NUTRITION AND PHYSICAL ACTIVITY CANCER PREVENTION GUIDELINE ADHERENCE AND ASSOCIATION WITH CIRCULATING CONCENTRATIONS OF VITAMIN D AND PRECANCEROUS LESIONS

by

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DEDICATION

To my husband and sons

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ABSTRACT

Background: Many studies have reported that adherence to health promotion guidelines for diet, physical activity, and maintenance of healthy body weight may decrease cancer incidence and mortality, including site-specific cancers such as colorectal cancer. To date, there have been no studies investigating adherence to the American Cancer Society's (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines and the development and characteristics of premalignant lesions. Several individual lifestyle factors targeted by the ACS guidelines have also been associated with circulating concentrations of vitamin D metabolites. These associations suggest that adherence to the ACS guidelines may be related to improved vitamin D status. This dissertation sought to 1) synthesize the evidence from published prospective cohort studies regarding adherence to the ACS and World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) nutrition and physical activity cancer prevention guidelines and the risk of overall cancer incidence and/or cancer mortality and 2) to further explore the role of adhering to a healthy lifestyle pattern as outlined by the ACS guidelines on a) colorectal adenoma occurrence and b) circulating concentrations of vitamin D metabolites using secondary data analyses from completed large prevention trials.

Methods: A systematic review was performed to examine associations between adherence to established cancer prevention guidelines for diet and physical activity and overall cancer incidence and mortality. PubMed, Google Scholar, and Cochrane Reviews databases were searched following the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA). Cross-sectional

and prospective analyses of pooled participants were also conducted from the Wheat Bran Fiber (n=503) and Ursodeoxycholic Acid (n=854) trials. A cumulative adherence score was constructed using baseline data regarding body size, diet, physical activity, and alcohol consumption. Continuous vitamin D metabolite concentrations and clinically significant vitamin D categories were evaluated with adherence score category using multiple linear and logistic regression models, respectively. Baseline adenoma characteristics and new colorectal adenomas were evaluated by adherence score category using multivariate logistic regression models.

Results: Twelve studies met inclusion criteria for the systematic review. High versus low adherence to established nutrition and physical activity cancer prevention guidelines was consistently and significantly associated with decreases of 10-61% in overall cancer incidence and mortality. Consistent significant reductions were also shown for breast cancer incidence (19-60%), endometrial cancer incidence (23-60%), and colorectal cancer incidence in both men and women (27-52%). Findings for lung cancer incidence were equivocal and no significant relationships were found between adherence and ovarian or prostate cancer. In the pooled analyses, concentrations of circulating 25-hydroxycholecalciferol [25(OH)D] were statistically significantly higher among participants with high versus low adherence to guidelines (31.4 ±0.8 and 26.3 ±0.8 ng/ml, respectively; $p<0.001$). For $1,25(OH)_2D$ concentrations, high adherence was again significantly related to greater metabolite levels, with mean concentrations of 36.4 ±1.1 and 31.2 ±1.2 pg/mL for high- and low-adherers, respectively ($p<0.001$). Furthermore, the odds of attaining sufficient 25(OH)D status were 4.30 times higher for those most

adherent versus those least adherent (95% CI: 2.43-7.60). Significantly reduced odds of having three or more adenomas at baseline were shown for moderate (odds ratio [OR]=0.67, 95% confidence intervals [CI]: 0.46-0.99) and highly adherent (OR=0.50, 95% CI: 0.31-0.81) participants compared to those with low adherence (*p*-trend=0.005). Conversely, guideline adherence was not associated with the development of a new colorectal adenoma (moderate adherence OR=1.16, 95% CI: 0.85-1.59, high adherence OR=1.23, 95% CI: 0.85-1.79).

Conclusion: From the systematic review, greater adherence to cancer prevention guidelines for diet and physical activity was consistently associated with lower risks of overall cancer incidence and mortality, including for some site-specific cancers. In addition, adherence to the ACS guidelines was associated with higher concentrations of both of 25(OH)D and 1,25$(OH)_2$D. Following the ACS guidelines could potentially increase 25(OH)D levels as much as that observed by a supplement of 1000 IU/d in a population similar to ours, and therefore may be a viable strategy for increasing both 25(OH)D and 1,25$(OH)_2$D concentrations. Further, our findings suggest that following the ACS Nutrition and Physical Activity guidelines may lead to a lower odds of multiple adenomas when at least one adenoma is detected. Finally, these guidelines and recommendations are consistent with strategies for the prevention of major diseases, and if followed, will ultimately lead to healthier lives overall.

CHAPTER 1

INTRODUCTION

A. Explanation of the Problem

Despite decreasing incidence rates for colorectal cancer over the past two decades in the United States (US), the American Cancer Society (ACS) estimates that there will be 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer in 2016, with a combined 49,190 deaths from these malignancies (1). Increased screening rates for those aged 50 years and older have contributed to the reduction in colorectal cancer rates over the past 20 years (2) by detection and removal of adenomatous polyps, the precursors to colorectal cancer (3). However, only half of those recommended for colorectal screening are currently following the screening guidelines (4).

In addition to recommended screening, nutrition and physical activity guidelines for cancer prevention have been designed by the United States Department of Health and Human Services along with leading cancer organizations (5, 6). Large cohort studies (7-10) have found that following behavior-associated cancer prevention guidelines for factors such as body size, physical activity, diet and alcohol consumption are associated with a reduced risk of cancer incidence, cancer mortality, and all-cause mortality (5, 6). Further, it has been suggested that a healthy diet alone could help prevent some colorectal cancers (11), and one dietary component that has been studied extensively in relation to colorectal adenoma and cancer is vitamin D (12-15). In two separate meta-analyses, Yin et al. found statistically significant inverse associations with serum concentrations of the

vitamin D biomarker 25-hydroxycholecalciferol [25(OH)D] and both colorectal adenoma and colorectal cancer risk (15, 16). Factors that have been demonstrated to affect 25(OH)D concentrations include physical activity, body size, and dietary intake (17-19), which suggests that following cancer prevention guidelines may additionally affect circulating concentrations of 25(OH)D, though to our knowledge, this analysis has not yet been conducted.

B. Specific Aims and Hypotheses

The relationship between adherence to nutrition and physical activity cancer prevention guidelines and cancer outcomes, circulating concentrations of 25(OH)D, and colorectal adenoma recurrence will be investigated by conducting: 1) a systematic review of the literature, and 2) pooled, secondary analyses utilizing data and samples from two completed clinical trials of colorectal adenoma recurrence, the Wheat Bran Fiber (WBF) trial (20) and the Ursodeoxycholic Acid (UDCA) trial (21).

Specific Aim 1: Conduct a systematic review of the literature regarding adherence to nutrition and physical activity cancer prevention guidelines in prospective cohort studies to estimate the impact on cancer incidence and mortality.

Specific Aim 2: Examine the association between adherence to the ACS Nutrition and Physical Activity Cancer Prevention Guidelines and circulating concentrations of vitamin D metabolites.

Specific Aim 3: Examine the association between adherence to the ACS Nutrition and Physical Activity Cancer Prevention Guidelines and risk of new colorectal adenoma occurrence.

We hypothesize that participants in the published prospective cohort studies that had high adherence to nutrition and physical activity cancer prevention guidelines at baseline will have reduced overall cancer incidence and mortality versus those with low adherence to the guidelines at baseline. In addition, we hypothesize that participants in the WBF and UDCA trials with higher baseline adherence to the guidelines will have higher levels of baseline circulating concentrations of 25(OH)D and reduced odds for colorectal adenoma occurrence.

C. Role of Author in the Research

In order to fulfill the objective stated in Specific Aim 1, the author conducted a systematic review of adherence to nutrition and physical activity cancer prevention guidelines and cancer outcomes. The author wrote the protocol and registered it with PROSPERO International. She conducted the search, reviewed output from the search to identify eligible studies, extracted data from articles, examined studies for quality and bias, and synthesized the data. The author also wrote the manuscript entitled "Adherence to Nutrition and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review," (Appendix A) which was accepted for publication in *Cancer Epidemiology, Biomarkers and Prevention*. This study is discussed in detail in Chapter 2, Section A.

For Specific Aims 2 and 3, the author developed and performed secondary data analyses, pooling data from two clinical trials completed at the University of Arizona Cancer Center (UACC) with the outcome of colorectal adenoma recurrence. The first study was a phase III, randomized, double-blind clinical trial measuring the effects of a high wheat bran fiber (WBF) intake (13.5 g/day) versus low WBF intake (2.0 g/day) on colorectal adenoma recurrence. The second study was a phase III, randomized, double-blind, placebo-controlled trial examining the effect of Ursodeoxycholic Acid (UDCA) on colorectal adenoma recurrence. The UDCA and WBF trials were previously approved by the University of Arizona Human Subjects Protection Program. The author completed an Internal Data Use Agreement (Appendix B) with the Biostatistics Shared Resource to receive a limited data set for the secondary analysis. A Determination of Human Research form (Appendix C) was submitted to the Human Subjects Protection Program and this work was deemed not human subjects research on August 14, 2015 (Appendix D). The current work investigated the association of adherence to the American Cancer Society (ACS) nutrition and physical activity cancer prevention guidelines and 1) circulating concentrations of 25(OH)D and 2) risk of colorectal adenoma recurrence. These analyses are discussed in detail in Chapter 2, Sections B and C, respectively.

The author interpreted the findings for all three aims mentioned above and wrote the manuscripts. The second manuscript entitled "Adherence to cancer prevention guidelines as a strategy for improving circulating concentrations of vitamin D" (Appendix E) was submitted to *The Journal of Nutrition*. The third manuscript entitled "Odds of new

colorectal adenoma when adhering to nutrition and physical activity cancer prevention guidelines" (Appendix F) will be submitted for publication at a later date.

D. Background

1. Nutrition and Physical Activity Cancer Prevention Guidelines

Individuals can be predisposed to cancer by genetic inheritance, but most cancer risk is not related to genetic factors (22, 23). Two-thirds of cancer deaths can be attributed to modifiable behaviors, including exposure to tobacco products, diet, physical activity, and body size (5, 6, 22-24). To help guide individuals and communities toward healthier lifestyles, entities such as the ACS have formed advisory committees, which include national panels of experts in cancer research and prevention, epidemiology, public health and policy (25). These committees examine the most current, evidence-based research on diet, physical activity, and cancer risk from laboratory experiments, human studies, and comprehensive reviews and publishes cancer prevention recommendations for individuals and community action (6). The goal is for these to help Americans lead healthier lives by providing strategies to make smart choices about food and being physically active. Such evidence-based guidelines such as these can also influence policy, such as employer wellness programs, and provide direction for governmental programs. The most recent update from the ACS Nutrition and Physical Activity Guidelines Advisory Committee was in 2012 (Table 1) (6). These cancer prevention guidelines contain lifestyle recommendations with specific strategies to adhere to the recommendations of achieving and maintaining a healthy weight throughout life, adopting a physically active lifestyle,

consuming a healthy diet with an emphasis on plant foods, and limiting consumption of alcohol.

Table 1. ACS Recommendations and Strategies for Individual Choices for Adults (6)

Recommendation	Strategies
1. Achieve and maintain a healthy weight throughout life.	• Be as lean as possible throughout life without being underweight. • Avoid excess weight gain at all ages. For those who are currently overweight or obese, losing even a small amount of weight has health benefits and is a good place to start. • Engage in regular physical activity and limit consumption of high-calorie foods and beverages as key strategies for maintaining a healthy weight.
2. Adopt a physically active lifestyle.	• Adults should engage in at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week, with vigorous intensity activity occurring at least 3 days each week. • Limit sedentary behavior such as sitting, lying down, watching television, or other forms of screen-based entertainment. • Doing some physical activity above usual activities, no matter what one's level of activity, can have many health benefits.
3. Consume a healthy diet, with an emphasis on plant foods.	• Choose foods and beverages in amounts that help achieve and maintain a healthy weight. • Limit consumption of processed meat and red meat. • Eat at least 2.5 cups of vegetables and fruits each day. • Choose whole grains instead of refined grain products.
4. If you drink alcoholic beverages, limit consumption.	• Drink no more than 1 drink per day for women or 2 per day for men.

2. Overview of Vitamin D

Obesity, advancing age, limited sun exposure, poor diet, and higher skin pigmentation are all risk factors for vitamin D deficiency (26-32) which is common in the United States (33). Vitamin D deficiency has been linked to several major causes of death including cardiovascular disease, diabetes, and cancer (34). While the definition of clinical vitamin D deficiency has been updated in recent years (35, 36) it remains debated (34). Both the Institute of Medicine (IOM) and the Endocrine Society (ES) have issued vitamin D status guidelines (Table 2) (26, 37). Classically, the threshold for vitamin D deficiency has been defined as less than 10 ng/mL of circulating 25(OH)D, however the IOM suggests levels less than 12 ng/mL should be considered deficient as that is the level rickets in children and osteomalacia in adults present. The ES suggests deficiency should be defined as <20 ng/mL based upon suboptimal levels of parathyroid hormone (PTH), an important hormone in the bone remodeling process. It is also important to bear in mind that 25(OH)D is a biomarker for vitamin D exposure. It is unclear if it also serves as a biomarker of effect (health outcomes), or to what extent (26).

Table 2. Institute of Medicine (IOM) and Endocrine Society (ES) Vitamin D Status Guidelines

Serum 25(OH)D concentration (ng/mL)	Defining entity	Health indicators
<12 ng/mL	IOM	Rickets in children; osteomalacia in adults
12 to <20 ng/mL	IOM	Inadequate for bone and overall health
<20 ng/mL	ES	Deficiency; suboptimal PTH levels
21 to <30 ng/mL	ES	Insufficiency; suboptimal PTH levels and bone health
≥20 ng/mL	IOM	Adequate for bone and overall health
>50 ng/mL	IOM	Potential adverse effects
30-100 ng/mL	ES	Optimal PTH, bone mineral density, and overall health

Furthermore, the optimal level of vitamin D intake required to meet definitions of vitamin D sufficiency also remains unclear (38-40). Vitamin D supplementation with cholecalciferol (vitamin D_3) is the primary clinical strategy used to increase circulating concentrations of 25-hydroxycholecalciferol [25(OH)D], the metabolite most often measured to determine vitamin D status in adults (41). However, studies of vitamin D supplementation and health outcomes have produced equivocal results (42, 43). In addition, there are emerging data that genetic background may influence response to vitamin D supplementation (44, 45). Humans can also produce 25(OH)D via exposure to ultraviolet B (UVB) radiation (46); but this route is rarely promoted as excessive sunlight exposure can cause sunburns and increase the risk of skin cancer (34). With regard to diet, naturally-occurring vitamin D can be found in only a limited number of foods such as fatty fish, while fortified foods such as dairy products, ready-to-eat cereals, and orange

juice are more common (34). Therefore, the optimal strategy for improving vitamin D status remains equivocal.

ACS Guidelines and Vitamin D

Vitamin D may be obtained via endogenous synthesis from UVB exposure to the skin or by consumption of a limited number of foods in the diet or supplements (46). Vitamin D status is most often measured by the metabolite 25(OH)D in epidemiological studies because it accounts for both endogenous synthesis and dietary intake vitamin D intake (41). However, levels of 25(OH)D can also vary due to factors such as body size, physical activity levels, skin pigmentation, sex, genetic background, season and geography (47, 48). Compared to normal weight adults, obese adults have been found to have significantly lower levels of vitamin D possibly due to lower dietary intakes and lesser exposure of skin to sunlight (49, 50). Healthy weight adults with higher levels of physical activity are more likely to meet Dietary Reference Intakes (DRIs) for vitamin D and other micronutrients (51). Although to date no studies have examined the association between following the ACS guidelines for cancer prevention and 25(OH)D concentrations, this vitamin D biomarker has been linked to numerous cancers and health outcomes (17, 52-54). These outcomes include colorectal cancer, with potential mechanisms of action including anti-proliferative and pro-differentiation effects, induction of apoptosis, anti-inflammation, inhibition of invasion and metastasis, and suppression of angiogenesis (55). Several lifestyle factors targeted by the American Cancer Society (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines, including body size, diet, and physical activity are also associated with circulating

concentrations of vitamin D. Interestingly, the study by Kabat et al. reported a statistically significant association between adherence to the ACS guidelines and melanoma incidence, demonstrating that those with greater adherence to the guidelines had a higher risk of melanoma (9). These findings suggest that adherence to the ACS guidelines is possibly associated with increased sun exposure and as such may also improve vitamin D status. Improving vitamin D status through lifestyle modifications as opposed to supplementation allows for strategies that may avoid any potential toxicities such as renal calcifications. The incidence of renal calcifications were significantly increased among participants in the Women's Health Initiative (WHI) in response to supplementation with 400 IU vitamin D and 1200 mg calcium/d, and is likely to incur other health benefits as well. These findings strongly suggest that in addition to the documented benefits on cancer and cardiovascular disease prevention, adherence to the ACS guidelines may be an optimal strategy for improving vitamin D status.

3. Overview of Colorectal Cancer and Adenomas

Colorectal Cancer Epidemiology

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the third leading cancer killer in both men and women in the United States (1). One in 20 Americans can expect to be diagnosed with colon or rectal cancer in their lifetime (4). Despite decreasing incidence rates for colorectal cancer over the past two decades in the United States, the American Cancer Society (ACS) estimates that there will be 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer in 2016, with a combined 49,190 deaths from these malignancies (1). The burden of colorectal cancer

varies greatly within racial and ethnic groups with non-Hispanic black men (63.8%) and women (47.6%) experiencing the highest incidence and Asian/Pacific Islander men (40.8%) and women (31.0%) experiencing the lowest incidence (4). The data analyzed in this dissertation consisted mainly of non-Hispanic whites, which according to the Colorectal Cancer Facts & Figures 2014-2016, experienced incidence rates of 50.9% and 38.6% for men and women, respectively (4). Overall, men experience incidence and mortality rates 30% to 40% greater than incidence and mortality rates for women (4). Increasing age is also a risk factor for colorectal cancer incidence and mortality. People aged 50 years and older comprise 90% of new cases and 93% of colorectal cancer deaths (4). Other non-modifiable risk factors include a personal or family history of colorectal cancer or adenomas, inherited Lynch syndrome, a personal history of chronic inflammatory bowel disease, and type 2 diabetes (1, 4).

Screening for early disease and modification of risk factors can prevent colorectal cancer. Increased screening rates for those aged 50 years and older have contributed to the reduction in colorectal cancer rates over the past 20 years (2) by detection and removal of adenomatous polyps, the precursors to colorectal cancer (3). The United States Preventive Services Task Force (USPSTF) recommends adults aged 50 to 75 years get screened for colorectal cancer every one to ten years depending on screening test. Stool-based (every 1-3 years) and direct visualization (every 5-10 years) tests are available as tools to detect adenomas and early-stage cancer (56). Fecal occult blood tests, barium enema, sigmoidoscopy, and colonoscopy are available screening tools to detect adenomas for removal to prevent progression to cancer (4). However, currently only half of those

individuals recommended for colorectal screening are following the guidelines (4). Colorectal carcinoma is a slowly progressing tumor taking 10 to 15 years to develop (57). Colorectal cancer development is a multistep process that begins with the accumulation of early genetic alterations and subsequent formation of abnormal cells that cluster to generate an adenomatous polyp that is a benign lesion (57, 58). Polyps are detected upon screening and can be removed to prevent progression to CRC. To prevent CRC in those unable or unwilling to undergo the current colorectal screening procedures, further strategies for preventing colorectal neoplasia are essential.

Colorectal Adenoma Epidemiology

Approximately 96% of colorectal cancers are adenocarcinomas, which develop in glandular cells that provide lubrication via mucus production in the colorectum (59). Well-known precursors in most cases of colorectal cancer, adenomas are benign lesions that will present in an estimated 20 to 53% of the US population over the age of 50 (60-62). Fewer than 10% of adenomas will eventually progress to invasive cancer (63). However, while adenomas typically cause few symptoms, they may silently progress to cancer unless removed (64). Of those patients that undergo colonoscopy, it is estimated that at least a quarter of men and 15% of women are found to have at least one adenoma detected and removed via endoscopic polypectomy (63). For those patients that have had an adenoma removed, regular screening is recommended as their risk of developing another lesion is increased two- to four-fold (63). More frequent screening is recommended for those patients that have adenomas characterized as advanced for villous features, high-grade dysplasia, large size (>1cm), or multiplicity (63).

Colorectal carcinogenesis

Carcinogenesis, the process in which normal cells transform into cancer cells, consists of three basic stages: initiation, promotion, and progression (65). This process for CRC has been described by Fearon and Volgelstein (58). They detail the multistage process in the following: accumulation of mutations in oncogenes and tumor suppressor genes; development of benign adenomas that slowly advance by increasing in size, dysplasia, and acquiring villous morphology; colorectal carcinoma and metastasis (58, 66). Thus, colorectal adenomas present as an ideal intervention point for the prevention of CRC.

ACS Guidelines, Colorectal Adenomas, and Colorectal Cancer

There are several innate factors that may increase the risk of colorectal cancer that cannot be changed (4), but as reviewed by Giovannucci, there are also several modifiable risk factors for CRC such as physical inactivity, overweight and obesity from overconsumption of energy, high consumption of red and/or processed meat, deficiency in some micronutrients or phytochemicals, moderate to heavy alcohol consumption, and smoking early in life (67) that can be altered to reduce the risk for CRC. Colorectal cancer incidence and mortality have been declining in part due to screening and subsequent removal of precancerous polyps (68) but even greater potential for prevention may lie in the modification of behavior-associated risk factors like diet and exercise.

E. Summary of the Introduction

Colorectal cancer, as the third most diagnosed and third leading killer for cancer, is an important public health priority due to the potential for prevention through adenoma

detection and removal and modification of several risk factors including diet and physical activity. Alternate approaches to CRC prevention need to be undertaken as screening alone reaches only half of those at risk. Specific Aim 1 will carefully review the literature for studies examining adherence to national cancer prevention guidelines and cancer outcomes. The findings from the systematic review will help summarize the effects of adherence to nutrition and physical activity cancer prevention guidelines on all-cancer incidence, cancer mortality, and some site-specific cancers such as colorectal cancer. Specific Aims 2 and 3 will evaluate adherence to ACS cancer prevention guidelines as an alternative approach to screening by considering precancerous indicators. Specific Aim 2 will evaluate adherence and circulating concentrations of 25(OH)D, a much-studied nutrient that has limited, suggestive evidence for chemopreventive effects in the progression of colorectal cancer. This work seeks to demonstrate that high adherence to ACS guidelines will be directly associated with increased vitamin D levels. Specific Aim 3 explores whether adherence to ACS guidelines has an inverse association with new adenoma occurrence, the precursor lesion to CRC. The overall goal of this work is to demonstrate increased circulating concentrations of vitamin D as well as alternate avenues for colorectal neoplasia prevention through adherence to ACS nutrition and physical activity cancer prevention guidelines.

CHAPTER 2

PRESENT STUDY

A. Introduction

An estimated 1,685,210 new cancer diagnoses and 595,690 cancer deaths are expected in the United States (U.S.) in 2016 (1). Behaviors such as poor diet choices, physical inactivity, excess alcohol consumption and unhealthy body weight could account for more than 20% of cancer cases and therefore be prevented with lifestyle modifications (1). Two-thirds of U.S. cancer deaths can also be attributed to these modifiable behaviors when including exposure to tobacco products (6, 22-24, 69).

To help guide individuals and communities toward healthier lifestyles, nutrition and physical activity guidelines for cancer prevention have been designed by the U.S. Department of Health and Human Services along with leading health organizations such as the American Cancer Society (ACS) (70) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (71). These cancer prevention and health promotion guidelines focus on specific lifestyle recommendations to 1) achieve and maintain a healthy weight throughout life; 2) adopt a physically active lifestyle; 3) consume a healthy diet with an emphasis on plant-based foods; and 4) limit alcohol consumption (6).

Often epidemiological studies attempt to parse out specific, individual risk factors; however, examination of an overall risk pattern also provides key information when considering health-related behaviors which often co-occur (72). For example, a general

risk profile pattern can be ascertained by measuring adherence to cancer prevention guidelines. A score can be constructed based on multiple lifestyle aspects including body mass index (BMI), physical activity, alcohol intake, and various aspects of a healthy diet such as intake of fruit and vegetables, whole grains, and red/processed meat. Utilization of such an adherence score would allow for investigation of overall behavior patterns.

The ACS and WCRF/AICR examine the most current, evidence-based research on diet, physical activity, and cancer risk from laboratory experiments, human studies, and comprehensive reviews, and then publish cancer prevention recommendations for individuals and community action. The most recent update from the ACS Nutrition and Physical Activity Guidelines Advisory Committee was published in 2012 (6). The ACS guidelines contain specific strategies to adhere to the aforementioned recommendations. Similarly, WCRF/AICR guidelines focus on improving modifiable risk profiles, with the most recently-published recommendations for healthy lifestyles in 2007 (69). These recommendations also proffer guidelines for remaining as lean as possible within the normal range of body weight, being physically active as a part of everyday life, eating mostly plant foods, limiting intake of red meat and avoiding processed meat, limiting consumption of alcohol, limiting consumption of energy dense foods, avoiding sugary drinks, and limiting salt consumption.

B. Specific Aim 1: Systematic Review

The aim of the systematic review was to synthesize the evidence from prospective cohort studies regarding the relationship between adherence to the ACS and WCRF/AICR

nutrition and physical activity cancer prevention guidelines and the risk of overall cancer incidence and/or cancer mortality.

1. Methods

Search Strategy and Identification of Studies

Two independent reviewers executed the following comprehensive search strategy following the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA) (73). Key search terms were used to maximize the identification of prospective cohort studies that examined associations between adherence to nutrition and physical activity cancer prevention guidelines and cancer incidence and mortality. Databases were searched in March 2016, using the following search parameters: PubMed key terms “cancer prevention guidelines”, “nutrition,” physical activity,” “adherence,” “cancer incidence and/or cancer mortality”; Google Scholar search “cancer prevention guideline adherence AND nutrition AND physical activity AND cancer incidence” with the exact phrase “cancer prevention guidelines” and at least one of the words “incidence mortality”; and Cochrane reviews strategy “adherence to nutrition physical activity cancer prevention guidelines”. Filters included human studies in English only, articles that had full text available, and papers published within the past ten years. All eligible full-text articles selected for inclusion were examined for citations of relevant studies.

Titles and abstracts were screened by two reviewers; data were extracted by the author and double-checked by a second reviewer using a pre-designed data extraction form. Data extracted from each study included the author’s first and last names, title,

publication year, study population (cohort and sample size), follow-up period, guidelines utilized and how adherence score was generated, covariates, and study outcomes including relative risks (RR) or hazard ratios (HR) and confidence intervals (CI). The Critical Appraisal Skills Programme's *Making sense of evidence* (74) was the predetermined tool used to assess the risk of bias. The tool was used to assess recruitment procedures, measurement of exposure, confounding variables, study outcomes, and generalizability. A third reviewer resolved any disagreement. The protocol was registered with PROSPERO International Prospective Register of systematic reviews (Ref: CRD42015026614).

Inclusion and exclusion criteria

Only prospective cohort studies were eligible for inclusion as the focus was to ascertain cancer incidence and cancer mortality. Minimally, studies must have collected data for physical activity and diet, generated an adherence score based on either ACS or WCRF/AICR cancer prevention guidelines (5, 6), and reported cancer outcomes of incidence and/or mortality in order to be deemed eligible for this review. Overall cancer incidence and cancer mortality were the primary outcomes of interest. However, site-specific cancer risks were also considered when data were available from at least two studies meeting the eligibility criteria. Commentaries and summary documents were excluded unless they presented additional data.

2. Results

A total of 2,033 potentially relevant studies were reviewed; after removal of duplicates and exclusion on the basis of title or abstract, 25 full papers on nutrition and physical

activity cancer prevention guideline adherence were retained for in-depth consideration. The selection process for the articles is shown in Figure 1. We identified 12 manuscripts that met the *a priori* criteria for inclusion (Table 3). These studies represented analyses of data from 10 cohorts including the Cancer Prevention Study-II (CPS-II) nutrition cohort (75), the Women's Health Initiative (WHI) cohort (76), the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort (77), the Framingham Offspring (FOS) cohort (78), the Vitamins and Lifestyle (VITAL) Study cohort (79), the Canadian National Breast Screening Study (NBSS) (80), the Swedish Mammography Cohort (SMC) (81), the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (82, 83), the Southern Community Cohort Study (SCCS) (84), and the Iowa Women's Health Study (IWHS) cohort (85). Adherence scores for these studies were constructed utilizing recommendations from the American Cancer Society (ACS) (Table 4) (70) or the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (Table 5) (71).

Figure 1. Article selection process. The PRISMA diagram details the search and selection of manuscripts for the review.

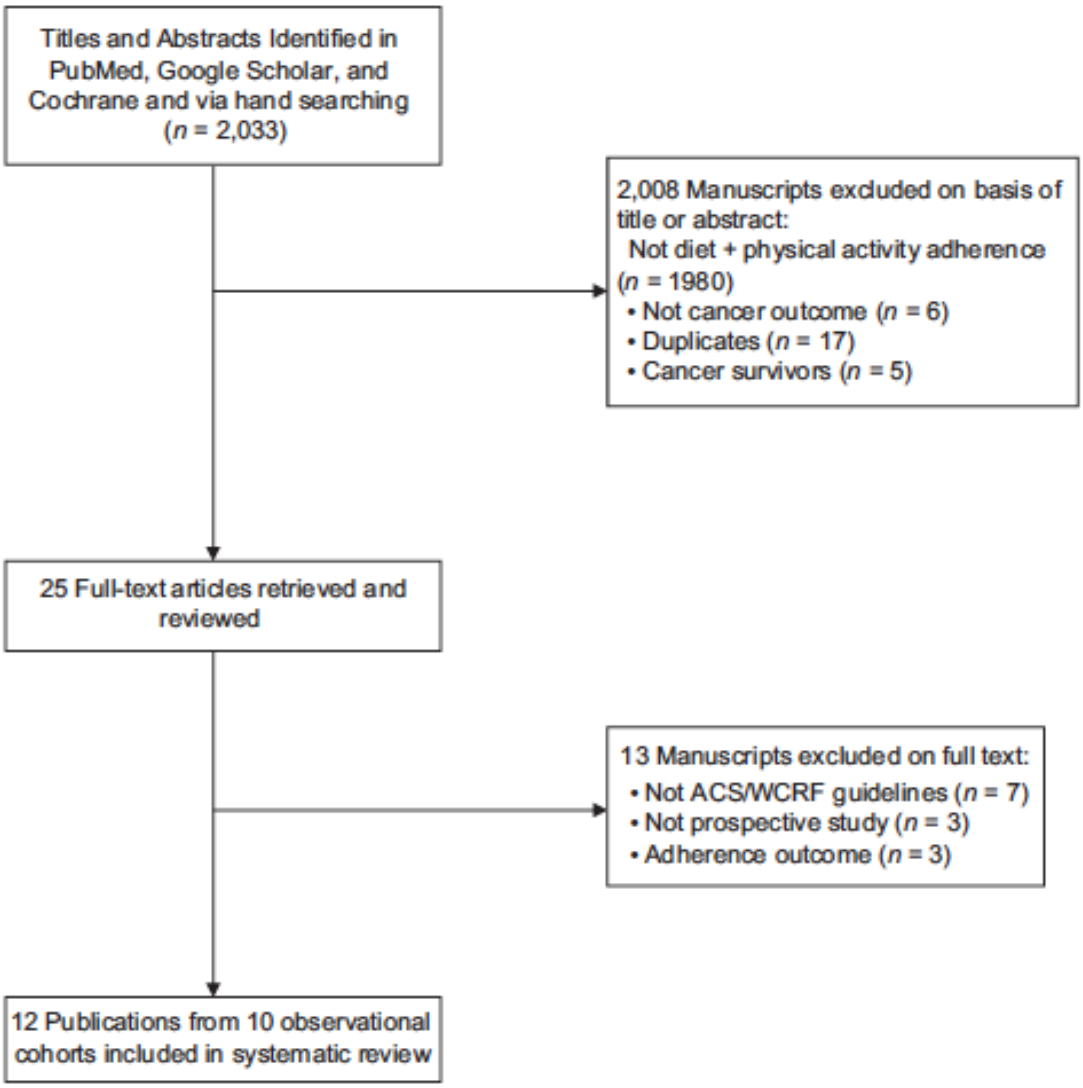

Table 3. Characteristics and findings of included prospective studies.

