat intake during CRC survivorship had little to no impact on CRC-specific mortality risk, which appears to be consistent across a range of consumption levels. This finding is not surprising given the heterogeneity of fatty acids and their pro- or anti-carcinogenic properties. The role of dietary fat in CRC survivorship may be manifested partly via bodyweight as a result of an individual's metabolic state and energy balance post-cancer.

Interestingly, the change in fat intake—neither increased nor decreased, had no impact on CRC-specific mortality risk in our cohort. One potential explanation is that cancer, as a disease state, and its related treatment is known to increase the patient's risk of cancer cachexia that may last beyond the active cancer phase. Also, GI functions may be altered following curative treatment and interfere with nutritional status. Consequently, total fat intake likely affects each individual differently, elucidating a consistent pattern on long-term health outcomes among CRC survivors.

On the contrary, the intake of fish and shellfish has been suggested to be protective against incident-CRC (Aglago et al., 2020; Schwingshackl, et al., 2018) However, such health benefits may be highly specific to one type of PUFA, marine ω-3 fatty acids. For example, Song et al. (2014) reported no significance between fish or total PUFAs intake and incident-CRC risk. But when Japanese researchers examined the relationship between marine ω-3 PUFAs and rectal cancer in a large-scale cohort, they reported a U-shape association. The intake level in the highest quintile showed a slightly elevated incident-rectal cancer risk. Whereas, intake levels in the middle quintiles were

protective (Sasazuki et al., 2010). Later, Song et al., (2017) examined the effect of marine ω-3 PUFAs on CRC-specific mortality risk and reported a trend in mortality risk reduction among survivors who consumed at least 0.3 g/d compared to 0.1 g/d (HR = .59, 95% CI [.35, 1.01]). Meanwhile, an increase of at least 0.15 g/d from prediagnosis intake was associated with a 70% CRC-specific mortality risk reduction compared to those who did not change their intake. However, the same association and trend were not observed in our analysis.

This contradicting finding suggests that first, seafood consumption was not a surrogate to marine ω-3 PUFAs intake, likely due to the full array of fatty acids besides ω-3 PUFAs and only deep-water fish such as salmon and tuna are rich in ω-3 PUFAs. Second, the top 10 most consumed seafood in the United States were shrimp, salmon, canned tuna, tilapia, Alaska pollock, pangasius, cod, catfish, crab, and clams (National Marine Fisheries Service, 2020). As such, risk estimates based on fat from fish and shellfish are likely less granular compared to estimating from marine ω-3 PUFAs.

Other factors that were significantly associated with CRC-specific mortality risk were older age at diagnosis, cigarette smoking postdiagnosis, and having a history of intestinal polyps was. In particular, smokers exhibited over three times the risk compared to participants who reported never smoked. On the other hand, consistent with the evidence that regular screening can identify pre- and early-stage cancerous polyps, a positive history may be a surrogate to early detection thus timely treatment.

Strengths and Limitations

The present study has several strengths, as well as limitations. To my knowledge, this is the first study on this topic among a racially diverse cohort of CRC survivors. Additionally, the calibration of a culturally validated FFQ used in the MEC demonstrated a high degree of reliability specific to fat intake, with correlation coefficients ranging from 0.46 to 0.77 among race-sex pairings (Stram et al., 2002). Furthermore, there were 12 years between incident-CRC diagnosis and the end of study or death. The robust length of follow-up allowed for a meaningful observation period to capture deaths where CRC was listed as the primary cause. On the other hand, the cohort's location in the Western region may involve socioenvironmental factors that may limit the findings generalizability. Finally, it is uncertain if the sources and types of fish and shellfish may contain toxins that could potentially affect secondary CRC risk.

Conclusion

Dietary fat has been a controversial nutrient for its role in chronic diseases, including CRC. However, there has yet been consistent evidence on the types and thresholds of fat that may protect against cancer recurrences. Emerging data points to the lack of association between total fat intake and mortality risk among CRC survivors, whereas there may be a protective effect by ω-3 PUFAs. The present study found no association between postdiagnosis intake or the change in consumption and CRC-specific mortality risk from total fat and seafood intake, aligning with existing literature. One practice implication may be that nutrition education post-CRC can benefit from precise

and specific communications regarding fish and shellfish selection and differentiate ω-3 PUFAs as the only fatty acids that have shown promising results in long-term survivorship. Future studies may consider estimating CRC recurrence and mortality risks with multiple variables to understand better the role of various types of fatty acids and their sources. Further subanalysis on cultural preferences on the types of fish and shellfish consumed and cooking methods may also be of interest.

