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Dietary patterns and cancer in the United States

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by

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2021

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General Abstract

Cancer incidence and mortality are growing in the US; however, the dietary contribution to the increase in cancer cases has not yet been elucidated. The Insulin-like Growth Factor-I (IGF-I) pathway is a hormonal pathway that connects diet and cancer. Nutritional studies have shown that IGF-I levels are dependent on nutrient consumption in a persons' diet. The IGF-I protein is the most reliable nutritional biomarker in malnourishment and fasting. Furthermore, the IGF-I levels in blood depend on nutrient intake characteristics and the amount of nutrients consumed. IGF-I protein influences several metabolic processes, including normal and malignant cell growth. Previous studies have shown that increased IGF-I levels are related to a higher risk of breast, prostate, and colorectal cancer.

Although efforts have been made to clarify the role of dietary components in cancer, researchers have failed to determine with accuracy its impact on cancer risk. Furthermore, prevention strategies to improve current cancer risk have failed, possibly due to inappropriate strategies to inform the public. This dissertation has the following objectives: to provide an overview of previous research in the form of a literature review to identify current research gaps; to investigate the association between a previous history of cancer and adherence to dietary patterns in the US; to examine the relationship between dietary patterns and IGF-I levels in the blood; and to investigate the association between dietary patterns, total mortality, and cancer mortality.

Chapter 1. General Introduction

According to estimates from the World Health Organization (WHO), cancer was the second leading cause of death globally during 2018(Bray et al., 2018). Cancer incidence and mortality are rapidly growing worldwide (Kanavos, 2006; Wagner & Brath, 2012). Epidemiological studies on migration and cancer have shown that people living in countries with low cancer rates increase their cancer risk when migrating to western countries. The reasons are multifactorial but reflect aging, population growth, and the increase of the main risk factors for cancer, including diet. Dietary components can exert changes in hormones.

The Insulin-like Growth Factor-I (IGF-I) pathway is a hormonal pathway that connects diet and cancer (Macaulay, 1992). Nutritional studies have shown that IGF-I levels are dependent on nutrient consumption in a persons' diet (Underwood et al., 1986). The IGF-I protein is the most reliable nutritional biomarker in malnourishment and fasting (Estívariz & Ziegler, 1997). Furthermore, the IGF-I levels in blood depend on nutrient intake characteristics and the amount of nutrients consumed (Norat et al., 2007). IGF-I protein influences several metabolic processes, including normal and malignant cell growth(Hankinson et al., 1998; Yakar et al., 2005). Previous studies have shown that increased IGF-I levels are related to a higher risk of breast, prostate, and colorectal cancer(Macaulay, 1992; Mantzoros et al., 1997).

Although efforts have been made to clarify the role of dietary components in cancer, researchers have failed to determine with accuracy its impact on cancer risk. Furthermore, prevention strategies to improve current cancer risk have failed, possibly

due to inappropriate strategies to inform the public. This dissertation examines the relationship between diet and cancer in several aspects.

The second chapter of this dissertation is a literature review that provides an overview of the existing literature of epidemiological studies on the association between diet and breast, prostate, and colorectal cancer risk and breast, prostate, and colorectal cancer. We discuss findings from epidemiological studies that provide evidence of the link between diet and cancer, with a specific focus on select biologically essential nutrients. Individual nutrient intake and dietary patterns in relationship to cancer will be discussed separately to provide better insight into the impact of diet on cancer development.

The third chapter is a study that examined the association between the previous history of cancer and adherence to dietary patterns in the US. While achieving optimal nutrition is ideal for cancer survivors, no studies investigated the adherence to dietary patterns after a cancer diagnosis in this population to the best of our knowledge. We hypothesized that previous diagnose of cancer is associated with healthy dietary pattern adherence. We used cross-sectional data from The Third National Health and Nutrition Examination Survey (NHANES III) study to test this hypothesis.

The fourth chapter is a study that investigates the relationship between dietary patterns and IGF-I levels in the blood. The research hypothesizes that a dietary pattern with high amounts of protein, processed carbohydrates, and fats increases IGF-I levels, and a dietary pattern with high amounts of complex carbohydrates from fruits,

vegetables, and legumes decreases IGF-I levels. This is the first epidemiological study investigating this relationship in the United States, to the best of our knowledge.

Chapter five includes a study investigating the association between dietary patterns, total mortality, and cancer mortality. Like the previous studies, this study used information from a nationally representative cohort and provides evidence valid for changes in nutritional guidelines for cancer prevention and cancer mortality reduction.

In the last chapter, we discuss the outstanding findings from this work. We will discuss the impact of adherence to the major dietary pattern in the US population on breast, prostate, and colorectal cancer risk and mortality.

Hypotheses

The research hypothesis developed for this dissertation are:

1. Research has not quantified the influence of overall diet on cancer. To test this hypothesis, we conducted a thorough literature review of epidemiological studies that provide evidence of the link between diet and cancer. Individual nutrient intake and dietary patterns in relationship to cancer were reviewed separately. We conducted searches in Google Scholar and PubMed databases and included only original research and peer-reviewed articles in English published before 1985.

2. Previous history of cancer is related to adherence to a healthier dietary pattern. This hypothesis was tested using cross-sectional data on sociodemographic, lifestyle characteristics, nutritional characteristics, and medical history from civilian non-

institutionalized adults 18 years of age and older participants of the Third National Health and Nutrition Examination Survey (NHANES III). Then, we examined the association between previous personal diagnosis of cancer and adherence to the major dietary patterns in the United States.

3. The prudent dietary pattern is associated with lower IGF-I levels in the blood, and the western dietary pattern is related to higher blood IGF-I levels. To investigate this hypothesis, we used data from noninstitutionalized adults aged 20 years and older with complete dietary intake information and laboratory data from NHANES III, IGF-I subsample. Then, we correlated IGF-I levels with the major dietary patterns found in this nationally representative population.

4. We hypothesize that dietary patterns characterized by consumption of nutrient-rich foods are associated with lower total mortality, and mortality due to cancer in the United States; conversely, we hypothesize that dietary patterns that reflect poor nutrition are associated with higher total mortality and mortality due to cancer. To verify these hypotheses, we used data from NHANES III participants and linked it to the National Death Index through December 31, 2015. We examined the relationship between dietary pattern adherence with total mortality (deaths from all causes) and cancer-specific mortality using the International Classification of Diseases, 10th Edition, Clinical Modification System codes (ICD-10).

Chapter 2. Nutrition and cancer: A review of population-based studies on the connection between breast, prostate, and colorectal cancer and diet

Abstract

Purpose: This narrative review examined the association between diet and breast, prostate, and colorectal cancer risk and breast, prostate, and colorectal cancer.

Methods*:* We conducted searches in the databases for eligible, peer-reviewed, English language articles examining the relationship between individual nutrient consumption, dietary pattern consumption, breast, prostate, and colorectal cancer.

Results*:* The findings suggest that consuming carbohydrates with a high Glycemic Index (GI) and high Glycemic Load (GL) increase the risk for these cancers, increasing IGF-I levels due to insulin-mediated effects. Consuming large amounts of protein from animal sources such as dairy products and meat increased the cancer risk in most studies reviewed directly through the IGF-I pathway. The consumption of dietary fat can increase cancer risk through inflammation pathways. Not enough research has been done on the relationship between dietary patterns and the cancer risk for these types of cancer.

Conclusion: Studies investigating the effect of the overall quality of diet on cancer are needed to further clarify this evidence.

Keywords*:* Insulin-like Growth Factor-1; cancer; nutrients; dietary patterns

Introduction

Cancer incidence and mortality are growing worldwide (Kanavos, 2006; Wagner & Brath, 2012). Epidemiological studies on populations that migrate from countries with low cancer rates showed an increase in their cancer risk when they migrated to western countries (John, 2005; Popkin, 2007; Ziegler et al., 1993). The reasons are multifactorial; nevertheless, it reflects the aging, population growth, and the increase of primary risk factors for cancer, including diet (Bray et al., 2018). Dietary components can produce changes in hormonal pathways (Caiozzi et al., 2012) and inflammation(Müller & Kersten, 2003; Pan et al., 2010).

The Insulin-like Growth Factor-I (IGF-I) pathway is a hormonal pathway that connects diet and cancer. Each component of the IGF-I pathway has a different metabolic function; the IGF-I protein is the most often associated with malignancies when its levels are above the normal range (Macaulay, 1992; Mantzoros et al., 1997). IGF-I protein influences several metabolic processes, including normal and malignant cell growth(Hankinson et al., 1998; Yakar et al., 2005). Nutritional studies have shown that IGF-I levels are dependent on nutrient consumption in a persons' diet (Underwood et al., 1986). The IGF-I protein is the most reliable nutritional biomarker in malnourishment and fasting (Estívariz & Ziegler, 1997). Furthermore, the IGF-I levels in blood depend on nutrient intake characteristics, and the amount of nutrients consumed (Norat et al., 2007).

This narrative review examines the connection between food and cancer development through the IGF-I pathway. First, we describe the link between diet and breast, prostate, and colorectal cancer, the most common cancer types in the western world. Second, we explain the mechanisms involved in cancer development through the IGF-I

pathway. We conducted searches in the database Google Scholar and PubMed using keyword combinations of the phrases “diet and cancer”, “Insulin like Growth Factor 1 (IGF-I) and cancer” “Insulin like Growth Factor 1 (IGF-I) and diet”, as well as more specific nutrition-related phrases such as “protein intake and cancer”. The type of scholarly sources used were original research and peer reviewed articles. Articles published in a language other than English were excluded from the literature review. Additionally, articles that were published before 1985 were not included in the literature review to guarantee most recent information.

Diet and cancer

The role of diet as a factor contributing to cancer risk is hard to determine; distinguishing one food component's effects from another due to the possibility of synergistic or inhibiting effects on cancer risk makes nutritional research difficult. Herein, we discuss findings from epidemiological studies that provide evidence of the link between diet and cancer, with a specific focus on select biologically essential nutrients. Individual nutrient intake and dietary patterns in relationship to cancer will be discussed separately to provide better insight into the impact of diet on cancer development.

Individual nutrient intake and cancer

While many nutrients are believed to have a protective role, and others are known as risk factors for cancer development, the evidence remains inconclusive. In this section, we examine current evidence from epidemiological studies showing the association between each group of macronutrients and micronutrients and cancer breast, prostate, and colorectal cancer risk are summarized in **Table 1** and **Table 2**, respectively.

Macronutrients

Protein. Scientific evidence shows that protein intake can increase IGF-I levels significantly compared to other groups of nutrients; and that higher levels of IGF-I increase the risk of cancer (Marcello Maggio et al., 2013; Thissen et al., 1994). Extensive cross-sectional studies in western populations demonstrated that high consumption of foods high in protein, such as dairy products, is associated with increased circulating IGF-I levels (Crowe et al., 2009; L.-Q. Qin et al., 2009). Nonetheless, the sources of protein may have different effects on the IGF-I levels. A study that included two different populations, one in Mongolia and one in the US, showed that protein consumption from milk and soy-derived products raised IGF-I concentrations in both populations(Rich-Edwards et al., 2007); while another study found that milk consumption and not meat raised IGF-I levels significantly(Hoppe et al., 2004). The hormones and growth factors found in dairy products may also influence the production of IGF-I. Studies on farm animals used in the dairy industry provide evidence that IGF-I in milk products can be altered during the processing procedures; therefore, consuming milk can significantly increase IGF-I levels (Meyer et al., 2017). Research examining the differences between animal protein intake and vegetable protein intake in relationship with IGF-I levels supports these findings (Giovannucci et al., 2003; Gunnell et al., 2003).

Similarly, breast, prostate, and colorectal cancers were associated with diets with high amounts of protein. Studies on breast cancer risk (Lê et al., 1986; Toniolo et al., 1989) and breast cancer mortality (La Vecchia, 1993; McGuire et al., n.d.) showed a positive correlation between milk consumption and IGF-I levels. However, a few studies attribute these findings to the amount of fat in the milk (Ewertz & Gill, 1990; La Vecchia, 1993;

Serra-Majem et al., 1993). Additionally, dairy consumption may influence IGF-I levels through an indirect mechanism concerning synergism with estrogens (C. L. Arteaga et al., 1990; Dickson et al., 1986; Huff et al., 1988), and the estrogens in cow's milk may further increase IGF-I levels. Worldwide, several studies found an increased risk of prostate cancer when consuming high protein foods such as milk and meat(Chan, Giovannucci, et al., 1998; De Stefani et al., 1995; Talamini et al., 1986; Vecchia et al., 1991). Likewise, meat and dairy consumption increases colorectal cancer risk and is highly influenced by consumption frequency (Baena & Salinas, 2015).

Fat. Dietary fats can contribute to prostaglandins production, increase inflammatory agents in the gut, and produce tumorigenesis due to chronic inflammation (Laparra & Sanz, 2010; Maslowski & Mackay, 2011; X. Qin, 2012; Valdés-Ramos & Benítez-Arciniega, 2007; G. D. Wu et al., 2011; H.-N. Yu et al., 2014). Saturated fatty acids are proinflammatory (Frommer et al., 2015; Liu et al., 2014) and inhibit cancer cells' programmed cell death (Busch et al., 2005; Yao et al., 2005). Conversely, unsaturated fatty acids are considered healthy, except for the polyunsaturated fat omega-6 (ω-6), which is linked to a proinflammatory response due to its effect on immune cell receptors (Galli, n.d.) and the production of inflammatory mediators (Calder, 2009; Innis, 2007; Kuhnt et al., 2006). Omega-3 (ω-3) has anti-inflammatory effects and decreases inflammatory gene expression(Calder, 2009, 2010; Weylandt et al., 2012). Additionally, it inhibits cytokines' production in innate immunity (J. Y. Lee et al., 2001) and regulates the immune response through resolvins, protectins, and other anti-inflammatory mediators(Ariel & Serhan, 2007; Levy, 2010; Weylandt et al., 2012).

Epidemiological studies in breast, prostate, and colorectal cancer have shown that consuming diets with a high amount of fats can increase cancer risk (Butler et al., 2009; Ewertz & Gill, 1990; Mariette Gerber & Cenée, 1991; Lê et al., 1986; J. Lin, 2004; Murff et al., 2009; Toniolo et al., 1989; Willett et al., 1990). Populations with previous low risk of breast cancer have been shown to increase their risk when increasing fat intake and decreasing carbohydrate intake (Chen et al., 2006; Jin et al., 1999). Conversely, a reduction of breast cancer risk in women occurred after reducing fat intake and decreasing the ω-6/ω-3 ratio of polyunsaturated fatty acids.(Stoll, 1999) Furthermore, synergism between IGF-I and estradiol is hypothesized since IGF-I seems to stimulate the growth of breast cancer cells (Thorsen et al., 1992), and drugs that lower estradiol can decrease IGF-I levels as well (Pollak, 1998). Similarly, a high-fat diet may also contribute to the development of colorectal cancer, depending on the type of fats consumed and the sources (Butler et al., 2009; J. Lin, 2004; Murff et al., 2009; Willett et al., 1990).

ω-3 seems to have a protective role in colorectal cancer risk development. A study found that supplementation of ω-3 for six months can reduce polyps' size among those with familial adenomatous polyposis(N. J. West et al., 2010). Nonetheless, the benefits of ω-3 to prevent colorectal cancer were inconclusive in other studies(Shen et al., 2012; N. J. West et al., 2010). Long-term consumption of ω-3 may reduce colorectal cancer risk, while recent intake may not have a substantial effect(Butler et al., 2009; Song et al., 2014). Studies were inconclusive in the role of ω-6 in colorectal cancer risk(Butler et al., 2009; Murff et al., 2009). There is evidence that saturated and monounsaturated fatty acids from animal sources, but not from vegetable sources, may increase the risk (Willett et al., 1990).

Despite this evidence, the influence of consuming fat on cancer risk is still unclear since these nutrients are rarely consumed isolated.

Carbohydrate. Nutritional modifications that improve insulin sensitivity and decrease inflammation have been linked with decreased cancer risk. Consumption of simple carbohydrates increases inflammatory cytokine markers in the blood (Sanchez et al., 1973; Sørensen et al., 2005); while complex carbohydrate consumption from fruits and vegetables reduces inflammation in humans (Kuo, 2013; Suter, 2005) and animals (Trompette et al., 2014). Consumption of carbohydrates produces a wide range of postprandial blood glucose levels. These levels are measured by the glycemic index (GI) and the glycemic load (GL). These measurements are considered risk factors for carcinogenesis when their levels are high (L. S. Augustin et al., 2002; L. S. A. Augustin et al., 2001; Livia S. A. Augustin et al., 2003; Barnard et al., 2002; Franceschi et al., 2001; Hsing et al., 2003; Michaud et al., 2002). Studies linked high sugar consumption, high GI, and high GL with increased cancer risk (Aune et al., 2012; Ruxton et al., 2009). Furthermore, IGF-I and insulin are closely related. Carbohydrates with higher GI increase the IGF-I levels due to insulin-mediated effects (Giovannucci et al., 2003; Gunnell et al., 2003; Holmes, Pollak, & Hankinson, 2002), and carbohydrates with lower GI decrease IGF-I levels (Holmes, Pollak, & Hankinson, 2002).

Similarly, epidemiological studies support that high carbohydrate consumption is associated with breast cancer risk, depending on the ability to increase insulin (Gupta et al., 2002; R. Kaaks & Lukanova, 2001; Rudolf Kaaks, 2008). The Canadian National Breast Screening Study found a diet with high GL and GI increased breast cancer risk in postmenopausal women(Silvera et al., 2005). Comparable results were found among

premenopausal women(Wen et al., 2009), and case-control studies(L. S. A. Augustin et al., 2001; Lajous et al., 2005). Conversely, a diet with carbohydrates with high fiber content and lower GL and GI levels, such as fruits and vegetables, demonstrated a protective effect for breast cancer (Challier et al., 1998; Ronco et al., 1999). Fiber can reduce circulating estrogens, consequently reducing the risk of breast cancer (Cohen, 1999; M. Gerber, 1998).

Carbohydrate intake with low IG, from legumes, whole grains, and fruit, decreased IGF-I levels by 20%, and prostate cancer cell growth in vitro was significantly reduced in an interventional study(Ngo et al., 2002). Studies worldwide support these findings. A study on Swedish men demonstrated that the effect of consuming carbohydrates on the risk of prostate cancer depends on the level of refinement and the amount of carbohydrates consumed(Drake et al., 2012). Consuming large amounts of sugar was linked with insulin resistance and a higher risk of prostate cancer in other epidemiological studies(Franceschi et al., 2001; Sanchez et al., 1973). Conversely, low GI foods have also been associated with low insulin levels and lower cancer risk(L. S. A. Augustin et al., 2001). Similar effects were found on colorectal cancer risk studies, supporting the negative effect of consuming refined carbohydrates (Franceschi et al., 2001; Giovannucci, 1995; G. McKeown-Eyssen, 1994).