	Author, year	Study name, data collection years, sample size, years follow-up, guidelines	Relevant Outcome(s)	Key Findings
1	McCullough, 2011	CPS-II Nutrition Cohort, 1992-1993, n=111,966, 14 years, ACS[i]-8 point score	All cancer mortality	Men: RR[ii]=0.70, 95% CI[iii]: 0.61-0.80 Women: RR=0.76, 95% CI: 0.65-0.89
2	Thomson, 2014	Women's Health Initiative, 1993-1998, n=65,838, 12.6 years, ACS-8 point score	All cancer incidence, and mortality, site-specific cancer incidence	Cancer incidence: HR[iv]=0.83, 95% CI: 0.75-0.92 Cancer mortality: HR=0.80, 95% CI: 0.71-0.90 Colorectal: HR=0.48, 95% CI: 0.32-0.73 Breast: HR=0.78, 95% CI: 0.67-0.92 Endometrial: HR=0.73, 95% CI: 0.49-1.09 Ovarian: HR=1.13, 95% CI: 0.68-1.87 Lung: HR=1.14, 95% CI: 0.81-1.60
3	Kabat, 2015	NIH-AARP Diet and Health Study, 1995-1996, n=476,396, 10.5-12.6 years, ACS-11 point score	All cancer incidence, site-specific cancer incidence, all cancer mortality	All cancer incidence: Men HR=0.90, 95% CI: 0.87-0.93 Women HR=0.81, 95% CI: 0.77-0.84 All cancer mortality: Men HR=0.75, 95% CI: 0.70-0.80 Women HR=0.76, 95% CI: 0.70-0.83 Colon: Men HR=0.52, 95% CI: 0.47-0.59 Women HR=0.65, 95% CI: 0.54-0.78 Rectal: Men HR=0.60, 95% CI: 0.51-0.72 Women HR=0.64, 95% CI: 0.49-0.83 Lung: Men HR=0.85, 95% CI: 0.78-0.93 Women HR=0.94, 95% CI: 0.84-1.05

				Breast: HR=0.81, 95% CI: 0.76-0.87 Endometrial: HR=0.40, 95% CI: 0.34-0.46 Ovarian: HR=0.95, 95% CI: 0.73-1.23
5	Hastert, 2013	VITAL cohort, 2000-2002, n=30,797 post-menopausal women, 7.7 years, WCRF/AICR Met/didn't meet	Breast cancer incidence	HR=0.40, 95% CI 0.25-0.65
4	Hastert, 2014	VITAL cohort, 2000-2002, n=57,841, 7.7 years, WCRF/AICR met/didn't meet	All cancer mortality	HR=0.39, 95% CI 0.24-0.62)
6	Makarem, 2015	FOS cohort, 1991, n=2,983, 11.5 years, WCRF/AICR 7 point score	Incidence of obesity-related cancers and site-specific: breast, prostate, and colon	Obesity-related: HR=0.94, CI 0.86-1.02 Breast: HR=0.87, 95% CI: 0.74-1.03 Prostate: HR=1.08, 95% CI: 0.92-1.27 Colorectal: HR=0.87, 95% CI: 0.68-1.12
7	Harris, 2016	SMC, 1987-1990, n=31,514, 15 years, WCRF/AICR 7 point score	Breast cancer incidence	HR=0.49, 95% CI: 0.35-0.70
8	Catsburg, 2014	Canadian NBSS, 1980-1985, n=47,130 WCRF/AICR and n=46,298 ACS, 16.6 years	Breast cancer incidence	ACS: HR=0.69, 95% CI: 0.49-0.97 WCRF/AICR: HR= 0.69, 95% CI: 0.47-1.00
9	Vergnauad, 2013	EPIC Study, 1992-2000, n=378,864, 12.8 years, WCRF/AICR 6 point score for men, 7 point score for women	All cancer mortality	Total: HR=0.80, 95% CI: 0.69-0.93 Men: HR=0.86, 95% CI: 0.69-1.07 Women: HR=0.76, 95% CI: 0.62-0.93
10	Romaguera, 2012	EPIC Study, 1992-2000, n=386,355, 11.0 years, WCRF/AICR 6 point score for men, 7 point score for women	All cancer incidence, site-specific cancer incidence	All cancer incidence: Men HR=0.84, 95% CI: 0.72-0.99 Women HR=0.81, 95% CI: 0.72-0.91 Colorectal: HR=0.73, 95% CI: 0.65-0.81 Lung: HR=0.86, 95% CI: 0.74-1.00 Breast: HR= 0.84, 95% CI: 0.78-0.90 Endometrial: HR= 0.77, 95% CI: 0.62-0.94

				Ovarian: HR= 0.99, 95% CI: 0.79-1.25 Prostate: HR=1.02, 95% CI: 0.91-1.14
11	Nomura, 2016	IWHS, 1986, n=36,626 post-menopausal, >23 years, WCRF/AICR 8 point score	Breast cancer incidence	HR=0.76, 95% CI: 0.67-0.87
12	Warren Andersen, 2016	SCCS, 2002-2009, n=61,098 low-income racially diverse adults, 6 years, ACS 4 point score	All cancer incidence	HR=0.96, 95% CI: 0.65-1.42[v] HR=0.55, 95% CI: 0.31-0.99[vi]

[1] American Cancer Society
[ii] Relative Risk
[iii] Confidence Interval
[iv] Hazard Ratio
[v] Total analytic population. P-trend 0.09
[vi] Participants without chronic disease at baseline. P-trend 0.003

Table 4. ACS recommendations and adherence score breakdown of selected studies.

American Cancer Society						
Recommendation	**McCullough, 2011 Thomson, 2014[i]**		**Kabat, 2015**		**Catsburg, 2014**	**Warren Andersen, 2016**
"Maintain a healthy weight throughout life"	0: Obese at both time points or obese at 1 and overweight at the other 1: All others 2: BMI[ii] 18-<25 at both times		0: >35.0 1: 30-34.9 2: 25-29.9 3: 18.5-24.9		18.5 ≤ BMI ≤25	18.5 ≤ BMI ≤25
"Adopt a physically active lifestyle"	0: <8.75 MET[iii] h/wk 1: 8.75-17.5 MET h/wk 2: >17.5 MET h/wk		0: ≤ 3x/mo 1: 1-2x/wk 2: 3-4x/wk 3: ≥5x/wk		≥ 150 min/week	≥ 150 min/wk of moderate, ≥ 75 min/wk of vigorous or ≥ 150 min/wk of moderate + vigorous
"Eat 5 or more servings of a variety of vegetables and fruits each day"	1: ≥5 servings/d fruits +veg +1 or 2 "variety" points for 2nd or 3rd tertile of unique fruits or veg consumed/month		Quartiles		>400g vegetables and fruit per day	≥2.5 cups vegetables + fruits/d
"Choose whole grains instead of refined grains"	Quartiles of the ratio of whole grains to total grains		Quartiles of the ratio of whole grains to total grains		Ratio of whole: refined grains >1	Highest quartile of the ratio of whole grains to total grains
"Limit consumption of processed and red meats"	Quartiles of red + processed meat intake (servings/wk)		Quartiles of red + processed meats		<500g red and processed meat per week	Lowest quartile of red + processed meats
"If you drink, limit consumption to 1 drink/day	Women: 0: >1	Men: 0: >2	Women: 0: ≥2	Men: 0: ≥3	≤1 standard drink/d	Women ≤1 drink/d Men ≤2 drinks/d

for women or 2 drink/day for men"	1: >0-≤1 2: Non	1: >0-≤2 2: Non	1: Non 2: 1	1: Non 2: 1-2		

[1] Thomson evaluated BMI as <18.5 excluded 0: BMI >=30 kg/m^2 at age 18 or at baseline, 1: BMI 25-<30 at age 18 or baseline, 2: BMI <25 kg/m^2 at age 18 and baseline; diet score plus 1 or 2 "quality" points for being in the 2nd or 3rd tertile of total carotenoids; alcohol score 2 points for nondrinker at baseline

[ii] Body mass index, kg/m^2

[iii] Metabolic Equivalent of Task

Table 5. WCRF/AICR recommendations and adherence score breakdown of selected studies.

World Cancer Research Fund/American Institute for Cancer Research						
Recommendation	**Hastert, 2013 & 2014**	**Catsburg, 2014**	**Makarem, 2015**	**Harris, 2016**	**Vergnaud, 2013 Romaguera, 2012**	**Nomura, 2016**
"Be as lean as possible within the normal range of body weight"	18.5 ≤ BMI[i]<25	18.5 ≤ BMI ≤25	0: <18.5 BMI >30.0 0.5: 25-29.9 1: 18.5-24.9	18.5 ≤ BMI <25	0: <18.5 BMI >30.0 0.5: 25-29.9 1: 18.5-24.9	0: <18.5 BMI ≥30.0 0.5: 25-<30 1: 18.5-<25
"Be physically active as part of everyday life"	≥30 min/d of moderate/fast walking and/or moderate/strenuous activity ≥5 days/wk in ≥7 of the past 10 yrs	≥210 min/wk	0: <30 PAI[ii] 0.5: 30-33 1: >33	≥30 min/d[iii]	0: <15 min/d[iv] 0.5: 15-30 min/d 1: Manual/heavy manual job, or >2h/wk vigorous, or >30 min/d	0: all other 0.5: 2-4x/wk moderate or 1x/wk vigorous 1: ≥2x/wk vigorous or ≥5x/wk moderate
"Eat mostly foods of plant origin"	≥5 servings of fruits + veg and ≥1 serving whole grains and/or legumes/d	>400g veg +fruit plus ≥25g whole grains + legumes/d	<u>Fruit + Veg</u> (servings/d) 0: <2.5 0.5: 2.5-<5 1: ≥5 <u>Refined Grains</u> (g/d) Tertiles <u>Vegetables</u>	>400g veg + fruit plus ≥25g whole grains and legumes/d	<u>Fruit + Veg (g/d)</u> 0: <200 0.5: 200 to <400 1: >400 <u>Dietary Fiber (g/d)</u> 0: <12.5 0.5: 12.5 to <25	<u>Fruit + Veg</u> (servings/d) 0: <3 0.5: 3-<5 1: ≥5 <u>Dietary Fiber (g/d)</u> 0: <12.5 0.5: 12.5 to <25 1: ≥25

			(g/week) 0: S[v]>503; NS[vi]<2,471.4 or S<503;NS <2,471.4 0.5: S>503; NS>2,471.4 1: S<503; NS>2,471.4		1: ≥25	
"Limit intake of red meat and avoid processed meat"	<18 oz red and/or processed meat per week	<500g red and <25g processed meat per week	0: ≥500 g/wk or ≥50 g/d 0.5: <500 g/wk & 3 to <50 g/d 1: <500 g/wk & <3 g/d	<500g red and <25g processed meat/wk	0: ≥500 g/wk or ≥50 g/d 0.5: <500 g/wk & 3 to <50 g/d 1: <500 g/wk & <3 g/d	0: ≥500 g/wk RP[vii] or ≥50 g/wk P[viii] 0.5: <500 g/wk RP & 3 to <50 g/wk P 1: <500 g/wk RP & <3 g/wk P
"Limit alcoholic drinks"	≤1 drink/d for women; ≤2 drink/d for men	≤1 standard drink per day	Women g/day: 0: >21 0.5: 14-24 1: ≤14 Men g/day: 0: >42 0.5: 28-42 1: ≤28	<10g alcohol/d	Women g/d: 0: >20 0.5: >10-20 1: ≤10 Men g/d: 0: >30 0.5: >20-30 1: ≤20	0: >20 g/d 0.5: >10-20 1: ≤10
"Limit consumption of ED[ix] foods; avoid sugary drinks"	ED of diet <125 kcal/100g or <1 sugary drink/wk	ED of food <125kcal/100g. No soda or drinks with added sugar	<u>ED Foods</u> (servings/wk) Tertiles	<14 servings/wk of ED foods and <2 glasses/d of soda/juice	0: ED: >175[x] 0.5:>125 to <175 1: ≤125 0: >250 g/d sugary drink 0.5: ≤250 g/d	0: ≥250 g/d sugary drink 0.5: <250 g/d 1: 0 g/d

					1: 0 g/d	
"Limit consumption of salt"	Not included	<2.4g sodium/d	Salty Foods Tertiles Sodium Intake g/d 0: >3.6 0.5: 2.4-3.6 1: <2.4	Not included	Not included	0: >2400 mg/d 0.5: >1500-2400 mg/d 1: ≤1500 mg/d
"Dietary supplements not recommended for cancer prevention"	Not included	Not included	Not included	Did not report consuming on a regular basis	Not included	Not included
"Mothers to breastfeed"	Not included	Not included	Not included	Not included	0: No BF[xi] 0.5: >0 to <6 months 1: ≥6 months	Not included

[1] Body Mass Index kg/m^2
[ii] Physical Activity Index
[iii] Walking/cycling + leisure time exercise
[iv] Cycling or sports
[v] Starchy vegetable
[vi] Non-starchy vegetable
[vii] Red and processed meat
[viii] Processed meat
[ix] Energy dense/density
[x] kcal/100g/day
[xi] Breastfeeding

Overall Cancer

Seven studies evaluated the association between guideline adherence for diet, physical activity, healthy body weight, and alcohol consumption and overall cancer incidence and/or mortality. After adjustment for covariates, there were statistically significant effects of guideline adherence on cancer risk. Participants with high adherence to the ACS guidelines were less likely to develop or die from any cancer compared to those participants that had low adherence to the ACS guidelines (7, 8, 86, 87). Likewise, meeting or highly adhering to WCRF/AICR recommendations versus low or no adherence to the recommendations also demonstrated statistically significant risk reduction in overall cancer incidence (88) and mortality (89, 90).

The study by McCullough et al. (8) developed an original scoring system to reflect adherence to the ACS guidelines with the goal of evaluating the association between following the recommended guidelines and risk of death from cancer, cardiovascular disease, and all causes. The authors evaluated 111,966 non-smoking men and women in the CPS-II Nutrition cohort, which is a subset of the larger CPS-II (75). Participants were primarily healthy, Caucasian adults aged 50-74 years from 21 states in the U.S. (75). The scoring system weighted each recommendation equally from 0 to 2 possible points, with 0 points representing not meeting the recommendation at all, 1 point for partially meeting the recommendation, and 2 points for fully meeting the recommendation. The overall adherence scores in the study population ranged from 0 for those participants who did not follow any of the guidelines to 8 for those participants that were fully adherent to all four lifestyle factor recommendations (Table 4). High

adherence was a score of 7-8 points and low adherence was a score of 0-2 points. McCullough et al. reported a 24% reduction (RR=0.76, 95% CI: 0.65-0.89) and a 30% reduction (RR=0.70, 95% CI: 0.61-0.80) in cancer mortality over 14 years of follow up for men and women, respectively, with high adherence compared to those with low adherence to the ACS guidelines. (8).

Thomson et al. (7) used similar methodology to examine the impact of adherence to the ACS guidelines in 65,838 postmenopausal women aged 50-79 years from the Women's Health Initiative Observational Study (WHI-OS) (76). The WHI-OS was a prospective study of health outcomes in postmenopausal women that were enrolled in 40 U.S. clinical centers from 1993 to 1998 (91). Overall baseline adherence components were similar to those from the CPS-II cohort, differing only slightly. The recommendation to "maintain a healthy weight throughout life" was assessed from reported weight at 18 years and measured at study baseline. The score for the recommendation to "consume a healthy diet with an emphasis on plant sources" included an extra point or two for diet quality determined by being in the second or third tertile of total carotenoids, respectively (Table 4). Similar to the previous study, the overall adherence scores ranged from 0 for those participants not adherent to any of the guidelines to 8 for fully adherent participants and were collapsed into categories for comparison. The overall cancer incidence or mortality analyses included a comparison of highly adherent participants with a score of 7 or 8 compared to low adherence participants scoring less than 2 points. Cancer-specific mortality analyses further collapsed categories of the score (0-3, 4-5, 6-8) due to smaller numbers of events. In women that had high adherence to the ACS guidelines, Thomson et

al. demonstrated a 17% reduction in cancer incidence over the 12.6 years of follow-up (HR=0.83, 95% CI: 0.75-0.92) and 20% reduction in cancer-specific mortality (HR=0.80, 95% CI: 0.71-0.90) compared to women with low adherence to the ACS guidelines (7).

In the third study utilizing the ACS guidelines, nearly half a million men and women aged 50-71 in the NIH-AARP Diet and Health Study (n=476,396) were included from 6 states and 2 metropolitan areas with existing population-based cancer registries from 1995-1996 (77). Adherence scores were modified somewhat from prior ACS-based studies by using only one baseline measurement for BMI, categorizing physical activity by times per week instead of metabolic equivalents of task (MET) hours per week, not including a variety or quality of diet measure, and giving moderate drinkers (1-2 drinks per day for men and 1 drink per day for women) the most adherent score of 2 points for the alcohol consumption recommendation (Table 4). Participants were categorized as most adherent if they scored 8-11 points and least adherent if they scored 0-3 points overall. As shown in Table 2, Kabat et al. reported a statistically significant decrease in cancer incidence over the 10.5 years of follow-up for both highly adherent men (HR=0.90, 95% CI: 0.87-0.93) and women (HR=0.81, 95% CI: 0.77-0.84). A statistically significant reduction in cancer mortality was also reported during the 12.6 years of follow-up for both highly adherent men (HR=0.75, 95% CI: 0.70-0.80) and women (HR=0.76, 95% CI: 0.70-0.83) (87).

Warren Andersen et al. (86) performed the most recent evaluation between adherence to the ACS guidelines and overall cancer incidence utilizing the Southern Community

Cohort Study (SCCS) (n=61,098) with a focus on representing low-income Whites and African Americans in the southeastern United States. Adherence scores ranged from 0 to 4 points with 1 point assigned for each recommendation met upon study entry (Table 4). A comparison of the most adherent participants (score=4) versus non-adherent participants (score=0) demonstrated a nonsignificant 4% reduction in overall cancer incidence (HR=0.96, 95% CI: 0.65-1.42) in the SCCS participants. However, when evaluating only participants free of chronic disease at baseline, a statistically significant 45% reduction in cancer risk (HR=0.55, 95% CI: 0.31-0.99) was found (86).

Romaguera et al. (88) assessed the association between adherence to WCRF/AICR guidelines and overall cancer incidence as well as specific types of cancer incidence in the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort study (n=386,355) (82, 83). The constructed adherence score (Table 5) operationalized the WCRF/AICR recommendations of body fatness, physical activity, intake of food and drinks that promote weight gain, intake of plant foods, intake of animal foods, intake of alcoholic drinks, and breastfeeding. One point was assigned for each recommendation that was fully met, a half point was assigned for partially meeting the recommendation, and all others received zero points for not meeting the recommendation. For women, high adherence to the score was denoted if the score summed to 6-7 points compared to low adherence scoring 0-3 points. For men, high adherence was considered a score of 5-6 compared to low adherence scoring 0-2 points. Romaguera et al. reported a statistically significant decrease in overall cancer incidence over the 11.0 years of follow-up for both highly adherent men (HR=0.84, 95% CI: 0.72-0.99) and women (HR=0.81, 95% CI:

0.72-0.91). In addition, a 1-point increment of the adherence score was associated with a statistically significant 5% reduction in overall cancer incidence (HR=0.95, 95% CI: 0.93-0.97) (88).

Similarly, Vergnaud et al. (90) investigated whether adherence to WCRF/AICR recommendations was associated with risk of death in the EPIC cohort study (n=378,864) after a median follow-up time of 12.8 years (82, 83). The adherence score (Table 5) was modeled after the previous work of Romaguera et al. utilizing the same recommendations and collapsing the score into the same sex-specific high and low adherence categories. A significant reduction in cancer-specific mortality was found among women who were most adherent to WCRF/AICR recommendations (HR=0.76, 95% CI: 0.62-0.93). Statistical significance was not reached in the association for men (HR=0.86, 95% CI: 0.69-1.07); however, an 8-9% reduction in risk per 1-point increase of WCRF/AICR adherence score was statistically significant for both men (HR=0.92, 95% CI: 0.89-0.95) and women (HR=0.91, 95% CI: 0.88-0.94) (90).

Finally, Hastert et al. (2014) also operationalized the WCRF/AICR guidelines (Table 5) to examine the association between meeting guidelines on nutrition and physical activity and cancer mortality in a cohort of men and women (n=57,841) aged 50 to 76 years from the VITAL study (79). Adherence to the WCRF/ AICR guidelines was classified as met or did not meet (DNM) for each of the 6 included recommendations (Table 3). Recommendations to limit salt preserved foods and supplements were not considered as the former was not considered common in the U.S. food supply and the latter because the

guidelines did not recommend for or against supplementation for the prevention of cancer. Adherence was measured as follows: BMI by self-reported height and weight, physical activity by minutes per day and intensity, energy density, plant foods, red meat, and alcohol based on responses to the food frequency questionnaire (FFQ). Meeting at least five recommendations compared to meeting none demonstrated a 61% reduction in cancer-specific mortality over 7.7 years of follow-up (HR=0.39, 95% CI: 0.24-0.62) (89).

Breast Cancer

In addition to overall cancer incidence, eight studies reported results for female breast cancer incidence as an outcome (7, 87, 92-95). Consistent reductions in breast cancer incidence were demonstrated in the WHI, NIH-AARP, and EPIC cohorts for high adherence to nutrition and physical activity cancer prevention guidelines versus low adherence, with HRs (95% CIs) of HR=0.78, 95% CI: 0.67-0.92 (7), HR=0.81, 95% CI: 0.76-0.87 (87), and HR=0.84, 95% CI: 0.78-0.90, respectively (88). Hastert et al. also investigated breast cancer incidence as an outcome using the WCRF/AICR guidelines in a cohort of postmenopausal women aged 50 to 76 years from the VITAL study (n = 30,797). Meeting at least five WCRF/AICR recommendations compared with meeting none was associated with a 60% reduction in breast cancer incidence (HR: 0.40, 95% CI: 0.25-0.65). Furthermore, each additional recommendation met was associated with an 11% reduction in breast cancer risk (HR=0.89, 95% CI: 0.84-0.95). (92). Similarly, Harris et al. demonstrated a 51% reduction in breast cancer incidence (HR: 0.49, 95% CI: 0.35-0.70) (93) for those most adherent (score≥6) compared to least adherent (score ≤2) to the WCRF/AICR guidelines in the primarily post-menopausal women in the Swedish

Mammography Cohort (SMC) (n=31,514) that were followed for 15 years (81). Makarem et al. (96) also used the WCRF/AICR guidelines to examine the relationship between meeting the recommendations and obesity-related cancer incidence in a sample of men and women from the Framingham Offspring (FOS) cohort (n=2,983) (78). Cancers were considered obesity-related if clearly or possibly linked to excess adiposity by the ACS. Participants received 1, 0.5, or 0 points for fully meeting, partially meeting or not meeting the WCRF/AICR recommendation, respectively (Table 3). Similar to the VITAL study, hazard ratios for every 1-unit increment in the overall adherence score were computed for obesity-related cancers and site-specific cancers. Conversely, no statistically significant association was found between adherence and breast cancer incidence (HR=0.87, 95% CI: 0.74-1.03) on a per-recommendation basis (96). Catsburg et al. (94) operationalized both ACS and WCRF/AICR guidelines in the Canadian National Breast Screening study (NBSS) (n=47,130 WCRF, n=46,298 ACS)(80). Adherence to all six ACS guidelines compared to at most one guideline was associated with a statistically significant 31% reduction in breast cancer incidence (HR=0.69, 95% CI: 0.49-0.97). Adhering to six or seven WCRF/AICR guidelines compared to at most one guideline was associated with a 21% reduction in risk (HR=0.79, 95% CI: 0.57-1.10) but did not reach statistical significance. Meeting each additional guideline was associated with a 5% (HR=0.95, 95% CI: 0.91-0.98) or 6% (HR=0.94, 95% CI: 0.91-0.98) reduction in breast cancer incidence utilizing the WCRF/AICR and ACS recommendations, respectively (94). Most recently, Nomura et al. (95) evaluated adherence to the WCRF/AICR guidelines and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors in the Iowa

Women's Health Study (IWHS) (n=36,626). The eight point adherence score was collapsed into 4 categories: 0-3.5 points (low adherence), 4.0-4.5, 5.0-5.5, 6.0-8.0 (high adherence). High adherence compared to low adherence to WCRF/AICR guidelines was significantly associated with a reduction in breast cancer incidence (HR=0.76, 95% CI: 0.67-0.87) (95).

Colorectal Cancer

A total of four studies reported results for colorectal cancer specifically (7, 87, 88, 96). Significant inverse associations were found between adherence to ACS guidelines and colorectal cancer incidence in the WHI cohort (HR=0.48, 95% CI: 0.32-0.73) (7) as well as the NIH-AARP cohort for women (HR=0.65, 95% CI: 0.54-0.78) and men (HR=0.52, 95% CI: 0.47-0.59) (87). Consistently, a statistically significant reduction in colorectal cancer was associated with higher adherence in the EPIC cohort (HR=0.73, 95% CI: 0.65-0.81) (88). In contrast, the FOS cohort demonstrated no significant association for colorectal cancer incidence and adherence to WCRF/AICR guidelines (HR=0.87, 95% CI: 0.68-1.12) (96).

Lung Cancer

The association between ACS guideline adherence and lung cancer incidence is equivocal. Three studies reported results for the association between nutrition and physical activity guideline adherence and lung cancer incidence (7, 87, 88). In the NIH-AARP cohort, effect modification by sex was demonstrated with a statistically significant inverse association found among highly adherent men (HR=0.85, 95% CI: 0.78-0.93), but

not highly adherent women (HR=0.94, 95% CI: 0.84-1.05) (87). Results from the WHI are consistent with these reporting no statistical significance between lung cancer incidence in women and ACS guideline adherence (HR=1.14, 95% CI: 0.81-1.60) (7). The association between high adherence and lung cancer incidence was not statistically significant when evaluated for both sexes combined in the EPIC study (HR=0.86, 95% CI: 0.74-1.00) (88).

Endometrial Cancer

To date, three prospective studies have reported results for the association between nutrition and physical activity guideline adherence and endometrial cancer incidence. The large NIH-AARP and EPIC cohorts both found significant inverse associations demonstrated by higher adherence and lower risk of endometrial cancer (HR=0.40, 95% CI: 0.34-0.46; HR=0.77, 95% CI: 0.62-0.94), respectively (87, 88); while findings from the WHI cohort suggest no significant association (HR=0.73, 95% CI: 0.49-1.09) (7). Although analysis of the adherence score as a categorical variable (high vs. low) in the latter study was not statistically significant for risk of endometrial cancer, the overall trend using ACS score as an ordinal variable (0-8 points) suggested a significant 7% reduction in endometrial cancer incidence (HR=0.93, 95% CI: 0.87-0.98) (7).

Other Cancers

Data were also available from three studies meeting the eligibility criteria for ovarian (7, 87, 88) and prostate (87, 88, 96) cancer incidence. No statistically significant associations were found between ovarian cancer incidence and ACS guideline adherence in the WHI

or NIH-AARP cohorts or WCRF/AICR guideline adherence in the EPIC cohort. Likewise, no significant associations were identified for prostate cancer incidence utilizing the ACS guidelines in the NIH-AARP cohort or the WCRF/AICR guidelines in the EPIC or FOS cohorts.

C. Specific Aim 2: Adherence and Vitamin D

We hypothesized that greater adherence to the guidelines would be associated with higher concentrations of vitamin D metabolites. Data were employed from a pooled sample of two completed chemoprevention trials to construct an adherence score to the ACS nutrition and physical activity cancer prevention guidelines and assess the relationship between adherence and levels of 25(OH)D (n=1,357) and 1α,25-dihydroxyvitamin D [$1,25(OH)_2D$] (n=854).

1. Methods

Study Sample

Data were pooled from two randomized, controlled, double blind, Phase III clinical trials conducted at the University of Arizona Cancer Center (UACC) from 1990 to 1999. These studies evaluated the effect of either a wheat bran fiber supplement (WBF) (20, 97) or ursodeoxycholic acid (UDCA) (21) on the development of a new colorectal adenoma in patients with previously- removed colorectal adenomas. The present analyses were conducted using data for baseline diet, physical activity, and vitamin D biomarkers from the pooled sample. The University of Arizona Human Subjects Protection Program approved both studies. Written informed consent was obtained from each participant prior to trial enrollment.

Recruitment and Data Collection: Phoenix and Tucson gastroenterology practices served as recruitment centers from 1990-1995 for WBF and 1995-1999 for UDCA. Men and women between the ages of 40 and 80 years who had one or more adenomas measuring ≥3 mm removed during a colonoscopy within a 6-month period prior to study registration were included in the study. Participants in the WBF trial were randomized to a daily wheat bran fiber supplement (13.5 g/day) or a low-fiber supplement (2.0 g/day) (20). Participants in the UDCA trial were randomized to receive 8-10 mg UDCA per kilogram of body weight or placebo daily (21). Primary findings from the trials were null; neither the WBF supplement nor the UDCA treatment prevented new colorectal adenomas (21, 97). For the present analysis, participants from the pooled sample (n=3,221) were excluded if they did not have serum 25(OH)D data (n=1,253), had missing body mass index (BMI) data (n=16), were underweight (BMI < 18.5kg/m^2) (n=16), had unreliable (<600kcal/d) dietary data (n=14), had missing baseline physical activity data (n=544), or were missing any other covariate included in the models (race, n=16; education, n=5). The analytic cohort for 25(OH)D was thus comprised of 1,357 participants; while $1,25(OH)_2D$ data were only available from the UDCA trial (n=854).