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Tables and Figures

Table 8

Participant Characteristics at Baseline and Follow-up by Lowest and Highest Quartiles of Total Fat Intake and Fat From Fish and Shellfish Among CRC survivors in the MEC

	Baseline				Follow-up			
	Total fat		Fish and shellfish		Total fat		Fish and shellfish	
Quartile	Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Cases	278	276	281	276	286	284	275	268
Median intake								
Total Fat, % kcal/d	21.5	37.5	29.2	30.8	23.9	39.1	30.2	33.2
Fat from fish and shellfish, g/d	0.60	0.87	0.17	1.81	0.49	0.69	0.16	1.94
Total fat, g/d	50.9	72.7	51.9	87.7	40.1	77.7	42.9	85.2
Saturated fat, g/d	14.1	21.1	16.1	24.6	11.3	23.1	13.7	23.9
Monounsaturated fat, g/d	17.9	26.3	18.9	31.5	14.6	30.1	16.5	32.4
Polyunsaturated fat, g/d	11.9	17.1	11.5	22.1	9.6	16.8	9.8	20.4
Men %	48.6	58.0	49.5	64.5	50.0	59.9	43.6	63.1
Women %	51.4	42.0	50.5	35.5	50.0	40.1	56.4	36.9
Ethnicity %								
White	18.7	23.6	27.0	17.8	16.4	22.5	25.5	16.0
African American	9.4	21.7	16.0	12.7	10.5	21.8	16.7	11.9
Native Hawaiian	5.4	8.0	2.8	14.1	4.2	7.0	5.1	13.1
Japanese American	55.0	29.7	23.1	51.1	54.5	35.2	21.8	53.4
Latino	11.5	17.1	30.9	4.3	14.3	13.4	30.9	5.6
BMI[a], kg/m^2	25.8	27.3	27.2	26.9	25.6	27.2	27.1	26.3
(SD)	(5.2)	(5.1)	(5.5)	(4.8)	(4.9)	(4.8)	(5.6)	(5.0)
Calories	1967	2150	1770	2651	1655	1816	1484	2353
(SD)	(781)	(841)	(738)	(867)	(665)	(755)	(660)	(765)

(Table continues)

	Baseline				Follow-up			
	Total fat		Fish and shellfish		Total fat		Fish and shellfish	
Alcohol, g ethanol/d	10.7	11.0	8.1	11.8	8.4	3.3	5.7	7.5
(SD)	(26.7)	(26.6)	(19.2)	(23.3)	(17.9)	(6.6)	(14.7)	(14.5)
Education %								
Less than high school	12.6	13.8	17.4	9.1	13.3	12.7	17.1	9.3
High school	30.2	32.2	25.6	34.1	25.5	29.9	28.4	29.9
Some college and college	43.2	44.2	46.6	44.2	49.3	46.1	44.4	47.4
Post-college	14.0	9.8	10.3	12.7	11.9	11.3	10.2	13.4
Physical activity[b] %								
No moderate to vigorous activity	0.7	3.7	2.9	0.7	3.8	6.3	6.5	4.9
< 150 min/day	84.1	79.5	84.0	81.5	82.2	84.5	83.3	78.7
>150 min/day	15.2	16.8	13.1	17.8	14.0	9.2	10.2	16.4
Smoking %								
Never	46.4	27.4	41.7	33.1	42.7	27.8	37.8	28.7
Past	43.8	51.8	46.7	52.0	53.5	63.7	58.5	66.4
Current	9.8	20.8	11.6	14.9	3.8	8.5	3.6	4.9
Family history[c], %	11.5	10.5	7.8	10.5	21.7	17.3	22.9	24.3
History of intestinal polyps, %	6.8	5.8	6.4	5.1	51.4	57.0	47.3	60.4
NSAIDs use[d], current %	26.2	37.5	33.6	32.0	43.0	45.1	46.5	42.5

Note.(N = 1,141). MEC, Multiethnic cohort; kcal, kilocalories; g/d, grams per day; BMI, body mass index; SD, standard deviation; NSAIDs, non-steroid anti-inflammatory drugs.

[a] BMI was calculated from self-reported height and weight at follow-up.

[b] Physical activity level was specified as moderate to vigorous.

[c] Family history of CRC was defined as participants' baseline response of the disease in mother, father, and/or siblings.

[d] NSAIDs use was based on self-reported use at follow-up as never used, past, or current usage of at least twice a week for longer than one month.