Table 1. Epidemiological studies assessing macronutrient intake and the risk of breast, prostate and colorectal cancer.

Study	Location	Population	Evidence
Protein intake			
(Talamini et al., 1986)	Italy	**Cases:** 166 prostatic carcinoma patients aged 48-79. **Controls:** 202 patients hospitalized for acute diseases aged 50-79.	**(+) *** PC risk and frequency of intake of milk, dairy products and meat.
(Mariette Gerber & Cenée, 1991)	France	**Cases:** 409 BRCA hospitalized patients. **Controls:** 515 non-BRCA hospitalized patients.	**(0) *** odds of BRCA and intake of animal derived protein.
(Toniolo et al., 1989)	U.S.	**Cases:** 250 BRCA patients < 70 years of age. **Controls:** 499 healthy patients < 70 years of age.	**(+) *** BRCA risk and intake of animal protein.
(Vecchia et al., 1991)	Italy	**Cases:** 96 prostatic cancer patients median age 65. **Controls:** 292 hospitalized patients for acute diseases median age 58.	**(+) *** PC risk and high intake of milk.
(Chan, Stampfer, et al., 1998)	Sweden	**Cases:** 526 prostatic carcinoma patients mean aged 70.7. **Controls:** 536 healthy participants mean aged 70.6.	**(+) *** PC risk and high intake of dairy products. (+) * PC risk and meat intake for advanced cases.
(D.-H. Lee et al., 2004)	China	**Cohort**: 73,224 participants and 394 incident CRC patients. **Follow-up:** mean length 7.4 years.	**(-) *** CRC risk and intake of animal protein and dairy.
Fat intake			
(Toniolo et al., 1989)	Italy	**Cases:** 250 BRCA patients less than 70 years old. **Controls:** 499 healthy participants less than 70 old.	**(+) *** BRCA risk and intake of saturated fat.
(Ewertz & Gill, 1990)	Denmark	**Cases:** 1,486 BRCA patients. **Controls:** 1,336 women from the general population.	**(+) *** BRCA risk and intake of fats.
(Willett et al., 1990)	U.S.	**Cohort:** 88,751 women aged 34-59 and 150 incident colon cancer cases. **Follow-up:** 6 years.	**(+) *** risk of colon cancer and high intake of animal derived fats.
(Mariette Gerber & Cenée, 1991)	France	**Cases:** 409 BRCA hospitalized patients. **Controls:** 515 non- BRCA hospitalized patients.	**(+) *** odds of BRCA and intake of animal derived fat.

(La Vecchia, 1993)	Italy	**Cases:** 2,564 BRCA hospitalized patients. **Controls:** 2,588 non- BRCA hospitalized patients.	**(-) *** odds of BRCA and intake of olive oil and other vegetable fats.
(Lê et al., 1986)	France	**Cases:** 1,010 BRCA patients mean aged 58.2. **Controls:** 1,950 patients with non-malignant diseases mean age 58.	**(+) *** BRCA risk and intake of cheese and the level of fat in milk.
(Järvinen et al., 2001)	Finland	**Cohort**: 9,959 participants and 109 incident CRC cases **Follow-up time:** 32 years.	**(0)** between CRC and fat intake.
(Flood et al., 2003)	U.S.	**Cohort**: 45,496 participants and 487 incident CRC cases **Follow-up time:**1987–1989, 1992–1995, and 1995–1998	**(0)** between CRC and fat intake.
(J. Lin, 2004)	U.S.	**Cohort**: 39,876 healthy women aged <45 and 202 incident CRC patients. **Follow-up:** mean length 8.7 years.	**(+) *** risk of CRC and high intake of fried food.
(Butler et al., 2009)	China, Singapore	**Cohort**: 61,321 participants and 921 incident CRC patients. **Follow-up:** mean length 9.8 years.	**(+) *** risk of localized colon cancer and intake of saturated fat.
(Murff et al., 2009)	China	**Cohort**: 73,242 women ages 40-70; subset 150 CRC patients and 150 control patients. **Follow-up time:** 10.5 years.	**(+) *** risk of CRC and n-6/n-3 ratio.
(Sasazuki et al., 2011)	Japan	**Cohort**: 827,833 participants and 1,268 incident CRC cases. **Follow-up:** mean length 9.3. years.	**(0)** risk CRC and n-6 intake or n-3/n-6 ratio; (-) risk of CRC and n-3 intake.
(Song et al., 2014)	U.S.	**Cohort**: 76,386 male and 47,143 female participants and 1,469 incident CRC cases. **Follow-up:** 26 years.	**(0)** risk CRC and n-6 intake or n-3 intake
Carbohydrate intake			
(Challier et al., 1998)	France	**Cases:** 345 BRCA patients. **Controls:** 345 healthy participants.	**(-) *** risk of BRCA and increased fiber intake.
(Ronco et al., 1999)	Uruguay	**Cases:** 400 breast cancer patients. **Controls:** 405 patients hospitalized for acute conditions.	**(-) *** risk of BRCA and increased vegetable and fiber intake.
(Deneo-Pellegrini et al., 1999)	Uruguay	**Cases:** 175 PC patients. **Controls:** 233 patients hospitalized for acute conditions.	**(-) *** risk of PC and increased vegetable and fruit intake.
(Franceschi et al., 2001)	Italy	**Cases:** 1,125 men and 828 women hospitalized CRC patients. **Controls:** 2073 men and 2081 women control patients hospitalized with acute conditions.	**(+) *** risk of CRC and high GI and GL.

(Jonas et al., 2003)	U.S.	**Cohort:** 63,307 postmenopausal women aged 40-87 and 12,442 incident BRCA patients. **Follow-up**: 5 years.	**(0)** risk of BRCA and high GI or GL.
(Cho et al., 2004)	U.S.	**Cohort**: 90,655 women aged 26-46 and 714 incident BRCA cases**.** **Follow-up:** 8 years.	**(0)** risk of BRCA and carbohydrate intake, GI or GL
(Higginbotham et al., 2004)	U.S.	**Cohort:** 39,876 women ages 45 and older and 946 incident BRCA cases. **Follow-up:** mean length 6.8 years.	**(0)** BRCA risk and GI or GL.
(Holmes et al., 2004)	U.S.	**Cohort**: 88,678 aged 34-59 and 4,092incident BRCA cases. **Follow-up:** 18 years.	**(0)** risk of BRCA and GI, GL or carbohydrate intake
(Lajous et al., 2005)	Mexico	**Cases:** 475 BRCA patients. **Controls:** 1,391 control participants from the general population.	**(+) *** risk of BRCA and carbohydrate intake.
Nielsen T. et al, 2005(T. G. Nielsen et al., 2005)	Denmark	**Cohort**: 28,870 women aged 50-65 and 634 incident BRCA cases. **Follow-up:** mean length 6.6 years.	**(0)** risk of BRCA and carbohydrate intake, GL or GI.
(Silvera et al., 2005)	Canada	**Cohort:** 49,613 women aged 40-59 and 1,461 incident BRCA cases. **Follow-up:** mean length16.6 years.	**(+) *** risk of BRCA on postmenopausal women and carbohydrate intake with high GI.
(Giles et al., 2006)	Australia	**Cohort:** 12,273 post-menopausal women and 324 incident BRCA cases. **Follow-up:** mean length 9.1 years.	**(0)** BRCA risk and high consumption of carbohydrates.
(Cade et al., 2007)	U.K.	**Cohort:** 35,792 pre- and post-menopausal women and 602 incident BRCA cases. **Follow-up:** mean length 7.5 years.	**(-) *** BRCA risk and intake of cereal derived fiber among premenopausal women.
(Suzuki et al., 2008)	Sweden	**Cohort:** 51,823 postmenopausal women and 1,888 incident BRCA cases. **Follow-up:** mean length 8.3 years.	**(-) *** BRCA risk and high intake of total fiber and cereal derived fiber.
(Wen et al., 2009)	China	**Cohort:** 74,942 women aged 40-70 and 616 incident BRCA cases. **Follow-up:** mean length 7.35 years.	**(+) *** risk of BRCA on premenopausal women and carbohydrate intake with high GL.
(Drake et al., 2012)	Sweden	**Cohort**: 8,128 men aged 45-73 and 817 incident PC patients. **Follow-up:** 15 years.	**(+) *** risk of PC and refined carbohydrate intake.

(+) = positive association; (-) = negative association; (0) = no association
*statistically significant association
Abbreviations: U.S United States; UK: United Kingdom; CRC: colorectal cancer; BRCA: breast cancer; PC: prostate cancer.

Micronutrients

Minerals

Few epidemiological studies investigated the relationship between mineral intake and cancer in humans. Minerals such as selenium, zinc, magnesium, and calcium possibly have a protective influence against cancer. Minerals produce a wide variety of functions on human cells. There is evidence that minerals such as selenium, zinc, magnesium, and calcium can influence IGF-I levels and their functions in cells and tissues. Additionally, these minerals' imbalances may be involved in chronic inflammation and frailty(Marcello Maggio et al., 2013). Proper mineral levels are required to maintain health and the IGF-I pathway in balance.

Selenium. Selenium plays a crucial role in multiple functions on cells and tissues in the human body. It is involved in antioxidation processes (Kryukov et al., 2003), cellular transcription (Makropoulos et al., 1996), the cellular cycle, and apoptosis (Kaeck et al., 1997). There is evidence that selenium modulates IGF-I bioavailability(Marcello Maggio et al., 2010; Moreno-Reyes et al., 2001). Selenium deficiency is associated with growth retardation, demonstrating that selenium plays a role in normal cell growth(Moreno-Reyes et al., 2001). Laboratory studies demonstrated that optimal levels of selenium protect against cancer(Amaral et al., 2010; Etminan et al., 2005). Nonetheless, only a few epidemiological studies found that selenium intake may decrease cancer risk(Vecchia et al., 1997; Verhoeven et al., 1997). A randomized controlled trial showed that supplementation of selenium reduced colorectal cancer incidence by 61%(John A. Baron et al., 2003). However, selenium supplementation may only benefit those with deficiencies(Rayman, 2012). Individuals' requirements vary depending on genetic

variation(Diwadkar-Navsariwala & Diamond, 2004; Rayman, 2000) and individual characteristics such as sex(Combs et al., 2012; Méplan et al., 2008; Waters et al., 2004). Therefore, more research is needed to clarify the protective role of selenium in cancer risk.

Zinc. Zinc is a micronutrient with an essential role in enzymatic functions in the human body. Among the most critical functions zinc is involved in are cellular growth, protein and DNA synthesis, neural and sensorial functions, and cell-mediated immunity(Meunier et al., 2005). Low levels of zinc are associated with inflammation, decreased immunity, and degenerative diseases (Hambidge, 2000). Zinc influence IGF-I bioavailability by increasing its endogenous synthesis (Makropoulos et al., 1996; Matsui & Yamaguchi, 1995).In animal studies, severe zinc deficiency was associated with low IGF-I hepatic production(Droke et al., 1993; McNall et al., 1995). Additionally, zinc influences insulin and GH concentrations and affects the IGF-I levels indirectly(Roth & Kirchgessner, 1994). Studies in humans support this evidence by demonstrating that poor zinc status is related to IGF-I low levels(Cossack, 1991; Dørup et al., 1991). Studies suggest that zinc decreases oxidative damage of membranes and acts as an antioxidant; however, abnormally high zinc levels could also be pro-oxidation(Abdallah & Samman, 1993). Even though there is evidence on zinc's protective role for cancer, only a few epidemiological studies have investigated this relationship. All of them found that zinc has a protective role for breast, prostate, and colorectal cancer.

Magnesium. Magnesium is a crucial mineral for many structural and human functions. Magnesium acts as a fundamental cofactor in protein and DNA synthesis(Wolf & Cittadini, 2003). Low magnesium levels are associated with hypertension, atherosclerosis, type 2 diabetes, metabolic syndrome, and increased C-reactive protein

(CRP), an acute inflammation marker(Barbagallo et al., 2003; Champagne, 2008). It can also produce increased oxidative stress and immune dysfunction at the molecular level (Barbagallo et al., 2003; Champagne, 2008). A study showed that magnesium levels were closely associated with IGF-I levels(M. Maggio et al., 2011). Another study demonstrated that IGF-I increases intracellular magnesium levels in a dose and time-dependent way(Dominguez et al., 1998), supporting IGF-I's role in this mineral's cellular metabolism. Nonetheless, epidemiological studies investigating the role of magnesium and cancer risk are needed.

Calcium. Dietary consumption of calcium is essential since the human body cannot produce it. Calcium supplementation produced the inhibition of the proliferation and promotion of apoptosis of cancer cells in colorectal cancer patients(Bostick et al., 1995) and patients at high risk(Gregoire et al., 1989; P. Rozen et al., 1989). Additionally, calcium may have a role in diminishing oxidative DNA damage when used in conjunction with vitamin D and protect against cancer through antioxidative mechanisms(Fedirko et al., 2010). Cohort studies demonstrated that consuming calcium is associated with a decreased risk of colorectal cancer (Flood et al., 2005; Ishihara et al., 2008; Kesse et al., 2005; Park et al., 2007; Peters et al., 2008; Shin et al., 2006; K. Wu et al., 2002) and its recurrence(Bonithon-Kopp et al., 2000; Martínez et al., 2002). This evidence was supported by randomized controlled trials(J.A. Baron et al., 1999; Wallace et al., 2004) and a prospective study with a 20-year follow up(Garland et al., 1985). However, a study found that consuming calcium was beneficial for diminishing distal colorectal cancer risk and not cancer on other colon sites(Oh et al., 2007). The results could be due to the different functionality and metabolism of the gastrointestinal tract. Calcium and other nutrients such

as vitamin D have a synergistic effect in decreasing cancer risk (K. Wu et al., 2002; Zheng et al., 1998). Studies investigating the role of both have shown a protective effect on cancer risk(Boyapati et al., 2003; Connelly-Frost et al., 2009; Dai et al., 2011; Hughes et al., 2015; Larsson et al., 2005, 2009; D.-H. Lee et al., 2004; Leitzmann et al., 2003; Jennifer Lin et al., 2007; McCullough et al., 2003; Peters et al., 2006; Whelan et al., 1983; Yücel et al., 1994).

Vitamins and antioxidants intake

Antioxidants prevent oxidative stress and inflammation(Reuter et al., 2010). Consumption of vitamins and antioxidants and the reduction of colorectal cancer risk was demonstrated in several cohort epidemiological studies(Bussey et al., 1982; Ferraroni et al., 1994; Howe et al., 1992; Gail McKeown-Eyssen et al., 1988; Rider et al., 1984; Paul Rozen et al., 1981).Additionally, antioxidant consumption reduced colonic adenoma recurrence, a pre-cancer condition(Roncucci et al., 1993). Nonetheless, the beneficial effect on cancer risk has not been consistent with other studies, possibly due to different sources and amounts of vitamins and antioxidants examined(Hercberg et al., 2004; Key et al., 2012; D.-H. Lee et al., 2004; Jennifer Lin et al., 2007; Lippman et al., 2009; Malila et al., 2002; Roswall et al., 2010). The effect of vitamin and antioxidant consumption on cancer risk warrants further investigation.

Table 2. Epidemiological studies assessing micronutrient intake and the risk of breast, prostate and colorectal cancer.

Study	Location	Population	Evidence
Selenium Intake			
(Van T' Veer et al., 1990)	Netherlands	**Cases:** 133 BRCA patients ages 25-44 & 55-64. **Controls:** 238 participants from the general population ages 25-44 & 55-64.	**(0)** BRCA risk and Se intake.
(D. W. West et al., 1991)	U.S.	**Cases:** 358 PC patients ages 45-74. **Controls:** 679 healthy participants age 45-64.	(**0)** PC risk and Se intake.
(Peters et al., 2006)	U.S.	**Cases:** 758 advanced colorectal adenoma patients mean aged 63.1. **Controls:** 767 healthy participants mean aged 61.8.	**(-) *** advanced colorectal adenoma risk and Se levels in blood among smokers.
(Peters et al., 2008)	U.S.	**Cohort:** 35,242 men aged 50-76 and 830 PC incident cases. **Follow-up time:** mean length 10 years.	**(0)** PC risk and Se intake.
(Connelly-Frost et al., 2009)	U.S.	**Cases:** 100 CRC patients mean ages 40-80. **Controls:** 100 healthy participants mean ages 40-80.	**(-) *** CRC risk and high Se and Folate levels jointly in blood.
(Hughes et al., 2015)	Europe	**Cases:** 966 CRC patients mean aged 63.1. **Controls:** 966 healthy participants mean aged 61.8.	**(-) *** CRC risk in women and Se levels in blood.
Zinc Intake			
(Whelan et al., 1983)	U.K.	**Cases:** 19 PC patients ages 70-80. **Controls:** 27 patients with benign prostatic hyperplasia ages 62-78.	**(-) *** PC risk and Zn levels in blood
(Yücel et al., 1994)	Turkey	**Cases:** 31 BRCA patients ages 28-75. **Controls:** 35 healthy participants ages 35-80.	**(-) *** BRCA risk and Zn levels in blood.
(Leitzmann et al., 2003)	U.S.	**Cohort:** 46,974 men aged 40-75 and 2,901 PC incident cases. **Follow-up:** 14 years.	**(-) *** PC risk and low dose of Zn intake. (+) * PC risk and low dose of Zn intake.