Analysis of Serum Vitamin D Metabolites

Baseline vitamin D metabolites were measured in a blinded fashion at Heartland Assays (Ames, IA) utilizing an established radioimmunoassay (RIA)(98). Quality assurance and control measures including pooled serum samples, and duplicates in different batches were performed. The coefficient of variation was <7.0% for 25(OH)D and 11.5% for

$1,25(OH)_2D$. Serum $1,25(OH)_2D$ was assessed as a continuous variable and 25(OH)D was assessed as both a continuous and a categorical variable, in which clinically important categories were defined as deficient (<20 ng/mL) insufficient (≥20 to <30 ng/mL), or sufficient (≥30 ng/mL) (12, 35, 36, 48, 99).

Nutrition and Physical Activity Cancer Prevention Guidelines Score

An *a priori* score was constructed, based upon previously published work by Thomson and colleagues (7), for adherence to the 2012 ACS cancer prevention guidelines for nutrition and physical activity (6) (Table 6). These guidelines focus on overall patterns of lifestyle behaviors that included body size, physical activity, diet, and alcohol consumption. Baseline diet and physical activity were collected using frequency questionnaires. The Arizona Food Frequency Questionnaire (AFFQ) is a semi-quantitative, 175-item validated questionnaire that asks respondents to report how often (per day, week, or month) and how much (small, medium, or large usual portion) participants consumed each food item over the past 12-month period (100). The Arizona Activity Frequency Questionnaire (AAFQ) is a 59-item, validated questionnaire that groups physical activity by leisure, recreational, household, and "other" activity categories (101). The provided output contains metabolic equivalents of task (MET) units per day and per activity, kilojoules, number of hours per day per activity, and number of activities reported by respondents for each category, which were used to generate the physical activity score. Each ACS recommendation was equally weighted 0-2 points. Zero points were allocated for not meeting the recommendation at all, 1 point for partially meeting the recommendation, and 2 points for fully meeting the

recommendation. The overall score, summed from individual recommendations, ranged from 0 for those participants that were not adherent at all to the recommendations to 8 for those participants that were fully adherent to all four lifestyle factor recommendations. Adherence categories were defined as low (0-2 points), moderate (3-5 points), and high (6-8 points). Table 6 outlines the recommendations for each lifestyle factor, how they were measured, how scores were assigned based upon the guidelines, and the proportion of the study population within each category. While the ACS guidelines recommend choosing whole grains over refined grains, the proportion of whole grain consumption was not included in the adherence score for these analyses because 1) questions related to grains in the food frequency questionnaire were not focused on delineating whole versus refined grains and 2) the food frequency questionnaire was updated between the WBF and UDCA trials and grains were not captured in the same manner. Smoking status was not included in the ACS adherence scoring, but was included as a potential confounder in the current analyses.

Table 6. Components of the adherence score and distribution in the study sample.

Adherence score component	Score	Description	Percentage of study sample		
			All	Men	Women
Body mass index (BMI)	0	>30 kg/m^2	29.9	30.1	29.7
	1	>25-≤30 kg/m^2	43.8	48.6	32.8
	2	18.5-≤25 kg/m^2	26.1	21.2	37.4
Physical Activity (PA)	0	<8.75 MET h/wk	40.4	35.8	50.9
	1	8.75-17.5 MET h/wk	25.1	25.5	24.1
	2	>17.5 MET h/wk	34.4	38.6	24.8
Diet*	0		23.9	23.4	24.9
	1		64.4	64.5	64.3
	2		11.7	12.1	10.9
Fruit & Vegetables	0	<5 servings/d fruits plus veg	51.9	52.0	51.7
	1	≥5 servings/d fruits plus veg	48.1	48.0	48.3
Quality	0	1st tertile of total carotenoids	32.3	33.0	30.7
	1	2nd tertile of total carotenoids	33.8	33.4	34.8
	2	3rd tertile of total carotenoids	33.9	33.6	34.5
Red & processed meat	0	Quartiles of red + processed meat intake	25.2	25.0	25.6
	1		25.4	25.1	26.1
	2		25.1	25.0	25.1
	3	Lowest Quartile	24.3	24.8	23.2
Alcohol	0	Men ≥3, Women ≥2 drinks/day	9.3	10.6	6.3
	1	Men 1-2, Women 1 drink/day	53.8	57.7	44.9
	2	Non-drinker	36.9	31.7	48.8

*Diet score is generated from the summation of the fruit & vegetable, quality, whole grains, and red & processed meat scores. Summed for up to 6 points and then collapsed into 4 categories (0-1, 2-4, 5-6) for subsequent diet adherence values (0, 1, 2)

The first recommendation "to maintain a healthy weight throughout life" was scored based upon calculated body mass index (BMI, in kg/m^2) from height and weight reported at baseline. The best score (2 points) was given to those with a BMI within normal range (18.5-25 kg/m^2). The worst score (0 points) was given to those with a BMI in the obese category (>30.0 kg/m^2). One point was given those with a BMI in the overweight range (25-30 kg/m^2). Underweight participants (<18.5 kg/m^2) were excluded from the present analysis.

The second recommendation to "adopt a physically active lifestyle with at least 30 minutes of moderate to vigorous intentional physical activity at least 5 days a week; 45-60 minutes are preferable" was evaluated by MET (102) scores from the AFFQ recreational activities section. The minimum standard of 30 minutes on 5 days (2.5 hours/week) of moderate activity (3.5 METs) is equal to 8.75 MET-hours per week. Any participant doing less than the minimum recommendation (less than 8.75 MET-hours per week) received a score of zero points. One hour per day, 5 days a week (5.0 hours/week), of moderate activity (3.5 METs) is equal to 17.5 MET-hours/ week. Therefore, 8.75 to 17.5 MET-hours/week earned a score of 1 point. Participants meeting "preferable" levels, greater than 17.5 MET-hours/week, earned a score of 2 points.

The third recommendation to "consume a healthy diet with an emphasis on plant sources" was assessed with three separate diet scores that were constructed and summed to capture the recommended dietary pattern. The first diet score for the recommendation "eat 5 or

more servings of a variety of vegetables and fruits each day" was assigned 1 point for meeting the recommended number of servings. The number of servings was measured from food group categories Fruits, Fruit Juice, Vegetables, and Vegetable Juice. An additional 1 or 2 points was assigned for diet quality based upon being in the 2nd or 3rd sex-specific tertile of total carotenoids, respectively, which included beta carotene, alpha carotene, beta cryptoxanthin, lycopene, and lutein plus zeaxanthin combined. The second diet score for the recommendation "choose whole grains in preference to processed (refined) grains" was not evaluated due to the reasons mentioned above. The third diet score for the recommendation "limit consumption of processed and red meats" was assessed by sex-specific quartile distribution with the lowest quartile receiving 3 points and the highest quartile receiving zero points. The two utilized diet scores were summed for a potential total of 6 points. Dietary pattern scores were further collapsed into 0 points for those with 0-1 summed diet scores, 1 point for those with 2-4 summed diet scores, and 2 point for those with 5-6 summed diet scores.

The fourth recommendation employed in this analysis was "if you drink alcohol, limit consumption to 1 drink per day for women or 2 drinks per day for men." Alcohol was captured in the AFFQ in terms of total grams of alcohol per day. One drink was estimated as 14 grams of alcohol or approximately a 12 ounce regular beer, 5 ounce glass of wine, or 1.5 ounce shot of 80-proof distilled spirit (103). Nondrinkers were assigned 2 points, moderate drinkers consuming the limit or less were assigned 1 point, and heavy drinkers consuming more than the limit were assigned zero points.

Statistical analysis

Descriptive statistics were generated for vitamin D metabolites, adherence scores, and demographic variables. Bivariate analyses were performed to assess differences in demographic characteristics between the trials. Unadjusted means and standard errors were estimated for continuous variables.

Multiple linear regression models were utilized to assess the relationships of circulating concentrations of 25(OH)D and $1,25(OH)_2D$ with adherence score categories and estimate mean concentrations of 25(OH)D and $1,25(OH)_2D$ for individuals in the reference categories centered on mean age and energy intake of the strata using linear combinations of parameters. Reference categories were selected to represent the majority of the pooled population (white, male, not a college graduate, non-smoker in the UDCA trial). Clinically significant categories for serum 25(OH)D were evaluated using multinomial logistic regression models to estimate odds ratios (ORs) for association with adherence scores. Adjusted mean concentrations of 25(OH)D and $1,25(OH)_2D$ were also estimated by individual adherence score components. Potential confounders included age, education, race, smoking status, supplement use, and energy intake (47, 104-107). A covariate was considered a confounder if it changed the measure of association by 10% or more when included in a regression model (108). To assess whether the associations between adherence score and vitamin D metabolites were modified by 1) sex as a biological variable 2) study or 3) smoking status, likelihood ratio tests were used to determine if there was a difference in the log-likelihoods from models with and without

interaction terms. Data from the trials were merged and managed using Stata version 14.1 software (StataCorp LP, College Station, Texas).

2. Results

Table 6 demonstrates more women than men met the BMI recommendation of a healthy body size (18.5-25kg/m^2); while more men than women met preferable physical activity levels of more than one hour per day, 5 days a week (>5.0 hours/week) of moderate activity (3.5 METs), or greater than 17.5 MET-hours/week total. Men and women had similar adherence to diet recommendations overall; however, a greater percentage of women were non-drinkers at baseline than men. Baseline characteristics of men and women by category of ACS score are shown in Table 7. In general, participants in the most adherent overall category of ACS score (6-8 points) were more likely to be older, white, and a non-smoker than those participants in the least adherent category (0-2 points).

Table 7. Baseline characteristics of participants in the pooled sample (n=1357) by categories of adherence score to the ACS Nutrition and Physical Activity Cancer Prevention guidelines, stratified by sex[1].

	Adherence Score (points)					
	Men			Women		
	0-2	3-5	6-8	0-2	3-5	6-8
n (%)	121 (12.8)	652 (69.1)	170 (18.0)	52 (12.6)	280 (67.6)	82 (19.8)
Age, years	61.4 ± 7.8	65.9 (8.7)	67.8 (8.2)	64.0 (8.9)	64.5 (8.5)	67.2 (8.7)
White, n (%)	115 (95.0)	610 (93.6)	161 (94.7)	50 (96.2)	262 (93.6)	79 (96.3)
College graduate, n (%)	44 (36.4)	274 (42.0)	72 (42.4)	10 (19.2)	61 (21.8)	16 (19.5)
BMI, kg/m^2	32.2 ± 4.3	28.5 ± 3.8	25.1 ± 2.6	33.8 ± 4.6	27.8 ± 5.2	23.7 ± 3.1
Physical activity, MET-h/wk	3.9 ± 4.2	17.9 ± 17.8	31.9 ± 17.9	3.8 ± 5.2	11.3 ± 15.5	26.5 ± 17.3
Diet						
Total energy, kcal/d	2342.3 ± 803.4	2114.3 ± 768.5	2169.7 ± 759.9	1718.4 ± 576.0	1545.9 ± 591.1	1590.9 ± 568.8
Fruit and veg, servings/d	5.1 ± 3.6	5.4 ± 3.2	6.8 ± 3.9	5.0 ± 3.0	5.7 ± 4.3	7.0 ± 3.8
Total carotenoids, μg/d	14625.1 ± 10577.4	13810.4 ± 8422.8	15356.2 ± 7347.4	10868.0 ± 5067.1	12125.5 ± 8766.8	13777.4 ± 7869.9
Red & processed meat, serv/d	2.2 ± 1.0	1.5 ± 0.8	1.3 ± 0.8	1.5 ± 0.9	0.9 ± 0.6	0.8 ± 0.6
Whole grains, g/d	17.6 ± 40.5	23.6 ± 52.6	36.8 ± 67.5	8.9 ± 17.2	16.9 ± 32.2	31.4 ± 67.2
Dietary vitamin D intake	136.7 ± 105.5	161.4 ± 118.0	168.1 ± 112.7	142.4 ± 114.9	135.3 ± 103.6	146.5 ± 130.1
Vitamin D supplement, IU/d	171.5 ± 228.2	205.4 ± 257.3	231.5 ± 222.4	219.8 ± 224.0	226.3 ± 277.3	319.9 ±262.1
Supplement use, n (%)	65 (53.7)	417 (64.0)	135 (79.4)	37 (71.2)	200 (71.4)	72 (87.8)
Alcohol						
Nondrinker at baseline, n (%)	10 (8.3)	196 (30.1)	93 (54.7)	10 (19.2)	134 (47.9)	58 (70.7)
Intake among drinkers, drinks/d	1.7 ± 1.9	0.9 ± 1.1	0.8 ± 0.8	0.4 ± 0.5	0.4 ± 0.5	0.4 ± 0.3
Current smoker, n (%)	21 (17.4)	76 (11.7)	17 (10.0)	7 (13.5)	39 (13.9)	14 (17.1)
Vitamin D Biomarkers						
25(OH)D, ng/mL	26.9 ± 9.3	29.3 ± 9.9	31.0 ± 10.0	20.6 ± 7.6	23.7 ± 9.8	27.4 ± 11.4
$1,25(OH)_2D$, pg/mL[3]	32.4 ± 11.2	34.0 ± 10.6	36.4 ± 10.8	26.6 ± 8.9	32.9 ± 12.5	34.3 ± 11.2

[1]Some percentages do not add up to 100% because of missing data or rounding. BMI, body mass index; MET-h/wk, metabolic equivalent hours per week; 25(OH)D, 25-hydroxycholecalciferol.
[2]Mean ± SD (all such values)
[3]Only UDCA trial measured $1,25(OH)_2D$ (n=854)

Table 8 shows adjusted mean circulating 25(OH)D and 1,25$(OH)_2$D concentrations for each adherence score category from multivariate linear regression models for individuals in reference categories (white, male, not a college graduate, non-smoker in UDCA trial) centered on mean age and energy intake. In the pooled sample, those in the highest adherence category to the ACS guidelines (6-8 points) had an average 25(OH)D concentration of 31.4 ±0.8 ng/mL and 1,25$(OH)_2$D concentration of 36.4 ±1.1 pg/mL, with significant dose-dependent trends for both metabolites (*P*-trend <0.001; *P*-trend <0.001) (Table 3). For 25(OH)D, there were no statistically significant interactions for sex (*P*=0.0.3306), smoking (*P*=0.1162), study (*P*=0.3576), or trial arm (*P*=0.6487). Study interaction was not evaluated for 1,25$(OH)_2$D as it was only available for the UDCA study. There was no statistically significant interaction between score and sex (*P*=0.9114), smoking (*P*=0.4728), or UDCA trial arm (*P*=0.5992) for 1,25$(OH)_2$D.

Table 8. Mean circulating 25(OH)D and $1,25(OH)_2D$ concentrations and adherence score category[1]

	25(OH)D, ng/mL				$1,25(OH)_2D$, ng/mL			
		ACS score				ACS score		
Serum 25(OH)D	*n*	0-2	3-5	6-8	*n*	0-2	3-5	6-8
Pooled sample	1357	26.3 ± 0.8[1]	29.2 ± 0.5	31.4 ± 0.8	854	31.2 ± 1.2	34.1 ± 0.7	36.4 ± 1.1
Stratified Analyses								
Non-smoker	1183	25.7 ± 0.9	29.3 ± 0.5	31.5 ± 0.8	750	31.5 ± 1.2	34.1 ± 0.7	36.8 ± 1.1
Current smoker	174	27.9 ± 1.9	27.0 ± 1.2	29.3 ± 2.0	104	29.8 ± 3.3	34.8 ± 1.8	33.4 ± 3.3
p-Interaction[2]		0.1162				0.4728		
Men	943	20.4 ± 1.6	23.1 ± 1.4	24.7 ± 1.5	586	32.7 ± 2.2	35.2 ± 1.9	37.9 ± 2.2
Women	414	14.2 ± 2.6	17.6 ± 2.2	21.4 ± 2.4	268	26.5 ± 3.7	30.0 ± 3.2	31.8 ± 3.6
p-Interaction[2]		0.3306				0.9114		
UDCA Trial	854	25.7 ± 1.0	28.9 ± 0.6	31.4 ± 0.9	854	31.1 ± 1.2	34.0 ± 0.7	36.3 ± 1.1
WBF Trial[2]	503	28.6 ± 1.4	30.5 ± 0.8	32.8 ± 1.1	0	-	-	-
p-Interaction		0.3576						
Low fiber	214	28.3 ± 2.4	32.4 ± 1.2	34.5 ± 2.0	0	-	-	-
High fiber	289	28.5 ± 1.7	29.0 ± 1.0	31.9 ± 1.3	0	-	-	-
Placebo	418	24.8 ± 1.5	28.4 ± 0.9	32.4 ± 1.4	418	30.0 ± 1.5	33.3 ± 0.9	36.4 ± 1.5
UDCA	436	26.1 ± 1.4	29.6 ± 0.7	30.3 ± 1.2	436	32.0 ± 1.7	34.6 ± 1.0	36.0 ± 1.5
p-Interaction		0.6487				0.5992		

[1] Means ±SE computed from linear regression for individuals in reference categories (white, male, not a college graduate, non-smoker in UDCA trial) centered on mean age and energy intake. Adjusted (or stratified) for study, mean age, race, education, smoking status, and mean energy intake.

[2] *p*-Interaction calculated using a likelihood ratio test

[3] WBF trial (low fiber vs. high fiber) did not measure $1,25(OH)_2D$

Table 9 demonstrates a statistically significant (*P*<0.001) unadjusted association between adherence score category and 25(OH)D status (Pearson χ^2 = 22.2584).

Table 9. Unadjusted association between category of adherence score and 25(OH)D status[1].

	n (%)		
Vitamin D status	Deficient <20ng/mL n=296	Insufficient ≥20 & <30ng/mL n=575	Sufficient ≥30ng/mL n=486
Low (0-2)	56 (18.9)	71 (12.4)	46 (9.5)
Moderate (3-5)	202 (68.2)	399 (69.4)	331 (68.1)
High (6-8)	38 (12.8)	105 (18.3)	109 (22.4)

[1]Pearson χ^2 = 22.2584; p-value <0.001

Table 10 presents the results of multinomial logistic regression models for the association between categories of adherence scores and clinically-defined categories of 25(OH)D. The odds of having an insufficient vitamin D status (≥20 and <30 ng/mL) versus a deficient status (<20 ng/mL) was 1.75 times (95% CI: 1.20-2.55) greater for those who were moderately adherent to the guidelines and 2.29 times greater (95% CI: 1.50-3.49) for those individuals who had high adherence, versus those with low adherence. The odds of having a sufficient vitamin D status (≥30 ng/mL) versus a deficient status was 2.30 times (95% CI: 1.35-3.93) greater for those achieving moderate adherence and 4.30 times greater (95% CI: 2.30-7.60) for those who were highly adherent, versus those within the lowest adherence category.

Table 10. Association between 25(OH)D status and adherence score category[1]

25(OH)D Adherence Score Category	OR (95% CI)
<20ng/mL	
Least (0-2)	1.00 (Ref)
≥20 & <30ng/mL	
Moderate (3-5)	1.75 (1.20-2.55)
High (6-8)	2.29 (1.50-3.49)
≥30ng/mL	
Moderate (3-5)	2.30 (1.35-3.93)
High (6-8)	4.30 (2.43-7.60)

[1]OR (95% CI) obtained from multinomial logistic regression. Adjusted for study, age, sex, race, education, smoking status, and energy intake.

Adjusted mean concentrations of 25(OH)D and $1,25(OH)_2D$ for individuals in the reference categories (white male, not a college graduate, and a non-smoker in the UDCA trial) by adherence score components are displayed in Table 11. An inverse relationship between BMI categories and both 25(OH)D and $1,25(OH)_2D$ exhibited a dose-dependent trend (*P*-trend for both comparisons <0.001). Similarly, a significant trend was seen for higher levels of physical activity and higher concentrations of both vitamin D metabolites (*P*-trend<0.001). In contrast, no significant associations were observed between diet score and either vitamin D metabolite. A significant trend was seen for increasing alcohol consumption and increasing concentrations of both 25(OH)D (*P*-trend 0.009) and $1,25(OH)_2D$ (*P*-trend 0.035).

Table 11. Mean concentrations of 25(OH)D and $1,25(OH)_2D$ by adherence score components.

Score components	Overall Study Sample[1]			
	25(OH)D, ng/mL		$1,25(OH)_2D$, pg/mL	
	n	Mean ± SE	n	Mean ± SE
Diet				
0	167	26.3 ± 1.2	50	31.8 ± 1.7
1	1018	27.7 ± 1.1	371	33.7 ± 1.5
2	172	27.2 ± 1.3	82	32.3 ± 1.9
P-trend		0.455		0.604
BMI, kg/m^2				
≥30	407	26.3 ± 1.2	117	31.8 ± 1.7
≥25 and <30	595	28.7 ± 1.2	647	33.5 ± 1.7
≥18.5 and <25	355	30.4 ± 1.3	90	35.9 ± 1.8
P-trend		<0.001		<0.001
Physical activity, MET-hours/week				
<8.75	549	26.3 ± 1.2	344	31.8 ± 1.7
≥8.75 and ≤17.5	341	26.8 ± 1.3	210	34.3 ± 1.8
>17.5	467	30.6 ± 1.3	300	35.4 ± 1.7
P-trend		<0.001		<0.001
Alcohol				
Heavy (mean 3.0 drinks/day)	126	26.3 ± 1.2	91	31.8 ± 1.7
Moderate (mean 0.5 drinks/day)	730	25.3 ± 0.9	458	29.2 ± 1.3
Never (0 drinks/day)	501	24.1 ± 1.0	305	28.6 ± 1.4
P-trend		0.009		0.035

[1] Means computed from adjusted linear regression for individuals in reference categories (white male, not a college graduate, non-smoker in the UDCA trial) centered on mean age and energy intake. Adjusted for sex, age, race, education, smoking status, energy intake, and all other score components. $1,25(OH)_2D$ was not measured for WBF trial.

D. Specific Aim 3: Adherence and New Colorectal Adenoma

1. Methods

Study Sample

Data were pooled from separate randomized, controlled, double blind, Phase III clinical trials conducted at the University of Arizona Cancer Center (UACC). These studies evaluated the effect of either wheat bran fiber (WBF) (20) or ursodeoxycholic acid (UDCA) (21) on the development of a new colorectal adenoma. Analyses for aim 3 were conducted using the same, pooled sample as aim 2. Data for baseline diet, physical activity, and new colorectal adenomas were complete for 1,670 participants in the pooled sample. The University of Arizona Human Subjects Protection Program approved both studies and written informed consent was obtained from each participant prior to trial enrollment.

For the present analysis, participants from the pooled sample (n=2,478) were excluded if they had missing BMI data (n=26), were underweight (BMI < 18.5kg/m^2) (n=17) or extremely obese (BMI>50kg/m^2) (n=1), had unreliable (<600kcal/d) dietary data (n=15), or missing physical activity data (n=749). The analytic cohort comprised 1,670 participants.

Outcome Ascertainment

Medical records and pathology reports were used to collect baseline and new adenoma characteristics such as number, size, location, and histology (20, 21). Any new colorectal adenoma was defined as yes or no. New advanced colorectal adenoma was defined as an

adenoma >1cm in size, having tubulovillous/villous histology (yes/no), or adenocarcinoma.

Nutrition and Physical Activity Cancer Prevention Guidelines Score

An *a priori* adherence score was constructed, as described above in section C for adherence to the 2012 ACS cancer prevention guidelines for nutrition and physical activity (6). The guidelines focused on an overall pattern of lifestyle behaviors that included body weight, physical activity, diet, and alcohol consumption. Frequency questionnaires were used to collect baseline diet and physical activity data. Diet was assessed utilizing the Arizona Food Frequency Questionnaire (AFFQ) which is a semi-quantitative, 175-item validated questionnaire that queries participants to report how often and how much they consumed each food item over the past 12-month period (100). Physical activity was assessed utilizing the Arizona Activity Frequency Questionnaire (AAFQ) is a 59-item, validated questionnaire that asks participants about usual physical activity in the past four weeks (101). For this analysis, smoking status was not included in the adherence score, but was included as a potential confounder in the current analyses.

Statistical analysis

Descriptive statistics were generated for outcome variables, exposure variables, and demographic variables. Chi-square tests will be used to test associations of the chosen variables for participants with and without a new adenoma occurrence. Current literature suggests potential confounders include age, previous polyps, family history of colorectal adenomas and/or cancer, and aspirin use (13, 109, 110). Additional covariates were

examined and included if the measure of association changed by at least 10% when entered in the model (108). Multiple logistic regression models were utilized to assess the association of adherence score with new adenoma occurrence and to evaluate interaction between adherence score and 1) sex as a biological variable 2) study and 3) smoking. Statistical significance was determined at an α level of 0.05, and assumptions for all statistical tests will be assessed. Data from the trials were merged and managed using Stata version 14.1 software (StataCorp LP, College Station, Texas).

2. Results

Table 12 demonstrates high adherence to the guidelines was achieved by 19.1% (n=319) of the sample population while 12.2% (n=204) and 68.7% (n=1147) attained low and moderate adherence, respectively. Baseline characteristics by category of ACS score are shown in Table 13.

Table 12. Components of the adherence score and distribution in the study sample.

	Score	Description	All N (%)
Overall adherence score	Low	0-2 points	204 (12.2)
	Moderate	3-5 points	1147 (68.7)
	High	6-8 points	319 (19.1)
Adherence score component			
Body mass index (BMI)	0	>30 kg/m^2	476 (28.5)
	1	>25-≤30 kg/m^2	749 (44.9)
	2	18.5-≤25 kg/m^2	445 (26.7)
Physical Activity (PA)	0	<8.75 MET h/wk	658 (39.4)
	1	8.75-17.5 MET h/wk	421 (25.2)
	2	>17.5 MET h/wk	591 (35.4)
Diet*	0	Summed and collapsed scores from diet components	209 (12.5)
	1		947 (56.7)
	2		514 (30.8)
Fruit & Vegetables	0	<5 servings/day fruits plus veg	836 (50.1)
	1	≥5 servings/day fruits plus veg	834 (49.9)
Quality	0	1st tertile of total carotenoids	540 (32.3)
	1	2nd tertile of total carotenoids	564 (33.8)
	2	3rd tertile of total carotenoids	566 (33.9)
Red & processed meat	0	Highest quartile	421 (25.2)
	1		423 (25.3)
	2		420 (25.2)
	3	Lowest quartile	406 (24.3)
Alcohol	0	Men ≥3, Women ≥2 drinks/day	153 (9.2)
	1	Men 1-2, Women 1 drink/day	921 (55.2)
	2	Non-drinker	596 (35.7)

*Diet score is generated from the summation of the fruit & vegetable, quality, and red & processed meat scores. Summed for up to 6 points and then collapsed into 3 categories (0-1, 2-4, 5-6) for subsequent diet adherence values (0, 1, 2)

Table 13. Baseline characteristics of participants in the pooled sample (n=1670) by categories of adherence [1].

	Adherence Score Category (points)		
	0-2	3-5	6-8
n (%)	204 (12.2)	1147 (68.7)	319 (19.1)
Age, years[3]	62.8 (8.4)	65.8 (8.6)	68.0 (8.1)
White, n (%)	195 (95.6)	1085 (94.6)	303 (95.0)
College graduate, n (%)	60 (29.4)	409 (35.7)	113 (35.4)
BMI, kg/m^2	32.5 (4.4)	28.2 (4.3)	24.5 (2.7)
Physical activity, MET-h/wk	4.1 (5.0)	16.7 (29.2)	31.3 (32.2)
Diet			
Total energy, kcal/d	2135.0 (797.2)	1955.7 (757.8)	1946.8 (726.4)
Fruit and veg, servings/d	5.0 (3.3)	5.7 (3.7)	6.9 (3.7)
Total carotenoids, µg/d	13449.0 (9127.9)	13846.0 (8676.4)	15054.2 (7414.7)
Red and processed meat,	2.0 (1.0)	1.4 (0.8)	1.1 (0.7)
Alcohol			
Nondrinker at baseline, n (%)	22 (10.8)	391 (34.1)	183 (57.4)
Intake among drinkers, drinks/d	1.3 (1.7)	0.8 (1.2)	0.7 (0.7)
Current smoker, n (%)	34 (16.7)	137 (11.9)	38 (11.9)
Family history CRC, n (%)	51 (25.0)	267 (23.3)	66 (20.7)
Previous polyps, n (%)	78 (38.2)	489 (42.6)	131 (41.1)
Aspirin use in last 4 weeks, n (%)	49 (24.0)	340 (29.6)	113 (35.4)
Number of colonoscopies during study period	1.8 (0.8)	1.8 (0.8)	1.8 (0.9)
Baseline adenoma characteristics			
Multiplicity, ≥3 adenomas, n (%)	42 (15.0)	192 (68.3)	47 (16.7)
Large size, >1cm, n (%)	89 (13.1)	463 (67.9)	130 (19.1)
Tubulovillous/villous histology,	49 (14.1)	228 (65.5)	71 (20.4)
Proximal location, n (%)	109 (12.8)	594 (69.6)	150 (17.6)

[1]Some percentages do not add up to 100% because of missing data or rounding. BMI, body mass index; MET-h/wk, metabolic equivalent hours per week; CRC, colorectal cancer.

[2]Mean ± SD (all such values)

Table 14 presents the adjusted odds ratios for the association between adherence score categories and baseline colorectal adenoma characteristics from multivariate logistic regression models. In the pooled sample, reduced odds of having three or more adenomas at baseline were shown for moderately adherent (OR=0.67, 95% CI: 0.46-0.99) and highly adherent (OR=0.50, 95% CI: 0.31-0.81) participants compared to those with low adherence (*p*-trend=0.005). No statistically significant associations were shown between guideline adherence and baseline adenoma size or villous histology in the pooled sample. No heterogeneity of effect was demonstrated between sexes for the relationship between adherence score category and any of the baseline adenoma characteristics. However, the odds of at least three adenomas at baseline were significantly lower among men for those highly adherent (OR=0.62, 95% CI: 0.40-0.97) and moderately adherent (OR=0.47, 95% CI: 0.27-0.82), versus those with low adherence (*p*-trend=0.011). Significant study interaction was demonstrated between adherence score category and baseline villous histology (*P*=0.0224).