Table 9

Cohort Participants' Ages at Cohort Entry, CRC Diagnosis, Death, and CRC-Specific Mortality by Quartiles of Fat Intakes at Postdiagnosis

	Total fat as % energy		Fat from fish and shellfish	
Quartiles	Q1	Q4	Q1	Q4
Age at entry, years (*SD*)	62.7 (7.7)	62.0 (8.4)	63.0 (7.8)	61.8 (8.0)
Age at diagnosis, years (*SD*)	69.0 (8.3)	68.6 (8.5)	69.5 (8.1)	68.6 (8.2)
Age at death, years (*SD*)	81.6 (7.2)	82.2 (7.5)	81.9 (7.2)	81.2 (7.6)
Years from cohort entry to CRC diagnosis	5.8 (3.3)	6.1 (3.4)	6.0 (3.3)	6.3 (3.3)
Years from CRC diagnosis to death or 12/31/2014	13.3 (4.4)	12.5 (4.6)	12.5 (4.6)	12.3 (4.6)
CRC-specific mortality, %	23.1	28.3	37.5	19.8

Note. (*N* = 1,141). CRC, colorectal cancer; SD, standard deviation.

Table 10

CRC-Specific Mortality Risk by Quartiles of Postdiagnosis Total Fat, Fat From Fish and Shellfish, and Their Changes in the MEC

			HR	95% CI	*p*
Total fat intake, % kcal/d	9.1-27.1 (1st)	Reference			
	36.0-52.9 (4th)	Model 1	1.40	.79-2.46	.249
		Model 2	1.48	.74-2.95	.264
Change in total fat intake,	> 5% decrease	Reference			
% kcal/d	> 5% increase	Model 1	.74	.42-1.33	.315
		Model 2	.56	.28-1.11	.095
Fat from fish and shellfish, g/d	0.0-0.30 (1st)	Reference			
	1.30-9.73 (4th)	Model 1	1.30	.77-2.21	.332
		Model 2	1.24	.58-2.66	.585
Change in fat from fish and	> 0.25 decrease	Reference			
shellfish, g/d	> 0.25 increase	Model 1	1.32	.80-2.19	.278
		Model 2	1.29	.69-2.39	.423

Note. (N = 1,141)[a]. CRC, colorectal cancer.

[a]HRs and 95% CIs were obtained by Cox regression.

Model 1: Unadjusted.

Model 2: Adjusted for sex, race, education level, BMI, physical activity level, energy intake, alcohol consumption, family history of CRC, history of intestinal polyps, age at diagnosis, smoking status, and NSAIDs use.

Part 3: Summary

Integration of the Studies

CRC diagnoses are life changing. For those who completed curative treatment, cancer recurrence and death from the disease are common concerns during long-term survivorship. The SEM, as applied in cancer prevention, considers dietary choices a personal-level factor in which an individual has significant decision-making power. Consequently, public health education could indirectly reduce CRC-specific mortality risk by encouraging survivors to adopt favorable dietary choices. Unfortunately, evidence regarding diet and CRC recurrence is inconsistent.

The present dissertation study examined the association between the HEI-2010 score, dietary fiber intake, and dietary fat intake and CRC-specific mortality risk among survivors. The results suggested that adherence to the DGA, intended for the general population, as well as dietary fat intake, had little to no effect on recurrence-related mortality risk. However, moderate to high dietary fiber intake was associated with reduced risk, regardless of the prediagnosis level. Together, the findings highlight a need to identify dietary indicators that reflect the altered GI physiology and anatomy post-CRC. This study provides several practice implications for consideration. First, it is critical to select appropriate dietary indices when evaluating diet quality among CRC survivors. For example, both the DASH diet and the Dietary Inflammatory Index have been observed to offer meaningful risk prediction among cancer patients. This observation may be, in part, due to their objectives in chronic disease management.

Second, the promotion of dietary fiber intake of at least 25 grams and toward the recommended intake level of 30 grams per day for older adults was beneficial. According to the results from the 2010 National Health and Nutrition Examination Survey, the average dietary fiber intake was 16 g/d in the United States, in which African Americans consumed the lowest level at 13 g/d and Hispanics reported the highest level at 17 g/d (Hoy & Goldman, 2014). As such, clinical and public health professionals are advised to incorporate personal-level factors within the SEM, including physical ability and cultural preferences when developing individual nutrition plans (U.S. Department of Health and Human Services and USDA, 2015). Finally, when discussing fish and shellfish consumption, it is critical to address the health benefits of fish as a food group and specific sources for marine ω-3 fatty acids that were associated with reducing mortality risk.