(D.-H. Lee et al., 2004)	U.S.	**Cohort:** 34,708 postmenopausal women aged 55-69 and 741 colorectal incident cases. **Follow-up:** 15 years.	**(-) *** CRC risk and Zn intake.
Magnesium Intake			
(Larsson et al., 2005)	Sweden	**Cohort:** 61,433 women aged 40-75 and 805 colorectal incident cases. **Follow-up:** mean length 14.8 years.	**(-) *** CRC risk and Mg intake.
(Dai et al., 2011)	U.S.	**Cases:** 133 PC patients with (+) biopsy ages 50-80. **Controls:** 163 patients with (-) biopsy ages 50-80.	**(-) *** PC risk and Mg levels in blood as a measurement of intake.
(Li et al., 2011)	Germany	**Cohort:** 24,323 participants aged 35-64 and 2,050 incident cancer cases. **Follow-up:** mean length 11 years.	**(0)** CRC, BRCA and PC risk and Mg intake.
Calcium Intake			
(Chan et al., 2001)	U.S.	**Cohort:** 20,885 men ages 43-65 and 1,012 incident PC cases. **Follow-up:** 11 years.	**(+) *** PC risk and calcium intake from dairy products.
(Kristal et al., 2002)	U.S.	**Cases:** 605 PC patients ages 40-64. **Controls:** 592 PC free patients ages 40-64.	**(+) *** PC risk and high calcium intake.
(McCullough et al., 2003)	U.S.	**Cohort:** 60,866 men and 66,883 women age 50-74; 412 and 262 incident CRC cases. **Follow-up:** 5 years.	**(-) *** CRC risk and calcium intake among men.
(Kesse et al., 2005)	France	**Cases:** 172 CRC patients ages 40-65. **Controls:** 67,312 cancer free patients ages 40-65.	**(0)** CRC risk and calcium intake.
(Jennifer Lin et al., 2007)	U.S.	**Cohort:** 10,578 premenopausal and 20,909 postmenopausal women aged > 45; 276 premenopausal and 743 postmenopausal BRCA cases. **Follow-up:** 10 years.	**(-) *** BRCA risk and calcium intake among premenopausal women.
(Larsson et al., 2009)	Sweden	**Cohort:** 61,433 women age 44-64 and 2,952 incident BRCA cases. **Follow-up:** 17.4 years.	**(-) *** BRCA risk and calcium intake among patients tested ER-negative/ PR-negative (ER-/PR-)
(Boyapati et al., 2003)	China	**Cases:** 1,459 BRCA patients ages 39-56. **Controls:** 1,724 participants general population ages 39-56.	**(-) *** BRCA risk and calcium intake from poultry.
Vitamins & antioxidants			

(Rohan et al., 1993)	Canada	**Cohort:** 56,837 women aged 40-59 and 519 incident BRCA cases. **Follow-up:** 5 years.	**(0)** BRCA risk and Vit. A, Vit C, Vit E, and B-carotene intake.
(Ferraroni et al., 1994)	Italy	**Cases:** 1,326 CRC patients aged 20-74. **Controls:** 2,024 hospitalized with acute non-neoplastic conditions aged 19-74.	**(-) *** CRC risk and Vit C and carotene intake.
(Kushi et al., 1996)	U.S.	**Cohort:** 34,387 postmenopausal women aged 40-59 and 879 incident BRCA cases. **Follow-up:** 4 years.	**(0)** BRCA risk and Vit. A, Vit C, Vit E, retinol and carotene intake.
(Verhoeven et al., 1997)	Netherland	**Cohort:** 62,573 women aged 55-69 and 650 incident BRCA cases. **Follow-up:** 4.3 years.	**(0)** BRCA risk and Vit C, Vit E, retinol and carotene intake.
(Vecchia et al., 1997)	Italy	**Cases:** 1,953 CRC patients aged 23-74. **Controls:** 4,154 hospitalized patients due to acute non-neoplastic conditions aged 20-74.	**(-) *** CRC risk and Vit C, Vit B2, carotene intake.
(Chan et al., 1999)	Finland	**Cohort:** 47,780 male participants aged 40-75 and 1,338 incident PC cases. **Follow-up:** 6.1 years.	(**0)** PC risk and supplemental Vit E intake.
(Kristal et al., 1999)	U.S.	**Cases:** 697 PC patients ages 40-64. **Controls:** 666 participants from the general population ages 40-64.	**(0)** PC risk and supplemental Vit. E, Vit. C and multivitamin intake.
(S. Zhang et al., 1999)	U.S.	**Cohort:** 83,234 women aged 33-60 and 2,697 incident BRCA cases. **Follow-up time:** 8 years.	**(-) *** BRCA r risk and Vit C, B-carotene, A-carotene derived from food among premenopausal women.
(Michels et al., 2001)	Sweden	**Cohort:** 59,036 women aged 40-76 and 1,271 incident BRCA cases. **Follow-up:** 10 years.	**(-) *** BRCA risk and supplemental Vit C among obese and overweight women.
(Kirsh et al., 2006)	U.S.	**Cohort:** 29361 male participants aged 55-74 and 1338 incident PC cases. **Follow-up:** 8 years.	**(-) *** PC risk and supplemental Vit E and B-carotene intake among male smokers.
(Roswall et al., 2010)	Denmark	**Cohort:** 56,322 participants aged 50-64 and 748 incident CRC cases. **Follow-up time:** mean length 10.6 years.	**(-) *** CRC risk and folate intake from food and not supplements.
(Key et al., 2012)	U.K.	**Cases:** 576 CRC patients aged 50-70. **Controls:** 1,951hospitalized with acute non-neoplastic conditions aged 50-70.	**(0)** CRC risk and Vit A, Vit B1, Vit B6, Vit B12, Vit D, and folate intake.

(+) = positive association; (-) = negative association; (0) = no association
*statistically significant association
Abbreviations: U.S United States; UK: United Kingdom; CRC: colorectal cancer; BRCA: breast cancer; PC: prostate cancer; Vit: vitamin.

Dietary patterns and cancer

Dietary patterns reflect the diet quality, account for interactions among nutrients and explain better the contribution of diet to health and disease than individual nutrients. A few dietary patterns described previously in the scientific literature concerning cancer risk are the western diet and the prudent diet. The western dietary pattern is characterized by a high consumption of red meat, fats, processed carbohydrates, and low consumption of vegetables, fruit, and fiber. The western pattern is linked with obesity and several chronic diseases (Mozaffarian et al., 2011). Furthermore, worldwide, the western diet consistently increased the risk of breast, prostate, and colorectal cancer (Cottet et al., 2005; X. Cui et al., 2007; Flood et al., 2008; Mizoue et al., 2005; Terry, Suzuki, et al., 2001; Walker et al., 2005) and cancer mortality (Meyerhardt et al., 2007). Conversely, the prudent dietary pattern with high consumption of fruits, vegetables, and fiber decreased the risk of obesity and metabolic syndrome (Meyerhardt et al., 2007), improved insulin sensitivity (Liese et al., 2003; Y. Lin et al., 2015), and has shown to decrease the risk of breast, prostate, and colorectal cancer(T. Fung et al., 2003; T. T. Fung et al., 2005; Magalhães et al., 2012; Tseng et al., 2004; G. D. Wu et al., 2011). Surprisingly, the scientific literature concerning these types of cancer risk and dietary patterns is still limited in the United States. **Table 3** summarizes the studies investigating the relationship between dietary patterns adherence and the risk of breast, prostate and colorectal cancer.

Table 3. Epidemiological studies assessing dietary patterns and the risk of breast, prostate and colorectal cancer.

Study	Location	Population	Evidence
(Terry et al., 2002)	Sweden	**Cohort:** 61,463 women aged 40-76 and 1,328 incident BRCA cases. **Follow-up time:** mean length 9.6 years.	**(+) *** BRCA risk and drinker pattern**. (0)** BRCA risk and western or healthy pattern.
(T. Fung et al., 2003)	U.S.	**Cohort:** 76,402 women aged 38-63 and 1,018 incident PC cases. **Follow-up time:** mean length 13,6 years.	**(+)** CRC risk and Western diet in postmenopausal smokers; **(-)** CRC risk and Prudent diet.
(Tseng et al., 2004)	U.S.	**Cohort:** 3,779 men aged 25-74 and 136 incident PC cases. **Follow-up time:** mean length 7.6 years.	**(-) *** PC risk and Southern pattern; (0) PC risk and western or healthy pattern.
(T. T. Fung et al., 2005)	U.S.	**Cohort:** 71,058 women aged 30-55 and 3,026 incident BRCA cases. **Follow-up time:** mean length 16 years.	**(+) *** BRCA risk and Western diet in postmenopausal smokers; **(-) *** breast cancer risk and Prudent diet.
(Walker et al., 2005)	Canada	**Cases:** 80 PC patients aged 50-80. **Controls:** 344 non-malignant urological conditions aged 50-80.	**(+) *** PC risk and processed pattern.
(X. Cui et al., 2007)	China	**Cases:** 1,446 BRCA patients aged 25-64. **Controls:** 1,549 general population aged 25-64.	**(+) *** BRCA risk and western diet in postmenopausal women.
(G. D. Wu et al., 2011)	U.S.	**Cohort:** 51,129 men aged 70-75 and 3,002 incident PC cases. **Follow-up time:** 14 years.	**(0)** PC risk and any dietary pattern.
(Muller et al., 2009)	U.S.	**Cohort:** 14, 627 men aged 34-75 and 546 incident PC cases. **Follow-up time:** mean length 12 years.	**(0)** PC risk and any dietary pattern.

(+) = positive association; (-) = negative association; (0) = no association
*statistically significant association
Abbreviations: U.S United States; UK: United Kingdom; CRC: colorectal cancer; BRCA: breast cancer; PC: prostate cancer.

The IGF-I pathway

The IGF-I pathway comprises the IGF-I protein, the IGF-I receptor (IGF-IR), and the IGF binding proteins (IGFBP's). The *IGF-I protein* is a small peptide with a chemical structure similar to insulin; this similarity explains its ability to bind to the insulin receptor and close bioactivity with insulin(Anders Juul, 2003; Laron, 2001). The IGF-I produces diverse effects on various biological processes in cells in all life stages, including normal cellular growth(Anders Juul, 2003). Nonetheless, elevated IGF-I levels influence malignant cell growth and tumorigenesis (Baserga, 1999).

Nutrition plays a vital role in regulating IGF-I levels and bioavailability. Nonetheless, other factors can influence IGF-I level such as age, lifestyle choices such as smoking, alcohol consumption, physical activity and fasting. IGF-I levels in blood depend highly on individuals' age. Higher IGF-I levels are found during childhood and puberty, followed by a marked decrease during adult life(A. Juul et al., 1994; Anders Juul et al., 1994) and elderly years(Janssen et al., 1998; O'Connor et al., 1998; Sugimoto et al., 1998). Alcohol intake produces an acute decrease in IGF-I levels in healthy subjects, followed by an increase in the next four days (Paassilta et al., 1999; Röjdmark et al., 2000). However, liver damage patients have lower IGF-I levels due to impaired liver function and IGF-I synthesis(Juul Anders et al., 2002).

Studies found that smoking affects IGF-I levels when considering smoking status, smoking duration, pack-years of smoking, and the number of cigarettes smoked [270,274]. Cross-sectional studies on physical activity demonstrated a positive association between IGF-I mean circulating levels and high physical activity (Ambrosio et al., 1996; P. J. Kelly

et al., 1990). Intense exercise with negative caloric balance decreased IGF-I levels similarly to starvation (Smith et al., 1987). Also, studies on patients with low mobility showed low levels of IGF-I (Abbasi et al., 1993; Eliakim et al., 1998). Also, fasting has an essential effect on the levels of IGF-I. IGF-I levels are markedly reduced after fasting for a few days; the normalization of these levels will depend on the diet composition in terms of quality and quantity of nutrients (Merimee et al., 1982; Underwood et al., 1986).

The *IGF-I receptor (IGF-IR)* is a glycoprotein found on the cell surface (Anders Juul, 2003), and it resembles the insulin receptor structurally (Seino et al., 1989). The IGF-IR is present in almost all tissues and cell types during embryogenesis; thus, it is considered ubiquitous in humans (Bondy et al., 1992).The liver is the organ with the highest IGF-I production and has almost undetectable expression of the IGF-IR. This mechanism preserves the homeostasis of the IGF-I levels. The research demonstrated that alterations in the IGF-IR could influence tumorigenesis through various molecular events (H. Cui, 2007; Hébert, 2006; Sarfstein et al., 2006; Yuen et al., 2007); however, it requires a functioning IGF-IR to mediate the proliferation and survival of the malignant cells(Baserga et al., 2003; C. Sell et al., 1994). Thus, the IGF-IR is a vital feature in cellular malignancy; and, in some cases, for the prognosis of cancer(Parker et al., 2002; Spentzos et al., 2007).

The *IGF Binding Proteins (IGFBP's)* are produced in various tissues and fluids in the human body. They function as carriers for specific growth factors(Baxter et al., 1998) and have many functions (Camacho-Hübner et al., 1999; F. C. Nielsen, 1992). Among the IGFBP's, only the IGFBP-3 can form a high molecular weight complex with the IGF-I protein, and more than 95 % of the IGF-I is bound to IGFBP-3 in the circulation(Holman

& Baxter, 1996). Therefore, the IGF-I protein and the IGFBP-3 levels are closely related and balanced through a negative feedback mechanism to conserve hormonal homeostasis. Not surprisingly, lower levels of the IGFBP-3 were associated with an increased risk of cancer(Gunnell et al., 2003).

Breast, Prostate and Colorectal cancer and IGF-I levels

The IGF-I pathway is involved in complex regulatory physiological and pathological functions in the human organism. The IGF-I pathway influences key stages of cancer development and progression at the molecular level. The IGF-I pathway's activation can produce cellular proliferation in various tissues after stimulation of signal transduction pathways. The Wnt pathway controls cells' proliferation in mature tissues, and its regulation is crucial for tissues with high rates of cell renewal, such as the epithelia found in the colon (P. J. Jenkins & Bustin, 2004). IGF-I's proliferative effect was demonstrated in *in vivo* and *in vitro* tests that proved its biological activity as a growth factor similar to insulin (Jones & Clemmons, 1995). This was supported by evidence in patients with acromegaly with increased risk of colonic neoplasia due to IGF-I's direct stimulatory effects (Ma et al., 1999).

Another stage in cancer development influenced by the IGF-I pathway is the inhibition of apoptosis. Apoptosis, the programmed cell death, is a vital component of normal cell turnover and it is also part of pathological conditions such as degenerative disorders and cancer(Chun et al., 1994; Harrington et al., 1994; Resnicoff et al., 1995). Furthermore, IGF-I can regulate the Vascular Endothelial Growth Factor (VEGF)

expression in cancer cells; the expression of this factor indicates the level of aggressiveness of tumoral cells (Akagi et al., 1998; Fukuda et al., 2002). IGF-I can also influence cancer progression through the invasion of the adjacent tissues producing metastasis(Y. Wu et al., 2002; D. Zhang et al., 2003). The malignant progression occurs after the IGF-I activates the expression of metalloproteinases that destroy structural cellular components, allowing malignant cells to migrate and invade normal tissues (D. Zhang et al., 2003).

Considering that IGF-I protein has local and systemic effects, and the IGF-IR is considered ubiquitous in humans, the connection between the IGF-I pathway with several types of cancers is biologically feasible. However, this review focuses on breast, prostate, and colorectal cancer due to the amount of scientific evidence gathered, the high prevalence and the increasing incidence of these types of cancer in the western world and worldwide. **Table 4** shows the studies on the association between IGF-I levels and breast, prostate, and colorectal cancer.

Breast cancer is a leading cause of cancer death in women in over 100 countries and a leading cause of death in the United States(Siegel et al., 2019). There is currently evidence that breast cancer cells from fresh tumor biopsies have receptors for IGF-I(Peyrat et al., 1993), and studies support that the IGF-I protein is higher in primary breast cancer patients(Bohlke et al., 1998; Peyrat et al., 1993). Furthermore, the IGF-I protein has been shown to produce a powerful stimulus for mammary cell proliferation, increasing the likelihood of breast cancer development(Carlos L. Arteaga, 1992; Cullen et al., 1992; Leon et al., 1992). Besides, the IGF-I protein can produce mammary tissue enlargement, and changes in density have been proven clinically and through mammographic exams. For instance, two studies found that therapies that require supplementation with IGF-I can

produce gynecomastia in prepuberal children (Malozowski & Stadel, 1995) and older men(Cohn et al., 1993). Studies correlated the stimulating effect of IGF-I on mammary cells with mammographic results(Byrne et al., 2000; Guo et al., 2001). Premenopausal women with breast cancer had higher IGF-I levels than non-cancer patients(Bohlke et al., 1998; Bruning et al., 1995); however, studies on postmenopausal breast cancer patients did not support these findings (Favoni et al., 1995; H. Jernström & Barrett-Connor, 1999), possibly due to age decreasing the IGF-I levels.

Defects in the IGF-I gene, such as polymorphism in the CA repeats in breast cancer, were only investigated at a small scale(H. Yu et al., 2001). However, gene mutations' may explain why women with first- or second-degree breast cancer family had increased IGF-I levels compared to women without this family history(H. C. Jernström et al., 1997), even though these findings were not confirmed in another epidemiological study (Arends et al., 2002). Further, there is the possibility of a synergistic effect between IGF-I and estrogens based on studies in humans (Hartmann et al., 1998; Lukanova et al., 2004) and animals (Murphy et al., 1987) as well, where the IGF-I levels and the levels of estrogens in blood were positively correlated.

Prostate cancer is the second most common cancer worldwide and a leading cause of cancer death in men(Bray et al., 2018). The IGF-I pathway was linked with the development of prostate cancer through mechanisms that include increased IGF-I levels, activation of the IGF-IR, and possible interactions with male sex hormones. The IGF-I protein has mitogenic and antiapoptotic effects on prostate epithelial cells(LeRoith & Roberts, 2003; Weinstein et al., 2009). These findings encouraged researchers to investigate the influence of IGF-I levels in prostate carcinogenesis, and this correlation was

investigated in studies worldwide. For instance, a study in Greece showed that a 60 ng/mL level in the serum IGF-I level doubled prostate cancer(Mantzoros et al., 1997). A large case-control study showed a similar increase in prostate cancer risk(Chan, Stampfer, et al., 1998). A study in Sweden reported a 50 % increase in prostate cancer risk per 100 ng/mL increment in IGF-I(Wolk et al., 1998). Prospective studies demonstrated that having higher IGF-I levels at baseline was associated with a 3-4 times increased risk of prostate cancer in the follow-up period. The results did not differ while adjusting for confounders(Chan, Stampfer, et al., 1998; Harman et al., 2000); a large meta-analysis supports these findings(Shi et al., 2001). Besides, IGF-I levels could help diagnose prostate cancer in cases where the traditional marker Prostatic Specific Antigen (PSA) is within normal ranges since the IGF-I levels helped discriminate between benign and malignant prostate tumors(Djavan et al., 1999).

Colorectal cancer is third in terms of incidence and second in terms of mortality worldwide(Bray et al., 2018). The IGF-I pathway seems to influence the development of colorectal cancer due to mechanisms that depend on the IGF-I levels, the IGFBP-3 levels, the IGF-IR activation, and hormonal interactions at a local level. Increased IGF-I levels and decreased levels of IGFBP-3 in patients with colon cancer were found in cross-sectional studies(Manousos et al., 1999). Studies on the high-risk populations for colorectal cancer, such as acromegalic patients, showed a positive association between IGF-I levels and the risk of developing malignant lesions in the colon(P. J. Jenkins et al., 2000). Studies on healthy participants showed that those with higher IGF-I levels had an increased risk of developing colorectal cancer than those with lower levels(Giovannucci, 2001; Giovannucci

et al., 2000). These findings were supported with a large prospective study with a 14-year follow-up(Ma et al., 1999).