Table 14. Adjusted ORs (95% CI) for the association between category of guideline adherence and baseline colorectal adenoma characteristics for pooled sample and by sex and study

ACS adherence score category	Baseline adenoma characteristics (OR, 95% CI)[1]					
	Multiplicity (≥3 adenoma)		Large size (≥1 cm)		Villous histology	
	n (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Pooled sample						
Low (0-2)	204 (12.2)	1.00	89 (13.1)	1.00	49 (14.1)	1.00
Moderate (3-5)	1147 (68.7)	0.67 (0.46-0.99)	463 (67.9)	0.85 (0.63-1.15)	228 (65.5)	0.78 (0.55-1.11)
High (6-8)	319 (19.1)	0.50 (0.31-0.81)	130 (19.1)	0.85 (0.59-1.22)	71 (20.4)	0.89 (0.58-1.36)
p-Trend		0.005		0.455		0.765
Men						
Low (0-2)	141 (12.3)	1.00	57 (12.3)	1.00	34 (14.5)	1.00
Moderate (3-5)	791 (68.7)	0.62 (0.40-0.97)	319 (69.1)	0.92 (0.64-1.34)	153 (65.4)	0.73 (0.47-1.12)
High (6-8)	219 (19.0)	0.47 (0.27-0.82)	86 (18.6)	0.83 (0.53-1.30)	47 (20.1)	0.78 (0.46-1.30)
p-Trend		0.011		0.405		0.443
Women						
Low (0-2)	63 (12.1)	1.00	32 (14.6)	1.00	15 (13.2)	1.00
Moderate (3-5)	356 (68.6)	0.82 (0.38-1.79)	144 (65.5)	0.68 (0.40-1.17)	75 (65.8)	0.90 (0.48-1.70)
High (6-8)	100 (19.3)	0.56 (0.21-1.48)	44 (20.0)	0.85 (0.45-1.60)	24 (21.1)	1.16 (0.55-2.45)
p-Trend		0.221		0.809		0.577
p-Interaction[2]		0.8360		0.4363		0.8597
UDCA						
Low (0-2)	121 (13.4)	1.00	51 (13.3)	1.00	24 (13.0)	1.00
Moderate (3-5)	633 (70.3)	0.75 (0.42-1.31)	276 (71.9)	1.06 (0.71-1.57)	134 (72.8)	1.15 (0.70-1.88)
High (6-8)	147 (16.3)	0.59 (0.28-1.23)	57 (14.8)	0.85 (0.52-1.41)	26 (14.1)	0.93 (0.50-1.73)
p-Trend		0.162		0.485		0.763
WBF						
Low (0-2)	83 (10.8)	1.00	38 (12.8)	1.00	25 (15.2)	1.00
Moderate (3-5)	514 (66.8)	0.62 (0.36-1.05)	187 (62.8)	0.64 (0.40-1.03)	94 (57.3)	0.50 (0.30-0.85)
High (6-8)	172 (22.4)	0.44 (0.23-0.83)	73 (24.5)	0.78 (0.46-1.34)	45 (27.4)	0.76 (0.42-1.37)
p-Trend		0.013		0.730		0.903

p-Interaction[2]	0.8687	0.1224	0.0224

[1] ORs adjusted for age, sex (except for stratified analysis), and study (except for stratified analysis)
[2] *P* for interaction calculated by likelihood ratio test

Table 15 presents the association between new colorectal adenoma and adherence score category from multivariate logistic regression models. In the pooled sample, there were no significant associations between ACS guideline adherence and development of a new adenoma upon follow-up. The odds of having a new colorectal adenoma were 1.16 times (95% CI: 0.85-1.59) greater for those who were moderately adherent to the guidelines and 1.23 times greater (95% CI: 0.85-1.79) for those individuals who had high adherence compared to those with low adherence. There were no statistically significant interactions for smoking status (P=0.6412; data not shown), sex (P=0.2152), or study (P=0.3963). There were no significant associations with adherence score category and any new adenoma occurrence characteristics.

Table 15. Association between adherence score category and new colorectal adenoma occurrence for pooled sample and by sex and study

	New adenoma occurrence (OR, 95% CI)[1]							
	Any new occurrence		Multiplicity (≥3 adenoma)		Large size (≥1 cm)		Villous histology	
Adherence score category	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Pooled sample								
Low (0-2)	105 (13.8)	1.00	22 (11.2)	1.00	14 (8.4)	1.00	11 (9.2)	1.00
Moderate (3-5)	504 (66.2)	1.16 (0.85-1.59)	130 (66.0)	0.97 (0.58-1.59)	112 (67.1)	1.40 (0.78-2.51)	88 (73.3)	1.35 (0.70-2.58)
High (6-8)	152 (20.0)	1.23 (0.85-1.79)	45 (22.8)	1.11 (0.62-1.98)	41 (24.6)	1.83 (0.95-3.51)	21 (17.5)	1.08 (0.50-2.33)
p-Trend		0.294		0.611		0.055		0.938
Men								
Low (0-2)	67 (11.9)	1.00	18 (11.6)	1.00	12 (9.6)	1.00	10 (11.1)	1.00
Moderate (3-5)	385 (38.4)	1.00 (0.69-1.45)	98 (63.2)	0.85 (0.48-1.49)	85 (68.0)	1.12 (0.59-2.15)	65 (72.2)	1.00 (0.50-2.02)
High (6-8)	111 (19.7)	1.00 (0.64-1.56)	39 (25.2)	1.10 (0.58-2.12)	28 (22.4)	1.27 (0.61-2.67)	15 (16.7)	0.76 (0.32-1.77)
p-Trend		0.983		0.531		0.494		0.435
Women								
Low (0-2)	17 (8.6)	1.00	4 (9.5)	1.00	2 (4.8)	1.00	1 (3.3)	1.00
Moderate (3-5)	138 (69.7)	1.69 (0.92-3.09)	32 (76.2)	1.30 (0.43-3.89)	27 (64.3)	2.45 (0.56-10.64)	23 (76.7)	4.42 (0.58-33.38)
High (6-8)	43 (21.7)	2.02 (1.01-4.06)	6 (14.3)	0.92 (0.25-3.40)	13 (31.0)	4.58 (0.98-21.39)	6 (20.0)	4.15 (0.48-35.56)
p-Trend		0.061		0.750		0.021		0.306
p-Interaction[2]		0.2152		0.3877		0.3253		0.1281
UDCA								
Low (0-2)	45 (12.0)	1.00	8 (11.8)	1.00	11 (13.4)	1.00	8 (11.9)	1.00
Moderate (3-5)	272 (72.3)	1.22 (0.81-1.84)	47 (69.1)	0.94 (0.42-2.11)	59 (72.0)	0.97 (0.49-1.94)	52 (77.6)	1.12 (0.51-2.45)
High (6-8)	59 (15.7)	1.08 (0.65-1.80)	13 (19.1)	1.11 (0.42-2.89)	12 (14.6)	0.84 (0.35-2.03)	7 (10.5)	0.59 (0.21-1.72)
p-Trend		0.846		0.781		0.689		0.299
WBF								
Low (0-2)	39 (10.1)	1.00	14 (10.9)	1.00	3 (3.5)	1.00	3 (5.6)	1.00
Moderate (3-5)	251 (65.2)	1.11 (0.69-1.80)	83 (64.3)	0.95 (0.50-1.80)	53 (62.4)	2.95 (0.89-9.73)	36 (67.9)	1.95 (0.58-6.50)
High (6-8)	95 (24.7)	1.38 (0.80-2.40)	32 (24.8)	1.09 (0.53-2.24)	29 (34.1)	4.94 (1.44-16.98)	14 (26.4)	2.15 (0.59-7.80)

p-Trend	0.192	0.707	0.003	0.318
p-Interaction[2]	0.3963	0.9864	0.0238	0.2581

[1] ORs adjusted for age, study (except for stratified analysis), baseline multiplicity (except villous histology analyses), and sex (except for stratified analysis)

[2] *P* for interaction calculated by likelihood ratio test

Table 16 presents the results from multivariate logistic regression for the association between ACS adherence score individual components and new colorectal adenoma occurrence. There were no statistically significant associations between the diet scores, BMI categories, physical activity levels, or alcohol consumption, and the development of a new colorectal adenoma.

Table 16. Association of individual component scores for cancer prevention adherence and odds of new colorectal adenoma[1]

Adherence Score components	New Adenoma Occurrence, OR (95% CI)[1]
Diet	
0	1.00
1	1.03 (0.78-1.45)
2	0.96 (0.68-1.36)
BMI, kg/m^2	
≥30	1.00
≥25 and <30	0.96 (0.76-1.22)
≥18.5 and <25	0.82 (0.63-1.08)
Physical activity, MET-hours/week	
<8.75	1.00
≥8.75 and ≤17.5	1.03 (0.80-1.32)
>17.5	1.07 (0.84-1.35)
Alcohol	
Heavy	1.00
Moderate	1.01 (0.71-1.43)
Never	1.17 (0.81-1.69)

[1] OR (95% CI) obtained from multivariate logistic regression. Adjusted for age, sex, study, and other score components.

CHAPTER 3

DISSERTATION CONCLUSIONS AND FUTURE DIRECTIONS

A. Specific Aim 1: Systematic review of adherence to nutrition and physical activity cancer prevention guidelines and cancer outcomes

The systematic review included 12 studies from 10 different prospective cohorts evaluating the association between adherence to nutrition and physical activity cancer prevention guidelines and cancer outcomes. High versus low adherence to ACS or WCRF/AICR guidelines was consistently and significantly associated with decreases of 10-61% in overall cancer incidence and mortality. Consistent reductions were also shown for breast cancer incidence (19-60%), endometrial cancer incidence (23-60%), and colorectal cancer incidence in both men and women (27-52%) for those most adherent to the recommendations. Findings from three studies that reported results for adherence and lung cancer incidence were less clear. No significant relationships were found between adherence and ovarian or prostate cancers.

The greatest evidence for an association with the guidelines was seven out of eight studies that showed significantly significant findings between adherence and breast cancer incidence as an outcome. Regarding the studies specifically related to breast cancer, all eight included women 50 years and older, although WHI, IWHS, and VITAL cohorts included only postmenopausal women, and the SMC cohort consisted of primarily postmenopausal women. ACS guidelines were employed in the WHI, NIH-AARP, NBSS cohorts while the WCRF/AICR guidelines were used in the VITAL, FOS,

SMC, EPIC, IWHS, and NBSS cohorts. Unlike the other studies that compared high adherence to low adherence, the FOS adherence score was evaluated and interpreted in 1-point increments (96). Other differences in the FOS cohort include fewer incident cases of breast cancer (n=124) and inclusion of pre- and postmenopausal women, which may contribute to attenuation of findings.

Significant inverse associations were also found between adherence to the guidelines and colorectal cancer incidence in three out of the four studies reviewed. The inconsistency in the FOS cohort could be due to the difference in the set of guidelines used for generation of adherence score, the different analytic approach utilizing the adherence score as a continuous variable versus a dichotomous variable (high versus low), analyzing men and women together unlike other studies, or perhaps the number of incident cases of colorectal cancer (n=63) in the FOS cohort was too small to detect statistically significant associations.

Less clear were the findings from three studies that included lung cancer as an outcome. One study reported a significant reduction in lung cancer for only men who had high adherence compared to men with low adherence, but not for women. Similarly, a second study found no association for women adhering to the guidelines and lung cancer and a third study had null findings when men and women were reported together. Though smoking status is the strongest risk factor associated with lung cancer, broader health-related behaviors such as diet and physical activity may have a significant role in reducing lung cancer risk in men.

Three studies found an inverse relationship between guideline adherence and risk of endometrial cancer; however, only two of those studies showed a statistically significant result for the high versus low adherence comparison. The third study did suggest a significant trend with higher adherence leading to lower risk of endometrial cancer when the adherence score was evaluated as a continuous variable.

B. Specific Aim 2: Association between cancer prevention guideline adherence and circulating concentrations of 25(OH)D

Greater adherence to nutrition and physical activity cancer prevention guidelines, developed by ACS and other leading cancer organizations, has been found to be associated with reduced risk of overall cancer incidence and mortality, including some site-specific cancers (111). These guidelines are consistent with recommendations for the prevention of other major diseases as well, and if followed, will lead to healthier lives overall (25, 112, 113). To our knowledge, no studies have assessed the relationship between ACS guidelines for cancer prevention and circulating concentrations of vitamin D metabolites, which are biomarkers often linked to health outcomes (114). This current work offers evidence indicating greater adherence to an overall lifestyle pattern as outlined by the ACS nutrition and physical activity cancer prevention guidelines is associated with higher concentrations of both 25(OH)D and $1,25(OH)_2D$. Furthermore, significant dose-dependent trends are seen for BMI, physical activity, and alcohol intake and both vitamin D metabolites. The relationship between alcohol intake and higher

circulating concentrations of vitamin D has been reported previously with suggestions of residual confounding or heavier alcohol consumers have lifestyles favorable to higher concentrations of circulating vitamin D (115, 116). To our knowledge there is no clear biological mechanism for this observation and warrants further investigation.

Concentrations of 25(OH)D can vary due to many non-modifiable factors such as skin pigmentation, sex, genetic background, and season (47, 48). However, 25(OH)D also varies due to modifiable factors such as amount of sun exposure, dietary intake, and supplementation (46). Sun exposure increases vitamin D production, but also can cause skin damage or even skin cancer, the risk of which varies according to skin pigmentation and possibly body size (117, 118). Compared to normal weight adults, obese adults have been found to have significantly lower levels of the vitamin D metabolite 25(OH)D, possibly due to lower dietary intakes and lesser exposure of skin to sunlight (50, 118). Healthy-weight adults with higher levels of physical activity are more likely to meet Dietary Reference Intakes (DRIs) for vitamin D and other micronutrients than overweight adults (51). Furthermore, several studies have suggested that obese adults may need higher doses of supplementation than normal weight adults to achieve sufficient 25(OH)D status (38, 119).

A recent review of vitamin D supplementation trials estimates that 2990 IU per day is required to surpass deficient concentrations (20 ng/mL) of serum 25(OH)D in 97.5% of healthy individuals (39). The Recommended Dietary Allowance (RDA) for healthy adults aged 19-70 years is 600 IU, and is 800 IU for those over 70 years of age (26). However,

it has been suggested these recommendations have been miscalculated, are too low, and should be reconsidered (40). To address these concerns, selected vitamin D supplementation trials were reviewed. Table 17 presents the means and standard deviations of 25(OH)D for selected, large vitamin D supplementation trials presented in a recent review (39) as well as a trial conducted by the Arizona group (120). Three studies used doses of 400 IU/d with follow-up times of 4, 48, and 108 weeks resulting in mean 25(OH)D concentrations of 28.3 ±8.9 ng/mL in healthy men and women (120), and 36.9 ±9.5 ng/mL (121) and 24.4 ±12.2 ng/mL (122), in two separate studies of postmenopausal women. Doses of 800 IU/d were used in two trials with a range of follow-up time from 13 to 156 weeks, resulting in mean 25(OH)D concentrations of 28.39 ±9.18 and 29.91 ±8.78 ng/mL among women (123, 124). In a study evaluating the effect of a daily dose of 1000 IU in preventing new colorectal adenomas, healthy non-Hispanic whites aged 45-75 years, had mean concentrations of 31.5 ±8.9 ng/mL after one year (125). Comparable to the current analyses in the pooled chemoprevention trials, moderate and high adherence to the ACS guidelines demonstrated mean concentrations of 25(OH)D of 29.6 ±0.5 and 32.0 ±0.8 ng/mL, respectively. Therefore, following the ACS guidelines could potentially increase 25(OH)D levels as much as or more than a supplement of 1000 IU per day. Improving vitamin D status through lifestyle modifications as opposed to supplementation allows for a strategy that would avoid any potential toxicity such as renal calcifications (42), and is likely to incur other health benefits as well.

Table 17. Comparison of 25(OH)D concentrations in supplementation trials and adherence score category.

				Post-supplementation 25(OH)D, ng/mL	
Study	**Sample/ Population**	**Cholecalciferol Dose (IU/d)**	**Follow-up (weeks)**	**Mean**	**SD**
Aloia, et al., 2005 (123)	104 healthy, postmenopausal African-American women, 50-75 years	800	13	28.39	9.18
Baron, et al., 2014 (125)	1755 healthy, non-Hispanic whites, 45-75 years	1000 and/or 1200mg/d calcium	52	31.5	8.9
Dawson-Hughes, et al., 1991 (121)	125 postmenopausal women	400 + 377 mg/d calcium	48	36.93	9.46
Hibler, 2011 (120)	28 healthy adults	400	4	28.3	8.9
Karkkainen, et al., 2010 (124)	306 OSTPRE-FPS[1] Finnish women, >65 years	800 + 1000mg calcium	156	29.91	8.78
Lappe, JM, et al., 2007 (126)	288 postmenopausal women in rural Nebraska	1100 + 1400-1500mg/d	288	38.50	8.58
Schnatz, PF, et al., 2014 (122)	285 postmenopausal women, Women's Health Initiative	400 + 1000mg/d calcium	104	24.38	12.23
Current study	909 moderately adherent to ACS guidelines	-	-	29.6	0.5
Current study	233 highly adherent to ACS guidelines	-	-	32.0	0.8

[1]Osteoporosis Risk Factor and Prevention Study- Fracture Prevention Study

Less is known about lifestyle factors that may be associated with circulating concentrations of $1,25(OH)_2D$ (127). Few epidemiological studies have evaluated the association between $1,25(OH)_2D$ and physical activity. The first examined the effects of long-term aerobic exercise and omega-3 supplementation on bone health in postmenopausal women and found $1,25(OH)_2D$ increased with the intervention (128). Similarly, in a study within the UDCA cohort included in the present study, moderate to vigorous physical activity was positively associated with $1,25(OH)_2D$, with women experiencing the greatest increase (104). Body mass index, the measure used to estimate body size in our study, has a well-known inverse relationship with 25(OH)D, but has limited evidence with $1,25(OH)_2D$. A statistically significant association between higher circulating concentrations of $1,25(OH)_2D$ and lower risk of metabolic syndrome, which consists of waist circumference, triglycerides, blood pressure, glucose, and high-density lipoprotein, has also been reported in a sample population from the UDCA and WBF cohorts (129).

C. Specific Aim 3: Association between cancer prevention guideline adherence and new colorectal adenoma occurrence

The results of the present study demonstrate that adherence to nutrition and physical activity cancer prevention guidelines was associated with lower odds of advanced adenoma features at baseline. Those who were more adherent to the guidelines were significantly less likely to present with multiple adenomas, which are established precursors of colorectal cancer. In contrast, there were no statistically significant associations observed for ACS guideline adherence and odds of developing a new

adenoma over a 3 year follow-up period. These findings suggest that adherence to a healthy lifestyle pattern may not be most relevant in the irreversible initiation phase of carcinogenesis, but in the reversible promotion phase, where premalignant adenomas may advance into invasive colorectal cancer.

To date, few studies have evaluated the association between healthy lifestyle adherence and colorectal adenoma risk. Similar to the presented findings, a recent study demonstrated a statistically significant inverse association between adherence to health guidelines and detection of advanced colorectal neoplasia defined as high-risk adenomas (≥3 adenomas or any adenoma ≥1 cm in diameter or villous/tubulovillous/severe dysplasia) or colorectal cancer (130). Fu et al. also found strong evidence that lifestyle modification was important for the prevention of colorectal polyps, especially advanced and multiple adenomas (131). In contrast to the findings from the current study, a case-control study by Tabung et al. found that for participants who reported no use of NSAIDs, those in the healthy lifestyle category had a 72% lower odds of any colorectal adenoma as compared to those in the unhealthy category (OR 0.28; 95% CI 0.08, 0.98) (132). Further, a one-unit increase in the index significantly reduced odds of any adenoma by 53% (OR 0.47; 95% CI 0.26, 0.88), however the sample size was fairly small (n=143) (132).

In summary, these results suggest that following an overall pattern of healthy behaviors as recommended in the ACS Nutrition and Physical Activity Cancer Prevention guidelines is associated with a reduction in colorectal adenoma multiplicity at baseline.

However, no association with adhering to the guidelines and odds of developing a new colorectal adenoma was observed over the 3-year follow-up period in our sample population. This is an important area for further research as the presence of multiple adenomas increases the risk of development of CRC. Prevention of multiple adenomas may have an impact on colonoscopy screening rates as well, as multiplicity is an indicator for more frequent surveillance.

D. Strengths and Limitations

To our knowledge, this was the first systematic review of dietary and physical activity cancer prevention guidelines and cancer outcomes. Strengths of this systematic review include strict inclusion criteria to include only prospective studies that constructed adherence scores to the established cancer prevention guidelines by ACS or WCRF/AICR. All of the studies contained sizeable cohorts with multiple years of follow-up leading to sufficient sample sizes, ample power to detect associations, and sufficient number of outcomes, enabling them to evaluate associations for some site-specific cancers. However, there are also some limitations that must be considered. First, all studies generated their own adherence scores based upon recommendations from either the ACS or WCRF/AICR. Most studies assigned points for meeting or partially meeting recommendations while others categorized adherence as “met” or “did not meet” recommendations. Including multiple levels of exposure may better capture the degree of adherence to the guidelines. Although ACS and WCRF/AICR guidelines are very similar, interpretations of how to measure the recommendations varied. Notably, physical activity was assessed several ways including in metabolic equivalents, times per week, and even a physical activity index. Furthermore, studies utilized frequency questionnaires

to capture diet and physical activity data. These self-reported measures are well-known sources of measurement error, which may bias findings toward the null, lending to conservative findings in this review. Components of the adherence score were measured singularly at baseline and used to assess cancer risk over time. Repeated measurements of diet and physical activity may have provided an improved exposure assessment of long-term behavior and risk over time. Follow-up times ranged from 7.7-14 years, which may not be sufficient for assessing the protective role of adherence to nutrition and physical activity cancer prevention guidelines. In addition, although the studies evaluated large cohorts, there was limited population heterogeneity with regard to race or ethnicity, with the exception of the WHI and SCCS studies. Furthermore, analyses varied somewhat among the studies. All studies evaluating associations with ACS guideline adherence made comparisons of high versus low adherence. One study used WCRF/AICR guidelines to compare "met" versus "did not meet" recommendations (89), while a single study evaluated adherence to WCRF/AICR guidelines based upon point increments of the overall score (96). Finally, the potential for publication bias is always of concern. Studies with significant findings are more likely to be published than those with null or unimportant findings. Grey literature was included in the search via Google Scholar in an attempt to capture any work that hasn't been formally published (abstracts, conference proceedings, etc.). Even though the studies differed in some measurements of individual score components, construction of the adherence score, specifics of the set of guidelines used, and analytic methods, it is important to note that studies generally demonstrated agreement in their findings even across countries with varying diet and physical activity patterns.

The major strengths for the analyses focused on the pooled data analysis of large chemoprevention trials include availability of data from a prospective cohort of over 1,300 participants with complete data on a wide range of available baseline nutrition, physical activity, adenoma characteristics, new adenoma occurrence, and serum vitamin D metabolite data. However, even though the original trials were prospective cohorts, the majority of this secondary data analysis is cross-sectional in nature with measurements coming from baseline assessments with the exception of evaluating new adenoma occurrences. Only one measure of 25(OH)D was used for the assessment of vitamin D status, although previous findings suggest that single, baseline 25(OH)D measurements provide reasonably representative measures of the biomarker (133). In addition, the "maintenance of a healthy weight throughout life" ACS guideline could not be precisely assessed because height and weight data were not available for earlier periods in life. Although the instruments used to collect lifestyle data asked for usual dietary consumption in the prior 12-month period and the last 4 four weeks for physical activity, the reported behaviors may not be representative of the participants' longer-term behaviors. While self-reports of physical activity, dietary and alcohol intake are susceptible to measurement error or misclassification bias, the frequency questionnaires used had been validated in the study sample. Finally, there is the potential issue that the various healthy behaviors included in the ACS adherence score may cluster in individuals making it difficult to separate the effect of the score components. Nonetheless, these findings indicate the potential for increasing levels of vitamin D when the overall guidelines are more closely followed. We were unable to adjust for the number of

previous colonoscopies. Perhaps those who were more adherent to the guidelines were more likely to have regular screening colonoscopies and therefore less likely to have multiple adenomas discovered at a given colonoscopy. The null findings for any new colorectal adenomas could be due to many reasons including follow-up time too short, residual confounding, or inadequate power in stratification analyses.

E. Conclusions and Future Directions

The work completed within this dissertation provides evidence for the benefit of following the ACS Nutrition and Physical Activity Cancer Prevention Guidelines on not only cancer incidence and mortality, but also for achieving higher concentrations of vitamin D metabolites and reduction in colorectal adenoma multiplicity. The systematic review of Aim 1 found strong and consistent evidence from ten large prospective cohorts in 12 publications indicating that adherence to ACS and WCRF/AICR cancer prevention guidelines was associated with significant reductions in cancer incidence and cancer mortality for both men and women. Additionally, significant inverse associations were consistently found between guideline adherence and breast, colorectal, and endometrial cancer incidence. These findings provide an easy-to-use guide to health practitioners who are required to pass along large amounts of information to their patients. Further research in this area might be to examine the knowledge of physicians and other healthcare professionals regarding these guidelines and/or testing an education module to further promote these guidelines. It may also be worthwhile to examine alternate pathways of delivering this healthcare message, such as through social media and via patient portals. To further illustrate the association between adherence to nutrition and

physical activity cancer prevention guidelines and cancer outcomes, specific dietary and physical activity interventions may need to be evaluated in randomized controlled trials.

The secondary analyses conducted for Aim 2 suggest that following an overall pattern of healthy behaviors as recommended in the ACS Nutrition and Physical Activity Cancer Prevention guidelines may be associated with higher concentrations of both 25(OH)D and $1,25(OH)_2D$. In addition, adherence score components also demonstrated significant associations. Therefore, adhering to the ACS nutrition and physical activity cancer prevention guidelines may be a viable public health strategy for increasing both 25(OH)D and $1,25(OH)_2D$ concentrations. This is a key finding as there remains controversy over the optimal dosage of vitamin D supplementation, which itself may be associated with adverse outcomes. Future epidemiological studies need to include more diverse populations, specifically populations with different skin pigmentation and from different geographic areas. Intervention studies should also be considered to further evaluate the effect of adherence to the guidelines on vitamin D levels over time. In addition, it will be important to ascertain if there is a specific mechanism of action related to specific guidelines, such as physical activity, that may promote the synthesis of vitamin D; or whether higher levels of vitamin D metabolites are an indirect effect of characteristics such as having lower BMI.

The results of Aim 3 suggest that following the recommendations outlined by the ACS Nutrition and Physical Activity Cancer Prevention guidelines is associated with a reduction in colorectal adenoma multiplicity at study baseline. In contrast, we found no association with adhering to the guidelines and odds of developing a new colorectal adenoma during the 3-year follow-up period. These findings suggest that the protective effect of following the ACS Nutrition and Physical Activity guidelines may occur not

with prevention of new adenomas, but in inhibiting the formation of multiple adenomas. This is an important area for further research as the presence of multiple adenomas increases the risk of development of CRC. Prevention of multiple adenomas may have an impact on colonoscopy screening rates as well, as multiplicity is an indicator for more frequent surveillance.

To summarize, the work from this dissertation contributes to the literature on healthy lifestyle patterns such as that outlined in the ACS Nutrition and Physical Activity Cancer Prevention Guidelines and the association with cancer outcomes, circulating concentrations of vitamin D metabolites, and colorectal adenomas. By maintaining a healthy body size, focusing on a healthy diet of mostly plant-based foods, minimizing consumption of red and processed meat, and limiting alcohol intake, Americans can significantly reduce their risk of getting cancer or dying from cancer. In addition, adherence may lead to increased circulating concentrations of vitamin D levels which have been linked to not only cancer but also cardiovascular disease and diabetes. To fully understand the association between guideline adherence and development of colorectal adenomas, further studies need to be performed. It is possible that follow-up time too brief to capture the protective effect of guideline adherence on new colorectal adenomas or perhaps the benefit occurs by preventing a field effect that results in the development of fewer lesions. Physicians and public health officials need to continue to emphasize the importance of following health promotion guidelines.

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APPENDIX A: MANUSCRIPT 1

Kohler LN, Garcia DO, Harris RB, Oren E, Roe DJ, Jacobs ET. Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review. Cancer epidemiology, biomarkers & prevention. 2016 Jul;25(7):1018-28. PubMed PMID: 27340121. http://cebp.aacrjournals.org/content/25/7/1018.long

Adherence to Diet and Physical Activity Cancer Prevention Guidelines and Cancer Outcomes: A Systematic Review

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Abstract

Many studies have reported that adherence to health promotion guidelines for diet, physical activity, and maintenance of healthy body weight may decrease cancer incidence and mortality. A systematic review was performed to examine associations between adherence to established cancer prevention guidelines for diet and physical activity and overall cancer incidence and mortality. PubMed, Google Scholar, and Cochrane Reviews databases were searched following the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA). Twelve studies met inclusion criteria for this review. High versus low adherence to established nutrition and physical activity cancer prevention guidelines was consistently and significantly associated with decreases of 16-61% in overall cancer incidence and mortality. Consistent significant reductions were also shown for breast cancer incidence (19-60%), endometrial cancer incidence (23-60%), and colorectal cancer incidence in both men and women (35-52%). Findings for lung cancer incidence were equivocal and no significant relationships were found between adherence and ovarian or prostate cancers. Adhering to cancer prevention guidelines for diet and physical activity is consistently associated with lower risks of overall cancer incidence and mortality, including for some site-specific cancers.

Introduction

An estimated 1,685,210 new cancer diagnoses and 595,690 cancer deaths are expected in the United States (U.S.) in 2016 (1). Behaviors such as poor diet choices, physical inactivity, excess alcohol consumption and unhealthy body weight could account for more than 20% of cancer cases and therefore be prevented with lifestyle modifications (1). Two-thirds of U.S. cancer deaths can also be attributed to these modifiable behaviors when including exposure to tobacco products (6, 22-24, 69).

To help guide individuals and communities toward healthier lifestyles, nutrition and physical activity guidelines for cancer prevention have been designed by the U.S. Department of Health and Human Services along with leading health organizations such as the American Cancer Society (ACS) (70) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (71). These cancer prevention and health promotion guidelines focus on specific lifestyle recommendations to 1) achieve and maintain a healthy weight throughout life; 2) adopt a physically active lifestyle; 3) consume a healthy diet with an emphasis on plant-based foods; and 4) limit alcohol consumption (6).

Often epidemiological studies attempt to parse out specific, individual risk factors; however, examination of an overall risk pattern also provides key information when considering health-related behaviors which often co-occur (72). For example, a general

risk profile pattern can be ascertained by measuring adherence to cancer prevention guidelines. A score can be constructed based on multiple lifestyle aspects including body mass index (BMI), physical activity, alcohol intake, and various aspects of a healthy diet such as intake of fruit and vegetables, whole grains, and red/processed meat. Utilization of such an adherence score would allow for investigation of overall behavior patterns.

The ACS and WCRF/AICR examine the most current, evidence-based research on diet, physical activity, and cancer risk from laboratory experiments, human studies, and comprehensive reviews, and then publish cancer prevention recommendations for individuals and community action. The most recent update from the ACS Nutrition and Physical Activity Guidelines Advisory Committee was published in 2012 (6). The ACS guidelines contain specific strategies to adhere to the aforementioned recommendations. Similarly, WCRF/AICR guidelines focus on improving modifiable risk profiles, with the most recently-published recommendations for healthy lifestyles in 2007 (69). These recommendations also proffer guidelines for remaining as lean as possible within the normal range of body weight, being physically active as a part of everyday life, eating mostly plant foods, limiting intake of red meat and avoiding processed meat, limiting consumption of alcohol, limiting consumption of energy dense foods, avoiding sugary drinks, and limiting salt consumption.

The aim of the systematic review was to synthesize the evidence from prospective cohort studies regarding adherence to the ACS and WCRF/AICR nutrition and physical activity

cancer prevention guidelines and the risk of overall cancer incidence and/or cancer mortality.