Together, the studies point to the dietary needs of CRC survivors being different from that of noncancer individuals. There is a need for assessment tools and nutrition recommendations tailored to CRC survivors inclusive of racial minorities' cultural practices. As seen in the study using the HEI as an evaluation tool, increasing conformity to the DGA may not produce mortality risk reduction benefits compared to the DASH diet index or the ACS's dietary index promoting anti-inflammatory food choices in existing literature. Meanwhile, education on adequate fiber intake, fish and shellfish selection, smoking cessation, and routine monitoring also play critical roles in CRC recurrence and mortality risk.

Social Change

This study's results contribute to existing literature that in which recurrence-related mortality risk was not associated with postdiagnosis intake of dietary fat, rather, reduced by moderate to high fiber intake. The evidence improves our understanding on CRC secondary prevention and for the first time, it extends the knowledge to America's racial minorities. The diversity of the sample cohort could propel CRC survivorship care to transcend upstream through the SEM beyond the personal level. For example, health promotion of high fiber foods may increase the demand of in ethnic enclaves, thus encourages food companies and grocers to scale up supplies. Such an increase in availability may potentially raise consumption over time, creating a positive cycle. From a population health standpoint, healthcare professional organizations and health insurance carriers are potential stakeholders at the organizational level with vested interests to participate in reducing CRC recurrence by applying these data.

Lasting behavioral changes require both willingness and capability to apply health knowledge. In this context, America's social infrastructure remains an essential social determinant in CRC survivors' dietary choices. Through acknowledging a potential path to empower dietary decision-making, progress may be made toward greater health equality.

Conclusion

A healthy diet is integral to long-term CRC survivorship. However, much research is needed to improve the understanding of the optimal timing and consumption

level following treatment. The takeaway is that CRC affects each person differently and individually tailored diets based on a balance of nutritional value and GI tolerate are critical as part of the survivor care plan. Finally, regular monitoring is one of the most effective tools in early detection in both incident and recurrent CRC prevention.

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Appendix: The Healthy Eating Index 2010

The Healthy Eating Index-2010 (HEI-2010)[1] Components and Scoring Standards (NCI, 2020).

Component	Maximum points	Standard for maximum score	Standard for minimum score of zero
Adequacy:			
Total fruits[2]	5	≥ 0.8 cup equiv. per 1,000 kcal	No fruit
Whole fruits[3]	5	≥ 0.4 cup equiv. per 1,000 kcal	No whole fruit
Total vegetables[4]	5	≥ 1.1 cup equiv. per 1,000 kcal	No vegetables
Greens and beans[4]	5	≥ 0.2 cup equiv. per 1,000 kcal	No dark green vegetables or beans and peas
Whole grains	10	≥ 1.5 oz equiv. per 1,000 kcal	No whole grains
Dairy[5]	10	≥ 1.3 cup equiv. per 1,000 kcal	No dairy

Component	Maximum points	Standard for maximum score	Standard for minimum score of zero
Total protein foods[6]	5	≥ 2.5 oz equiv. per 1,000 kcal	No protein foods
Seafood and plant proteins[6,7]	5	≥ 0.8 oz equiv. per 1,000 kcal	No seafood or plant proteins
Fatty acids[8]	10	(PUFAs + MUFAs)/SFAs ≥ 2.5	(PUFAs + MUFAs)/SFAs ≤ 1.2
Moderation:			
Refined grains	10	≤ 1.8 oz equiv. per 1,000 kcal	≥ 4.3 oz equiv. per 1,000 kcal
Sodium	10	≤ 1.1 gram per 1,000 kcal	≥ 2.0 grams per 1,000 kcal
Empty calories[9]	20	≤ 19% of energy	≥ 50% of energy

Kcal, kilocalories; Equiv., equivalent; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

[1]Intakes between the minimum and maximum standards are scored proportionately.

[2]Includes 100% fruit juice.

[3]Includes all forms except juice.

[4]Includes any beans and peas not counted as total protein foods.

[5]Includes all milk products, such as fluid milk, yogurt, and cheese, and fortified soy beverages.

[6]Includes beans and peas when the total protein foods standard is otherwise not met.

[7]Includes seafood, nuts, seeds, soy products (other than beverages), and beans and peas.

[8]Ratio of poly- and monounsaturated fatty acids to saturated fatty acids.

[9]Calories from solid fats, alcohol, and added sugars; threshold for counting alcohol is > 13 grams/1,000 kcal.

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