Further, possible hormonal interactions between the IGF-I pathway and other hormones such as Growth Hormone (GH) and insulin seem to increase the likelihood of colorectal cancer. Patients with acromegaly, a population with higher GH and IGF-I levels, increased the expression of IGF-I receptor, increased epithelial cell proliferation, and precancerous lesions of the colon such as adenomatous polyps(Cats et al., 1996). Further, having hyperinsulinemia, a condition that increases free IGF-I protein levels may also increase the risk of colorectal neoplasia(P. J. Jenkins & Bustin, 2004; Jones & Clemmons, 1995).

Table 4. Studies showing the link between breast, prostate, and colorectal cancer and IGF-I

Study	Population	Evidence
Breast cancer		
(Peyrat et al., 1993)	**Cases:** 47 female cancer patients ages 31-86 **Controls:** 134 control patients ages 20-80.	**(+) *** IGF-I plasma levels in cancer patients compared to control patients.
(Favoni et al., 1995)	**Cases:** 85 female patients with early cancer, 20 female patients with late breast cancer ages 35-81. **Controls:** 33 control patients aged 35-81.	**(0)** IGF-I plasma levels in cancer patients and controls.
(Bohlke et al., 1998)	**Cases:** 94 premenopausal cancer patients aged <50. **Controls:** 76 control patients aged <50.	**(+) *** IGF-I plasma levels in cancer patients in the upper two tertiles.
(H. Jernström & Barrett-Connor, 1999)	**Cases:** 45 female cancer patients aged 53-90. **Controls:** 393 control patients aged 53-90.	**(0)** IGF-I plasma levels in cancer patients and controls.
(Byrne et al., 2000).	**Cases:** Mammographic breast density as a predictor of breast cancer of 65 premenopausal. **Controls:** 162 postmenopausal women.	Premenopausal**: (+) *** IGF-I plasma levels; Postmenopausal: **(-) *** IGF-I plasma levels.

Prostate cancer		
(Mantzoros et al., 1997)	**Cases:** 52 male cancer patients; 52 males with benign prostatic hyperplasia. **Controls:** 52, healthy male control patients.	**(+) *** IGF-I plasma levels in cancer patients compared to benign prostatic hyperplasia and control patients.
(Chan, Stampfer, et al., 1998)	**Cases:** 152 male cancer patients aged 40-80. **Controls:** 152 male control patients aged 40-80.	**(+) *** IGF-I plasma levels in cancer patients compared to control patients.
(Wolk et al., 1998)	**Cases:** 210 male cancer patients. **Controls:** 224 control patients.	**(+)** * mean IGF-I plasma levels in cancer patients compared to control patients
(Djavan et al., 1999)	**Cases:** 245 males aged 56-79 with increased Prostatic Specific Antigen (PSA) levels. **Follow-up:** 6 weeks.	**(+) *** IGF-I plasma levels in cancer patients compared to those with the benign condition.
(Harman et al., 2000)	**Cases:** 72 male cancer patients mean age 64.8. **Controls:** 127 male control patients mean age 65.7.	**(+) *** IGF-I plasma levels in cancer patients compared to control patients.
Colorectal cancer		
(Ma et al., 1999)	**Cases:** 193 male cancer patients. **Controls:** 318 male control patients.	**(+) *** IGF-I levels and risk of developing cancer.
(Manousos et al., 1999)	**Cases:** 46 cancer patients. **Controls:** 50 control patients.	**(+)** IGF-I plasma levels in cancer patients compared to control patients.
(Giovannucci et al., 2000)	**Cases:** 79 female cancer patients. **Controls:** 158 female controls.	**(+)** IGF-I plasma levels in cancer patients compared to control patients.
(P. J. Jenkins et al., 2000)	**Cases:** 66 patients with acromegaly and colonoscopy screening. **Follow-up:** 32.7 months.	**(+)** IGF-I levels and risk of developing cancer.

(+) = positive association; (-) = negative association; (0) = no association
*statistically significant association

Discussion

Diet has a significant influence on the increase in cancer numbers, especially in the western world(*Cancer*, n.d.; Kanavos, 2006; Wagner & Brath, 2012). In this review, the role of diet in relationship with the risk of prostate, breast, and colorectal cancer was described while considering the IGF-I pathway. Diet composition can influence cancer

development depending on the nutrients consumed and the ability to modify IGF-I levels. The assessment of individual nutrients showed that macronutrient consumption might influence breast, prostate, and colorectal cancer through different mechanisms. For instance, protein intake seems to significantly influence the circulating IGF-I levels(Crowe et al., 2009; Ketelslegers et al., 1995; Marcello Maggio et al., 2013; L.-Q. Qin et al., 2009; Rich-Edwards et al., 2007; Thissen et al., 1994). The reduction of protein intake may be an essential dietary intervention for cancer prevention and risk reduction. Even though few epidemiological studies on protein intake and cancer, these studies show the influence of protein consumption on breast cancer(La Vecchia, 1993; Lê et al., 1986; McGuire et al., n.d.; Toniolo et al., 1989), prostate cancer(Chan, Giovannucci, et al., 1998; De Stefani et al., 1995; Talamini et al., 1986; Vecchia et al., 1991), and colorectal cancer(Baena & Salinas, 2015).Nonetheless, the results of these studies varied depending on the amount and sources of protein consumed.

Fat intake showed inconsistent findings in the cancer relationship, even though consuming fats may have a role in modulating inflammation(Laparra & Sanz, 2010; Maslowski & Mackay, 2011; X. Qin, 2012; Valdés-Ramos & Benítez-Arciniega, 2007; G. D. Wu et al., 2011; H.-N. Yu et al., 2014)and saturated fatty acids are considered proinflammatory (Frommer et al., 2015; Liu et al., 2014). In contrast, unsaturated fatty acids have an anti-inflammatory effect(Calder, 2009, 2010; Weylandt et al., 2012) except for ω-6 fatty acids(Liao et al., 2005).Additionally, current evidence shows that an imbalance in the ω-6/ω-3 ratio may better show a relationship to cancer than considering each fatty acid's effect separately (Stoll, 1999) .Therefore, the relationship between the consumption of specific types of fats warrants further investigation. So far, there is limited

evidence supporting its role in cancer; however, having a diet high in fats may predispose a person to other factors such as obesity, which can indirectly influence cancer risk.

Carbohydrate intake may influence cancer depending on the GI and GL of diet(D. J. Jenkins et al., 1981) and modulates insulin sensitivity, close to IGF-I levels and possibly cancer. Furthermore, inflammation may be another causal mechanism since consuming simple sugars increases inflammatory cytokine markers in the blood(Sanchez et al., 1973; Sørensen et al., 2005). In contrast, consuming complex carbohydrates reduces inflammation(Kuo, 2013; Suter, 2005) and the risk of cancer(Franceschi et al., 2001; Holmes, Pollak, & Hankinson, 2002).

Most of the studies reviewed showed the protective effect on cancer risk of selenium, zinc, magnesium, and calcium. These minerals showed protective effects for cancer through many biological processes. Selenium modulates the IGF-I bioavailability(Kryukov et al., 2003; Makropoulos et al., 1996), and it is involved in processes that protect cells from damage, such as antioxidation(Kryukov et al., 2003), normal cellular transcription(Makropoulos et al., 1996) ,cellular cycle, and apoptosis(Kaeck et al., 1997). Nonetheless, epidemiological studies showed that selenium's protective role might only be significant in populations with deficiencies (Diwadkar-Navsariwala & Diamond, 2004; Goyal et al., 2013). Zinc is involved in critical enzymatic functions in cellular growth, protein and DNA synthesis, and immunity(Meunier et al., 2005) and influencing IGF-I bioavailability(Matsui & Yamaguchi, 1995; Yamaguchi & Hashizume, 1994).

Magnesium is a fundamental cofactor in protein and DNA synthesis(Wolf & Cittadini, 2003) and is associated with increased inflammation and oxidative stress when

the levels are low(Champagne, 2008; M. Maggio et al., 2011). Further, magnesium levels are closely associated with IGF-I levels(M. Maggio et al., 2011) . Calcium inhibited the proliferation of cancer cells in vitro(Bostick et al., 1995; Gregoire et al., 1989; P. Rozen et al., 1989), reduced oxidative DNA damage (Fedirko et al., 2010), and has a protective and synergistic effect with vitamin D(K. Wu et al., 2002; Zheng et al., 1998). The reviewed evidence suggests that minerals have synergistic effects with other nutrients; therefore, there is a possibility that consuming isolated nutrients from vitamin supplements may not have the same effect on cancer risk as consuming nutrients through a wholesome diet. Similarly, antioxidants and vitamin consumption may help prevent oxidative stress, inflammation, and cancer(Reuter et al., 2010). Nonetheless, existing research has not demonstrated with certainty that their consumption is beneficial. Many of the studies included in this review demonstrated a protective effect of consuming vitamins and antioxidants; however, the types and sources of vitamins and antioxidants varied in each study. Furthermore, it is possible that consuming these nutrients as supplements is not as beneficial as consuming them through a regular diet.

Dietary patterns demonstrate the overall quality of diet and account for possible interactions among nutrients. Therefore, dietary patterns explain better the effect of diet on cancer risk. The current evidence shows that dietary patterns with higher consumption of meat, fats, and processed foods such as the western diet, showed an increased risk for breast, prostate, and colorectal cancer. Conversely, the prudent dietary pattern, with high consumption of fruits, vegetables, and fiber, decreases these cancers' risk[240–242] Nonetheless, only a few studies on dietary patterns and cancer risk and mortality have been done in the United States.

Finally, the IGF-I pathway is involved in critical stages of cancer development and links diet with cancer. The stages include malignant cell proliferation, inhibition of apoptosis, tumoral angiogenesis, metastasis, and resistance to chemotherapeutics. Individual characteristics, such as age, comorbidities, physical activity level and fasting influence IGF-I levels. Most of the epidemiological studies reviewed here focused on individual nutrients and did not account for cancer status at baseline; therefore, the effect of diet in cancer development cannot be entirely inferred.

Conclusion

The IGF-I pathway connects diet with the risk of breast, prostate, and colorectal cancer. Nonetheless, most studies have focused on individual nutrients. Dietary pattern studies that include IGF-I levels in the design are needed to produce dietary guidelines for cancer risk management and prevention.

Chapter 3: Adherence to dietary patterns among cancer survivors in the United States

Abstract

Purpose: This study aims to investigate the association between previous history of cancer and adherence to dietary patterns in the US.

***Methods*:** This cross-sectional study included 13,751 adults ages 18 and older from the Third National Health and Nutrition Examination Survey (NHANES III). We used Principal Component Analysis (PCA) to identify major dietary patterns. We used linear regression models to assess the association between previous history of cancer and adherence to dietary patterns.

***Results*:** Previous history of cancer was not associated with adherence to the prudent dietary pattern. The western dietary pattern was positively related previous history of cancer (b= 0.13, CI: 0.05 to 0.20, p=0.001; b_{adj}= 0.23, CI: 0.15 to 0.31, p = <0.001); and the traditional dietary pattern was negatively related to previous history of cancer (b= -0.58, CI: -0.65 to - 0.51, p=<0.001; b_{adj}= -0.22, CI: -0.29 to - 0.15, p = <0.001). The alcohol dietary pattern was positively associated with previous history of cancer only before adjusting for possible confounders. (b= 0.13, CI: 0.06 to 0.20, p=<0.001; b_{adj}= 0.03, CI: 0.03 to 0.10, p = <0.365).

Conclusion: Our findings suggest that cancer survivors do not follow a healthy dietary pattern and need guidance to adopt and maintain a healthy diet. The promotion of healthy dietary behaviors may improve the length and the quality of life of this population.

***Keywords**:* Dietary patterns, adherence, principal component analysis, cancer survivors

3.1 Introduction

Cancer diagnosis can be the driver for making significant lifestyle changes. Cancer survivors commonly attempt to make healthier changes after cancer diagnosis(Humpel et al., 2007); these changes include decreasing or discontinuing harmful behaviors, such as heavy consumption of alcoholic beverages(Allison, 2001) and smoking(PHD et al., 2000), increasing their physical activity and improving their diet(Patterson et al., 2003). Nutrition can influence cancer incidence and outcome(Chlebowski, 2013). Dietary changes are made in hopes that better nutrition would improve health and prevent cancer recurrence.(Maskarinec et al., 2001)

Cancer patients frequently experience severe malnutrition as a result of elevated energy requirements, increased catabolism and muscle wasting. In the post-diagnose period, cancer survivors report making dietary improvements that include increasing consumption of fruits and vegetables(Patterson et al., 2003; Satia et al., 2004) and decreasing the consumption of fatty foods(Patterson et al., 2003). Nonetheless, there is evidence suggesting that significant dietary modifications are difficult to achieve and sustain over time. For instance, a study found that women after breast cancer diagnosis made modest dietary changes over 2 years postdiagnosis(Wayne et al., 2004). Similarly, a study found that cancer survivors increased their weight and body fat during the first to third year post-diagnosis period(Irwin et al., 2005). And a literature review found that while cancer survivors frequently initiate a healthier diet, still only 25% to 42% of survivors consume adequate amounts of fruits and vegetables(Demark-Wahnefried et al., 2005).

Even though achieving optimal nutrition is ideal for cancer survivors(Mourouti et al., 2017), to the best of our knowledge there are no studies investigating the adherence to dietary patterns after cancer diagnosis in this population. Dietary patterns explain the overall quality of diet of the survivors and provide substantial information regarding their nutritional behaviors. We hypothesize that previous diagnose of cancer is associated with healthy dietary patterns. To test this hypothesis, we used cross-sectional data from The Third National Health and Nutrition Examination Survey, (NHANES III) and examined the association between previous personal diagnosis of cancer and adherence to the major dietary patterns in the United States.

3.2 Materials and Methods

Study population

This cross-sectional study included a total of 13,751 civilian non-institutionalized adults 18 years of age and older with complete information of the household survey, examination and dietary intake from the Third National Health and Nutrition Examination Survey, NHANES III. The data set contains information that describes the health and nutritional status of the U.S. population using high quality standards of measurements. The survey was conducted from 1988 through 1994 and had an overall examined response rate of 78 percent. The survey includes a household interview, a physical examination, and laboratory tests. The examination component involves examinations by a physician, a dentist, and health technicians. Detailed information of the standardized protocols used in

NHANES III have been previously published("Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1," 1994).

Data collection

The sociodemographic and lifestyle characteristics information was collected during the face-to-face interviews following the NHANES III protocol("Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1," 1994). The characteristics included in the analysis were: age (years at time of the recruitment); sex (male or female); race/ethnicity (Non-Hispanic White; Non-Hispanic Black; Mexican-American and Other); educational attainment (years of schooling completed); physical activity (average, more active or less active compared to those at the same age); and current smoking status (yes, no or missed to answer). The collection of the anthropometric measurements was done during the examination part of the NHANES III, following standard procedures. The measurements were taken with subjects wearing light clothing and without shoes. Standing height and weight were obtained and used to calculate the Body mass index (BMI) as kg/m^2.

The information on the medical history of cancer was obtained during the household interview including all adults over the age of 18 years. The National Coalition for Cancer Survivorship (NCCS) defines a survivor as being any person diagnosed with cancer, from the time of initial diagnosis until his or her death(*DCCPS*, 2011). This definition has been adopted by The National Cancer Institute (NCI)(*Office of Cancer Survivorship | DCCPS/NCI/NIH*, n.d.). In agreement with this definition and previous research (Deshmukh et al., 2018; Karavasiloglou et al., 2019; *Sugar Intake from Sugar-*

Sweetened Beverage among Cancer and Non-Cancer Individuals: The NHANES Study - Tseng - Translational Cancer Research, n.d.), we defined cancer status based on the questions: *Has a doctor ever told you had cancer skin cancer?* and *Has a doctor ever told you had cancer other cancer?* Participants that answered "yes" to these questions were defined as cancer survivors (n=1,030).

The medical history of chronic diseases including ischemic heart disease, stroke, hypertension, diabetes, was also collected during the household interview. The variables were dichotomized as yes or no. The questions participants were asked were: *"Has a doctor ever told you that you had a heart attack?"; "Has a doctor ever told you that you had a stroke?"; "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" ;"Have you ever been told by a doctor that you have diabetes?"*. For this analysis, we did not categorize as diabetes to females who were diabetic only during pregnancy.

Dietary assessment

The dietary assessment contained information from the food frequency questionnaire (FFQ) and the 24-hour food recall. The FFQ is a validated, semi-quantitative, interviewer-administered questionnaire that includes approximately 60 food items and beverages, as well as standard portion sizes and nutrient intakes calculated as grams per day. FFQ has been shown to be a valid and reliable method for assessing average consumption of nutrients (Feskanich et al., 1993; F. B. Hu et al., 1999). Information on the percentage of daily calories and macronutrients was included on the 24-h food recall interview. Subjects who reported excessively high or low values for total food or energy

intake (less than 600 kcal/day in or more than 4200 kcal/day) or those with missing answers were excluded from the analysis. Food groups were classified based on their nutrient profiles based according to the USDA food composition data (USDA). The food groups and items are shown in **Table 5.**

Table 5. Food groups used in the dietary pattern analysis

Food Groups	Food items
Milk and milk products	Chocolate milk, milk, yogurt, beverages made with milk and creams, cheese and cheese dishes.
Meat	Beef, pork, poultry, processed meat, entrails.
Fish	Fish and seafood.
Eggs	Eggs and egg products.
Vegetables	Soups and dishes with vegetables, all types of vegetables.
Fruit	Fruits and fruit juices,
Legumes and beans	Beans including kidney, pinto and black beans, lentils, chickpeas and rice
Potatoes	All types of potatoes including sweet potatoes and yams.
Nuts and seeds.	Nuts and seeds.
Cereal	Bran, fiber, cold and hot cereals, box cereals,
Breads	Breads, tortillas and pasta.
Sweets and pastries	Pastries, chocolate, candy.
Caffeinated beverages	Tea, coffee and other caffeinated beverages
Soda	Regular and diet sodas, colas, drinks with vitamin C.
Alcoholic beverages	Beer, wine, champagne, hard liquors.
Oils	Margarine, butter, vegetable oils and oil-based salad dressings.