Methods and Materials

Search Strategy and Identification of Studies

Two independent authors (LNK, DOG) executed the following comprehensive search strategy following the current recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analysis Approach (PRISMA) (73). Key search terms were used to maximize the identification of prospective cohort studies that examined associations between adherence to nutrition and physical activity cancer prevention guidelines and cancer incidence and mortality. Databases were searched in March 2016, using the following search parameters: PubMed key terms "cancer prevention guidelines", "nutrition," physical activity," "adherence," "cancer incidence and/or cancer mortality"; Google Scholar search "cancer prevention guideline adherence AND nutrition AND physical activity AND cancer incidence" with the exact phrase "cancer prevention guidelines" and at least one of the words "incidence mortality"; and Cochrane reviews strategy "adherence to nutrition physical activity cancer prevention guidelines". Filters included human studies in English only, articles that had full text available; and papers published within the past ten years. All eligible full-text articles selected for inclusion were examined for citations of relevant studies.

Titles and abstracts were screened by two reviewers; data were extracted by one reviewer (LNK) and double-checked by the second reviewer (DOG) using a pre-designed data

extraction form. Data extracted from each study included the author's first and last names, title, publication year, study population (cohort and sample size), follow-up period, guidelines utilized and how adherence score was generated, covariates, and study outcomes including relative risks (RR) or hazard ratios (HR) and confidence intervals (CI). The Critical Appraisal Skills Programme's *Making sense of evidence* (74) was the predetermined tool used to assess the risk of bias. The tool was used to assess recruitment procedures, measurement of exposure, confounding variables, study outcomes, and generalizability. A third reviewer (ETJ) resolved any disagreement. The protocol was registered with PROSPERO International Prospective Register of systematic reviews (Ref: CRD42015026614).

Inclusion and exclusion criteria

Only prospective cohort studies were eligible for inclusion as the focus was to ascertain cancer incidence and cancer mortality. Minimally, studies must have collected data for physical activity and diet, generated an adherence score based on either ACS or WCRF/AICR cancer prevention guidelines (5, 6), and reported cancer outcomes of incidence and/or mortality in order to be deemed eligible for this review. Overall cancer incidence and cancer mortality were the primary outcomes of interest. However, site-specific cancer risks were also considered when data were available from at least two studies meeting the eligibility criteria. Commentaries and summary documents were excluded unless they presented additional data.

Results

A total of 2,033 potentially relevant studies were reviewed; after removal of duplicates and exclusion on the basis of title or abstract, 25 full papers on nutrition and physical activity cancer prevention guideline adherence were retained for in-depth consideration. The selection process for the articles is shown in Figure 1. We identified 12 manuscripts that met the *a priori* criteria for inclusion (Table 1). These studies represented analyses of data from 10 cohorts including the Cancer Prevention Study-II (CPS-II) nutrition cohort (75), the Women's Health Initiative (WHI) cohort (76), the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort (77), the Framingham Offspring (FOS) cohort (78), the Vitamins and Lifestyle (VITAL) Study cohort (79), the Canadian National Breast Screening Study (NBSS) (80), the Swedish Mammography Cohort (SMC) (81), the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (82, 83), the Southern Community Cohort Study (SCCS) (84), and the Iowa Women's Health Study (IWHS) cohort (85). Adherence scores for these studies were constructed utilizing recommendations from the American Cancer Society (ACS) (Table 2) (70) or the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) (Table 3) (71).

Overall Cancer

Seven studies evaluated the association between guideline adherence for diet, physical activity, healthy body weight, and alcohol consumption and overall cancer incidence and/or mortality. After adjustment for covariates, there were statistically significant effects of guideline adherence on cancer risk. Participants with high adherence to the ACS guidelines were less likely to develop or die from any cancer compared to those

participants that had low adherence to the ACS guidelines (7, 8, 86, 87). Likewise, meeting or highly adhering to WCRF/AICR recommendations versus low or no adherence to the recommendations also demonstrated statistically significant risk reduction in overall cancer incidence (88) and mortality (89, 90).

The study by McCullough et al. (8) developed an original scoring system to reflect adherence to the ACS guidelines with the goal of evaluating the association between following the recommended guidelines and risk of death from cancer, cardiovascular disease, and all causes. The authors evaluated 111,966 non-smoking men and women in the CPS-II Nutrition cohort, which is a subset of the larger CPS-II (75). Participants were primarily healthy, Caucasian adults aged 50-74 years from 21 states in the U.S. (75). The scoring system weighted each recommendation equally from 0 to 2 possible points, with 0 points representing not meeting the recommendation at all, 1 point for partially meeting the recommendation, and 2 points for fully meeting the recommendation. The overall adherence scores in the study population ranged from 0 for those participants who did not follow any of the guidelines to 8 for those participants that were fully adherent to all four lifestyle factor recommendations (Table 2). High adherence was a score of 7-8 points and low adherence was a score of 0-2 points. McCullough et al. reported a 24% reduction (RR=0.76, 95% CI: 0.65-0.89) and a 30% reduction (RR=0.70, 95% CI: 0.61-0.80) in cancer mortality over 14 years of follow up for men and women, respectively, with high adherence compared to those with low adherence to the ACS guidelines. (8).

Thomson et al. (7) used similar methodology to examine the impact of adherence to the ACS guidelines in 65,838 postmenopausal women aged 50-79 years from the Women's Health Initiative Observational Study (WHI-OS) (76). The WHI-OS was a prospective study of health outcomes in postmenopausal women that were enrolled in 40 U.S. clinical centers from 1993 to 1998 (91). Overall baseline adherence scores were similar to those from the CPS-II cohort, differing only slightly. The recommendation to "maintain a healthy weight throughout life" was assessed from reported weight at 18 years and measured at study baseline. The score for the recommendation to "consume a healthy diet with an emphasis on plant sources" included an extra point or two for diet quality determined by being in the second or third tertile of total carotenoids, respectively (Table 2). Similar to the previous study, the overall adherence scores ranged from 0 for those participants not adherent to any of the guidelines to 8 for fully adherent participants and were collapsed into categories for comparison. The overall cancer incidence or mortality analyses included a comparison of highly adherent participants with a score of 7 or 8 compared to low adherence participants scoring less than 2 points. Cancer-specific mortality analyses further collapsed categories of the score (0-3, 4-5, 6-8) due to smaller numbers of events. In women that had high adherence to the ACS guidelines, Thomson et al. demonstrated a 17% reduction in cancer incidence over the 12.6 years of follow-up (HR=0.83, 95% CI: 0.75-0.92) and 20% reduction in cancer-specific mortality (HR=0.80, 95% CI: 0.71-0.90) compared to women with low adherence to the ACS guidelines (7).

In the third study utilizing the ACS guidelines, nearly half a million men and women aged 50-71 in the NIH-AARP Diet and Health Study (n=476,396) were included from 6

states and 2 metropolitan areas with existing population-based cancer registries from 1995-1996 (77). Adherence scores were modified somewhat from prior ACS-based studies by using only one baseline measurement for BMI, categorizing physical activity by times per week instead of metabolic equivalents of task (MET) hours per week, not including a variety or quality of diet measure, and giving moderate drinkers (1-2 drinks per day for men and 1 drink per day for women) the most adherent score of 2 points for the alcohol consumption recommendation (Table 2). Participants were categorized as most adherent if they scored 8-11 points and least adherent if they scored 0-3 points overall. As shown in Table 1, Kabat et al. reported a statistically significant decrease in cancer incidence over the 10.5 years of follow-up for both highly adherent men (HR=0.90, 95% CI: 0.87-0.93) and women (HR=0.81, 95% CI: 0.77-0.84). A statistically significant reduction in cancer mortality was also reported during the 12.6 years of follow-up for both highly adherent men (HR=0.75, 95% CI: 0.70-0.80) and women (HR=0.76, 95% CI: 0.70-0.83) (87).

Warren Andersen et al. (86) performed the most recent evaluation between adherence to the ACS guidelines and overall cancer incidence utilizing the Southern Community Cohort Study (SCCS) (n=61,098) with a focus on representing low-income Whites and African Americans in the southeastern United States. Adherence scores ranged from 0 to 4 points with 1 point assigned for each recommendation met upon study entry (Table 2). A comparison of the most adherent participants (score=4) versus non-adherent participants (score=0) demonstrated a nonsignificant 4% reduction in overall cancer incidence (HR=0.96, 95% CI: 0.65-1.42) in the SCCS participants. However, when

evaluating only participants free of chronic disease at baseline, a statistically significant 45% reduction in cancer risk (HR=0.55, 95% CI: 0.31-0.99) was found (86).

Romaguera et al. (88) assessed the association between adherence to WCRF/AICR guidelines and overall cancer incidence as well as specific types of cancer incidence in the European Prospective Investigation into Nutrition and Cancer (EPIC) cohort study (n=386,355) (82, 83). The constructed adherence score (Table 3) operationalized the WCRF/AICR recommendations of body fatness, physical activity, intake of food and drinks that promote weight gain, intake of plant foods, intake of animal foods, intake of alcoholic drinks, and breastfeeding. One point was assigned for each recommendation that was fully met, a half point was assigned for partially meeting the recommendation, and all others received zero points for not meeting the recommendation. For women, high adherence to the score was denoted if the score summed to 6-7 points compared to low adherence scoring 0-3 points. For men, high adherence was considered a score of 5-6 compared to low adherence scoring 0-2 points. Romaguera et al. reported a statistically significant decrease in overall cancer incidence over the 11.0 years of follow-up for both highly adherent men (HR=0.84, 95% CI: 0.72-0.99) and women (HR=0.81, 95% CI: 0.72-0.91). In addition, a 1-point increment of the adherence score was associated with a statistically significant 5% reduction in overall cancer incidence (HR=0.95, 95% CI: 0.93-0.97) (88).

Similarly, Vergnaud et al. (90) investigated whether adherence to WCRF/AICR recommendations was associated with risk of death in the EPIC cohort study (n=378,864)

after a median follow-up time of 12.8 years (82, 83). The adherence score (Table 3) was modeled after the previous work of Romaguera et al. utilizing the same recommendations and collapsing the score into the same sex-specific high and low adherence categories. A significant reduction in cancer-specific mortality was found among women who were most adherent to WCRF/AICR recommendations (HR=0.76, 95% CI: 0.62-0.93). Statistical significance was not reached in the association for men (HR=0.86, 95% CI: 0.69-1.07); however, an 8-9% reduction in risk per 1-point increase of WCRF/AICR adherence score was statistically significant for both men (HR=0.92, 95% CI: 0.89-0.95) and women (HR=0.91, 95% CI: 0.88-0.94) (90).

Finally, Hastert et al. (2014) also operationalized the WCRF/AICR guidelines (Table 3) to examine the association between meeting guidelines on nutrition and physical activity and cancer mortality in a cohort of men and women (n=57,841) aged 50 to 76 years from the VITAL study (79). Adherence to the WCRF/ AICR guidelines was classified as met or did not meet (DNM) for each of the 6 included recommendations (Table 2). Recommendations to limit salt preserved foods and supplements were not considered as the former was not considered common in the U.S. food supply and the latter because the guidelines did not recommend for or against supplementation for the prevention of cancer. Adherence was measured as follows: BMI by self-reported height and weight, physical activity by minutes per day and intensity, energy density, plant foods, red meat, and alcohol based on responses to the food frequency questionnaire (FFQ). Meeting at least five recommendations compared to meeting none demonstrated a 61% reduction in cancer-specific mortality over 7.7 years of follow-up (HR=0.39, 95% CI: 0.24-0.62) (89).

Breast Cancer

In addition to overall cancer incidence, eight studies reported results for female breast cancer incidence as an outcome (7, 87, 92-95). Consistent reductions in breast cancer incidence were demonstrated in the WHI, NIH-AARP, and EPIC cohorts for high adherence to nutrition and physical activity cancer prevention guidelines versus low adherence, with HRs (95% CIs) of HR=0.78, 95% CI: 0.67-0.92 (7), HR=0.81, 95% CI: 0.76-0.87 (87), and HR=0.84, 95% CI: 0.78-0.90, respectively (88). Hastert et al. also investigated breast cancer incidence as an outcome using the WCRF/AICR guidelines in a cohort of postmenopausal women aged 50 to 76 years from the VITAL study (n = 30,797). Meeting at least five WCRF/AICR recommendations compared with meeting none was associated with a 60% reduction in breast cancer incidence (HR: 0.40, 95% CI: 0.25-0.65). Furthermore, each additional recommendation met was associated with an 11% reduction in breast cancer risk (HR=0.89, 95% CI: 0.84-0.95). (92). Similarly, Harris et al. demonstrated a 51% reduction in breast cancer incidence (HR: 0.49, 95% CI: 0.35-0.70) (93) for those most adherent (score≥6) compared to least adherent (score ≤2) to the WCRF/AICR guidelines in the primarily post-menopausal women in the Swedish Mammography Cohort (SMC) (n=31,514) that were followed for 15 years (81). Makarem et al. (96) also used the WCRF/AICR guidelines to examine the relationship between meeting the recommendations and obesity-related cancer incidence in a sample of men and women from the Framingham Offspring (FOS) cohort (n=2,983) (78). Cancers were considered obesity-related if clearly or possibly linked to excess adiposity by the ACS. Participants received 1, 0.5, or 0 points for fully meeting, partially meeting or not

meeting the WCRF/AICR recommendation, respectively (Table 2). Similar to the VITAL study, hazard ratios for every 1-unit increment in the overall adherence score were computed for obesity-related cancers and site-specific cancers. Conversely, no statistically significant association was found between adherence and breast cancer incidence (HR=0.87, 95% CI: 0.74-1.03) on a per-recommendation basis (96). Catsburg et al. (94) operationalized both ACS and WCRF/AICR guidelines in the Canadian National Breast Screening study (NBSS) (n=47,130 WCRF, n=46,298 ACS)(80). Adherence to all six ACS guidelines compared to at most one guideline was associated with a statistically significant 31% reduction in breast cancer incidence (HR=0.69, 95% CI: 0.49-0.97). Adhering to six or seven WCRF/AICR guidelines compared to at most one guideline was associated with a 21% reduction in risk (HR=0.79, 95% CI: 0.57-1.10) but did not reach statistical significance. Meeting each additional guideline was associated with a 5% (HR=0.95, 95% CI: 0.91-0.98) or 6% (HR=0.94, 95% CI: 0.91-0.98) reduction in breast cancer incidence utilizing the WCRF/AICR and ACS recommendations, respectively (94). Most recently, Nomura et al. (95) evaluated adherence to the WCRF/AICR guidelines and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors in the Iowa Women's Health Study (IWHS) (n=36,626). The eight point adherence score was collapsed into 4 categories: 0-3.5 points (low adherence), 4.0-4.5, 5.0-5.5, 6.0-8.0 (high adherence). High adherence compared to low adherence to WCRF/AICR guidelines was significantly associated with a reduction in breast cancer incidence (HR=0.76, 95% CI: 0.67-0.87) (95).

Colorectal Cancer

A total of four studies reported results for colorectal cancer specifically (7, 87, 88, 96). Significant inverse associations were found between adherence to ACS guidelines and colorectal cancer incidence in the WHI cohort (HR=0.48, 95% CI: 0.32-0.73) (7) as well as the NIH-AARP cohort for women (HR=0.65, 95% CI: 0.54-0.78) and men (HR=0.52, 95% CI: 0.47-0.59) (87). Consistently, a statistically significant reduction in colorectal cancer was associated with higher adherence in the EPIC cohort (HR=0.73, 95% CI: 0.65-0.81) (88). In contrast, the FOS cohort demonstrated no significant association for colorectal cancer incidence and adherence to WCRF/AICR guidelines (HR=0.87, 95% CI: 0.68-1.12) (96).

Lung Cancer

The association between ACS guideline adherence and lung cancer incidence is equivocal. Three studies reported results for the association between nutrition and physical activity guideline adherence and lung cancer incidence (7, 87, 88). In the NIH-AARP cohort, effect modification by sex was demonstrated with a statistically significant inverse association found among highly adherent men (HR=0.85, 95% CI: 0.78-0.93), but not highly adherent women (HR=0.94, 95% CI: 0.84-1.05) (87). Results from the WHI are consistent with these reporting no statistical significance between lung cancer incidence in women and ACS guideline adherence (HR=1.14, 95% CI: 0.81-1.60) (7). The association between high adherence and lung cancer incidence was not statistically significant when evaluated for both sexes combined in the EPIC study (HR=0.86, 95% CI: 0.74-1.00) (88).

Endometrial Cancer

To date, three prospective studies have reported results for the association between nutrition and physical activity guideline adherence and endometrial cancer incidence. The large NIH-AARP and EPIC cohorts both found significant inverse associations demonstrated by higher adherence and lower risk of endometrial cancer (HR=0.40, 95% CI: 0.34-0.46; HR=0.77, 95% CI: 0.62-0.94), respectively (87, 88); while findings from the WHI cohort suggest no significant association (HR=0.73, 95% CI: 0.49-1.09) (7). Although analysis of the adherence score as a categorical variable (high vs. low) in the latter study was not statistically significant for risk of endometrial cancer, the overall trend using ACS score as an ordinal variable (0-8 points) suggested a significant 7% reduction in endometrial cancer incidence (HR=0.93, 95% CI: 0.87-0.98) (7).

Other Cancers

Data were also available from three studies meeting the eligibility criteria for ovarian (7, 87, 88) and prostate (87, 88, 96) cancer incidence. No statistically significant associations were found between ovarian cancer incidence and ACS guideline adherence in the WHI or NIH-AARP cohorts or WCRF/AICR guideline adherence in the EPIC cohort. Likewise, no significant associations were identified for prostate cancer incidence utilizing the ACS guidelines in the NIH-AARP cohort or the WCRF/AICR guidelines in the EPIC or FOS cohorts.

Discussion

This systematic review included 12 studies from 10 different prospective cohorts evaluating the association between adherence to nutrition and physical activity cancer prevention guidelines and cancer outcomes. High versus low adherence to ACS or WCRF/AICR guidelines was consistently and significantly associated with decreases of 16-61% in overall cancer incidence and mortality. Consistent reductions were also shown for breast cancer incidence (19-60%), endometrial cancer incidence (23-60%), and colorectal cancer incidence in both men and women (35-52%) for those most adherent to the recommendations. Findings from three studies that reported results for adherence and lung cancer incidence were less clear. No significant relationships were found between adherence and ovarian or prostate cancers.

The greatest evidence for an association with the guidelines was significant findings in seven out of eight studies that included breast cancer incidence as an outcome. Regarding the studies specifically related to breast cancer, all eight included women 50 years and older, although WHI, IWHS, and VITAL cohorts included only postmenopausal women, and the SMC cohort consisted of primarily postmenopausal women. ACS guidelines were employed in the WHI, NIH-AARP, NBSS cohorts while the WCRF/AICR guidelines were used in the VITAL, FOS, SMC, EPIC, IWHS, and NBSS cohorts. Unlike the other studies that compared high adherence to low adherence, the FOS adherence score was evaluated and interpreted in 1-point increments (96). Other differences in the FOS cohort include fewer incident cases of breast cancer (n=124) and inclusion of pre- and postmenopausal women, which may contribute to attenuation of findings.

Significant inverse associations were also found between adherence to the guidelines and colorectal cancer incidence in three out of the four studies reviewed. The inconsistency in the FOS cohort could be due to the difference in the set of guidelines used for generation of adherence score, the different analytic approach utilizing the adherence score as a continuous variable versus a dichotomous variable (high versus low), analyzing men and women together unlike other studies, or perhaps the number of incident cases of colorectal cancer (n=63) in the FOS cohort was too small to detect statistically significant associations.

Less clear were the findings from three studies that included lung cancer as an outcome. One study reported a significant reduction in lung cancer for only men who had high adherence compared to men with low adherence, but not for women. Similarly, a second study found no association for women adhering to the guidelines and lung cancer and a third study had null findings when men and women were reported together. Though smoking status is the strongest risk factor associated with lung cancer, broader health-related behaviors such as diet and physical activity may have a significant role in reducing lung cancer risk in men.

Three studies found an inverse relationship between guideline adherence and risk of endometrial cancer; however, only two of those studies showed a statistically significant result for the high versus low adherence comparison. The third study did suggest a

significant trend with higher adherence leading to lower risk of endometrial cancer when the adherence score was evaluated as a continuous variable.

To our knowledge, this is the first systematic review of dietary and physical activity cancer prevention guidelines and cancer outcomes. Strengths of this systematic review include strict inclusion criteria to include only prospective studies that constructed adherence scores to the established cancer prevention guidelines by ACS or WCRF/AICR. All of the studies contained sizeable cohorts with multiple years of follow-up leading to sufficient sample sizes, ample power to detect associations, and sufficient number of outcomes, enabling them to evaluate associations for some site-specific cancers. However, there are also some limitations that must be considered. First, all studies generated their own adherence scores based upon recommendations from either the ACS or WCRF/AICR. Most studies assigned points for meeting or partially meeting recommendations while others categorized adherence as "met" or "did not meet" recommendations. Including multiple levels of exposure may better capture the degree of adherence to the guidelines. Although ACS and WCRF/AICR guidelines are very similar, interpretations of how to measure the recommendations varied. Notably, physical activity was assessed several ways including in metabolic equivalents, times per week, and even a physical activity index. Furthermore, studies utilized frequency questionnaires to capture diet and physical activity data. These self-reported measures are well-known sources of measurement error, which may bias findings toward the null, lending to conservative findings in this review. Components of the adherence score were measured singularly at baseline and used to assess cancer risk over time. Repeated measurements of

diet and physical activity may have provided an improved exposure assessment of long-term behavior and risk over time. Follow-up times ranged from 7.7-14 years, which may not be sufficient for assessing the protective role of adherence to nutrition and physical activity cancer prevention guidelines. In addition, although the studies evaluated large cohorts, there was limited population heterogeneity with regard to race or ethnicity, with the exception of the WHI and SCCS studies. Furthermore, analyses varied somewhat among the studies. All studies evaluating associations with ACS guideline adherence made comparisons of high versus low adherence. One study used WCRF/AICR guidelines to compare "met" versus "did not meet" recommendations (89), while a single study evaluated adherence to WCRF/AICR guidelines based upon point increments of the overall score (96). Finally, the potential for publication bias is always of concern. Studies with significant findings are more likely to be published than those with null or unimportant findings. Grey literature was included in the search via Google Scholar in an attempt to capture any work that hasn't been formally published (abstracts, conference proceedings, etc.). Even though the studies differed in some measurements of individual score components, construction of the adherence score, specifics of the set of guidelines used, and analytic methods, it is important to note that studies generally demonstrated agreement in their findings even across countries with varying diet and physical activity patterns.

In conclusion, strong and consistent evidence from ten large prospective cohorts in 12 publications indicates that adherence to ACS and WCRF/AICR cancer prevention guidelines was associated with significant reductions in cancer incidence and cancer

mortality for both men and women. Additionally, significant inverse associations were consistently found between guideline adherence and breast, colorectal, and endometrial cancer incidence. Adherence to a pattern of healthy behaviors, as outlined in cancer prevention guidelines from either the ACS or WCRF/AICR, may reduce cancer incidence and mortality.

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Table 1. Characteristics and findings of included prospective studies.

	Author, year	Study name, data collection years, sample size, years follow-up, guidelines	Relevant Outcome(s)	Key Findings
1	McCullough, 2011	CPS-II Nutrition Cohort, 1992-1993, n=111,966, 14 years, ACS[i]-8 point score	All cancer mortality	Men: RR[ii]=0.70, 95% CI[iii]: 0.61-0.80 Women: RR=0.76, 95% CI: 0.65-0.89
2	Thomson, 2014	Women's Health Initiative, 1993-1998, n=65,838, 12.6 years, ACS-8 point score	All cancer incidence, and mortality, site-specific cancer incidence	Cancer incidence: HR[iv]=0.83, 95% CI: 0.75-0.92 Cancer mortality: HR=0.80, 95% CI: 0.71-0.90 Colorectal: HR=0.48, 95% CI: 0.32-0.73 Breast: HR=0.78, 95% CI: 0.67-0.92 Endometrial: HR=0.73, 95% CI: 0.49-1.09 Ovarian: HR=1.13, 95% CI: 0.68-1.87 Lung: HR=1.14, 95% CI: 0.81-1.60
3	Kabat, 2015	NIH-AARP Diet and Health Study, 1995-1996, n=476,396, 10.5-12.6 years, ACS-11 point score	All cancer incidence, site-specific cancer incidence, all cancer mortality	All cancer incidence: Men HR=0.90, 95% CI: 0.87-0.93 Women HR=0.81, 95% CI: 0.77-0.84 All cancer mortality: Men HR=0.75, 95% CI: 0.70-0.80 Women HR=0.76, 95% CI: 0.70-0.83 Colon: Men HR=0.52, 95% CI: 0.47-0.59 Women HR=0.65, 95% CI: 0.54-0.78 Rectal: Men HR=0.60, 95% CI: 0.51-0.72 Women HR=0.64, 95% CI: 0.49-0.83 Lung: Men HR=0.85, 95% CI: 0.78-0.93 Women HR=0.94, 95% CI: 0.84-1.05

				Breast: HR=0.81, 95% CI: 0.76-0.87 Endometrial: HR=0.40, 95% CI: 0.34-0.46 Ovarian: HR=0.95, 95% CI: 0.73-1.23
5	Hastert, 2013	VITAL cohort, 2000-2002, n=30,797 post-menopausal women, 7.7 years, WCRF/AICR Met/didn't meet	Breast cancer incidence	HR=0.40, 95% CI 0.25-0.65
4	Hastert, 2014	VITAL cohort, 2000-2002, n=57,841, 7.7 years, WCRF/AICR met/didn't meet	All cancer mortality	HR=0.39, 95% CI 0.24-0.62)
6	Makarem, 2015	FOS cohort, 1991, n=2,983, 11.5 years, WCRF/AICR 7 point score	Incidence of obesity-related cancers and site-specific: breast, prostate, and colon	Obesity-related: HR=0.94, CI 0.86-1.02 Breast: HR=0.87, 95% CI: 0.74-1.03 Prostate: HR=1.08, 95% CI: 0.92-1.27 Colorectal: HR=0.87, 95% CI: 0.68-1.12
7	Harris, 2016	SMC, 1987-1990, n=31,514, 15 years, WCRF/AICR 7 point score	Breast cancer incidence	HR=0.49, 95% CI: 0.35-0.70
8	Catsburg, 2014	Canadian NBSS, 1980-1985, n=47,130 WCRF/AICR and n=46,298 ACS, 16.6 years	Breast cancer incidence	ACS: HR=0.69, 95% CI: 0.49-0.97 WCRF/AICR: HR= 0.69, 95% CI: 0.47-1.00
9	Vergnauad, 2013	EPIC Study, 1992-2000, n=378,864, 12.8 years, WCRF/AICR 6 point score for men, 7 point score for women	All cancer mortality	Total: HR=0.80, 95% CI: 0.69-0.93 Men: HR=0.86, 95% CI: 0.69-1.07 Women: HR=0.76, 95% CI: 0.62-0.93
10	Romaguera, 2012	EPIC Study, 1992-2000, n=386,355, 11.0 years, WCRF/AICR 6 point score for men, 7 point score for women	All cancer incidence, site-specific cancer incidence	All cancer incidence: Men HR=0.84, 95% CI: 0.72-0.99 Women HR=0.81, 95% CI: 0.72-0.91 Colorectal: HR=0.73, 95% CI: 0.65-0.81 Lung: HR=0.86, 95% CI: 0.74-1.00 Breast: HR= 0.84, 95% CI: 0.78-0.90 Endometrial: HR= 0.77, 95% CI: 0.62-0.94

				Ovarian: HR= 0.99, 95% CI: 0.79-1.25 Prostate: HR=1.02, 95% CI: 0.91-1.14
11	Nomura, 2016	IWHS, 1986, n=36,626 post-menopausal, >23 years, WCRF/AICR 8 point score	Breast cancer incidence	HR=0.76, 95% CI: 0.67-0.87
12	Warren Andersen, 2016	SCCS, 2002-2009, n=61,098 low-income racially diverse adults, 6 years, ACS 4 point score	All cancer incidence	HR=0.96, 95% CI: 0.65-1.42[v] HR=0.55, 95% CI: 0.31-0.99[vi]

[1] American Cancer Society
[ii] Relative Risk
[iii] Confidence Interval
[iv] Hazard Ratio
[v] Total analytic population. P-trend 0.09
[vi] Participants without chronic disease at baseline. P-trend 0.003

Table 2. ACS recommendations and adherence score breakdown of selected studies.

American Cancer Society				
Recommendation	**McCullough, 2011 Thomson, 2014[i]**	**Kabat, 2015**	**Catsburg, 2014**	**Warren Andersen, 2016**
"Maintain a healthy weight throughout life"	0: Obese at both time points or obese at 1 and overweight at the other 1: All others 2: BMI[ii] 18-<25 at both times	0: >35.0 1: 30-34.9 2: 25-29.9 3: 18.5-24.9	18.5 ≤ BMI ≤25	18.5 ≤ BMI ≤25
"Adopt a physically active lifestyle"	0: <8.75 MET[iii] h/wk 1: 8.75-17.5 MET h/wk 2: >17.5 MET h/wk	0: ≤ 3x/mo 1: 1-2x/wk 2: 3-4x/wk 3: ≥5x/wk	≥ 150 min/week	≥ 150 min/wk of moderate, ≥ 75 min/wk of vigorous or ≥ 150 min/wk of moderate + vigorous
"Eat 5 or more servings of a variety of vegetables and fruits each day"	1: ≥5 servings/d fruits +veg +1 or 2 "variety" points for 2nd or 3rd tertile of unique fruits or veg consumed/month	Quartiles	>400g vegetables and fruit per day	≥2.5 cups vegetables + fruits/d
"Choose whole grains instead of refined grains"	Quartiles of the ratio of whole grains to total grains	Quartiles of the ratio of whole grains to total grains	Ratio of whole: refined grains >1	Highest quartile of the ratio of whole grains to total grains
"Limit consumption of processed and red meats"	Quartiles of red + processed meat intake (servings/wk)	Quartiles of red + processed meats	<500g red and processed meat per week	Lowest quartile of red + processed meats

"If you drink, limit consumption to 1 drink/day for women or 2 drink/day for men"	Women: 0: >1 1: >0-≤1 2: Non	Men: 0: >2 1: >0-≤2 2: Non	Women: 0: ≥2 1: Non 2: 1	Men: 0: ≥3 1: Non 2: 1-2	≤1 standard drink/d	Women ≤1 drink/d Men ≤2 drinks/d

[1] Thomson evaluated BMI as <18.5 excluded 0: BMI >=30 kg/m^2 at age 18 or at baseline, 1: BMI 25-<30 at age 18 or baseline, 2: BMI <25 kg/m^2 at age 18 and baseline; diet score plus 1 or 2 "quality" points for being in the 2nd or 3rd tertile of total carotenoids; alcohol score 2 points for nondrinker at baseline

[ii] Body mass index, kg/m^2

[iii] Metabolic Equivalent of Task

Table 3. WCRF/AICR recommendations and adherence score breakdown of selected studies.