Statistical analysis

We performed principal component analysis (PCA) based on the 16 food groups to assess the major dietary patterns in the cohort. We performed principal component analysis (PCA), a method used for dimensionality reduction of data that transforms correlated variables into a smaller number of uncorrelated variables(Abdi & Williams, 2010; Tipping & Bishop, 1999).The PCA analysis was based on the afore mentioned food groups. The components with eigenvalues greater than 1 were considered in the analysis and the major dietary patterns (components) were identified(Girden, 2001). We confirmed the choice with the scree test. The sample adequacy was tested using the Kaiser-Meyer-Olkin (KMO) test(Cerny & Kaiser, 1977; Kaiser, 1974). We used the factor loading matrix to extract the factor loadings for each food group. Scores were calculated for each of the components retained by summing the standardized values of the food groups weighted by their scoring coefficients. Thus, each individual received a score for each dietary pattern retained. Food groups with absolute scoring coefficients >0.2 were considered important contributors to a pattern. This criterion for factor loading cutoff has been previously described (Hinkin, 1998; Howard, 2016). The distribution of population characteristics was evaluated by quintiles of dietary patterns scores and tested for trend analysis. We used 1-way ANOVA for quantitative variables and chi-square tests for qualitative variables to identify significant differences across quintile of dietary scores. For the dietary variables, we calculated energy-adjusted means across quintiles. We used multiple linear regression to determine the association between previous history of cancer and the adherence to the dietary patterns. We fitted unadjusted and adjusted models to calculate the regression coefficients and 95% confidence intervals. The adjusted models controlled for age, BMI,

sex, smoking status and previous history of chronic diseases including diabetes, hypertension, stroke, and ischemic heart disease. Sample weights adapted to our total population were used to account for the complex survey design and provide nationally representative estimates. All analyses were performed on the weighted data using STATA version 13. 1.

3.3 Results

Assessment of the dietary patterns

The principal component analysis procedure generated eigenvalues that indicated four major dietary patterns and ten minor dietary patterns. The extracted factors accounted for 63% of the total variance, a value considered satisfactory(Hair, 2012; Peterson, 2000). Considering the scores obtained, we named the four major components as dietary patterns. The four major patterns identified are shown in **Table 6.** The first dietary pattern was named a 'Prudent' because it was characterized by a high score for vegetables, fruits, fish, legumes, potatoes, eggs, cereals, nuts and seeds. This pattern was consistent with previous studies on dietary patterns in the United States population (T. Fung et al., 2003; Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011). The second dietary pattern was named 'Western' since it was characterized by a high score for sweets and oils and very low scores for fruits, vegetables and legumes; and had similar characteristics to previous studies (T. Fung et al., 2003; Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011). We named the third dietary pattern 'traditional' because of the high score for traditional foods that included: fish, eggs, legumes and bread and low score for fruits, cereals and soda. The traditional pattern has

been previously described(Noel et al., 2009; Velie et al., 2005). And finally, the fourth dietary pattern was labelled as ‘Alcohol’ due to the extremely high score for alcoholic beverages compared to other foods. The alcohol dietary pattern is consistent with previous studies as well(Shikany James M. et al., 2015; Terry, Suzuki, et al., 2001). The variables were calculated as linear combinations of the standardized values of the predefined food groups using the factor scores found in the principal component analysis as coefficients. All patterns were normally distributed.

Table 6. Factor scores for the four major dietary patterns identified by using food consumption data from NHANES III. [a]

	Prudent dietary pattern	**Western dietary pattern**	**Traditional dietary pattern**	**Alcohol dietary pattern**
Dairy	-	-	-	-
Meat	-	0.20	-	-
Fish	0.21	-	0.52	0.32
Eggs	0.20	-	0.48	-0.24
Vegetables	0.47	-0.31	-	-
Fruits	0.37	-0.32	-0.30	-
Legumes and rice	0.25	-0.35	0.49	-
Potatoes	0.32	0.24	-	-
Bread	0.37	-	0.30	-
Cereals	0.24	-	-0.37	-0.39
Sweets	-	0.52	-	-
Oils	0.28	0.39	-	-
Caffeinated beverages	-	-	-	-
Alcoholic beverages	-	-	-	0.59
Soda	-	-	-0.23	-
Nuts and Seeds	0.26	0.23	-	-

[a] Absolute values <0.2 were not listed in the table.

Demographic characteristics

The study included 13,751 adults from the NHANES III. The distribution of characteristics across quintile categories of adherence to dietary patterns are shown in **Table 7.** The demographic characteristics, the nutrient intakes and previous history of diseases differed across quintiles of dietary patterns. Healthier nutritional and lifestyle

behaviors were seen among those that had the highest consumption of the prudent diet, in contrast with the participants with the highest consumption of the western pattern. The participants with highest consumption of the prudent dietary pattern were older, had lower BMI and were less likely to be current smokers compared to the participants in the lowest consumption. Moreover, they consumed more protein, carbohydrates and fiber, and less fat and alcoholic beverages. They were also less likely to have previous history of cancer.

In contrast with those that followed the prudent diet, the participants with the highest consumption of the western pattern were younger, had higher BMI and were more likely to be current smokers, despite having more years of education than those in the lowest group of consumption. Their diet included less amount of protein, carbohydrates and fiber, while consuming more fat and alcoholic beverages. In addition, they were more likely to report previous diagnose of hypertension and cancer. Among the participants that followed the traditional pattern, those in the highest consumption group were less likely to have had previous history of chronic diseases and cancer than those in the lowest group. However, they were older, less educated and more likely to be current smokers compared to those in the lowest consumption group. They also consumed more alcoholic beverages and less fat, carbohydrates and fiber. And finally, those with highest consumption of the alcohol pattern were younger, had more years of education and were more likely to be smokers. Consistently, the evaluation of the nutritional intake indicated that they consumed a high percentage of alcohol, low percentage of fat, carbohydrates and fiber. Nonetheless, they were less likely to report having a previous history of ischemic heart disease, stroke, or hypertension.

Table 7. Characteristics and nutrient densities of the study population by quintiles of dietary pattern consumption[1]

	'Prudent' pattern			'Western' pattern			'Traditional' Pattern			'Alcohol' pattern		
	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*
Age, (y)	39.54	50.93	<0.001	45.84	43.67	<0.001	42.57	54.79	<0.001	52.01	45.24	<0.001
BMI, (kg/m²)	26.83	26.12	<0.001	25.77	26.78	<0.001	26.50	26.5	0.967	26.10	26.45	0.002
Education, (y)	11.47	10.81	0.001	10.23	11.42	<0.001	12.23	9.06	<0.001	9.88	12.16	<0.001
Sex, % Female	11.63	10.63	0.052	12.72	11.02	0.023	12.68	11.32	0.013	10.58	11.43	0.011
Race, % White	6.67	7.90	0.002	4.28	10.68	0.001	12.76	2.61	0.001	7.91	8.61	0.003
Current smoker, %	5.74	3.58	<0.001	3.34	6.41	<0.001	2.52	6.56	<0.001	3.59	5.95	<0.001
Nutrient Intake[2]												
Total energy (MJ)	1932.86	2039.28	<0.001	1865.06	2195.48	<0.001	1830.41	2142.85	<0.001	1919.05	2108.19	<0.001
Total fat (E%)	34.26	32.48	<0.001	30.35	34.71	<0.001	32.63	32.25	<0.001	33.35	32.56	0.009
Protein (E%)	15.08	16.11	<0.001	16.49	14.63	<0.001	15.9	15.80	0.001	15.76	15.74	0.006
Carbohydrates (E%)	49.23	51.4	<0.001	52.76	49.11	<0.001	51.2	49.47	<0.001	49.72	47.43	<0.001
Alcohol (E%)	1.43	0.01	<0.001	0.40	1.55	<0.001	0.27	2.48	<0.001	1.17	4.27	<0.001
Dietary Fiber (g/MJ)	13.54	18.79	<0.001	17.79	13.25	<0.001	18.46	17.12	<0.001	17.35	15.5	<0.001
Chronic diseases, %												
Heart Disease	0.71	1.09	0.001	0.78	0.66	0.103	1.34	0.56	<0.001	1.26	0.53	<0.001
Stroke	0.39	0.59	0.002	0.57	0.51	0.853	0.89	0.31	<0.001	1.09	0.26	<0.001
Hypertension	5.13	5.52	0.047	4.17	5.58	<0.001	6.69	4.47	<0.001	6.28	4.86	<0.001
Diabetes	9.92	8.90	0.043	9.53	9.08	0.176	9.21	8.62	0.003	8.81	8.65	0.005
History of cancer	1.86	0.94	<0.001	1.14	1.52	<0.001	2.65	0.59	<0.001	1.81	1.25	0.005

*Q1: quintile 1, lowest consumption; Q5: quintile 5, highest consumption; E%: Energy percentage; MJ: megajoules.

[1] ANOVA for quantitative variables and chi-square for qualitative variables indicating differences in characteristics between quintiles of each dietary pattern.

[2] Values are energy-adjusted means.

Previous history of cancer and adherence to dietary patterns

The regression coefficients and confidence intervals (95%) for the previous history of cancer associated with the adherence to the four major dietary patterns are shown in **Table 8.** Previous history of cancer was not significantly associated with adherence to the prudent dietary pattern in the adjusted and unadjusted models. The western dietary pattern, characterized by high consumption of sweets and oils; and low consumption of vegetables, fruits and legumes, was positively related to a previous history of cancer (b= 0.13, CI: 0.05 to 0.20, p=0.001); demonstrating that those with a previous history of cancer were more likely to adhere to the western dietary pattern compared to those without. Furthermore, after controlling for confounders, the association remained significant (b= 0.23, CI: 0.15 to 0.31, p = <0.001). Conversely, the traditional dietary pattern was negatively associated with previous history of cancer (b= -0.58, CI: -0.65, - 0.51, p=<0.001); and the association remained significant after controlling for confounders (b= -0.22, CI: -0.29, - 0.15, p = <0.001). Thus, participants with a previous history of cancer were less adherent to the traditional dietary pattern compared to those without it. The alcohol dietary pattern was positively associated with previous history of cancer in the unadjusted model (b= 0.13, CI: 0.06 to 0.20, p=<0.001); however, after adjustment for confounders, the estimates were not statistically significant (b= 0.03, CI: 0.03 to 0.10, p=0.367).

Table 8. Previous history of cancer association with adherence to the major dietary patterns

	Prudent dietary pattern					
	Unadjusted Model			Adjusted Model		
	b	**p- value**	**CI (95 %)**	**b**	**p- value**	**CI (95 %)**
No previous history of cancer		†			†	
Previous history of cancer	0.09	0.085	(-0.01, 0.20)	0.07	0.172	(-0.03, 0.19)
	Western dietary pattern					
	Unadjusted Model			**Adjusted Model**		
	b	**p- value**	**CI (95 %)**	**b**	**p- value**	**CI (95 %)**
No previous history of cancer		†			†	
Previous history of cancer	0.13	0.001	(0.05, 0.20)	0.23	**<0.001**	(0.15, 0.31)
	Traditional dietary pattern					
	Unadjusted Model			**Adjusted Model**		
	b	**p- value**	**CI (95 %)**	**b**	**p- value**	**CI (95 %)**
No previous history of cancer		†			†	
Previous history of cancer	-0.58	**<0.001**	(-0.65, -0.51)	-0.22	**<0.001**	(-0.29, -0.15)
	Alcohol dietary pattern					
	Unadjusted Model			**Adjusted Model**		
	b	**p- value**	**CI (95 %)**	**b**	**p- value**	**CI (95 %)**
No previous history of cancer		†			†	
Previous history of cancer	0.13	**<0.001**	(0.06, 0.20)	0.03	0.367	(0.03, 0.10)

b: regression coefficient (a positive coefficient implies a higher adherence to the pattern).
CI, confidence interval.
† Reference category.

Discussion

We examined the association between previous personal diagnose of cancer and adherence to four major dietary patterns in the United States using cross-sectional data from the NHANES III study. To the best of our knowledge, this is the first study investigating adherence to dietary patterns after cancer diagnosis in the United States. Dietary patterns condense information about food consumption, reflect diet composition and capture the overall effect of dietary exposures in health and disease.

Four major dietary patterns were found in the analysis of participants from the NHANES III study. These patterns have been previously described in the United States adult population: the prudent dietary pattern with high intakes of legumes, fruits and vegetables (T. Fung et al., 2003; Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011); the western dietary pattern is characterized by high intakes of processed and fried foods, refined grains, sweets and desserts(T. Fung et al., 2003; Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011); the traditional pattern, characterized by high consumption of such as rice, beans eggs and fish(Noel et al., 2009; Velie et al., 2005); and the alcohol dietary pattern(Shikany James M. et al., 2015; Terry, Suzuki, et al., 2001).

Our study failed to prove the hypothesis that a previous diagnosis of cancer is associated with adherence to a healthy dietary pattern. Previous research suggests that cancer survivors are motivated to receive information and implement a healthy lifestyles and healthy dietary behaviors(Allison, 2001; Humpel et al., 2007; Maskarinec et al., 2001; Patterson et al., 2003; PHD et al., 2000). Adherence to good-quality diet is beneficial for

cancer prognosis(Meyerhardt et al., 2007; Weigl et al., 2018) and may reduce the risk of cancer recurrence(Meyerhardt et al., 2007).

While cancer survivors may strive to improve their diet, evidence shows that it can be challenging to adopt and maintain a healthy diet (Beeken et al., 2016; Hardcastle et al., 2018); especially among vulnerable and low-income populations(Cassady et al., 2007; Drewnowski & Eichelsdoerfer, 2010; Nicklas et al., 2013). Furthermore, evidence shows that the perception of the quality of their diet and the actual diet of cancer survivors differs significantly(Xue et al., 2020), demonstrating the need for comprehensive information and nutritional guidance for this population.

In this study, healthier behaviors were seen among those that had the highest consumption of the prudent and traditional diet patterns, contrasting with participants with the highest consumption of the western and alcohol patterns, in general. Our findings are supported by previous studies that demonstrated a correlation between dietary behaviors and lifestyle choices(Johansson et al., 1999; Marques-Vidal et al., 2015; Thiele et al., 2004). Health concerns are often the motivation for improving diet and health behaviors simultaneously(Phan & Chambers, 2016; Sun, 2008); nonetheless, the prudent diet was not associated with cancer survivorship in this study.

Current dietary guidelines for cancer survivors are similar to healthy diet guidelines for cancer prevention(Brown et al., 2001; Doyle et al., 2006; Rock et al., 2012).These guidelines recommend including fruits, vegetables, whole grains and other food rich in fiber; and to limit the consumption of high fat foods and alcoholic beverages. Nonetheless, there is evidence showing that cancer survivors may consume lesser amounts of the

recommended foods and more empty calories than the general population(F. F. Zhang et al., 2015). In fact, our findings showed that cancer survivors were more likely to adhere to the western dietary pattern compared to the rest of the participants. The consumption of the western diet has increased in the last decades. The western diet has been associated with obesity(T. T. Fung et al., 2001; Kanoski & Davidson, 2011; McCarty, 2000), type II diabetes(Qi et al., 2009), cardiovascular disease(T. T. Fung et al., 2001; Kerver et al., 2003) and several types of cancer in previous studies(Ahmed, 2004; Chan et al., 2013; M.L. Slattery et al., 2000; Stoll, 1999).

Interestingly, cancer survivors in this study were less likely to follow the traditional dietary pattern compared to the rest of the participants. Traditional foods serve as the foundation for the contemporary diet and its consumption seems to be related to cultural preferences(Dekker et al., 2015; García-Bailo et al., 2012; Kim et al., 2008) and cultural historical context(Brombach, 2017; Tucker, 2010). In the United States, traditional foods were inherited from the American Indian and Alaska Native Communities. In these populations, studies have shown that western acculturation had led to an increase to chronic diseases(Colby et al., 2012; Pollack et al., 1984); therefore, more research is needed to understand the factors that influence the consumption of traditional foods and the adherence to the traditional dietary pattern.

Alcohol consumption has been previously linked with increased risk of cancer (Hirayama, 1989; Pelucchi et al., 2011; Pollack et al., 1984) and risk cancer recurrence(Weigl et al., 2018). The current guidelines for cancer survivors recommend limiting the consumption of alcohol to improve survival. We found that the alcohol dietary pattern was associated with a previous history of cancer before controlling for possible

confounders. Cancer diagnosis can be a stressful event, and alcohol consumption may be related to lack of support systems. Further studies are required to determine the reasons of alcohol consumption among cancer survivors. Intervention and support programs to help manage alcohol consumption that is specific to this population may be required.

Strengths and limitations

This study used a large, nationally representative sample of adults in the United States and it is the first study investigating adherence to dietary patterns among cancer survivors in the US, to the best of our knowledge. This study provided significant information on dietary behaviors among cancer survivors and may serve as a catalyst for future research aiming to understand the barriers that challenge cancer survivors and prevent them from optimizing their diet and health. Nonetheless, we recognize that the use of self-reported data can be subject to recall bias and this limitation. This study lacks the validation by medical records to confirm the medical diagnoses. However, previous studies demonstrated that self-reported diagnosis of diseases is valid and reliable(Bush et al., 1989; Kehoe et al., 1994). Another limitation may be the consistency and the reproducibility of the dietary patterns; nonetheless, the dietary patterns analyzed in this study were consistent in nutritional characteristics with previous studies in the United States population. In addition, this cross-sectional study did not capture information about changes in diet over time; therefore, the participants' previous diet and its nutritional characteristics were not analyzed in this study.

Conclusion

Our findings suggest that cancer survivors need guidance to adopt and maintain healthy dietary habits. Cancer survivors are at increased risk for progressive disease, cancer recurrence and functional decline. Optimal nutrition may improve the length and the quality of life of this population. Good communication with health providers may create more awareness of the importance of optimal nutrition after cancer diagnose.

Chapter 4. The Connection between dietary patterns and Insulin-like Growth Factor I (IGF-I)

Abstract

***Background**:* Insulin-like Growth Factor-I (IGF-I) is a hormone essential for normal growth in children and maintains anabolic processes in adults. Nonetheless, high levels of the IGF-I hormone are associated with an increased risk of several cancers.

***Objective**:* This study investigates the relationship between dietary patterns and IGF-I levels in the blood.

Methods: The present cross-sectional study included 4,854 adults from NHANES III. Dietary patterns were identified using principal component analysis based on a validated food frequency questionnaire. Multiple linear regression models were used to analyze the association between dietary patterns and IGF-I levels in the blood.

***Results*:** The 'prudent' dietary pattern, with high consumption of fruits and vegetables and legumes, decreased IGF-I levels (b= -0.03, CI: -0.04 to 0.02, $p<0.001$; and b_{adj}= -0.01, CI: -0.02 to 0.01, $p<0.05$). Conversely, the 'western' pattern, with high consumption of oils, sweets, and soda, increased IGF-I (b= -0.03, CI: 0.02 to 0.04, $p<0.001$; and b_{adj}= 0.04, CI: 0.02 to 0.05, $p<0.001$). The 'traditional' and the 'alcohol' dietary pattern did not modify IGF-I levels when controlling for confounders.

Conclusion: Our findings suggest that it is possible to regulate IGF-I levels through consumption of a healthy diet.

***Keywords**:* Insulin-like Growth Factor-I, Principal component analysis, Cancer.

Introduction

The Insulin-like Growth Factor-I (IGF-I) is a hormone essential for normal growth in children (Blum et al., 1993) and maintenance of anabolic processes in adults (Nindl & Pierce, 2010). IGF-I levels reach maximum levels during puberty, followed by a continuous age-related decline (A. Juul et al., 1995; Anders Juul et al., 1994; Landin-Wilhelmsen et al., 2004). In adults, abnormally elevated levels of IGF-I have been linked with an increased risk of several cancers (Hankinson et al., 1998; P. J. Jenkins & Bustin, 2004; Anders Juul, 2003; LeRoith & Roberts, 2003; Ma et al., 1999; Macaulay, 1992; Manousos et al., 1999; Mantzoros et al., 1997). This evidence is supported by studies that showed that IGF-I promotes malignant cell growth and tumorigenesis(Akagi et al., 1998; Chun et al., 1994; Fukuda et al., 2002; Resnicoff et al., 1995; D. Zhang et al., 2003). Nutrition plays an essential role in regulating IGF-I levels (Hochberg et al., 1992; Ketelslegers et al., 1995; Thissen et al., 1994; Underwood et al., 1986, 1994) and mainly on protein intake(Bonjour et al., 1997; Castaneda et al., 2000; Holmes, Pollak, Willett, et al., 2002). Nonetheless, evidence suggests that carbohydrate and fat intake can influence IGF-I levels under conditions that require a change in metabolism to a catabolic state (Aronson William J. et al., 2010; Snyder et al., 1989).

Evidence from a large epidemiological study suggests that IGF-I mediates the relationship between nutrition and cancer's pathogenesis (Kaklamani et al., 1999). This evidence is supported by a clinical study on healthy individuals that consumed a low-fat diet resulting in in-vivo changes in IGF-I levels and reduced growth of LNCaP tumoral cells *in-vitro* (Ngo et al., 2002). Conversely, caloric restriction and fasting can produce a

transient reduction in IGF-I levels and decrease tumor progression (Dunn et al., 1997; Henning et al., 2013; Ch Sell, 2003). While previous studies demonstrated the role of individual nutrients on IGF-I levels, no studies investigate the influence of dietary patterns on IGF-I levels, to the best of our knowledge. Dietary patterns reflect the overall quality of diet and account for interactions among nutrients.

In this study, we hypothesize that dietary patterns with large amounts of protein, processed carbohydrates, and fats will increase IGF-I levels; conversely, a diet with high amounts of complex carbohydrates from fruits and vegetables will decrease IGF-I levels. We used information from 4,854 adults from the National Health and Nutrition Examination Survey III (NHANES III).

Methods

Study population

This study included noninstitutionalized adults aged 20 years and older with complete dietary intake information and laboratory data from NHANES III. The 6-year survey began in 1988 and ended in 1994 with a response rate of 78%. The survey included a household interview, a physical examination, and laboratory tests. The examination component involved examinations by a health professional, including physicians, dentists, and health technicians. Detailed information about the standardized protocols used in NHANES III has been previously published (*NHANES III (1988-1994)*, n.d.).

The sociodemographic and lifestyle characteristics information was collected during the face-to-face household interview. The characteristics included in the analysis

were: age (years at the time of the recruitment); sex (male or female); educational attainment (years of schooling completed); and current smoking status (yes, no, or missed to answer). The medical history of chronic diseases, including ischemic heart disease, stroke, hypertension, diabetes, was also collected during the household interview. The variables were dichotomized as yes or no. The questions participants were asked were: "Has a doctor ever told you that you had a heart attack?"; "Has a doctor ever told you that you had a stroke?"; "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?"; "Have you ever been told by a doctor that you have diabetes?"; "Has a doctor ever told you that you had skin cancer?" and "Has a doctor ever told you that you had any other cancer?".

The collection of anthropometric measurements during the physical examination included standing height and weight using standard protocols. We used these measurements to calculate body mass index (BMI) as kg/m^2. The laboratory results of the testing serum samples for IGF-I from adults age 20 and older that attended the morning session of the examination after an overnight fast are available were included in the NHANES III/IGF-I subsample. The IGF-I levels were measured using standard laboratory protocols by Diagnostic Systems Laboratories Inc (DSL, Webster TX). For quality control, a modified Levey Jennings Approach was used.

Dietary data

The dietary assessment was based on the food frequency questionnaire (FFQ) and the 24-hour food recall. The FFQ included 60 food items and beverages calculated in standardized portion sizes and nutrient intakes as grams per day. The percentage of daily calories and macronutrients was included in the 24-h food recall interview. Participants without complete dietary data and those that reported excessively high or low values for total food or energy intake (less than 600 kcal/day in or more than 4200 kcal/day) were excluded. The food groups were classified based on their nutrient profiles according to the USDA food composition data (USDA) (*USDA Nutrient Data Laboratory | Food and Nutrition Information Center | NAL | USDA*, n.d.). The food groups and items are shown in **Table 9**.

Table 9. Food groups and food items

Food Groups	Food items
Milk and milk products	Chocolate milk, milk, yogurt, beverages made with milk and creams, cheese, and cheese dishes.
Meat	Beef, pork, poultry, processed meat, entrails.
Fish	Fish and seafood.
Eggs	Eggs and egg products.
Vegetables	Soups and dishes with vegetables, all types of vegetables.
Fruit	Fruits and fruit juices.
Legumes and Beans	Bean including kidney, pinto and black beans, lentils, chickpeas, and rice.
Potatoes	All types of potatoes, including sweet potatoes and yams.
Nuts and seeds.	Nuts and seeds.
Cereal	Bran, fiber, cold and hot cereals, box cereals.
Bread	Bread, tortillas, and pasta.
Sweets and pastries	Pastries, chocolate, candy.
Caffeinated beverages	Tea and coffee.
Soda	Regular and diet sodas, colas, drinks with vitamin C.
Alcoholic beverages	Beer, wine, champagne, hard liquors.
Oils	Margarine, butter, oils, and salad dressings.

Statistical analysis

Principal component analysis (PCA) was used to assess the major dietary patterns. The sample adequacy was tested using the Kaiser-Meyer-Olkin (KMO) test. We identified the major dietary patterns based on the components with eigenvalues greater than one and a confirmatory scree test. Scores were calculated for each of the dietary patterns. Food groups with absolute scoring coefficients >0.3 were considered important contributors to a pattern. The distribution of population characteristics was evaluated by quintiles of dietary pattern scores and tested for trend analysis. The distribution of IGF-I levels was skewed; therefore, logarithmically transformed values were used in all analyses. We used 1-way ANOVA for quantitative variables and chi-square tests for qualitative variables to identify significant differences across quintile of dietary scores. The dietary variables were energy-adjusted.

Multiple linear regression models were used to determine the association between dietary patterns and IGF-I levels in the blood. We fitted unadjusted and adjusted models to calculate the regression coefficients and 95% confidence intervals. The adjusted models controlled for: age, BMI, sex, smoking status, and previous history of chronic diseases including diabetes, stroke, hypertension, ischemic heart disease and the previous history of cancer. Stepwise multiple regression analysis was conducted to identify predictors associated with IGF-I levels. Sample weights were used to account for the complex survey design and provide nationally representative estimates. All analyses were performed on the weighted data using STATA version 13. 1.

Results

Dietary pattern assessment

In the study population, the observed KMO was 0.65, which meant that the sample was adequate for principal component analysis. We identified four major dietary patterns that were consistent with previous studies. The first dietary pattern was named ‘traditional’ because it was characterized by high scores in traditional foods, including meat, vegetables, potatoes, and bread. The second dietary pattern was named ‘prudent’ because it was characterized by a high score for vegetables, fruits, and a low score in meat and oils. We named the third dietary pattern ‘western’ since it was characterized by a high score for sweets, oils, and soda and low scores for vegetables and fruits. Finally, the fourth dietary pattern was labeled as 'alcohol' due to the high score for alcoholic beverages compared to other foods. These patterns explained 45% of the variation in consumption of the foods and food groups. The factor loadings for these patterns are shown in **Table 10.**

Table 10. Factor loading matrix for the major factors identified by using food consumption data from NHANES III. [a]

	'Prudent' Pattern	**'Western' Pattern**	**'Traditional' Pattern**	**'Alcohol' Pattern**
Dairy	-	-	-	
Meat	-0.35	0.32	0.37	0.45
Fish	-	-	-	0.50
Eggs	-	0.36	-	-
Vegetables	0.40	-	0.39	-
Fruits	0.49	-	-	-
Legumes	0.33	-0.55	-	-
Potatoes	-	-	0.35	-
Bread	-	-	0.38	-
Cereals	-	-	-	-0.33
Sweets	-0.38	0.38	-	-
Oils	-	0.34	-	-
Caffeinated beverages	-	-	-	-
Alcoholic beverages	-	-	-	0.58
Soda	-	0.30	-	-
Nuts and Seeds	-	-	-	-

Absolute values < 0.30 were not listed in the table

Demographic characteristics

The study included 4,854 adults from NHANES III. In **Table 11**, characteristics are shown across the quintiles for the dietary patterns. Participants with the highest consumption scores of the 'prudent' dietary pattern were, on average, less likely to be a current smoker and less likely to have a history of hypertension and previous history of cancer, compared to those with the lowest consumption. In contrast, the participants with the highest consumption scores of the 'western' dietary pattern were more likely to have hypertension, ischemic heart disease, and previous cancer history than those with the lowest consumption scores; while those with the lowest scores of the ‘western’ dietary pattern were more likely to have less years of education compared to those with lowest consumption scores.

In general, individuals with the highest consumption scores of the 'prudent' dietary pattern exhibited healthier lifestyle and nutritional behaviors than individuals with the highest consumption scores of the 'western' dietary pattern. No significant differences in the previous history of diseases or nutrient intakes were seen among those with the lowest versus those with the highest consumption scores of the traditional dietary pattern. Participants with the highest scores of the alcohol dietary pattern were more likely to have a previous history of chronic diseases and cancer than those with the lowest consumption scores despite being younger. Interestingly, they were also more likely to have higher education than those with the lowest scores of the alcohol dietary pattern.

Table 11. Characteristics, nutrient consumption and plasma concentrations of the IGF-I biomarker by quintiles of dietary patterns[1]

	'Prudent' pattern			'Western' pattern			'Traditional' pattern			'Alcohol' pattern		
	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*
Age, *(y) (mean)*	41.78	52.37	<0.001	42.46	53.98	<0.001	44.37	48.38	<0.001	54.48	44.85	<0.001
BMI, (kg/m^2) *(mean)*	26.75	26.65	0.969	26.18	26.87	0.008	27.22	26.37	0.004	26.21	26.50	0.001
Education, *(y) (mean)*	11.24	11.28	0.428	11.98	8.93	<0.001	11.60	10.68	<0.001	9.95	12.47	<0.001
Sex, Female, *%*	9.27	13.21	<0.001	8.88	12.01	<0.001	12.44	10.26	<0.001	11.52	9.59	<0.001
Current smoker, *%*	7.40	2.49	<0.001	10.61	9.66	0.020	4.67	4.54	0.011	3.90	5.66	<0.001
Previous history of Diseases (%)												
Ischemic Heart Disease	0.44	0.97	0.064	0.50	1.28	<0.001	0.78	0.75	0.745	0.46	1.29	0.001
Stroke	0.49	0.58	0.735	0.29	00.66	0.130	0.41	0.50	0.619	0.16	1.02	<0.001
Hypertension	6.49	4.26	<0.001	453	6.02	<0.001	5.16	4.63	0.076	4.81	6.32	0.005
Diabetes	8.88	9.77	0.341	9.38	9.24	0.394	10.16	9.40	0.546	8.99	9.09	0.225
History of Cancer	1.98	0.75	<0.001	0.37	2.34	<0.001	1.41	1.39	0.263	1.20	1.77	0.011
Nutrients Intakes [2]												
Mean energy intake (MJ)	2251.17	1850.58	<0.001	1959.93	2056.76	<0.001	1836.39	2155.97	<0.001	1908.47	2082.22	<0.001
Total fat (E%)	35.78	29.79	<0.001	31.41	33.40	<0.001	34.12	32.98	0.004	33.01	33.18	0.354
Saturated fat(E%)	11.94	9.58	<0.001	10.14	10.14	<0.001	11.21	10.77	0.010	11.06	10.58	0.056
Monounsaturated fat(E%)	13.82	10.96	<0.001	11.74	12.68	<0.001	12.94	12.40	0.012	12.50	12.41	0.178
Polyunsaturated fat(E%)	7.26	6.79	0.001	6.83	7.26	0.072	7.35	7.14	0.008	6.83	7.57	<0.001
Protein (E%)	14.83	16.47	<0.001	16.15	15.36	<0.001	15.07	15.78	0.005	15.44	15.92	0.001
Carbohydrates (E%)	47.43	54.02	0.064	50.84	51.53	0.021	50.23	50.87	0.267	49.44	47.42	<0.001
Alcohol (E%)	1.96	0.80	<0.001	2.71	1.57	0.030	0.58	0.43	0.460	2.11	3.48	<0.001
Dietary Fiber (g/MJ)	14.46	19.47	<0.001	19.10	16.62	<0.001	14.60	17.62	<0.001	17.61	15.60	<0.001
Biomarker												
IGF-I (ng/ml) *(mean)*	275.51	239.51	<0.001	230.87	260.95	<0.001	266.36	248.96	<0.001	246.63	247.58	0.033

*Q1: quintile 1, lowest consumption; Q5: quintile 5, highest consumption; E%: Energy percentage; M.J.: megajoules.
[1]ANOVA for quantitative variables and chi-square for qualitative variables indicating differences between quintiles of each dietary pattern.
2 Values are energy adjusted means.

Association between dietary patterns and IGF-I blood levels

We fitted linear regression models to examine the relationship between dietary patterns and IGF-I levels in the blood. The 'prudent' dietary pattern was negatively associated with IGF-I blood levels in the adjusted and unadjusted models (b= -0.03, CI: -0.04 to 0.02, p<0.001; and b= -0.01, CI: -0.02 to 0.01, p<0.05, respectively), with evidence of a significant trend (p for trend <0.001 and 0.001, respectively). Conversely, the 'western' dietary pattern, was positively associated with IGF-I levels in both models (b= 0.03, CI: 0.02 to 0.04, p<0.001; and b= 0.04, CI: 0.02 to 0.05, p<0.001, respectively), also with a significant trend (p for trend <0.001). The 'traditional' and the 'alcohol' dietary patterns were significantly associated with IGF-I levels in the unadjusted models (b= -0.01, CI: -0.02 to -0.01, p<0.05 and b= 0.02, CI: 0.01 to 0.04, p<0.05, respectively). Nonetheless, after controlling for confounders, these patterns were not significantly related with IGF-I levels (b= -0.01, CI: -0.01 to 0.01, p=0.060 and b= -0.01, CI: -0.01 to 0.01, p=0.062, respectively). **Table 12** shows the adjusted and unadjusted models used to examine the association between the 'prudent' and the 'western' dietary patterns and the IGF-I levels in the blood.

Table 12. Relationship between the dietary patterns and IGF-I levels.

	Insulin-like Growth Factor I (IGF-I)								
				Quintiles of dietary patterns					
	β	**CI (95 %)**		**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	***p trend***
'Prudent' pattern									
IGF-I *(ng/ml)*				275.51	256.54	258.23	245.21	239.51	
Unadjusted Model	-0.03	(-0.04	-0.02) **	†	-0.06	-0.08	-0.11	-0.14	<0.001
Adjusted Model[1]	-0.01	(-0.02	-0.01) *	†	-0.01	-0.01	-0.02	-0.03	0.001
'Western' pattern									
IGF-I *(ng/ml)*				243.69	245.33	257.56	260.92	266.25	
Unadjusted Model	0.03	(0.02	0.04) **	†	0.06	0.07	0.08	0.10	<0.001
Adjusted Model[1]	0.04	(0.02	0.05) **	†	0.07	0.09	0.06	0.20	<0.001
'Traditional' pattern									
IGF-I *(ng/ml)*				266.36	259.60	251.18	247.22	248.96	
Unadjusted Model	-0.01	(-0.02	-0.01) *	†	-0.01	-0.04	-0.06	-0.05	0.860
Adjusted Model[1]	-0.01	(-0.01	0.01)	†	-0.01	-0.03	-0.03	-0.03	<0.001
'Alcohol' pattern									
IGF-I *(ng/ml)*				246.63	254.41	256.63	258.44	257.58	
Unadjusted Model	0.02	(0.01	0.04) *	†	0.09	0.12	0.13	0.10	0.796
Adjusted Model[1]	-0.01	(-0.01	0.01)	†	0.03	0.04	0.03	-0.01	<0.001

† Reference category.
* p <0.05; ** p <0.001
[1]Model adjusted for age, sex, energy intake, smoking status, and diseases (diabetes, stroke, hypertension, ischemic heart disease, and cancer).

Discussion

In this cross-sectional study, we investigated the association between dietary patterns and IGF-I levels in the blood from participants of the NHANES III. In this study,

we found that dietary patterns characterized with large amounts of animal protein, processed carbohydrates, and fats were correlated with an increase in IGF-I levels, and dietary patterns with high amounts of complex carbohydrates from fruits, vegetables, and legumes correlated with a decrease in IGF-I levels. This is the first epidemiological study investigating these relationships in the United States, to the best of our knowledge. IGF-I is an anabolic hormone that can influence normal cell growth and tumoral growth (Anders Juul, 2003). During childhood, IGF-I supports normal growth and development, reaching its peak around puberty (A. Juul et al., 1994, 1995; Landin-Wilhelmsen et al., 2004). In adulthood, there is no longer the need to support growth, and a continuous decline in IGF-I levels is observed(Landin-Wilhelmsen et al., 2004). Nonetheless, when IGF-I levels are above normal ranges for age, IGF-I can promote malignant cell growth (Akagi et al., 1998; Chun et al., 1994; Fukuda et al., 2002; Resnicoff et al., 1995; D. Zhang et al., 2003) and increase the risk of several cancers(Hankinson et al., 1998; P. J. Jenkins & Bustin, 2004; LeRoith & Roberts, 2003; Ma et al., 1999; Macaulay, 1992; Manousos et al., 1999; Mantzoros et al., 1997).