World Cancer Research Fund/American Institute for Cancer Research						
Recommendation	**Hastert, 2013 & 2014**	**Catsburg, 2014**	**Makarem, 2015**	**Harris, 2016**	**Vergnaud, 2013 Romaguera, 2012**	**Nomura, 2016**
"Be as lean as possible within the normal range of body weight"	18.5 ≤ BMI[i]<25	18.5 ≤ BMI ≤25	0: <18.5 BMI >30.0 0.5: 25-29.9 1: 18.5-24.9	18.5 ≤ BMI <25	0: <18.5 BMI >30.0 0.5: 25-29.9 1: 18.5-24.9	0: <18.5 BMI ≥30.0 0.5: 25-<30 1: 18.5-<25
"Be physically active as part of everyday life"	≥30 min/d of moderate/fast walking and/or moderate/strenuous activity ≥5 days/wk in ≥7 of the past 10 yrs	≥210 min/wk	0: <30 PAI[ii] 0.5: 30-33 1: >33	≥30 min/d[iii]	0: <15 min/d[iv] 0.5: 15-30 min/d 1: Manual/heavy manual job, or >2h/wk vigorous, or >30 min/d	0: all other 0.5: 2-4x/wk moderate or 1x/wk vigorous 1: ≥2x/wk vigorous or ≥5x/wk moderate
"Eat mostly foods of plant origin"	≥5 servings of fruits + veg and ≥1 serving whole grains and/or legumes/d	>400g veg +fruit plus ≥25g whole grains + legumes/d	<u>Fruit + Veg</u> (servings/d) 0: <2.5 0.5: 2.5-<5 1: ≥5 <u>Refined Grains</u> (g/d) Tertiles	>400g veg + fruit plus ≥25g whole grains and legumes/d	<u>Fruit + Veg (g/d)</u> 0: <200 0.5: 200 to <400 1: >400 <u>Dietary Fiber (g/d)</u> 0: <12.5 0.5: 12.5 to <25 1: ≥25	<u>Fruit + Veg</u> (servings/d) 0: <3 0.5: 3-<5 1: ≥5 <u>Dietary Fiber (g/d)</u> 0: <12.5 0.5: 12.5 to

			<u>Vegetables</u> (g/week) 0: S[v]>503; NS[vi]<2,471.4 or S<503;NS <2,471.4 0.5: S>503; NS>2,471.4 1: S<503; NS>2,471.4					<25 1: ≥25
"Limit intake of red meat and avoid processed meat"	<18 oz red and/or processed meat per week	<500g red and <25g processed meat per week	0: ≥500 g/wk or ≥50 g/d 0.5: <500 g/wk & 3 to <50 g/d 1: <500 g/wk & <3 g/d		<500g red and <25g processed meat/wk	0: ≥500 g/wk or ≥50 g/d 0.5: <500 g/wk & 3 to <50 g/d 1: <500 g/wk & <3 g/d		0: ≥500 g/wk RP[vii] or ≥50 g/wk P[viii] 0.5: <500 g/wk RP & 3 to <50 g/wk P 1: <500 g/wk RP & <3 g/wk P
"Limit alcoholic drinks"	≤1 drink/d for women; ≤2 drink/d for men	≤1 standard drink per day	Women g/day: 0: >21 0.5: 14-24 1: ≤14	Men g/day: 0: >42 0.5: 28-42 1: ≤28	<10g alcohol/d	Women g/d: 0: >20 0.5: >10-20 1: ≤10	Men g/d: 0: >30 0.5: >20-30 1: ≤20	0: >20 g/d 0.5: >10-20 1: ≤10

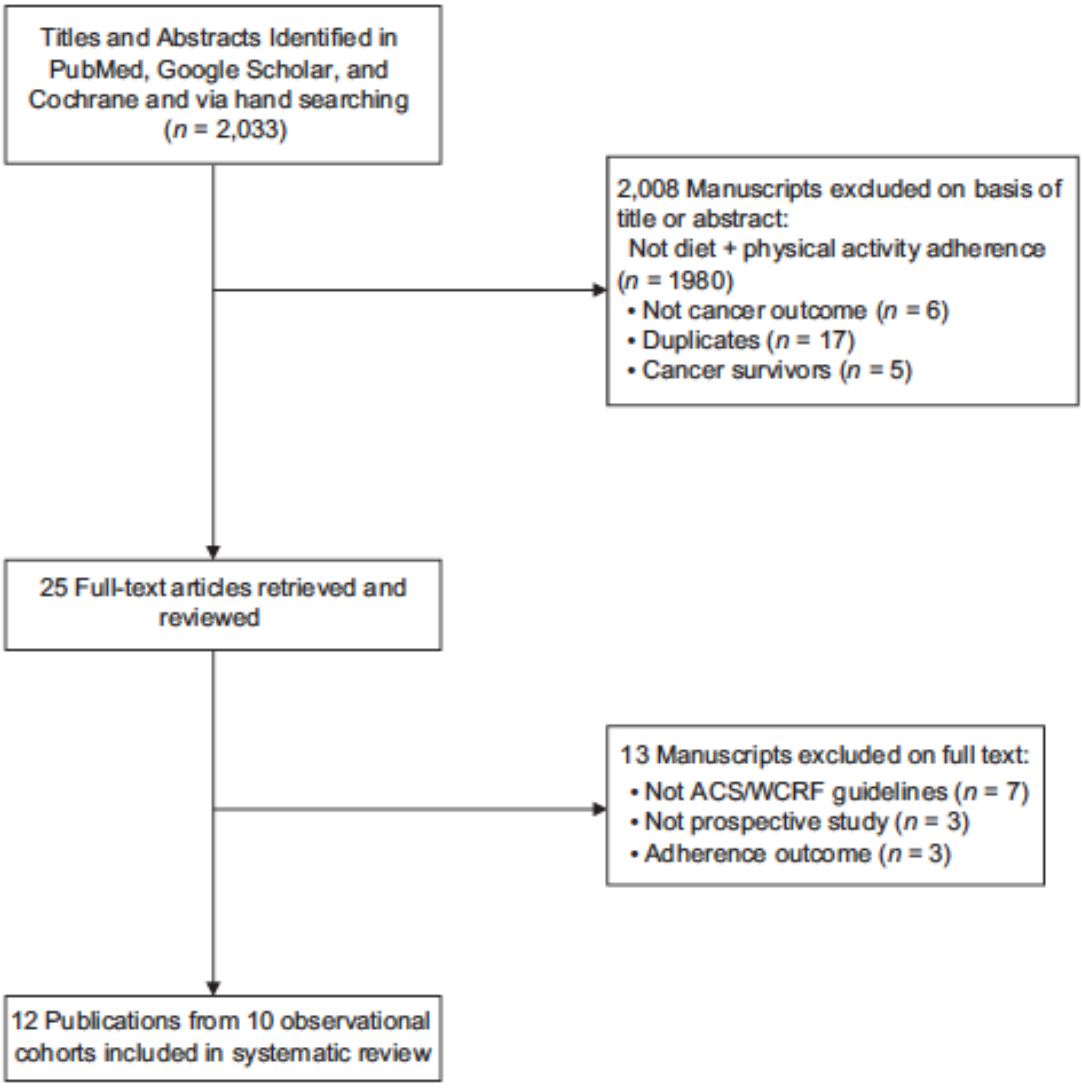
"Limit consumption of ED[ix] foods; avoid sugary drinks"	ED of diet <125 kcal/100g or <1 sugary drink/wk	ED of food <125kcal/100g. No soda or drinks with added sugar	<u>ED Foods</u> (servings/wk) Tertiles	<14 servings/wk of ED foods and <2 glasses/d of soda/juice	0: ED: >175[x] 0.5:>125 to <175 1: ≤125 0: >250 g/d sugary drink 0.5: ≤250 g/d 1: 0 g/d	0: ≥250 g/d sugary drink 0.5: <250 g/d 1: 0 g/d
"Limit consumption of salt"	Not included	<2.4g sodium/d	<u>Salty Foods</u> Tertiles <u>Sodium Intake g/d</u> 0: >3.6 0.5: 2.4-3.6 1: <2.4	Not included	Not included	0: >2400 mg/d 0.5: >1500-2400 mg/d 1: ≤1500 mg/d
"Dietary supplements not recommended for cancer prevention"	Not included	Not included	Not included	Did not report consuming on a regular basis	Not included	Not included
"Mothers to breastfeed"	Not included	Not included	Not included	Not included	0: No BF[xi] 0.5: >0 to <6 months 1: ≥6 months	Not included

[1] Body Mass Index kg/m^2
[ii] Physical Activity Index
[iii] Walking/cycling + leisure time exercise
[iv] Cycling or sports
[v] Starchy vegetable
[vi] Non-starchy vegetable
[vii] Red and processed meat
[viii] Processed meat

[ix] Energy dense/density
[x] kcal/100g/day
[xi] Breastfeeding

Figure Legend

Figure 1. Article selection process. The PRISMA diagram details the search and selection of manuscripts for the review.



APPENDIX B: DATA USE AGREEMENT

Internal Data Use Agreement:
Sharing and use of a coded data set within Biostatistics Shared Resource (BSR)

This Data Use Agreement serves to define the responsibilities of investigators and to document their agreement to abide by these terms.

Is this human subjects research?

If there is any possibility that individuals may be readily identifiable from the information in the data set, then IRB review is required prior to execution of this agreement.

Definitions

Coded: Identifiable information, such as name or social security number, has been replaced by a code (i.e. a number, letter, or combination thereof) AND there is a key to link between the code and the identifiable information.

Limited Data Set*:* The following Protected Health Information (PHI) may be used by Recipient(s). A complete description of the limited data set should be provided including the types of date fields and postal address fields that are included.

The Limited Data Set shall **not** contain any of the following identifiers of the individual who is the subject of the PHI, or of relatives, employers or household members of the individual:

• Names • Postal address information, other than town or city, State, and zip code • Telephone numbers • Fax numbers' • Electronic mail addresses • Social security numbers • Medical record numbers	• Health plan beneficiary numbers • Account numbers • Certificate/license numbers • Vehicle identifiers and serial numbers, including license plate numbers • Device identifiers and serial numbers;	• Web Universal Resource Locators (URLs); • Internet Protocol (IP) address numbers; • Biometric identifiers, including finger and voice prints; • Full face photographic images and any comparable images

Data Provider (holder of the key): the investigator, clinician, or other custodian of data who possesses and shares a limited data set with a recipient investigator.

Recipient Investigator (or Data User): the investigator who receives a limited data set from a provider.

Source of the Data Set: the original source for the creation and assembly of the data set. The source could be from medical charts, a clinical database, an IRB-approved research study or repository or a Quality Improvement review. If the data is from an IRB-approved study, the IRB study number should be included.

Name of the Data Provider: Biostatistics Shared Resource (Director: Dr. Denise Roe)
Source of the Data Set: Wheat Bran Fiber (IRB# 8800000256) and UDCA (IRB # 9400000371) trials (PI: Dr. Peter Lance)
Description of the Limited Data Set: Baseline characteristics, baseline diet and physical activity data, vitamin d levels, comorbidities and follow-up adenoma recurrence pathology

Obligations of Recipient Data User

a. *Performance of Activities.* Data User may use and disclose the Limited Data Set only in connection with the performance of the research activities described in the project summary (e.g., protocol, abstract, synopsis – whatever format the project is using) entitled, **Nutrition and Physical Activity Cancer Prevention Guideline Adherence Association with Vitamin D Levels and Precancerous Lesions** (the "Activities").

b. *Permitted Access to Limited Data Set.* Data User shall limit the use or receipt of the Limited Data Set to the individuals listed at the bottom of this document who need access to the Limited Data Set for the performance of the Activities.

c. Nondisclosure Except As Provided In Agreement. Data User shall not use or further disclose the Limited Data Set except as permitted or required by this Agreement. Access to the Limited Data Set by members of the research team who are not affiliated with University of Arizona (UA) requires the execution of a separate Data Use Agreement between the third party user and UA.

d. *Identification of Individual.* Data User may not use the Limited Data Set to re-identify or contact any individual who is the subject of the PHI from which the Limited Data Set was created. The data provider (holder of the key) will not release the key to the Data User under any circumstances.

e. *Disclosures Required By Law.* Data User shall not, without the prior written consent of the HIPAA Privacy Office, disclose the Limited Data Set on the basis that such disclosure is required by law without notifying the Privacy Office so that the UA shall have an opportunity to object to the disclosure and to seek appropriate relief. If the UA objects to such disclosure, Data User shall refrain from disclosing the Limited Data Set until the UA has exhausted all reasonably available alternatives for relief.

f. *Safeguards.* Data User shall use appropriate safeguards to prevent use or disclosure of the Limited Data Set other than as provided by this Agreement.

g. *Reporting.* Data User shall report to the HIPAA Privacy Office twenty-four (24) hours of Data User becoming aware of any use or disclosure of the Limited Data Set in violation of this Agreement or applicable law.

h. *Knowledge of Non-Compliance*. Any non-compliance by Data User with this Agreement or with HIPAA or the HIPAA Regulations automatically will be considered a breach or violation of a material term of this Agreement if Data User knew or reasonably should have known of such non-compliance and failed to immediately take reasonable steps to cure the non-compliance.

ASSURANCE OF COMPLIANCE WITH DATA USE AGREEMENT

The following individuals ("Data User(s)") are authorized to receive and use the Limited Data Set described in this Data Use Agreement for the purposes of conducting the research protocol listed above.

The Provider retains the original and the Recipient should retain a copy of the signed agreement.
By signing below, we acknowledge and agree to abide by the restrictions on our use and disclosure of the Limited Data Set in accordance with this Data Use Agreement.

Data Providers

Dr. Denise Roe	Dr. Peter Lance
Name	Name
	
Signature	Signature
07/28/15	07/29/15
Date	Date

Data Users (Recipient Investigators and members of the Study Team)

Dr. Elizabeth Jacobs	Lindsay Kohler
Name	Name
	
Signature	Signature
07/23/15	07/23/2015
Date	Date

Abstract

Despite decreasing incidence rates for colorectal cancer over the past two decades in the United States, the American Cancer Society (ACS) estimates that there will be 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer in 2015, with a combined 49,700 deaths from these malignancies. Increased screening rates for those aged 50 years and older have contributed to the reduction in colorectal cancer rates over the past 20 years by detection and removal of adenomatous polyps, the precursors to colorectal cancer. However, only half of those recommended for colorectal screening are currently following the guidelines. In addition to recommended screening, nutrition and physical activity guidelines for cancer prevention have been designed by the United States Department of Health and Human Services along with leading cancer organizations. Large cohort studies have found that following behavior-associated cancer prevention guidelines for factors such as body weight, physical activity, diet and alcohol consumption is associated with a reduced risk of cancer incidence, cancer mortality, and all-cause mortality. Further, it has been suggested that a healthy diet alone could help prevent some colorectal cancers, and one dietary component that has been studied extensively in relation to colorectal adenoma and cancer is vitamin D. In two separate meta-analyses, Yin et al. found statistically significant inverse associations with serum concentrations of the vitamin D biomarker 25-hydroxycholecalciferol [25(OH)D] and both colorectal adenoma and colorectal cancer risk. Factors that have been demonstrated to affect 25(OH)D concentrations include physical activity, body size, and dietary intake, which suggests that following cancer prevention guidelines may additionally affect circulating concentrations of 25(OH)D, though to our knowledge, this analysis has not yet been conducted. The objectives of the proposed work are to examine whether adherence to behavior-associated cancer prevention guidelines set by the ACS, as assessed by a previously established scoring system, are associated with 1) circulating concentrations of 25(OH)D and 2) colorectal adenoma recurrence. The planned study is a secondary analysis utilizing data and samples from two clinical trials of colorectal adenoma recurrence, the Wheat Bran Fiber (WBF) trial and the Ursodeoxycholic Acid (UDCA) trial.

APPENDIX C: DETERMINATION OF HUMAN RESEARCH

Determination of Human Research

This form should be used when it is unclear whether the proposed activities require review by an Institutional Review Board (IRB). **If the proposed study clearly is Human Research, do not complete this form! Instead, please submit the appropriate application for review and approval by the IRB.**

This form is required if the proposed study involves the following activities and it is unclear whether these activities require IRB review:

- Access to an electronic medical record;
- Use or disclosure of Protected Health Information (PHI);
- Requests for data or specimens from the AHSC Data Warehouse or Specimen Warehouse;
- The project is or will be supported by federal funds;
- The information will be used to support an application to the FDA or involves the use of a test article in a human;
- IRB certification for access to materials from dbGap; OR
- The project involves Native American/Alaskan Native or international indigenous populations.

The Human Subjects Protection Program (HSPP) will provide a written determination. This determination can be used to provide sponsors, collaborators, and journal editors who want verification from an impartial source that the activities do not require IRB approval. To have a successful determination, complete the entire form. Submit completed forms to the Human Subjects Protection Program through the departmental email account at VPR-IRB@email.arizona.edu.

If a written determination is needed in other instances than those described above, please contact HSPP for clarification using the departmental email account.

Section 1: Contact Information	
Principal Investigator Name, Degree(s):	Lindsay Kohler, MPH, BS
Principal Investigator **UA netID**	lschulz
Status/Rank:	Doctoral Student
Center:	
Department:	Epidemiology and Biostatistics
College:	MEZCOPH
Contact phone:	520-990-8587
Official Institutional Email:	lschulz@email.arizona.edu

Section 2: General Information

1. Project funding - If the proposed study is or will be funded, complete below:

a. UAccess
   i. Development Proposal #: 424593
   ii. Award #:
   iii. Unit #:
b. eDoc # (Required for For-profit sponsored research):
c. Total funding amount **OR** per subject amount: $153,354.00

Submit complete copy, cover-to-cover, of grant or award.

2. Conflict of Interest (COI):
The Principal Investigator hereby affirms that ALL individuals who meet the definition of *investigator* for this project in the current *Policy on Investigator Conflict of Interest in Research* have completed the mandatory Conflict of Interest training and Disclosure of Significant Financial Interests.

☒ Yes - All individuals who meet the definition of "investigator" have completed COI training and disclosure.

☐ No (explain):

3. Location of Research

Banner – University Medicine Group:

☐ Phoenix Campus		☐ Biological specimens	☐ Clinical Data
☒ Tucson Campus		☐ Biological specimens	☒ Clinical Data
☐ South Campus		☐ Biological specimens	☐ Clinical Data

University of Arizona Cancer Center:

☐ North Campus		☐ Biological specimens	☐ Clinical Data
☐ Orange Grove Clinics		☐ Biological specimens	☐ Clinical Data
☐ Phoenix		☐ Biological specimens	☐ Clinical Data

Other: Secondary data analysis only from the Biostatistics Shared Resource (See Data Use Agreement)

Section 3: Summary of Activities

2a. Title (If funded, provide exact title of funded project)
Cancer Prevention Guideline Adherence and Risk of Precancerous Lesions of the Colon

2b. Provide a concise description of the purpose or objectives of the project.

The objectives of the proposed work are to examine whether adherence to behavior-associated cancer prevention guidelines set by the American Cancer Society, as assessed by a previously established scoring system, are associated with 1) circulating concentrations of 25(OH)D and 2) colorectal adenoma recurrence. The planned study is a secondary analysis utilizing data and samples from two clinical trials of colorectal adenoma recurrence, the Wheat Bran Fiber (WBF) trial and the Ursodeoxycholic Acid (UDCA) trial.

2c. Describe the proposed methods and study procedures

This is a secondary analysis so there are no study procedures. Descriptive statistics will be generated for outcome variables, exposure variables, and demographic variables. Univariate analyses will be performed to assess whether there are any differences in demographic characteristics between the trials and within the trial arms. Unadjusted means and standard errors will be estimated. To assess whether the association between adherence score and each outcome is modified by sex, sex-specific estimates will be produced. The likelihood ratio test will be used to determine if there is a difference in the log-likelihoods from models with and without an interaction term (sex*adherence score). Differences between the WBF and UDCA study populations will be evaluated by producing trial arm-specific estimates. Cochran's Q statistic will be used to test if the treatments were equally effective and I^2 will be utilized to assess the proportion of variation in the effect size attributable to heterogeneity.

Multiple linear regression models will be utilized to assess the relationship of circulating concentrations of 25(OH)D with ACS adherence score. All linear models will be tested for assumptions of normality, linearity, and homoscedasticity. Clinically significant, ordinal categories for serum 25(OH)D will also be evaluated using ordered logistic regression models to estimate odds ratios for the association with adherence scores. Diagnostic tests will be performed to verify assumptions for ordered logistic regression models.

Chi-square tests will be used to test associations of the chosen variables for participants with and without adenoma recurrence, and for recurrent subjects by sex. Multiple logistic regression models will be utilized to assess the association of adherence score with adenoma recurrence and to evaluate interaction between adherence score and sex. Advanced adenoma recurrence will be evaluated in a similar fashion if necessary. Statistical significance will be determined at an α level of 0.05, and assumptions for all statistical tests will be assessed.

2d. Describe how data collection will occur, where the study will take place, and the type of information to be collected? If applicable, include a list of the data elements to be abstracted or collected.

Data has already been collected in previously approved clinical trials at the UACC and has been de-identified. Data elements include de-identified demographics such as sex, age, race; items from diet and physical activity; pathology results from colonoscopy; serum vitamin D concentrations and body measurements.

Section 3: *Research* per OHRP

Research is defined in the Code of Federal Regulations, 45 CFR 46.102(d), as *a systematic investigation designed to develop or contribute to generalizable knowledge.*

	Yes	No
Is there a systematic investigation, including (but not limited to) a hypothesis, research development, testing, pilot work, and evaluation?	☒ *	☐

Is the activity primarily designed to develop NEW knowledge that can be applied broadly to similar groups or conditions?	☒ *	☐
*If Yes to BOTH questions the study is Research. Proceed to Section 4. If the answers to one or both questions are NO, proceed to Section 5 to determine if the activity is subject to the Food and Drug Administration (FDA) regulations.		

Section 4: Involvement of *Human Subjects* per OHRP *Human Subject* is defined in the Code of Federal Regulations, 45 CFR 46.102(f), as *a living individual **about** whom an investigator obtains data through intervention or interaction, **or** their identifiable private information.*	Yes	No
Does the study involve interaction or intervention with a <u>living</u> individual or group of individuals (whether identifiable or not)? (e.g. surveys, interviews, medical or educational testing)	☐ *	☒
Does the study involve access to identifiable private information? *Private information is information that a person would reasonably expect that no observation or recording is taking place or that will not be made public. NOTE: Access to social media is typically considered private information.*	☐ *	☒
*If YES to either question, the research activity is *research* that involves *human subjects*. STOP and submit an IRB application for approval of human research. If the answers to one or both questions are NO, proceed to Section 5 to determine if the activity is subject to the Food and Drug Administration (FDA) regulations.		

Section 5: *Clinical investigation* per FDA *Clinical Investigation* is defined in the Code of Federal Regulations, 21 CFR 50.3(c), as *any experiment that involves a test article and one or more human subjects.*	Yes	No
Does the study involve the use of a drug or device (including in vitro diagnostic devices)? * If NO, proceed to section 6. If YES, complete all Section 5.	☐	☒*
Does the study include testing the safety and efficacy of a drug or device in a human subject, including analysis or comparison of outcome data about a drug or device?	☐ *	☐
Will a person receive a test article (i.e. drug, biologic, medical device, food additive, color additive, electronic article, or any other product or article subject to regulation) or serve as a control?	☐ *	☐
Will a person's specimen be subject to a medical device (i.e. in vitro	☐ *	☐

diagnostic device)? (This includes use of leftover specimens that are not individually identifiable such as clinical discard)	
*If YES to ANY question, the activity is subject to the FDA regulations. STOP and submit an IRB application for approval of human research. If ALL answers are NO, proceed to Section 6.	

Section 6: Coded private information and/or human biological specimens per OHRP *Coded* means *identifiable information, such as name or social security number has been replaced by a code (i.e. a number, letter, or combination thereof)* ***AND*** *there is a key to link between the code and the identifiable information.*	Yes	No
Does the study involve use of coded data/specimens? * If NO, proceed to section 7. If YES, complete Section 6.	☒	☐*
Please explain what data/specimens consists of (if it includes PHI elements please list them): Clinical and Specimen's.		
The data/specimens were collected for the proposed project?	☐	☒*
The provider of the data/specimens will remove the code before sending the data/specimens to the researcher? *If NO, STOP and submit an IRB application for approval of human research. *If any answer is YES, complete the section below. Identify the method for removing the code below.	☒	☐*
The holder of the key and researcher enter into an agreement prohibiting the release of the key to the researcher under any circumstances?	☒ *	☐
The researcher has documented written policies and procedures from a repository or data management center that prohibits the release of the key to the researcher under any circumstances?	☐ *	☒
There are other legal requirements prohibiting the release of the key to the researcher?	☐ *	☒
*STOP! For HSPP determination, submit copies of the informed consent from the study where the data/samples were collected, agreements, or policies and procedures preventing access to the code for review. *If NO to all questions, STOP and submit an IRB application for approval of human research.		

Section 7: Use or disclosure of Protected Health Information (PHI) per the HIPAA Privacy Rule	Yes	No
The private information/specimens come from a Covered Entity or medical record?	☐	☒*

Covered Entity means: (*1) a health plan; (2) a health care clearinghouse; or (3) a health care provider who transmits any health information in connection with a standard, electronic transaction.* *Medical record* means (*i) the medical records and billing records about individuals maintained by or for a covered health care provider; (ii) the enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (iii) used, in whole or in part, by or for the covered entity to make decisions about individuals.* *If YES, complete this Section. If NO, proceed to Section 8.	
Does the study involve the use or disclosure of a Limited Data Set? A *limited data set* is *PHI that excludes the following direct identifiers of the individual or of relatives, employers, or household members of the individual: (i) names; (ii) postal address information, other than town or city, state, and ZIP code; (iii) telephone numbers; (iv) fax numbers; (v) e-mail addresses; (vi) Social Security Numbers; (vii) medical record numbers; (viii) health plan beneficiary numbers; (ix) account numbers; (x) certificate/license numbers; (xi) vehicle identifiers and serial numbers, including license plate numbers; (xii) device identifiers and serial numbers; (xiii) Web Universal Resource Locators (URLs); (xiv) Internet Protocol (IP) address numbers; (xv) biometric identifiers, including finger and voice prints; and (xvi) full face photographic images and any comparable images*. *If YES, you must sign a Data Use Agreement (DUA). Please contact the HIPAA Privacy Program at PrivacyOffice@email.arizona.edu or (520) 621-1465 to receive a DUA. Please continue to Section 8. If NO, please continue to "Preparatory to Research" (directly below).	☒ * ☐
Preparatory to Research: Are you reviewing PHI preparatory to research? • The information is necessary and is used solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research. • No PHI is to be removed from the covered entity by the researcher in the course of the review. • Researchers outside of the Covered Entity may not contact or recruit potential research subjects. *If YES, you will be asked by the Covered Entity to attest to the above. Please continue to Section 8. If NO, please continue to "Decedents" (directly below).	☐ * ☒
Decedents: The activity is necessary and is limited to death records, autopsy materials, or cadaver specimens? • Note: Access to psychotherapy notes or information related to	☐ * ☒

HIV, mental health, genetic testing, or drug or alcohol abuse may not be applicable. • Note: PHI does not include information regarding a person who has been deceased for more than 50 years. *If YES, you will be asked by the Covered Entity to attest to the above statements. Please continue to Section 8.	

Section 8: De-identified private information or specimens *De-identified* means the *complete removal of all identifiers, (e.g. HIPAA identifiers – see appendix), and that the information or combination thereof cannot be combined to identify an individual or readily ascertained by the investigator*. *NOTE: Analysis of video, image, or digital recordings is considered identifiable.*	Yes	No
The investigator will only receive information/specimens that are fully de-identified? (Meaning, the investigator will not collect or remove the identifiers themselves.)	☒	☐
Proceed to Section 9.		

Section 9: Non-Human Research Activities Many proposed activities may involve people or their data, but may not be human research. The University of Arizona has determined the following activities to NOT represent Human Subjects Research. *NOTE: Investigators may have obligations under HIPAA (as noted below).*	Yes	No
Case Report: The proposed activity is a case report or case series of no more than three (3) cases describing an interesting treatment, presentation, or outcomes? • If case report requires PHI, a researcher outside of the Covered Entity must obtain a signed HIPAA Authorization from the subject/patient. • If you intend to disclose PHI as part of any case report, you must obtain a signed HIPAA Authorization from the subject/patient.	☐ *	☒
Program Evaluation/Quality Improvement/Quality Assurance: The proposed activity will assess, analyze, critique, and improve current processes of program or health care delivery in an institutional setting, involving data-guided, systematic activities designed to bring about prompt improvements in a program or health care delivery? • The activity will NOT involve randomization to different intervention groups.	☐ *	☒

• The activity WILL improve clinical care. • The activity will NOT be applied to populations beyond the specific study population (e.g. the knowledge gained from the activity is unique to the University of Arizona). • The activity will not affect clinical decision making for an individual patient vs. a population of patients. *NOTE:* Researchers outside of the Covered Entity may not conduct PE/QI/QA unless specifically authorized by the Covered Entity and pursuant to a Business Associate Agreement. Please contact the HIPAA Privacy Program at PrivacyOffice@email.arizona.edu or (520) 621-1465 for additional information.	
Course-Related Activities: The proposed activity is limited to course-related activities designed specifically for educational or teaching purposes? • The activity is part of a routine class exercise or assignment for a grade. • The activity is meant to teach research or professional methodology.	☐ * ☒
Oral History: The activity is limited to oral history activities, such as open ended interviews that only document a specific historical event or the experiences of individuals without the intent to draw conclusions or generalize findings.	☐ * ☒
Public Use Datasets: The activity is limited to analyzing de-identified data contained within a publically available dataset. *NOTE: This does not include reviewing or analyzing information from social media.* • Restricted use data sets do not qualify.	☐ * ☒
Journalism/Documentary Activities: The activities are limited to investigations and interviews that focus on specific events, views, etc., and that lead to publication in any medium (including electronic), documentary production, or are part of training that is explicitly linked to journalism. There is no intent to test a hypothesis? • IRB approval may be required when journalists conduct activities normally considered scientific research intended to produce generalizable knowledge.	☐ * ☒
Purchased cell lines: The activity involves commercially available, de-identified non-human embryonic cell lines.	☐ * ☒
Database creation: The primary reason for establishing this database is for clinical purposes or an improvement project (IRB approval of a new protocol must be obtained before any data from this database may be used for research purposes). *NOTE:* For some records and database research, a signed HIPAA Authorization may not be needed.	☐ * ☒
dbGap: Receipt of data from dbGap that requires IRB approval, but the data you will receive:	☐ * ☒

• Is de-identified, but the Data Use Committee requires IRB approval • The researcher did not submit any of the original data to dbGap • The researcher will not collaborate with others on the project who submitted the original data to dbGap Investigators must also submit an Institutional Certification form to be completed and signed by the Investigator and IRB. See …	
Native American/Alaskan Native: The activity involves access to tribal resources (e.g. cultural artifacts, environmental samples, or people), but the activity is not intended to produce generalizable knowledge.	☐ * ☒

*****If YES to any item the study does not involve human subjects. STOP! Submit to HSPP for a determination if required as noted in the bulleted instructions. Remember to submit copies of relevant materials to assist the review (e.g. informed consent from the study where the data/samples were collected, agreements, or policies and procedures).
***** If none of the areas above apply please submit to HSPP for review.