Previous studies demonstrated that nutrition regulates IGF-I levels in blood (Hochberg et al., 1992; Ketelslegers et al., 1995; Thissen et al., 1994; Underwood et al., 1986, 1994); however, most studies have focused on examining the effect of individual nutrient consumption on IGF-I levels. To expand these findings, we examined the relationship between the dietary pattern on IGF-I levels. In our study population, four previously described dietary patterns were found: the 'prudent' dietary pattern with high intakes of legumes, fruits, and vegetables (Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011); the 'western' dietary pattern with high intakes

of fried foods, sweets, and oils (Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011); the ‘traditional’ pattern, characterized by high consumption of traditional foods such as rice, beans, eggs, and fish (Noel et al., 2009; Velie et al., 2005); and the alcohol pattern (Shikany James M. et al., 2015; Terry, Bergkvist, et al., 2001).

Dietary patterns with large amounts of animal protein, processed carbohydrates, and fats correlated with an increase in IGF-I levels, and dietary patterns with high amounts of complex carbohydrates from fruits, vegetables, and legumes correlated with a decrease in IGF-I levels. While accounting for confounders, only the ‘prudent’ and the ‘western’ dietary pattern were significantly related to IGF-I levels. The ‘prudent’ pattern was associated with decreased IGF-I levels. Consumption of fresh fruits, vegetables, and legumes has been extensively recommended to prevent cancer, even though the exact mechanisms are yet to be clarified (Mariette Gerber et al., 2002; Hanausek et al., 2003; Temple & Kaiser Gladwin, 2003; Veer et al., 2000).

Additionally, previous studies have shown that consuming a ‘prudent’ diet, characterized by a high intake of fruits, vegetables, and whole grains, is associated with a decreased risk of chronic diseases (Gao et al., 2007; van Dam et al., 2002) and several cancers (Adebamowo et al., 2005; Chan et al., 2013; Hirose et al., 2007; Martha L. Slattery, 2010). Therefore, the regulation of IGF-I levels through consumption of a ‘prudent’ diet may decrease cancer risk when maintained in the normal ranges. Furthermore, among populations with increased risk of cancer, such as people with diabetes, those with a familial or personal history of cancer, maintaining optimal IGF-I levels through a healthy 'prudent' diet may reduce cancer recurrence risk.

Our findings showed that the ‘western’ diet correlated with increased IGF-I levels. Previous studies have shown that high consumption of meat and dairy products, which are an essential part of the western patterns, is associated with increased IGF-I levels (Giovannucci et al., 2003; Outwater et al., 1997). The 'western' dietary pattern is characterized by overconsumption of refined sugars, processed foods, salt, and saturated fats and has been associated with several chronic diseases (Carrera-Bastos et al., 2011) and cancers (Adlercreutz, 1990; Aronson William J. et al., 2010; Giovannucci, 2002; M.L. Slattery et al., 2000). Overconsumption of these foods increases inflammation and produces unfavorable changes in the gut microbiota (Myles, 2014). The results of this study demonstrate that certain dietary patterns correlate with IGF-I levels and increase cancer risk. Dietary composition regulates energy balance, glucose tolerance, gut microbiota, and hormonal balance, preventing chronic illnesses and cancer (Schwarz et al., 2011). Populations currently adhering to a ‘western’ diet may benefit from adopting a ‘prudent’ diet and maintaining IGF-I levels inside the normal ranges. Consuming a ‘prudent’ healthy diet may be a significant intervention to reduce cancer risk.

Strengths and limitations

This study used information from a large, nationally representative sample of adults in the United States. This information can provide important information to the general population and higher risk groups for cancer. Among the limitations of this study, the use of self-reported data can be subject to recall bias. The study lacks validation by medical records to confirm the medical diagnoses; however, previous studies demonstrated that self-reported diagnosis of diseases is a valid and reliable source of the medical history of the disease(Busch et al., 2005; Kehoe et al., 1994). Another limitation

is the consistency and reproducibility of the dietary patterns; however, the dietary patterns analyzed in this study were consistent with previous studies' nutritional characteristics in the United States population.

Conclusion

Our findings suggest that it is possible to regulate IGF-I levels through consumption of a 'prudent' dietary pattern. A healthy diet with high consumption of vegetables and fruits, and a low consumption of meats and oils lowers IGF-I blood levels. Future dietary interventions to reduce cancer risk should aim to regulate IGF-I using a nutritional approach and considering dietary pattern adherence.

Chapter 5. Dietary patterns, total and cancer mortality in the United States

Abstract

Background: Updated evidence on the association between adherence to specific dietary patterns and mortality is needed. This study aimed to investigate the association between dietary patterns, total mortality, and cancer mortality.

Methods: We included 13,466 participants from the NHANES III cohort. We assessed the usual diet at baseline with a validated semiquantitative food frequency questionnaire. The primary outcome measures were deaths, including all-causes, and the secondary outcome was deaths due to cancer, confirmed by the National Death Index. Dietary patterns were determined through principal component analysis based on predefined food groups. Cox regression models were used to estimate multivariable-adjusted hazard ratios and 95% confidence intervals for mortality.

Results*:* The major dietary patterns identified at baseline were the 'prudent' pattern, rich in vegetables, fish, fruits, and legumes; the 'western' dietary pattern, rich in sweets and oils and low in fruits and vegetables; the 'traditional' pattern, rich in bread, legumes, eggs; and the ‘alcohol’ pattern. After a mean follow-up of 19.9 years, 4963 deaths due to all causes were reported, and 1077 deaths were due to cancer. After adjustment for confounders, the lowest risk of total mortality was found among those with the highest adherence to the 'prudent' dietary pattern compared to those with the lowest (HR_{adj} 0.90, 95% CI: 0.82 to 0.99, $p < 0.05$) and showed a significant trend ($p=0.002$) demonstrating that as adherence to the ‘prudent’ pattern increased, the total mortality decreased. Those adhering to the 'western' and the 'traditional' dietary showed the highest risk of total

mortality (HR_{adj} 1.12, 95% CI 1.02 to 1.22, $p < 0.05$; and HR_{adj} 1.16, 95% CI 1.06 to 1.27, respectively); and the highest risk of mortality due to cancer (HR_{adj} 1.17, 95% CI 1.06 to 1.27, $p < 0.05$; and HR_{adj} 1.25, 95% CI 1.03 to 1.52, $p < 0.05$, respectively). The 'alcohol' dietary pattern showed no significant association with total mortality or mortality due to cancer in this study.

Conclusion: Adherence to 'prudent' dietary pattern was associated with reducing the risk of total mortality. Adherence to dietary patterns rich in sweets, oils, meat, and eggs, such as the western and the traditional dietary pattern, is associated with an increased risk of total mortality and mortality due to cancer.

Keywords: Dietary patterns; United States; total mortality; cancer mortality.

Introduction

In the last decades, efforts have been made to quantify the burden of disease attributable to specific dietary factors (Lock et al., 2005; Organization, 2009; Pomerleau et al., 2003). The study of diet and disease associations has traditionally originated from the consumption of single nutrients or foods. Dietary patterns describe diet quality and explain the total variability in food intake(Frank B. Hu, 2002; Moeller et al., 2007). Additionally, dietary patterns account for complex interactions that occur among foods and nutrients (Tapsell et al., 2016). Therefore, the study of dietary patterns provides a clearer view of food and nutrient consumption and could better predict long-term outcomes such as mortality due to dietary exposure (Michels & Schulze, 2005).

Several studies have evaluated the effect of different dietary patterns and mortality in other countries (Buckland et al., 2011; Huijbregts et al., 1997; Michels & Wolk, 2002; Trichopoulou et al., 2009). In the United States, many studies have shown the association between adherence to specific dietary habits and chronic diseases, including obesity (Aqeel et al., 2020; LeCroy et al., 2020), cardiovascular disease, and diabetes (Brunner et al., 2008). Moreover, only a few studies have investigated the relationship between specific dietary patterns and total mortality (Akinyemiju et al., 2016; Kant, 2004; J. T. Kelly et al., 2017; Orlich et al., 2013; Reedy et al., 2014). Most of these studies have focused on particular racial subpopulations (Akinyemiju et al., 2016), only older adults (Kant, 2004; J. T. Kelly et al., 2017), or participants with certain health conditions (Anderson et al., 2011). Therefore, the association between the adherence to dietary patterns and total mortality in the United States in the general population is still limited.

This study evaluates the association between dietary patterns, total mortality, and cancer mortality in the NHANES III adult cohort in the U.S. We hypothesize that dietary patterns characterized by consumption of nutrient-rich foods are associated with lower total mortality, and mortality due to cancer in the United States. Conversely, we hypothesize that dietary patterns that reflect poor nutrition are associated with higher total mortality and mortality due to cancer. We used data from 13,466 adults from the National Health and Nutrition Examination Survey III
(NHANES III). We identified the predominant dietary patterns in relationship with total mortality and mortality due to cancer.

4.2 Materials and Methods

Study Population

The study used data from the NHANES III, a nationally representative sample of the civilian, non-institutionalized U.S. population conducted between 1988 and 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The NHANES study protocol obtained ethical approval from the CDC/NCHS Ethics Review Board and received informed consent from all participants(*NHANES III (1988-1994)*). As determined by the Institutional Review Board at the University of California, Merced, the use of public datasets with de-identified information does not constitute research with human subjects. There was no interaction with the participants, and no identifiable private information was used; therefore, human subjects' approval was not required for this study. The current study included 13,466

participants 18 to 90 years old, with complete data on mortality status, diet, and relevant covariates. The examination component involved examinations by a health professional, including physicians, dentists, and health technicians. Detailed information on the standardized protocols used in NHANES III has been previously published (*NHANES III (1988-1994)*).

Assessment of Dietary Exposure

During the interviews, dietary records providing detailed information about the foods and beverages were collected using computer-assisted software. The usual diet assessment was based on the food frequency questionnaire (FFQ) and the 24-hour food recall. The FFQ included 60 food items and beverages calculated in standardized portion sizes and nutrient intakes as grams per day. The percentage of daily calories and macronutrients was calculated based on the information gathered during the 24-h food recall interview. Participants without complete dietary data and those that reported excessively high or low values for total food or energy intake (less than 600 kcal/day in or more than 4200 kcal/day) were excluded. The food groups were classified based on their nutrient profiles according to the USDA food composition data (USDA) (*USDA Nutrient Data Laboratory | Food and Nutrition Information Center | NAL | USDA*). The food groups and items are shown in **Table 13**.

Table 13. Food groups and food items

Food Groups	Food items
Milk and milk products	Chocolate milk, milk, yogurt, beverages made with milk and creams, cheese, and cheese dishes.
Meat	Beef, pork, poultry, processed meat, entrails.
Fish	Fish and seafood.
Eggs	Eggs and egg products.
Vegetables	Soups and dishes with vegetables, all types of vegetables.
Fruit	Fruits and fruit juices,
Legumes and Beans	Bean including kidney, pinto and black beans, lentils, chickpeas, and rice
Potatoes	All types of potatoes, including sweet potatoes and yams.
Nuts and seeds.	Nuts and seeds.
Cereal	Bran, fiber, cold and hot cereals, box cereals,
Bread	bread, tortillas, and pasta.
Sweets and pastries	pastries, chocolate, candy.
Caffeinated beverages	Tea and coffee.
Soda	Regular and diet sodas, colas, drinks with vitamin C.
Alcoholic beverages	Beer, wine, champagne, hard liquors.
Oils	Margarine, butter, oils, and salad dressings.

Assessment of covariates

The sociodemographic and lifestyle characteristics information was collected during the face-to-face household interview. The participants' characteristics included in

the analysis were: age (years at the time of the recruitment); sex (male or female); educational attainment (years of schooling completed); and current smoking status (yes, no, or missed to answer). The medical history of chronic diseases, including ischemic heart disease, stroke, hypertension, diabetes, was also collected during the household interview. The variables were dichotomized as yes or no. The questions participants were asked were: "Has a doctor ever told you that you had a heart attack?"; "Has a doctor ever told you that you had a stroke?"; "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?"; "Have you ever been told by a doctor that you have diabetes?"; "Has a doctor ever told you that you had skin cancer?" and "Has a doctor ever told you that you had any other cancer?".

The collection of anthropometric measurements during the physical examination included standing height and weight using standard protocols. We used these measurements to calculate body mass index (BMI) as kg/m2.

Assessment of the Outcome

The NHANES III cohort study's mortality information was identified through linkage to the National Death Index through December 31, 2015. The mortality data included the underlying cause of death. For total mortality, we included deaths from all causes. For cancer-specific mortality, we included deaths from malignant neoplasms coded from C00-C97 in the International Classification of Diseases, 10th Edition, Clinical Modification System codes (ICD-10). The follow-up time was determined based on the interval from the 24-hour recall interview to the date of death or to December 31, 2015, for those that were censored.

Statistical Analysis

We used principal component analysis (PCA) to assess the major dietary patterns in the NHANES III cohort. We tested the sample adequacy for PCA using the Kaiser-Meyer-Olkin (KMO) test. We identified the major dietary patterns based on the components with eigenvalues greater than one and a confirmatory scree test. Then, we calculated scores for each of the dietary patterns. Food groups with absolute scoring coefficients >0.3 were considered substantia contributors to a pattern. We evaluated the distribution of population characteristics by quintiles of dietary pattern scores and tested for trend analysis. We used 1-way ANOVA for quantitative variables and chi-square tests for qualitative variables to identify significant differences across quintile of dietary pattern scores. The nutritional variables were energy-adjusted.

We used Cox regression models with the length of follow-up as the primary time variable to test the association between dietary pattern adherence and mortality due to all-causes and cancer. Hazard ratios (H.R.) with 95% confidence intervals (C.I.) across quintiles of dietary patterns were calculated using the lowest quintile of adherence as the reference category. In the multivariable models, potential confounders included as covariates were age, sex, total energy intake, smoking status, baseline BMI and previous history of chronic diseases (diabetes, hypertension, stroke, heart attack) and cancer. Also, tests of linear trend across successive quintiles of adherence to each pattern were conducted, treating the variable as continuous. Sample weights were used to calculate population estimates to account for unequal probability of selection. All analyses were performed using STATA version 13. 1.

4.3 Results

Dietary pattern assessment

In the study population, the observed KMO was 0.64, demonstrating that the sample was adequate for principal component analysis. The mean age of the 13,446 participants was 46.89 years. The mean follow-up of participants was 19.59 years, with a minimum and maximum follow-up of 0.10 and 27.2 years, respectively. During this period, 4,963 deaths were registered. The leading causes of death were cardiovascular disease (23.65 %), cancer (21.89%), cerebrovascular disease (6.64%), and other reasons (47.8%). The median age at recruitment for deceased participants was 64.1 years. We identified four major dietary patterns, explaining 36% of the total variance in the food groups' consumption. The factor loadings are shown in **Table 14**.

The first dietary pattern was named 'prudent' because it was characterized by a high score for vegetables, fruits, and a low score in meat and oils. The second dietary pattern was named 'western' since it was characterized by a high score for sweets, fats, and soda and low scores for vegetables and fruits. The third pattern was named 'traditional' because it was characterized by high scores in traditional foods, including meat, vegetables, potatoes, and bread. Finally, the fourth dietary pattern was labeled as 'alcohol' due to the notably high score for alcoholic beverages compared to other foods.

Table 14. Factor loading matrix for the major factors identified by using food consumption data from NHANES III. [a]

	'Prudent' Pattern	**'Western' Pattern**	**'Traditional' Pattern**	**'Alcohol' Pattern**
Dairy	-	-	-	-
Meat	-	0.32	0.30	-
Fish	-	-	-	0.53
Eggs	-	0.30	0.48	-
Vegetables	0.47	-0.31	-	-
Fruits	0.37	-0.32	-0.31	-
Legumes	0.35	-0.35	0.48	-
Potatoes	0.32	-	-	-
Bread	0.37	-	0.30	-
Cereals	-	-	-0.37	-0.39
Sweets	-	0.52	-	-
Oils	-	0.39	-	-
Caffeinated beverages	-	-	-	-
Alcoholic beverages	-	-	-	0.57
Soda	-	-	-	-
Nuts and Seeds	-	-	-	-

Absolute values < 0.30 were not listed in the table

Demographic characteristics

In **Table 15**, the baseline characteristics of the participants are shown across the quintiles for the dietary patterns. On average, the participants with the highest adherence to the 'prudent' dietary pattern were more likely to be men, older, leaner, had more years of education, and were less likely to be current smokers. They were also less likely to have a previous history of chronic diseases and cancer. They consumed higher amounts of fiber, carbohydrates, and protein; and consumed a lower amount of fats, despite having a higher calorie intake.

The participants with the highest adherence to the 'western' dietary pattern were more likely to be male, younger, current smokers, to have a higher BMI, and have fewer years of education. Additionally, they were more likely to report a history of hypertension and cancer. The higher intake of total energy was probably related to higher total fat consumption from fried foods, eggs, and a higher alcohol intake. Those with the highest consumption of the 'traditional' and the 'alcohol' dietary patterns were more likely to be men, younger, and current smokers; however, those with the highest adherence to the traditional pattern were less likely to have a previous history of chronic diseases baseline.

Table 15. Baseline characteristics and nutrient consumption of the study population by quintiles of dietary patterns[1] (n=13,466).