Section 10: REQUIRED SIGNATURES

1. PRINCIPAL INVESTIGATOR (REQUIRED)

By signing below, I, the Principal Investigator, certify that I have accurately answered the items listed above.

Signature	Date	Print Name
		Lindsay Kohler, MPH

2. ADVISOR (REQUIRED FOR ALL STUDENTS AND RESIDENTS ACTING AS THE PI)

By signing below, I, the Advisor, certify that I have accurately reviewed and mentored the student/resident regarding completion of the items listed above.

Signature	Date	Print Name
	07/28/15	Elizabeth Jacobs, PhD

APPENDIX D: HUMAN SUBJECTS APPROVAL

Correspondence from University of Arizona Human Subjects Protection Program

THE UNIVERSITY OF ARIZONA

Human Subjects Protection Program

1618 E. Helen St.
P.O. Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://orcr.arizona.edu/hspp

Date:	August 14, 2015
Principal Investigator:	Lindsay Nicole Kohler
Protocol Number:	1508046848
Protocol Title:	Cancer Prevention Guideline Adherence and Risk of Precancerous Lesions of the Colon
Determination:	Human Subjects Review not Required

The project listed above does not require oversight by the University of Arizona because the project does not meet the definition of 'research' and/or 'human subject'.

- **Not Research as defined by 45 CFR 46.102(d):** As presented, the activities described above do not meet the definition of research as cited in the regulations issued by the U.S. Department of Health and Human Services which state that "research means a systematic investigation, including research development, testing and evaluation, designed to contribute to generalizable knowledge".
- **Not Human Subjects Research as defined by 45 CFR 46.102(f):** As presented, the activities described above do not meet the definition of research involving human subjects as cited in the regulations issued by the U.S. Department of Health and Human Services which state that "human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention ***or*** interaction with the individual, or identifiable private information".

Note: Modifications to projects not requiring human subjects review that change the nature of the project should be submitted to the Human Subjects Protection Program (HSPP) for a new determination (e.g. addition of research with children, specimen collection, participant observation, prospective collection of data when the study was previously retrospective in nature, and broadening the scope or nature of the research question). Please contact the HSPP to consult on whether the proposed changes need further review.

The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).

APPENDIX E: MANUSCRIPT 2

Adherence to cancer prevention guidelines as a strategy for improving circulating concentrations of vitamin D

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There are no conflicts of interest to disclose.

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Running Title: Cancer Prevention Guideline Adherence and Vitamin D
Abbreviations: 25-hydroxycholecalciferol [25(OH)D], 1α,25-dihydroxyvitamin D [1,25$(OH)_2$D], American Cancer Society (ACS), World Cancer Research Fund/American Institute for Cancer

Research (WCRF/AICR), University of Arizona Cancer Center (UACC), wheat bran fiber supplement (WBF), ursodeoxycholic acid (UDCA), ultraviolet B (UVB), body mass index (BMI), Arizona Food Frequency Questionnaire (AFFQ), Arizona Activity Frequency Questionnaire (AAFQ), metabolic equivalents of task (MET), odds ratios (ORs), confidence interval (CI)

Abstract

Background: Several lifestyle factors targeted by the American Cancer Society's (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines are also associated with circulating concentrations of vitamin D metabolites. This suggests that adherence to the ACS guidelines may be related to improved vitamin D status.

Objective: We examined the relationship between adherence to the ACS guidelines and circulating concentrations of two vitamin D metabolites, 25-hydroxycholecalciferol [25(OH)D] and 1α,25-dihydroxyvitamin D [$1,25(OH)_2D$].

Design: We conducted cross-sectional analyses of pooled participants from the Wheat Bran Fiber (n=503) and Ursodeoxycholic Acid (n=854) trials. A cumulative adherence score was constructed using baseline data regarding body size, diet, physical activity, and alcohol consumption. Continuous vitamin D metabolite concentrations and clinically significant categories were evaluated using multiple linear and logistic regression models, respectively.

Results: The most adherent participants were more likely to be older, white, and non-smokers compared to the least adherent. Concentrations of circulating 25(OH)D were statistically significantly higher among participants with high versus low adherence to guidelines (32.0 ±0.8 and 26.4 ±0.7 ng/ml, respectively; $p<0.001$). For $1,25(OH)_2D$ concentrations, high adherence was again significantly related to greater metabolite levels, with mean concentrations of 36.3 ±1.3 and 31.9 ±1.0 pg/mL for high- and low-adherers, respectively ($p=0.008$). Furthermore, the odds of attaining sufficient 25(OH)D status was 4.37 times higher for those most adherent versus those least adherent (95% CI: 2.47-7.71).

Conclusions: These findings demonstrate that adherence to the ACS guidelines is associated with higher concentrations of both of 25(OH)D and 1,25$(OH)_2$D. Following the ACS guidelines could potentially increase 25(OH)D levels as much as that observed by a supplement of 1000 IU/d in a population similar to ours.

Key Words: adherence, vitamin D, cancer prevention guidelines, diet, physical activity

Introduction

Obesity, advancing age, limited sun exposure, poor diet, and higher skin pigmentation are all risk factors for vitamin D deficiency (26-32) which is common in the United States (33). Vitamin D deficiency has been linked to several major causes of death including cardiovascular disease, diabetes, and cancer (34). While the definition of clinical vitamin D deficiency has been updated in recent years (35, 36) it remains debated (34). Furthermore, the optimal level of vitamin D intake required to meet definitions of vitamin D sufficiency also remains unclear (38-40). Vitamin D supplementation with cholecalciferol (vitamin D_3) is the primary clinical strategy used to increase circulating concentrations of 25-hydroxycholecalciferol [25(OH)D], the metabolite most often measured to determine vitamin D status in adults (41). However, studies of vitamin D supplementation and health outcomes have produced equivocal results (42, 43), In addition, there are emerging data that genetic background may influence response to vitamin D supplementation (44, 45). Humans can also produce 25(OH)D via exposure to ultraviolet B (UVB) radiation (46), but this route is rarely promoted as excessive sunlight exposure can cause sunburns and increase the risk of skin cancer. With regard to diet, naturally-occurring vitamin D can be found in only a limited number of foods such as fatty fish, while fortified foods such as dairy products, ready-to-eat cereals, and orange juice are more common. Therefore, the optimal strategy for improving vitamin D status remains equivocal.

Several lifestyle factors targeted by the American Cancer Society (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines, including body size, diet, and physical

activity are also associated with circulating concentrations of vitamin D. Our group recently completed a systematic review that found strong and consistent evidence indicating that adherence to the ACS or similar World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines was associated with significant reductions in cancer incidence and mortality (111). One study included in the review by Kabat et al. reported a statistically significant association between the higher adherence to the guidelines and increased melanoma incidence (9). One explanation for these findings is that adherence to the guidelines, particularly for physical activity, is related to increased sun exposure and potentially higher vitamin D concentrations. Thus, we hypothesized that greater adherence to the guidelines would be associated with higher concentrations of vitamin D metabolites. We employed data from a pooled population of two completed chemoprevention trials to construct an adherence score to the ACS nutrition and physical activity cancer prevention guidelines and assess the relationship between adherence and levels of 25(OH)D (n=1,357) and 1α,25-dihydroxyvitamin D [$1,25(OH)_2D$] (n=854).

Subjects and Methods

Study Population

Data were pooled from two randomized, controlled, double blind, Phase III clinical trials conducted at the University of Arizona Cancer Center (UACC) from 1990 to 1999. These studies evaluated the effect of either a wheat bran fiber supplement (WBF) (20, 97) or ursodeoxycholic acid (UDCA) (21) on the development of a new colorectal adenoma in patients with previously- removed colorectal adenomas. The present analyses were

conducted using data for baseline diet, physical activity, and vitamin D biomarkers from the pooled population. The University of Arizona Human Subjects Protection Program approved both studies. Written informed consent was obtained from each participant prior to trial enrollment.

Recruitment and Data Collection: Phoenix and Tucson gastroenterology practices served as recruitment centers from 1990-1995 for WBF and 1995-1999 for UDCA. Men and women between the ages of 40 and 80 years who had one or more adenomas measuring ≥3 mm removed during a colonoscopy within a 6-month period prior to study registration were included in the study. Participants in the WBF trial were randomized to a daily wheat bran fiber supplement (13.5 g/day) or a low-fiber supplement (2.0 g/day) (20). Participants in the UDCA trial were randomized to receive 8-10 mg UDCA per kilogram of body weight or placebo daily (21). Primary findings from the trials were null; neither the WBF supplement nor the UDCA treatment prevented new colorectal adenomas (21, 97). For the present analysis, participants from the pooled sample (n=3,221) were excluded if they did not have serum 25(OH)D data (n=1,253), had missing body mass index (BMI) data (n=16), were underweight (BMI < 18.5kg/m^2) (n=16), had unreliable (<600kcal/d) dietary data (n=14), had missing baseline physical activity data (n=544), or were missing any other covariate included in the models (race, n=16; education, n=5). The analytic cohort for 25(OH)D was thus comprised of 1,357 participants; while $1,25(OH)_2D$ data were only available from the UDCA trial (n=854).

Analysis of Serum Vitamin D Metabolites

Baseline vitamin D metabolites were measured in a blinded fashion at Heartland Assays (Ames, IA) utilizing an established radioimmunoassay (RIA)(98). Quality assurance and control measures including pooled serum samples, and duplicates in different batches were performed. The coefficient of variation was <7.0% for 25(OH)D and 11.5% for $1,25(OH)_2D$. Serum $1,25(OH)_2D$ was assessed as a continuous variable and 25(OH)D was assessed as both a continuous and a categorical variable, in which clinically important categories were defined as deficient (<20 ng/mL) insufficient (≥20 to <30 ng/mL), or sufficient (≥30 ng/mL) (12, 35, 36, 48, 99).

Nutrition and Physical Activity Cancer Prevention Guidelines Score

An *a priori* score was constructed, based upon previously published work by Thomson and colleagues (7), for adherence to the 2012 ACS cancer prevention guidelines for nutrition and physical activity (6) (**Table 1**). These guidelines focus on overall patterns of lifestyle behaviors that included body size, physical activity, diet, and alcohol consumption. Baseline diet and physical activity were collected using frequency questionnaires. The Arizona Food Frequency Questionnaire (AFFQ) is a semi-quantitative, 175-item validated questionnaire that asks respondents to report how often (per day, week, or month) and how much (small, medium, or large usual portion) participants consumed each food item over the past 12-month period (100). The Arizona Activity Frequency Questionnaire (AAFQ) is a 59-item, validated questionnaire that groups physical activity by leisure, recreational, household, and "other" activity categories (101). The provided output contains metabolic equivalents of task (MET) units per day and per activity, kilojoules, number of hours per day per activity, and number of

activities reported by respondents for each category, which were used to generate the physical activity score. Each ACS recommendation was equally weighted 0-2 points. Zero points were allocated for not meeting the recommendation at all, 1 point for partially meeting the recommendation, and 2 points for fully meeting the recommendation. The overall score, summed from individual recommendations, ranged from 0 for those participants that were not adherent at all to the recommendations to 8 for those participants that were fully adherent to all four lifestyle factor recommendations. Adherence categories were defined as low (0-2 points), moderate (3-5 points), and high (6-8 points). Table 1 outlines the recommendations for each lifestyle factor, how they were measured, how scores were assigned based upon the guidelines, and the proportion of the study population within each category. Smoking status was not included in the ACS adherence scoring, but was included as a potential confounder in the current analyses.

The first recommendation "to maintain a healthy weight throughout life" was scored based upon calculated body mass index (BMI, in kg/m^2) from height and weight reported at baseline. The best score (2 points) was given to those with a BMI within normal range (18.5-25 kg/m^2). The worst score (0 points) was given to those with a BMI in the obese category (>30.0 kg/m^2). One point was given those with a BMI in the overweight range (25-30 kg/m^2). Underweight participants (<18.5 kg/m^2) were excluded from the present analysis.

The second recommendation to "adopt a physically active lifestyle with at least 30

minutes of moderate to vigorous intentional physical activity at least 5 days a week; 45-60 minutes are preferable" was evaluated by MET (102) scores from the AFFQ recreational activities section. The minimum standard of 30 minutes on 5 days (2.5 hours/week) of moderate activity (3.5 METs) is equal to 8.75 MET-hours per week. Any participant doing less than the minimum recommendation (less than 8.75 MET-hours per week) received a score of zero points. One hour per day, 5 days a week (5.0 hours/week), of moderate activity (3.5 METs) is equal to 17.5 MET-hours/ week. Therefore, 8.75 to 17.5 MET-hours/week earned a score of 1 point. Participants meeting "preferable" levels, greater than 17.5 MET-hours/week, earned a score of 2 points.

The third recommendation to "consume a healthy diet with an emphasis on plant sources" was assessed with three separate diet scores that were constructed and summed to capture the recommended dietary pattern. The first diet score for the recommendation "eat 5 or more servings of a variety of vegetables and fruits each day" was assigned 1 point for meeting the recommended number of servings. The number of servings was measured from food group categories Fruits, Fruit Juice, Vegetables, and Vegetable Juice. An additional 1 or 2 points was assigned for diet quality based upon being in the 2^{nd} or 3^{rd} sex-specific tertile of total carotenoids, respectively, which included beta carotene, alpha carotene, beta cryptoxanthin, lycopene, and lutein plus zeaxanthin combined. The second diet score for the recommendation "choose whole grains in preference to processed (refined) grains" was evaluated by the percentage of grains consumed as whole grains. Points were assigned by the sex-specific quartile distribution with the highest quartile receiving 3 points and lowest quartile receiving 0 points. The third diet score for the

recommendation "limit consumption of processed and red meats" was measured similar to the whole grains. The recommendation was assessed by sex-specific quartile distribution with the lowest quartile receiving 3 points and the highest quartile receiving zero points. The three diet scores were summed for a potential total of 9 points. Dietary pattern scores were further collapsed into 0 points for those with 0-2 summed diet scores, 1 point for those with 3-6 summed diet scores, and 2 point for those with 7 to 9 summed diet scores.

The fourth recommendation employed in this analysis was "if you drink alcohol, limit consumption to 1 drink per day for women or 2 drinks per day for men." Alcohol was captured in the AFFQ in terms of total grams of alcohol per day. One drink was estimated as 14 grams of alcohol or approximately a 12 ounce regular beer, 5 ounce glass of wine, or 1.5 ounce shot of 80-proof distilled spirit (103). Nondrinkers were assigned 2 points, moderate drinkers consuming the limit or less were assigned 1 point, and heavy drinkers consuming more than the limit were assigned zero points.

Statistical analysis

Descriptive statistics were generated for outcome, exposure, and demographic variables. Bivariate analyses were performed to assess differences in demographic characteristics between the trials. Unadjusted means and standard errors were estimated. Potential confounders included age, education, race, smoking status, supplement use, and energy intake (47, 104-107). A covariate was considered a confounder if it changed the measure of association by 10% or more when included in a regression model (108). To assess

whether the associations between adherence score and vitamin D metabolites were modified by sex or study, likelihood ratio tests were used to determine if there was a difference in the log-likelihoods from models with and without interaction terms.

Multiple linear regression models were utilized to assess the relationships of circulating concentrations of 25(OH)D and $1,25(OH)_2D$ with ACS adherence score categories and estimate mean concentrations of 25(OH)D and $1,25(OH)_2D$ for individuals in the reference categories centered on mean age and energy intake of the strata using linear combinations of parameters. Reference categories were selected to represent the majority of the pooled population (white, male, not a college graduate, non-smoker in the UDCA trial). Clinically significant categories for serum 25(OH)D were evaluated using multinomial logistic regression models to estimate odds ratios (ORs) for association with adherence scores. Adjusted mean concentrations of 25(OH)D and $1,25(OH)_2D$ were also estimated by individual ACS adherence score components. Data from the trials were merged and managed using Stata version 14.1 software (StataCorp LP, College Station, Texas).

Results

Table 1 demonstrates more women than men met the BMI recommendation of a healthy body size (18.5-25kg/m^2); while more men than women met preferable physical activity levels of more than one hour per day, 5 days a week (>5.0 hours/week) of moderate activity (3.5 METs), or greater than 17.5 MET-hours/week total. Men and women had similar adherence to diet recommendations overall; however, a greater percentage of

women were non-drinkers at baseline than men. Baseline characteristics of men and women by category of ACS score are shown in **Table 2**. In general, participants in the most adherent overall category of ACS score (6-8 points) were more likely to be older, white, and a non-smoker than those participants in the least adherent category (0-2 points).

Table 3 shows adjusted mean circulating 25(OH)D and $1,25(OH)_2D$ concentrations for each adherence score category from multivariate linear regression models for individuals in reference categories (white, male, not a college graduate, non-smoker in UDCA trial) centered on mean age and energy intake. In the pooled sample, those with the highest adherence to the ACS guidelines (6-8 points) had an average 25(OH)D concentration of 32.0 ±0.8 ng/mL and $1,25(OH)_2D$ concentration of 36.3 ±1.3 pg/mL, with significant dose-dependent trends for both metabolites (*P*-trend <0.001; *P*-trend <0.008) (Table 3). For 25(OH)D, there were no statistically significant interactions for sex (*P*=0.42) or study (*P*=0.19). Study interaction was not evaluated for $1,25(OH)_2D$ as it was only available for the UDCA study. There was no statistically significant interaction between score and sex (*P*=0.86) for $1,25(OH)_2D$.

Table 4 presents the results of multinomial logistic regression models for the association between categories of ACS adherence scores and clinically-defined categories of 25(OH)D. The odds of having an insufficient vitamin D status (≥20 and <30 ng/mL) versus a deficient status (<20 ng/mL) was 1.76 times (95% CI: 1.21-2.57) greater for those who were moderately adherent to the guidelines and 2.29 times greater (95% CI:

1.35-3.90) for those individuals who had high adherence, versus those with low adherence. The odds of having a sufficient vitamin D status (≥30 ng/mL) versus a deficient status was 2.41 times (95% CI: 1.58-3.68) greater for those achieving moderate adherence and 4.37 times greater (95% CI: 2.47-7.71) for those who were highly adherent, versus those within the lowest adherence category.

Adjusted mean concentrations of 25(OH)D and $1,25(OH)_2D$ for individuals in the reference categories (white male, not a college graduate, and a non-smoker in the UDCA trial) by adherence score components are displayed in **Table 5**. An inverse relationship between BMI categories and both 25(OH)D and $1,25(OH)_2D$ exhibited a dose-dependent trend (*P*-trend for both comparisons <0.001). Similarly, a significant trend was seen for higher levels of physical activity and higher concentrations of both vitamin D metabolites (*P*-trend<0.001). In contrast, any association or trend between diet component and either vitamin D metabolite was less clear. A diet score of 1 point was significantly associated with 25(OH)D with a significant overall trend (*P*-trend=0.039). No significant association was observed between diet score and $1,25(OH)_2D$. A significant trend was seen for increasing alcohol consumption and increasing concentrations of both 25(OH)D (*P*-trend 0.009) and $1,25(OH)_2D$ (*P*-trend 0.040).

Discussion

Greater adherence to nutrition and physical activity cancer prevention guidelines, developed by ACS and other leading cancer organizations, has been found to be associated with reduced risk of overall cancer incidence and mortality, including some

site-specific cancers (111). These guidelines are consistent with recommendations for the prevention of other major diseases as well, and if followed, will lead to healthier lives overall (25, 112, 113). To our knowledge, no studies have assessed the relationship between ACS guidelines for cancer prevention and circulating concentrations of vitamin D metabolites, which are biomarkers often linked to health outcomes (114). Our work offers evidence indicating greater adherence to an overall lifestyle pattern as outlined by the ACS nutrition and physical activity cancer prevention guidelines is associated with higher concentrations of both 25(OH)D and $1,25(OH)_2D$. Furthermore, significant dose-dependent trends were seen for BMI, physical activity, and alcohol intake and both vitamin D metabolites. The relationship between alcohol intake and higher circulating concentrations of vitamin D has been reported previously with suggestions of residual confounding or heavier alcohol consumers have lifestyles favorable to higher concentrations of circulating vitamin D (115, 116). To our knowledge there is no clear biological mechanism and warrants further investigation.

Concentrations of 25(OH)D can vary due to many non-modifiable factors such as skin pigmentation, sex, genetic background, and season (47, 48). However, 25(OH)D also varies due to modifiable factors such as amount of sun exposure, dietary intake, and supplementation (46). Sun exposure increases vitamin D production, but also can cause skin damage or even skin cancer, the risk of which varies according to skin pigmentation and possibly body size (117, 118). Compared to normal weight adults, obese adults have been found to have significantly lower levels of the vitamin D metabolite 25(OH)D, possibly due to lower dietary intakes and lesser exposure of skin to sunlight (50, 118).

Healthy-weight adults with higher levels of physical activity are more likely to meet Dietary Reference Intakes (DRIs) for vitamin D and other micronutrients than overweight adults (51). Furthermore, several studies have suggested that obese adults may need higher doses of supplementation than normal weight adults to achieve sufficient 25(OH)D status (38, 119).

A recent review of vitamin D supplementation trials estimates that 2990 IU per day is required to surpass deficient concentrations (20 ng/mL) of serum 25(OH)D in 97.5% of healthy individuals (39). The Recommended Dietary Allowance (RDA) for healthy adults aged 19-70 years is 600 IU, and is 800 IU for those over 70 years of age (26). However, it has been suggested these recommendations have been miscalculated, are too low, and should be reconsidered (40). **Table 6** presents the means and standard deviations of 25(OH)D for selected, large vitamin D supplementation trials presented in the review (39) as well as a trial conducted by our group (120). Three studies used doses of 400 IU/d with follow-up times of 4, 48, and 108 weeks resulting in mean 25(OH)D concentrations of 28.3 ±8.9 ng/mL in healthy men and women (120), and 36.9 ±9.5 ng/mL (121) and 24.4 ±12.2 ng/mL (122), in two separate studies of postmenopausal women. Doses of 800 IU/d were used in two trials with a range of follow-up time from 13 to 156 weeks, resulting in mean 25(OH)D concentrations of 28.39 ±9.18 and 29.91 ±8.78 ng/mL among women (123, 124). In a study evaluating the effect of a daily dose of 1000 IU in preventing new colorectal adenomas, healthy non-Hispanic whites aged 45-75 years, had mean concentrations of 31.5 ±8.9 ng/mL after one year (125). Comparably in our study, moderate and high adherence to the ACS guidelines demonstrated mean concentrations

of 25(OH)D of 29.6 ±0.5 and 32.0 ±0.8 ng/mL, respectively. Therefore, following the ACS guidelines could potentially increase 25(OH)D levels as much as or more than a supplement of 1000 IU per day. Improving vitamin D status through lifestyle modifications as opposed to supplementation allows for a strategy that would avoid any potential toxicity such as renal calcifications (42), and is likely to incur other health benefits as well.

Less is known about lifestyle factors that may be associated with circulating concentrations of $1,25(OH)_2D$ (127). Few epidemiological studies have evaluated the association between $1,25(OH)_2D$ and physical activity. The first examined the effects of long-term aerobic exercise and omega-3 supplementation on bone health in postmenopausal women and found $1,25(OH)_2D$ increased with the intervention (128). Similarly, in a study within the UDCA cohort included in the present study, moderate to vigorous physical activity was positively associated with $1,25(OH)_2D$, with women experiencing the greatest increase (104). Body mass index, the measure used to estimate body size in our study, has a well-known inverse relationship with 25(OH)D, but has limited evidence with $1,25(OH)_2D$. A statistically significant association between higher circulating concentrations of $1,25(OH)_2D$ and lower risk of metabolic syndrome, which consists of waist circumference, triglycerides, blood pressure, glucose, and high-density lipoprotein, has also been reported in a sample population from the UDCA and WBF cohorts (129).

The major strengths of the current study include availability of data from a prospective cohort of over 1,300 participants with complete data on a wide range of available baseline nutrition, physical activity, and serum vitamin D metabolite data. However, even though the original trials were prospective cohorts, this secondary data analysis is cross-sectional in nature with measurements coming from baseline assessments. Only one measure of 25(OH)D was used for the assessment of vitamin D status, although previous findings suggest that single, baseline 25(OH)D measurements provide reasonably representative measures of the biomarker (133). In addition, the "maintenance of a healthy weight throughout life" ACS guideline could not be precisely assessed because height and weight data were not available for earlier periods in life. Although the instruments used to collect lifestyle data asked for usual dietary consumption in the prior 12-month period and the last 4 four weeks for physical activity, the reported behaviors may not be representative of the participants' longer-term behaviors. While self-reports of physical activity, dietary and alcohol intake are susceptible to measurement error or misclassification bias, the frequency questionnaires used had been validated in the study sample. Finally, there is the potential issue that the various healthy behaviors included in the ACS adherence score may cluster in individuals making it difficult to separate the effect of the score components. Nonetheless, these findings indicate the potential for increasing levels of vitamin D when the overall guidelines are more closely followed.

In summary, our results suggest that following an overall pattern of healthy behaviors as recommended in the ACS Nutrition and Physical Activity Cancer Prevention guidelines may be associated with higher concentrations of both 25(OH)D and $1,25(OH)_2D$. In

addition, score components also demonstrated significant associations. Therefore, adhering to the ACS nutrition and physical activity cancer prevention guidelines may be a viable public health strategy for increasing both 25(OH)D and 1,25$(OH)_2$D concentrations.

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LNK and ETJ designed secondary analysis, EAH designed, performed and analyzed the supplement trial; LNK analyzed secondary data; LNK, EAH, ETJ, RBH, EO, PWJ, and DJR wrote the paper; LNK and ETJ had primary responsibility for final content. All authors read and approved the final manuscript.

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Table 1. Components of the ACS adherence score and distribution in the study population.

Adherence score component	Score	Description	Percentage of study population		
			All	Men	Women
Body mass index (BMI)	0	>30 kg/m^2	29.9	30.1	29.7
	1	>25-≤30 kg/m^2	43.8	48.6	32.8
	2	18.5-≤25 kg/m^2	26.1	21.2	37.4
Physical Activity (PA)	0	<8.75 MET h/wk	40.4	35.8	50.9
	1	8.75-17.5 MET h/wk	25.1	25.5	24.1
	2	>17.5 MET h/wk	34.4	38.6	24.8
Diet*	0		23.9	23.4	24.9
	1		64.4	64.5	64.3
	2		11.7	12.1	10.9
Fruit & Vegetables	0	<5 servings/d fruits plus veg	51.9	52.0	51.7
	1	≥5 servings/d fruits plus veg	48.1	48.0	48.3
Quality	0	1st tertile of total carotenoids	32.3	33.0	30.7
	1	2nd tertile of total carotenoids	33.8	33.4	34.8
	2	3rd tertile of total carotenoids	33.9	33.6	34.5
Whole grains	0	Quartiles of whole:total grains	63.1	62.3	64.9
	1		0	0	0
	2		11.6	12.4	9.7
	3	Highest Quartile	25.3	25.2	25.4
Red & processed meat	0	Quartiles of red + processed meat intake	25.2	25.0	25.6
	1		25.4	25.1	26.1
	2		25.1	25.0	25.1
	3	Lowest Quartile	24.3	24.8	23.2
Alcohol	0	Men ≥3, Women ≥2 drinks/day	9.3	10.6	6.3
	1	Men 1-2, Women 1 drink/day	53.8	57.7	44.9
	2	Non-drinker	36.9	31.7	48.8

*Diet score is generated from the summation of the fruit & vegetable, quality, whole grains, and red & processed meat scores. Summed for up to 9 points and then collapsed into 4 categories (0-2, 3-6, 7-9) for subsequent diet adherence values (0, 1, 2)

Table 2. Baseline characteristics of participants in the pooled population (n=1357) by categories of adherence score to the ACS Nutrition and Physical Activity Cancer Prevention guidelines, stratified by sex[1].

	ACS Adherence Score (points)					
	Men			Women		
	0-2	3-5	6-8	0-2	3-5	6-8
n (%)	151 (16.0)	638 (67.7)	154 (16.3)	64 (15.5)	271 (65.5)	79 (19.1)
Age, years	62.7 ± 8.1[2]	65.8 ± 8.8	68.4 ± 7.6	64.1 ± 8.6	64.6 ± 8.7	67.1 ± 8.6
White, n (%)	142 (94.0)	598 (93.7)	146 (94.8)	62 (96.8)	252 (93.0)	77 (97.5)
College graduate, n (%)	54 (35.8)	279 (43.7)	57 (37.0)	12 (18.8)	61 (22.5)	14 (17.7)
BMI, kg/m^2	31.7 ± 4.3	28.4 ± 3.9	25.0 ± 2.4	33.5 ± 5.1	27.4 ± 5.1	24.0 ± 3.0
Physical activity, MET-h/wk	4.7 ± 4.7	18.8 ± 18.2	31.6 ± 18.1	3.7 ± 5.0	11.3 ± 15.3	28.2 ± 17.3
Diet						
Total energy, kcal/d	2302.3 ± 778.3	2120.7 ± 781.2	2144.1 ± 728.6	1648.5 ± 564.3	1548.9 ± 593.4	1613.0 ± 579.0
Fruit and veg, servings/d	4.9 ± 3.3	5.4 ± 3.2	6.9 ± 3.9	4.8 ± 3.1	5.8 ± 4.3	7.0 ± 3.6
Total carotenoids, μg/d	13525.4 ± 9724.8	13981.9 ± 8405.7	15725.8 ± 7851.1	10056.0 ± 5025.3	12449.0 ± 8934.4	13579.3 ± 7563.6
Red & processed meat, serv/d	2.0 ± 0.9	1.5 ± 0.8	1.3 ± 0.8	1.4 ± 0.9	1.0 ± 0.6	0.9 ± 0.6
Whole grains, g/d	11.2 ± 36.1	21.8 ± 48.2	52.9 ± 79.3	6.5 ± 15.5	15.8 ± 31.1	39.2 ± 68.6
Dietary vitamin D intake	155.8 ± 121.3	161.9 ±116.4	152.7 ± 107.5	143.4 ± 112.1	134.5 ± 104.0	147.8 ± 130.3
Vitamin D supplement, IU/d	186.5 ± 227.2	205.7 ±258.8	224.8 ± 220.9	239.6 ± 266.1	224.3 ± 268.3	315.4 ± 272.0
Supplement use, n (%)	85 (56.3)	412 (64.6)	120 (77.9)	49 (76.6)	191 (70.5)	69 (87.3)
Alcohol						
Nondrinker at baseline, n (%)	21 (13.9)	193 (30.3)	85 (55.2)	15 (23.4)	132 (48.7)	55 (69.6)
Intake among drinkers, drinks/d	1.7 ± 1.9	0.9 ± 1.1	0.7 ± 0.5	0.4 ± 0.4	0.4 ± 0.5	0.5 ± 0.4
Current smoker, n (%)	20 (13.3)	76 (11.9)	18 (11.7)	10 (15.6)	40 (14.8)	10 (12.7)
Vitamin D Biomarkers						
25(OH)D, ng/mL	26.4 ± 9.1	29.5 ± 9.9	31.1 ± 10.3	20.9 ± 7.5	23.6 ± 9.9	28.0 ± 11.4
$1,25(OH)_2D$, pg/mL[3]	32.3 ± 10.5	34.5 ± 10.8	35.8 ±10.8	31.1 ± 12.3	32.8 ± 11.7	34.4 ± 12.2

[1]Some percentages do not add up to 100% because of missing data or rounding. BMI, body mass index; MET-h/wk, metabolic equivalent hours per week; 25(OH)D, 25-hydroxycholecalciferol.