	'Prudent' pattern			'Western' pattern			'Traditional' pattern			'Alcohol' pattern		
	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*	*Q1**	*Q5**	*p*
Age, *(y) (mean)*	40.64	51.25	<0.001	46.83	43.33	<0.001	55.39	43.03	<0.001	53.69	44.54	<0.001
BMI, (kg/m^2) (*mean*)	26.96	26.15	0.001	25.83	26.80	<0.001	26.55	26.53	0.660	26.20	26.45	0.002
Education, *(y) (mean)*	10.87	11.43	<0.001	10.08	11.65	<0.001	12.26	9.06	<0.001	9.871	12.25	<0.001
Sex, Female, %	11.66	10.55	0.026	12.74	10.12	<0.001	12.69	8.14	<0.001	10.42	9.68	<0.001
Current smoker, *%*	5.86	3.66	<0.001	3.44	6.54	<0.001	2.49	6.65	<0.001	3.74	5.96	<0.001
History of Diseases												
Ischemic Heart Disease	1.13	0.73	0.001	1.34	3.14	0.487	1.36	0.57	<0.001	1.33	0.53	<0.001
Stroke	0.60	0.41	0.002	0.80	0.68	0.091	0.89	0.31	<0.001	1.13	0.25	<0.001
Hypertension	5.6	5.25	0.047	4.26	5.69	<0.001	6.76	4.47	<0.001	6.44	4.92	<0.001
Diabetes	9.27	8.8	0.013	9.62	0.09	0.298	0.93	0.32	<0.001	8.71	8.81	0.008
Cancer	1.91	0.95	<0.001	1.14	1.59	<0.001	0.27	0.60	<0.001	1.91	1.28	<0.001
***Nutrients Intakes*[2]**												
Mean energy intake (M.J.)	1926.50	2036.52	<0.001	1869.05	2192.73	<0.001	1826.45	2151.98	<0.001	1921.27	2099.39	<0.001
Total fat (E%)	34.04	32.64	<0.001	30.16	35.23	<0.001	32.54	32.35	<0.001	33.45	32.57	0.001
Saturated fat(E%)	11.26	10.49	<0.001	9.61	11.74	<0.001	10.59	10.44	<0.001	11.19	10.45	<0.001
Monounsaturated fat(E%)	12.94	12.25	<0.001	11.09	13.54	0.001	12.26	12.16	<0.001	12.67	12.26	0.001
Polyunsaturated fat(E%)	7.18	7.23	0.013	6.96	7.17	0.008	7.14	7.04	0.006	6.88	7.26	<0.001
Protein (E%)	15.16	16.07	<0.001	16.50	14.65	<0.001	15.95	15.82	<0.001	14.78	15.79	0.006
Carbohydrates (E%)	49.34	51.22	<0.001	52.65	48.92	<0.001	51.25	49.29	<0.001	50.55	47.50	<0.001
Alcohol (E%)	1.46	0.07	<0.001	0.69	1.02	0.010	0.26	2.54	<0.001	2.22	4.14	<0.001
Dietary Fiber (g/MJ)	13.18	19.14	<0.001	13.78	13.25	<0.001	18.58	17.03	<0.001	17.37	15.60	<0.001

Q1: quintile 1, lowest consumption; Q5: quintile 5, highest consumption; E%: Energy percentage; M.J.: megajoules.

[1]ANOVA for quantitative variables and chi-square for qualitative variables indicating differences between quintiles of each dietary pattern.

2 Values are energy adjusted means.

Dietary patterns and total mortality

The results of the study showed that the lowest risk of total mortality was found among those with the highest adherence to the 'prudent' dietary pattern compared to those with the lowest (HR: 0.89, 95% CI 0.81 to 0.98, p <0.05; HR_{adj}:0.90, 95% CI 0.82 to 0.99, p<0.05). Also, there was evidence of a significant trend (p for trend <0.05). Conversely, those in the highest group of consumption of the 'western' and the 'traditional' dietary patterns had the highest risk of total mortality (HR: 1.24, 95% CI 1.13 to 1.36, p<0.001 and HR_{adj}:1.12, 95% CI 1.02 to 1.22 for the western pattern; HR: 1.32, 95% CI 1.21 to 1.44, p<0.001 and HR_{adj}: 1.16, 95% CI 1.06 to 1.27, for the 'traditional' pattern). We did not find an association between the 'alcohol' dietary pattern and total mortality in the unadjusted and the adjusted model (HR: 0.82, 95% CI 0.62 to 1.02, p >0.05; HR_{adj}:0.77, 95% CI 0.41 to 1.01, p >0.05). Also, no statistically significant trend was evident (P for trend 0.771). The H.R. and 95% CI for total mortality according to baseline adherence to the four dietary patterns are shown in **Table 16**.

Table 16. Hazard ratios for total mortality according to quintiles of adherence categories of dietary patterns in NHANES III.

	Quintiles of dietary pattern consumption			
	Q1	***Q3***	***Q5***	***P for trend***
'Prudent' pattern				
All-cause of death (n)	761	973	1,210	
Person-years	56107.89	53509.59	49302.89	
Model I	†	0.89 (0.81 - 0.98) *	0.90 (0.81 - 0.98) *	0.002
Model II	†	0.94 (0.89 – 0.99) *	0.90 (0.82 - 0.99) *	0.049
'Western' pattern				
All-cause of death (n)	942	1,019	941	
Person-years	53472.49	52438.89	53451.19	
Model I	†	1.16 (1.06 - 1.27) **	1.24 (1.13 - 1.36) **	<0.001
Model II	†	1.10 (1.01 - 1.20) *	1.12 (1.02 - 1.22) *	0.632
'Traditional' pattern				
All-cause of death (n)	1,368	835	890	
Person-years	47488.89	54927.49	54195.39	
Model I	†	1.16 (1.06 - 1.27) *	1.32 (1.21 - 1.44) **	<0.001
Model II	†	1.04 (0.95 - 1.14)	1.16 (1.06 - 1.27) **	0.644
'Alcohol' pattern				
All-cause of death (n)	1,451	886	820	
Person-years	45289.09	54537.99	55569.49	
Model I	†	0.82 (0.62 - 1.02)	0.77 (0.50 – 1.04)	<0.001
Model II	†	0.79 (0.43 - 1.15)	0.71 (0.41 – 1.01)	0.771

† Reference category
* p <0.05; ** p <0.001
Model I: Adjusted for age. Model II: Adjusted for age, sex, energy intake, smoking status, and diseases (diabetes, stroke, hypertension, ischemic heart disease, and cancer).

Dietary patterns and mortality due to cancer

Participants with the highest consumption of the 'western' pattern had the highest risk of mortality due to cancer in the unadjusted and the adjusted models (HR 1.38, 95% CI 1.14 to 1.68, p<0.001; HR_{adj}: 1.17, 95% CI 1.06 to 1.29, p <0.05, respectively). Similar results were found among those with the highest consumption to the and the 'traditional' pattern (HR_{adj}: 1.50, 95% CI 1.25 to 1.80, p <0.001 and HR_{adj}: 1.25, 95% CI 1.03 to 1.52). We found no association between adherence to the 'prudent' or the 'alcohol' pattern and mortality due to cancer in the adjusted and the unadjusted models (HR: 1.02, 95% CI 0.83 to 1.24, p >0.05; and HR_{adj}: 1.05, 95% CI 0.86 to 1.28, p >0.05 for the 'prudent' pattern; and HR:0.90, 95% CI 0.75 to 1.08, p >0.05 for the 'alcohol' pattern). The H.R. and 95% CI for mortality due to cancer according to baseline adherence to the four dietary patterns are shown in **Table 17**.

Table 17. Hazard ratios for mortality due to cancer according to quintiles of adherence categories of dietary patterns in NHANES III.

	Quintile			
	Q1	***Q3***	***Q5***	***P for trend***
'Prudent' pattern				
Death due to cancer (n)	161	223	263	
Person-years	56107.89	53509.59	49302.89	
Model I	†	1.02 (0.83 - 1.25)	1.02 (0.83 - 1.24)	0.941
Model II	†	1.05 (0.86 - 1.29)	1.05 (0.86 - 1.28)	0.650
'Western' pattern				
All-cause of death (n)	197	207	224	
Person-years	53472.49	52438.89	53451.19	
Model I	†	1.31 (1.08 - 1.58) *	1.38 (1.14 - 1.68) **	<0.001
Model II	†	0.99 (0.81 - 1.21)	1.17 (1.06 - 1.29) *	0.456
'Traditional' pattern				
All-cause of death (n)	263	184	215	
Person-years	47488.89	54927.49	54195.39	
Model I	†	1.09 (0.90- 1.32)	1.50 (1.25- 1.80) **	<0.001
Model II	†	0.97 (0.90- 1.32)	1.25 (1.03- 1.52) *	0.568
'Alcohol' pattern				
All-cause of death (n)	272	216	213	
Person-years	45289.09	54537.99	55569.49	
Model I	†	0.93 (0.78 - 1.21)	0.90 (0.75 - 1.08)	0.041
Model II	†	0.91 (0.76 - 1.09)	0.78 (0.56 – 1.01)	0.861

† Reference category
* p <0.05; ** p <0.001
Model I: Adjusted for age; Model II: Adjusted for age, sex, energy intake, smoking status, and diseases (diabetes, stroke, hypertension, ischemic heart disease, and cancer)

Discussion

Most studies in the United States have focused on investigating associations between specific dietary factors and chronic diseases (Aqeel et al., 2020; Brunner et al., 2008; LeCroy et al., 2020). The association between the adherence dietary patterns and total mortality and mortality due to cancer in the general population is still limited. Dietary patterns condense information about food consumption, reflect diet composition, and capture the overall effect of dietary exposures on health and disease. This study evaluated the association between dietary patterns, total mortality, and cancer mortality in the NHANES III adult cohort in the U.S. Four previously described dietary patterns were found in this study at baseline. The 'prudent' dietary pattern, with high intakes of vegetables, fish, fruits, and legumes (T. Fung et al., 2003; Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011); the 'western' dietary pattern, rich in sweets and oils, and low in fruits and vegetables (T. Fung et al., 2003; Kerver et al., 2003; van Dam et al., 2002; Varraso et al., 2007; G. D. Wu et al., 2011); the 'traditional' dietary pattern, rich in bread, legumes, eggs (Noel et al., 2009; Velie et al., 2005); and the ‘alcohol’ dietary pattern (Shikany James M. et al., 2015; Terry, Bergkvist, et al., 2001).

On average, those with the highest consumption of the prudent dietary pattern were more likely to adhere to healthier behaviors and less likely to report a previous history of chronic diseases and cancer, in contrast with the participants with the highest consumption of the other patterns. Previous studies support this evidence and demonstrate a correlation between dietary behaviors and lifestyle choices (Marques-Vidal et al., 2015; Thiele et al., 2004).

Our findings confirmed the hypothesis that dietary patterns characterized by consuming nutrient-rich foods are associated with lower total mortality, and dietary patterns that reflect poor nutritional habits are associated with higher total mortality. Herein, the lowest risk of total mortality was among those with the highest adherence to the 'prudent' dietary pattern. The 'prudent' pattern is characterized by consuming nutrient-rich foods high in antioxidants and vitamins. Prudent diets contain a complex combination of antioxidant and prooxidant elements that can modify the human body's oxidative status. The oxidative stress resulting from imbalances between reactive oxygen species and the antioxidant defense is a common factor in many pathological conditions (Willcox et al., 2004). Oxidative stress has been related to cardiovascular disease, cancer, and other chronic diseases that account for a significant portion of deaths in the United States (FastStats, 2020).

In this study, participants with the highest consumption of the 'western' dietary pattern showed the highest risk of total mortality. The 'western' dietary pattern with high consumption of sweets and oils and low consumption of vegetables and fruits was associated with an increased risk of chronic diseases and cancer, probably due to micronutrient deficiencies that lead to several pathophysiological events increase the risk of chronic disease. Western diets are known to be deficient in magnesium, zinc, folate, and vitamins C, E, and K (Ames, 2006; McCann & Ames, 2009). Deficiencies in the micronutrients above were previously related to metabolic syndrome (Ford et al., 2007), cardiovascular disease (Hatzistavri et al., 2009; F. H. Nielsen et al., 2007), and coronary disease (Beulens et al., 2009; Gast et al., 2009), which are principal causes of mortality in the U.S.

Our findings did not show an association between the 'traditional' or the 'alcohol' pattern and total mortality. The 'traditional' dietary pattern has not been extensively studied in the United States, where traditional foods, inherited from the native communities, served as the foundation for the contemporary diet. Nonetheless, western acculturation led to increasing consumption of a westernized diet in native communities, increasing chronic diseases(Colby et al., 2012; Pollack et al., 1984); therefore, more research is needed to understand the factors that influence the adherence to the traditional dietary pattern and its effects on health and mortality. Alcohol consumption has been previously linked with increased mortality; nonetheless, the harmful effects depend on the level of alcohol consumption and the amount of time that individuals consume alcoholic beverages(Camargo et al., 1997; White et al., 2002). Furthermore, these effects depend on individuals' characteristics, such as their age and cardiovascular health (Fuchs et al., 1995; Thun et al., 1997). In line with these findings, our study showed that individuals with the highest adherence to the alcohol pattern were younger and less likely to have a previous history of chronic diseases and cancer.

We partially confirmed our second hypothesis and provided evidence that dietary patterns that reflect lower quality nutrition are associated with higher cancer mortality. Our findings suggest that participants with the highest consumption of the 'western' and the 'traditional' dietary pattern had the highest risk of mortality due to cancer, probably due to the high consumption of fats. Carrol and colleagues reviewed experimental and epidemiological studies on the role of dietary fat and cancer. Their findings suggested that high-fat diets increase cancer risk, and total dietary fat correlates with cancer mortality (Carroll et al., 1986). Similar findings were found across different types of

cancers (Rose et al., 1986; Sasaki et al., 1993). This study found no association between adherence to the 'prudent' or the 'alcohol' pattern and cancer mortality. Diets rich in fruits and vegetables are widely considered beneficial to health since they contain antioxidants, vitamins, and dietary fiber responsible for the benefits.

Nonetheless, the results of several studies have been inconsistent in the association between the consumption of fruits and vegetables and cancer risk. Additionally, a recent meta-analysis indicated that higher consumption of fruits and vegetables was not significantly associated with cancer mortality risk (Wang et al., 2014). The evidence presented herein suggests that efforts to increase consumption of a prudent dietary pattern may reduce the risk of total mortality, and the benefit for cancer mortality remains possible.

Strengths and limitations

This study's key strengths include the >27-year follow-up of a large, nationally representative sample of adults in the United States. Furthermore, it is the first study investigating the role of adherence to dietary patterns and total mortality, and mortality in the United States, to the best of our knowledge. Nonetheless, the study has limitations. First, the study used self-reported data that could be subject to recall bias due to the lack of medical records validation to confirm the medical diagnoses. Second, residual confounding may also be a limitation due to unmeasured socioeconomic variables. Finally, the study analyzed baseline dietary information and did not capture information about diet changes over time.

Conclusion

In this nationally representative cohort, adherence to the western and the traditional dietary pattern was strongly associated with an increased risk of total mortality and mortality due to cancer. The prudent dietary pattern was associated with a decreased risk of total mortality, but not due to cancer. The evidence presented herein suggests that efforts to increase consumption of a prudent dietary pattern may reduce the risk of total mortality, and the benefit for cancer mortality remains possible.

Chapter 6. Conclusion and recommendations.

This overall body of work illustrates the association between adherence to the major dietary patterns among cancer survivors, the general adult population in the United States and the risk of cancer and cancer mortality. In this collective study of eating patterns, we evaluated the effect of overall diet quality in cancer. Cancer incidence and mortality are growing worldwide. In the last decades, efforts have been made to quantify the burden of disease attributable to specific dietary factors. The role of diet as a factor contributing to cancer risk is hard to determine; distinguishing one food component's effects from another due to the possibility of synergistic or inhibiting cancer risk effects makes nutritional research difficult. A lack of understanding of the overall diet's role may be a fundamental reason why previous research has failed to determine the impact of diet on cancer risk and cancer mortality. Thus, this dissertation examined several aspects of the diet and cancer relationship.

In the second chapter, we conducted a thorough literature review that provided an overview of the existing literature of epidemiological studies on the association between diet and breast, prostate, and colorectal cancer. The literature review findings suggest that most studies have focused on individual nutrient consumption, and not enough research has been done on the relationship between dietary patterns and the cancer risk for breast, prostate and colorectal cancer. Dietary patterns reflect the overall quality of diet and account for possible interactions among nutrients. Therefore, the next chapters focused on dietary pattern consumption.

The first study in Chapter 3 aimed to investigate the association between the previous history of cancer and adherence to dietary patterns in the US. We identified four major dietary patterns in this population; the 'Prudent' dietary pattern characterized by a high score for vegetables, fruits, fish, legumes, potatoes, eggs, cereals, nuts, and seeds; 'Western' since it was characterized by a high score for sweets and oils and low scores for fruits, vegetables, and legumes; 'traditional' because of the high score for traditional foods that included: fish, eggs, legumes and bread and low score for fruits, cereals and soda; and finally the 'Alcohol' due to the extremely high score for alcoholic beverages compared to other foods. Our findings suggest that cancer survivors do not follow a healthy dietary pattern and need guidance to adopt and maintain a healthy diet. The promotion of healthy dietary behaviors may improve the length and the quality of life of this population.

Chapter 4 investigated the association between adherence to the previously described dietary patterns and IGF-I levels using data from a subsample of adults from the NHANES III study. We found similar dietary patterns to those in the previous chapter. The study's main findings were that the 'prudent' dietary pattern was associated with decreased IGF-I levels; conversely, the western dietary pattern was associated with increased IGF-I levels. The 'traditional' and the 'alcohol' dietary pattern did not modify IGF-I levels when controlling for confounders. These findings suggest that it is possible to regulate IGF-I levels through the consumption of a healthy diet.

The third study in Chapter 5 aimed to investigate the association between dietary patterns, total mortality, and cancer mortality. Dietary pattern adherence was assessed at

baseline, and participants were followed for almost 20 years on average. We found that adherence to the 'prudent' dietary pattern was associated with reducing the risk of total mortality, while adherence to the 'western' and the 'traditional' dietary pattern was associated with an increased risk of total mortality and mortality due to cancer. These findings suggest that efforts to increase consumption of a 'prudent' dietary pattern may reduce the risk of total mortality, and the benefit for cancer mortality remains possible.

Overall, adherence to a healthier diet such as the 'prudent' dietary pattern may decrease the risk of breast, prostate, and colorectal cancer. Furthermore, the prudent dietary pattern may lower total mortality and mortality due to cancer. Conversely, continuous consumption and adherence to dietary patterns rich in processed foods such as the ‘western’ diet may be associated with harmful long-term effects such as increased cancer risk and mortality. There is a need to continue studying the relationship between diet and cancer to improving cancer prevention guidelines and recommendations.

Implications for Future Research

The development of healthy eating patterns is of great importance for cancer management and cancer prevention. The entire work reveals that cancer survivors and the general population in the United States require dietary guidance. The dietary guidance should include information about increasing consumption of fresh fruits and vegetables, whole-grain intake, and reduction in processed food, and sugar beverage consumption in order to improve diet quality. More research is needed to determine what are the factors that prevent cancer survivors and the general population from adhering to and maintaining a healthy diet. Additionally, the possibility of brief screening for dietary

adherence during well-care visits to determine risks for low diet quality. Future studies should consider the use of mixed methods, including interviews to fully assess meal patterns in cancer survivors and the general population. The use of mixed methods may provide important information about eating behaviors, better-informing programs, and interventions targeting the improvement of diet quality for at-risk groups.

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