[2]Mean ± SD (all such values)

[3]Only UDCA trial measured 1,25$(OH)_2$D (n=854)

Table 3. Mean circulating 25(OH)D and $1,25(OH)_2D$ concentrations and category of ACS adherence score[1].

	25(OH)D, ng/mL					$1,25(OH)_2D$, pg/mL				
		ACS score					ACS score			
	n	0-2	3-5	6-8	*p-trend*	*n*	0-2	3-5	6-8	*p-trend*
Pooled population	1357	26.4 ±0.7[1]	29.6 ±0.5	32.0 ±0.8	<0.001	854	31.9 ±1.0	34.5 ±0.7	36.3 ±1.3	0.008

[1] Means ±SE computed from linear regression for individuals in reference categories (white, male, not a college graduate, non-smoker in UDCA trial) centered on mean age and energy intake. Adjusted for sex, study, mean age, race, education, smoking status, and mean energy intake. WBF trial (low fiber vs. high fiber) did not measure $1,25(OH)_2D$

Table 4. Adjusted ORs (95%) for the association between category of ACS adherence score and 25(OH)D status[1].

	Vitamin D status OR (95% CI)		
ACS score category	Deficient <20ng/mL n=296	Insufficient ≥20 & <30ng/mL n=575	Sufficient ≥30ng/mL n=486
Low (0-2)	1.00	1.00	1.00
Moderate (3-5)	1.00	1.76 (1.21-2.57)	2.41 (1.58-3.68)
High (6-8)	1.00	2.29 (1.35-3.90)	4.37 (2.47-7.71)

[1]Odds Ratios (95% CI) obtained from multinomial logistic regression adjusted for study, age, sex, race, education, and energy intake.

Table 5. Mean concentrations of 25(OH)D and $1,25(OH)_2D$ by adherence score components.

Score components	Overall Population[1]			
	25(OH)D, ng/mL		$1,25(OH)_2D$, pg/mL	
	n	Mean ±SE	n	Mean ±SE
Diet				
0	324	26.3 ±1.1	315	32.5 ±1.5
1	874	28.2 ±1.1	538	33.9 ±1.5
2	159	27.5 ±1.3	1	50.0 ±11.0*
P-trend		0.039		0.059
BMI, kg/m^2				
≥30	407	26.3 ±1.1	267	32.5 ±1.5
≥25 and <30	595	28.7 ±1.1	367	34.4 ±1.5
≥18.5 and <25	355	30.4 ±1.2	220	36.7 ±1.6
P-trend		<0.001		<0.001
Physical activity, MET-hours/week				
<8.75	549	26.3 ±1.1	344	32.5 ±1.5
≥8.75 and ≤17.5	341	26.8 ±1.2	210	35.0 ±1.6
>17.5	467	30.5 ±1.2	300	36.0 ±1.6
P-trend		<0.001		<0.001
Alcohol				
Heavy (mean 3.0 drinks/day)	126	26.3 ±1.1	91	32.5 ±1.5
Moderate (mean 0.5 drinks/day)	730	25.1 ±0.8	458	29.8 ±1.1
Never (0 drinks/day)	501	24.0 ±0.8	305	29.3 ±1.1
P-trend		0.009		0.040

[1] Means computed from adjusted linear regression for individuals in reference categories (white male, not a college graduate, non-smoker in the UDCA trial) centered on mean age and energy intake. Adjusted for sex, age, race, education, smoking status, energy intake, and all other score components. $1,25(OH)_2D$ was not measured for WBF trial.

*Only 1 observation in UDCA trial where diet score = 2.

Table 6. Comparison of 25(OH)D concentrations in supplementation trials and ACS adherence score category.

				Post-supplementation 25(OH)D, ng/mL	
Study	**Sample/ Population**	**Cholecalciferol Dose (IU/d)**	**Follow-up (weeks)**	**Mean**	**SD**
Aloia, et al., 2005 (123)	104 healthy, postmenopausal African-American women, 50-75 years	800	13	28.39	9.18
Baron, et al., 2014 (125)	1755 healthy, non-Hispanic whites, 45-75 years	1000 and/or 1200mg/d calcium	52	31.5	8.9
Dawson-Hughes, et al., 1991 (121)	125 postmenopausal women	400 + 377 mg/d calcium	48	36.93	9.46
Hibler, 2011 (120)	28 healthy adults	400	4	28.3	8.9
Karkkainen, et al., 2010 (124)	306 OSTPRE-FPS[1] Finnish women, >65 years	800 + 1000mg calcium	156	29.91	8.78
Lappe, JM, et al., 2007 (126)	288 postmenopausal women in rural Nebraska	1100 + 1400-1500mg/d	288	38.50	8.58
Schnatz, PF, et al., 2014 (122)	285 postmenopausal women, Women's Health Initiative	400 + 1000mg/d calcium	104	24.38	12.23
Current study	909 moderately adherent to ACS guidelines	-	-	29.6	0.5
Current study	233 highly adherent to ACS guidelines	-	-	32.0	0.8

[1]Osteoporosis Risk Factor and Prevention Study- Fracture Prevention Study

APPENDIX F: MANUSCRIPT 3

Odds of new colorectal adenoma when adhering to nutrition and physical activity cancer prevention guidelines

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Running Title: Cancer Prevention Guideline Adherence and Colorectal Adenoma Recurrence

Abbreviations

Abstract

Background: It has been shown that adherence to the American Cancer Society's (ACS) Nutrition and Physical Activity Cancer Prevention Guidelines is associated with reductions in overall cancer incidence and mortality, including site-specific cancers such as colorectal cancer (CRC). To date, there have been no studies investigating adherence to ACS guidelines and development and characteristics of premalignant lesions for CRC.

Objective: We examined the relationship between baseline adherence to the ACS guidelines and 1) baseline CRC adenoma characteristics and 2) odds of new colorectal adenomas.

Design: We performed cross-sectional and prospective cohort analyses of a pooled sample from the Wheat Bran Fiber (n=503) and Ursodeoxycholic Acid (n=854) trials. A cumulative adherence score was constructed using baseline data regarding body size, diet, physical activity, and alcohol consumption. Associations between adherence and baseline adenoma characteristics and new colorectal adenomas were evaluated using multivariate logistic regression models.

Results: In the pooled sample, significantly reduced odds of having three or more adenomas at baseline were shown for moderately adherent (odds ratio [OR]=0.67, 95% confidence intervals [CI]: 0.46-0.99) and highly adherent (OR=0.50, 95% CI: 0.31-0.81) participants compared to those with low adherence (*p*-trend=0.005). Conversely, guideline adherence was not associated with the development of a new colorectal adenoma (moderate adherence OR=1.16, 95% CI: 0.85-1.59, high adherence OR=1.23, 95% CI: 0.85-1.79).

Conclusions: These findings suggest that following the ACS Nutrition and Physical Activity guidelines may lead to a lower odds of multiple adenomas when at least one adenoma is detected.

Key Words: adherence, colorectal adenoma, cancer prevention guidelines, diet, physical activity

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the third leading cancer killer in both men and women in the United States (1). Despite decreasing incidence rates for colorectal cancer over the past two decades in the United States, the American Cancer Society (ACS) estimates that there will be 95,270 new cases of colon cancer and 39,220 new cases of rectal cancer in 2016, with a combined 49,190 deaths from these malignancies (1). Increased screening rates for those aged 50 years and older have contributed to the reduction in colorectal cancer rates over the past 20 years (2) by detection and removal of adenomatous polyps, the precursors to colorectal cancer (3).

Approximately 96% of colorectal cancers are adenocarcinomas, which develop in glandular cells that provide lubrication via mucus production in the colorectum (59). Adenomas are the most common type of polyps, which are benign lesions that up to 50% of all individuals will develop in their lifetime (60, 61). However, adenomas typically cause few symptoms and may silently progress to cancer unless removed. Adenoma are considered advanced when characteristics are displayed such as large size (>1cm), having tubulovillous/villous histology, or having multiple adenomas detected. The United States Preventive Services Task Force (USPSTF) recommends that adults aged 50 to 75 years get screened for colorectal cancer every one to ten years depending on screening test. Stool-based (every 1-3 years) and direct visualization (every 5-10 years) tests are available as tools to detect adenomas and early-stage cancer (56). However, currently only half of those recommended for colorectal screening are following the guidelines (4).

In order to prevent CRC in those unable or unwilling to undergo the current colorectal screening procedures, further strategies for preventing colorectal neoplasia are essential.

There are several innate factors that may increase the risk of colorectal cancer (4), but as reviewed by Giovannucci, there are also several modifiable risk factors for CRC such as physical inactivity, overweight and obesity (REF). Overconsumption of energy rich foods, high consumption of red and/or processed meat, deficiency in some micronutrients or phytochemicals, moderate to heavy alcohol consumption, and smoking early in life (67) have been shown to increase the risk for CRC. While CRC incidence and mortality have been declining in part due to screening and subsequent removal of precancerous polyps (68) an even greater potential for prevention may lie in the modification of behavior-associated risk factors like diet and exercise. Nutrition and physical activity guidelines for cancer prevention have been designed by the United States Department of Health and Human Services along with leading cancer organizations (5, 6). Our recent systematic review of 12 large cohort studies (111) found that following behavior-associated cancer prevention guidelines for factors, such as body weight, physical activity, diet and alcohol consumption, are associated with a reduced risk of cancer incidence, cancer mortality, and all-cause mortality (5, 6). The present study assesses the relationship between adherence to the American Cancer Society's (ACS) nutrition and physical activity cancer prevention guidelines and 1) baseline adenoma characteristics and 2) new colorectal adenoma occurrence.

Subjects and Methods

Study Sample

We pooled data from two randomized, controlled, double blind, Phase III clinical trials conducted at the University of Arizona Cancer Center (UACC). The effect of either wheat bran fiber (WBF) (20) or ursodeoxycholic acid (UDCA) (21) was evaluated against the development of a new colorectal adenoma. The present analyses were conducted for 1,357 participants in the pooled sample with complete data for baseline adenoma characteristics, diet and physical activity measures, and follow-up for evaluation of new colorectal adenomas. The University of Arizona Human Subjects Protection Program previously approved both studies. Each participant provided written informed consent prior to trial enrollment.

Recruitment and Data Collection: Participants were originally recruited from Phoenix and Tucson gastroenterology practices from 1990-1995 for WBF and 1995-1999 for UDCA. Inclusion criteria included men and women aged 40 to 80 years who had at least one adenoma (≥3 mm) removed via a colonoscopy within 6-months prior to study enrollment. Mean time from trial randomization to follow-up colonoscopy was 3.1 and 3.2 years for the WBF and UDCA trials, respectively (20, 21). WBF trial participants were randomized to a daily wheat bran fiber supplement (13.5 g/day) or a low-fiber supplement (2.0 g/day); UDCA trial participants were randomized to receive 8-10 mg UDCA per kilogram of body weight or placebo (21). Primary findings demonstrated that neither the WBF supplement nor the UDCA treatment reduced the number of new colorectal adenomas (21, 97). For the present analysis, participants from the pooled sample (n=2,478) were excluded if they had missing BMI data (n=26), were underweight

(BMI < 18.5kg/m^2) (n=17) or extremely obese (BMI>50kg/m^2) (n=1), had unreliable (<600kcal/d) dietary data (n=15), or missing physical activity data (n=749). The analytic cohort comprised 1,670 participants.

Outcome Ascertainment

Medical records and pathology reports were used to collect baseline and new adenoma characteristics such as number, size, location, and histology (20, 21). Presence of a new colorectal adenoma was defined as yes or no. New advanced colorectal adenoma was defined as an adenoma >1cm in size, having tubulovillous/villous histology (yes/no), or adenocarcinoma.

Nutrition and Physical Activity Cancer Prevention Guidelines Score

An *a priori* adherence score was constructed, based upon previous work (111) for adherence to the 2012 ACS cancer prevention guidelines for nutrition and physical activity (6). The guidelines focused on an overall pattern of lifestyle behaviors that included body weight, physical activity, diet, and alcohol consumption. Frequency questionnaires were used to collect baseline diet and physical activity data. Diet was assessed utilizing the Arizona Food Frequency Questionnaire (AFFQ) which is a semi-quantitative, 175-item validated questionnaire that queries participants to report how often and how much they consumed each food item over the past 12-month period (100). Physical activity was assessed utilizing the Arizona Activity Frequency Questionnaire (AAFQ) is a 59-item, validated questionnaire that asks participants about usual physical activity in the past four weeks (101).

Adherence scores were based upon each ACS recommendation that was equally weighted 0-2 points (not meeting the recommendation at all = 0 points, partially meeting the recommendation = 1 point, fully meeting the recommendation = 2 points). The overall score, summed from individual recommendations, ranged from not adherent at all to the recommendations (0 points) to fully adherent to all four lifestyle factor recommendations (8 points). Adherence scores were categorized into low (0-2 points), moderate (3-5 points), and high (6-8 points). Recommendations for each lifestyle factor, how they were measured, how scores were assigned based upon the guidelines, and the proportion of the study sample within each adherence score category are shown in Table 1. Although the ACS guidelines recommend choosing whole grains over refined grains, the proportion of whole grain consumption was not included in the adherence score for these analyses because 1) grains-related questions in the food frequency questionnaire were vague in distinguishing whole versus refined grains and 2) the food frequency questionnaire was updated between the WBF and UDCA trials. Smoking status was not included in the adherence score, but was included as a potential confounder in the current analyses.

Maintaining a healthy body weight was scored based upon body mass index (BMI, in kg/m^2) from height and weight reported at baseline. Fully meeting the recommendation (2 points) was given to those with a BMI within normal range (18.5-25 kg/m^2). Not meeting the recommendation at all (0 points) was given to those with a BMI in the obese category (>30.0 kg/m^2). One point was given to those partially meeting the recommendation with a BMI in the overweight range (25-30 kg/m^2). Underweight

participants (<18.5 kg/m^2) were excluded from the present analysis.

Adopting a physically active lifestyle was evaluated by MET (102) scores from the AFFQ recreational activities section. The minimum standard of 30 minutes on 5 days (2.5 hours/week) of moderate activity (3.5 METs) is equal to 8.75 MET-hours per week. Any participant doing less than 8.75 MET-hours per week received a score of zero points for not meeting the recommendation at all. One hour per day, 5 days a week (5.0 hours/week), of moderate activity (3.5 METs) is equal to 17.5 MET-hours/ week. Therefore, 8.75 to 17.5 MET-hours/week was considered partially meeting the recommendation and received 1 point. Meeting "preferable" levels of greater than 17.5 MET-hours/week received 2 points for fully meeting the recommendation.

Consumption of a healthy diet with an emphasis on plant sources was assessed with three sub-scores that were constructed and summed to capture the recommended dietary pattern. For the first diet sub-score 1 point was assigned for meeting the recommended number of 5 servings of fruits and vegetables each day. The number of servings was measured from food group categories Fruits, Fruit Juice, Vegetables, and Vegetable Juice. One or 2 points was assigned for diet quality based upon being in the 2nd or 3rd sex-specific tertile of total carotenoids, respectively, which included beta carotene, alpha carotene, beta cryptoxanthin, lycopene, and lutein plus zeaxanthin combined. Limiting the consumption of processed and red meats was assessed by sex-specific quartile distribution with the lowest quartile receiving 3 points and the highest quartile receiving zero points. The diet sub-scores were summed for a potential total of 6 points. Dietary

pattern scores were further collapsed into 0 points for those with 0-1 summed diet scores, 1 point for those with 2-4 summed diet scores, and 2 point for those with 5-6 summed diet scores.

Alcohol consumption was captured in the AFFQ in terms of total grams of alcohol per day. One drink was estimated as 14 grams of alcohol or approximately a 12 ounce regular beer, 5 ounce glass of wine, or 1.5 ounce shot of 80-proof distilled spirit (103). Nondrinkers were assigned 2 points, moderate drinkers consuming the limit or less (1 drink per day for women or 2 drinks per day for men) were assigned 1 point, and heavy drinkers consuming more than the limit were assigned zero points.

Statistical analysis

Descriptive statistics were generated for outcome variables, exposure variables, and demographic variables. Chi-square tests were used to test associations of the chosen variables for participants with and without adenoma recurrence, and for recurrent subjects stratified by sex. Current literature suggests potential confounders include age, previous polyps, family history of colorectal adenomas and/or cancer, and aspirin use (13, 109, 110). Additional covariates were examined and included if the measure of association changed by at least 10% when entered in the model (108). Multiple logistic regression models were utilized to assess the association of adherence score with adenoma recurrence and to evaluate potential interaction between adherence score and 1) sex as a biological variable 2) study and 3) smoking. Statistical significance was determined at an α level of 0.05, and assumptions for all statistical tests were assessed. Data from the trials

were merged and managed using Stata version 14.1 software (StataCorp LP, College Station, Texas).

Results

Table 1 demonstrates high adherence to the guidelines was achieved by 19.1% (n=319) of the sample population while 12.2% (n=204) and 68.7% (n=1147) attained low and moderate adherence, respectively. Baseline characteristics by category of adherence score are shown in **Table 2**.

Table 3 presents the adjusted odds ratios for the association between adherence score categories and baseline colorectal adenoma characteristics from multivariate logistic regression models. In the pooled sample, reduced odds of having three or more adenomas at baseline were shown for moderately adherent (OR=0.67, 95% CI: 0.46-0.99) and highly adherent (OR=0.50, 95% CI: 0.31-0.81) participants compared to those with low adherence (*p*-trend=0.005). No statistically significant associations were shown between guideline adherence and baseline adenoma size or villous histology in the pooled sample. No heterogeneity of effect was demonstrated between sexes for the relationship between adherence score category and any of the baseline adenoma characteristics. However, the odds of at least three adenomas at baseline were significantly lower among men for those highly adherent (OR=0.62, 95% CI: 0.40-0.97) and moderately adherent (OR=0.47, 95% CI: 0.27-0.82), versus those with low adherence (*p*-trend=0.011). Significant study interaction was demonstrated between adherence score category and baseline villous histology (*P*=0.0224).

Table 4 presents the association between new colorectal adenoma and adherence score category from multivariate logistic regression models. In the pooled sample, there were no statistically significant associations between guideline adherence and development of a new adenoma upon follow-up. The odds of having a new colorectal adenoma were 1.16 times (95% CI: 0.85-1.59) greater for those who were moderately adherent to the guidelines and 1.23 times greater (95% CI: 0.85-1.79) for those individuals who had high adherence compared to those with low adherence. There were no statistically significant interactions for smoking status (P=0.6412; data not shown), sex (P=0.2152), or study (P=0.3963). There were no significant associations with adherence score category and any new adenoma occurrence characteristics.

Table 5 presents the results from multivariate logistic regression for the association between adherence score individual components and new colorectal adenoma occurrence. There were no statistically significant associations between the diet scores, BMI categories, physical activity levels, or alcohol consumption, and the development of a new colorectal adenoma.

Discussion

The results of the present study demonstrate that adherence to the cancer prevention guidelines was associated with lower odds of multiple adenomas at baseline. Those who were more adherent to the guidelines were significantly less likely to have multiple adenomas, which are established precursors of colorectal cancer (134). In contrast, there

were no statistically significant associations observed for guideline adherence and odds of developing a new adenoma.

To date, few studies have evaluated the association between healthy lifestyle adherence and colorectal adenoma risk. Similar to our findings, a recent study demonstrated a statistically significant inverse association between adherence to health guidelines and detection of advanced colorectal neoplasia defined as high-risk adenomas (≥3 adenomas or any adenoma ≥1 cm in diameter or villous/tubulovillous/severe dysplasia) or colorectal cancer (130). Fu et al. also found strong evidence that lifestyle modification was important for the prevention of colorectal polyps, especially advanced and multiple adenomas (131). In contrast to our findings, a case-control study by Tabung et al. found that for participants who reported no use of NSAIDs, those in the healthy lifestyle category had a 72% lower odds of any colorectal adenoma as compared to those in the unhealthy category (OR 0.28; 95% CI 0.08, 0.98) (132). In addition, a one-unit increase in the index significantly reduced odds of any adenoma by 53% (OR 0.47; 95% CI 0.26, 0.88), however the sample size was fairly small (n=143) (132). Furthermore, although a statistically significant association between the adherence score and odds of a new adenoma recurrence was not seen in the present work, a recent review demonstrated a significant reduction in colorectal cancer risk (27-52%) for those that highly adhered to the guidelines versus those with low adherence to the guidelines (111).

The major strengths of the current study include availability of data from a prospective cohort of over 1,300 participants with complete data on a wide range of available

baseline nutrition, physical activity, and new colorectal adenoma outcome data. This study is not without limitations. The recommendation "maintenance of a healthy weight throughout life" could not be precisely assessed because height and weight data were only available at study baseline. In addition, the lifestyle pattern at the time of screening may not reflect participants' lifestyle leading up to the onset of their adenoma development. We were unable to adjust for the number of previous colonoscopies. Perhaps those who were more adherent to the guidelines were more likely to have regular screening colonoscopies and therefore less likely to have multiple adenomas discovered at a given colonoscopy. The null findings for any new colorectal adenomas could be due to many reasons including the brief follow-up time, residual confounding, or inadequate power in stratification analyses.

In summary, these results suggest that following an overall pattern of healthy behaviors as recommended in the ACS Nutrition and Physical Activity Cancer Prevention guidelines is associated with a reduction in colorectal adenoma multiplicity at baseline. However, no association with adhering to the guidelines and odds of developing a new colorectal adenoma was observed over the 3-year follow-up period in our sample population. This is an important area for further research as the presence of multiple adenomas increases the risk of development of CRC. Prevention of multiple adenomas may have an impact on colonoscopy screening rates as well, as multiplicity is an indicator for more frequent surveillance.

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LNK and ETJ designed research; LNK analyzed data; LNK, ETJ, RBH, EO, and DJR wrote the paper; LNK had primary responsibility for final content. All authors read and approved the final manuscript.

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Table 1. Components of the Cancer Prevention adherence score and distribution in the study sample.

	Score	Description	All N (%)
Overall adherence score	Low	0-2 points	204 (12.2)
	Moderate	3-5 points	1147 (68.7)
	High	6-8 points	319 (19.1)
Adherence score component			
Body mass index (BMI)	0	>30 kg/m^2	476 (28.5)
	1	>25-≤30 kg/m^2	749 (44.9)
	2	18.5-≤25 kg/m^2	445 (26.7)
Physical Activity (PA)	0	<8.75 MET h/wk	658 (39.4)
	1	8.75-17.5 MET h/wk	421 (25.2)
	2	>17.5 MET h/wk	591 (35.4)
Diet*	0	Summed and collapsed scores from diet components	209 (12.5)
	1		947 (56.7)
	2		514 (30.8)
Fruit & Vegetables	0	<5 servings/day fruits plus veg	836 (50.1)
	1	≥5 servings/day fruits plus veg	834 (49.9)
Quality	0	1st tertile of total carotenoids	540 (32.3)
	1	2nd tertile of total carotenoids	564 (33.8)
	2	3rd tertile of total carotenoids	566 (33.9)
Red & processed meat	0	Highest quartile	421 (25.2)
	1		423 (25.3)
	2		420 (25.2)
	3	Lowest quartile	406 (24.3)
Alcohol	0	Men ≥3, Women ≥2 drinks/day	153 (9.2)
	1	Men 1-2, Women 1 drink/day	921 (55.2)
	2	Non-drinker	596 (35.7)

*Diet score is generated from the summation of the fruit & vegetable, quality, and red & processed meat scores. Summed for up to 6 points and then collapsed into 3 categories (0-1, 2-4, 5-6) for subsequent diet adherence values (0, 1, 2)

Table 2. Baseline characteristics of participants in the pooled sample (n=1670) by categories of adherence [1].

	Adherence Score Category (points)		
	0-2	3-5	6-8
n (%)	204 (12.2)	1147 (68.7)	319 (19.1)
Age, years[3]	62.8 (8.4)	65.8 (8.6)	68.0 (8.1)
White, n (%)	195 (95.6)	1085 (94.6)	303 (95.0)
College graduate, n (%)	60 (29.4)	409 (35.7)	113 (35.4)
BMI, kg/m^2	32.5 (4.4)	28.2 (4.3)	24.5 (2.7)
Physical activity, MET-h/wk	4.1 (5.0)	16.7 (29.2)	31.3 (32.2)
Diet			
Total energy, kcal/d	2135.0 (797.2)	1955.7 (757.8)	1946.8 (726.4)
Fruit and veg, servings/d	5.0 (3.3)	5.7 (3.7)	6.9 (3.7)
Total carotenoids, µg/d	13449.0	13846.0	15054.2
Red and processed meat,	2.0 (1.0)	1.4 (0.8)	1.1 (0.7)
Alcohol			
Nondrinker at baseline, n (%)	22 (10.8)	391 (34.1)	183 (57.4)
Intake among drinkers, drinks/d	1.3 (1.7)	0.8 (1.2)	0.7 (0.7)
Current smoker, n (%)	34 (16.7)	137 (11.9)	38 (11.9)
Family history CRC, n (%)	51 (25.0)	267 (23.3)	66 (20.7)
Previous polyps, n (%)	78 (38.2)	489 (42.6)	131 (41.1)
Aspirin use in last 4 weeks, n (%)	49 (24.0)	340 (29.6)	113 (35.4)
Number of colonoscopies during study period	1.8 (0.8)	1.8 (0.8)	1.8 (0.9)
Baseline adenoma characteristics			
Multiplicity, ≥3 adenomas, n (%)	42 (15.0)	192 (68.3)	47 (16.7)
Large size, >1cm, n (%)	89 (13.1)	463 (67.9)	130 (19.1)
Tubulovillous/villous histology, n (%)	49 (14.1)	228 (65.5)	71 (20.4)
Proximal location, n (%)	109 (12.8)	594 (69.6)	150 (17.6)

[1]Some percentages do not add up to 100% because of missing data or rounding. BMI, body mass index; MET-h/wk, metabolic equivalent hours per week; CRC, colorectal cancer.

[2]Mean ± SD (all such values)

Table 3. Adjusted ORs (95% CI) for the association between category of guideline adherence and baseline colorectal adenoma characteristics for pooled sample and by sex and study

ACS adherence score category	Baseline adenoma characteristics (OR, 95% CI)[1]					
	Multiplicity (≥3 adenoma)		Large size (≥1 cm)		Villous histology	
	n (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Pooled sample						
Low (0-2)	204 (12.2)	1.00	89 (13.1)	1.00	49 (14.1)	1.00
Moderate (3-5)	1147 (68.7)	0.67 (0.46-0.99)	463 (67.9)	0.85 (0.63-1.15)	228 (65.5)	0.78 (0.55-1.11)
High (6-8)	319 (19.1)	0.50 (0.31-0.81)	130 (19.1)	0.85 (0.59-1.22)	71 (20.4)	0.89 (0.58-1.36)
p-Trend		0.005		0.455		0.765
Men						
Low (0-2)	141 (12.3)	1.00	57 (12.3)	1.00	34 (14.5)	1.00
Moderate (3-5)	791 (68.7)	0.62 (0.40-0.97)	319 (69.1)	0.92 (0.64-1.34)	153 (65.4)	0.73 (0.47-1.12)
High (6-8)	219 (19.0)	0.47 (0.27-0.82)	86 (18.6)	0.83 (0.53-1.30)	47 (20.1)	0.78 (0.46-1.30)
p-Trend		0.011		0.405		0.443
Women						
Low (0-2)	63 (12.1)	1.00	32 (14.6)	1.00	15 (13.2)	1.00
Moderate (3-5)	356 (68.6)	0.82 (0.38-1.79)	144 (65.5)	0.68 (0.40-1.17)	75 (65.8)	0.90 (0.48-1.70)
High (6-8)	100 (19.3)	0.56 (0.21-1.48)	44 (20.0)	0.85 (0.45-1.60)	24 (21.1)	1.16 (0.55-2.45)
p-Trend		0.221		0.809		0.577
p-Interaction[2]		0.8360		0.4363		0.8597
UDCA						
Low (0-2)	121 (13.4)	1.00	51 (13.3)	1.00	24 (13.0)	1.00
Moderate (3-5)	633 (70.3)	0.75 (0.42-1.31)	276 (71.9)	1.06 (0.71-1.57)	134 (72.8)	1.15 (0.70-1.88)
High (6-8)	147 (16.3)	0.59 (0.28-1.23)	57 (14.8)	0.85 (0.52-1.41)	26 (14.1)	0.93 (0.50-1.73)
p-Trend		0.162		0.485		0.763
WBF						
Low (0-2)	83 (10.8)	1.00	38 (12.8)	1.00	25 (15.2)	1.00
Moderate (3-5)	514 (66.8)	0.62 (0.36-1.05)	187 (62.8)	0.64 (0.40-1.03)	94 (57.3)	0.50 (0.30-0.85)
High (6-8)	172 (22.4)	0.44 (0.23-0.83)	73 (24.5)	0.78 (0.46-1.34)	45 (27.4)	0.76 (0.42-1.37)

p-Trend	0.013	0.730	0.903
p-Interaction[2]	0.8687	0.1224	0.0224

[1] ORs adjusted for age, sex (except for stratified analysis), and study (except for stratified analysis)
[2] *P* for interaction calculated by likelihood ratio test

Table 4. Adjusted ORs (95% CIs) for the association between category of adherence and new colorectal adenoma occurrence for pooled sample and by sex and study

	New adenoma occurrence (OR, 95% CI)[1]							
	Any new occurrence		Multiplicity (≥3 adenoma)		Large size (≥1 cm)		Villous histology	
Adherence score category	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Pooled sample								
Low (0-2)	105 (13.8)	1.00	22 (11.2)	1.00	14 (8.4)	1.00	11 (9.2)	1.00
Moderate (3-5)	504 (66.2)	1.16 (0.85-1.59)	130 (66.0)	0.97 (0.58-1.59)	112 (67.1)	1.40 (0.78-2.51)	88 (73.3)	1.35 (0.70-2.58)
High (6-8)	152 (20.0)	1.23 (0.85-1.79)	45 (22.8)	1.11 (0.62-1.98)	41 (24.6)	1.83 (0.95-3.51)	21 (17.5)	1.08 (0.50-2.33)
p-Trend		0.294		0.611		0.055		0.938
Men								
Low (0-2)	67 (11.9)	1.00	18 (11.6)	1.00	12 (9.6)	1.00	10 (11.1)	1.00
Moderate (3-5)	385 (38.4)	1.00 (0.69-1.45)	98 (63.2)	0.85 (0.48-1.49)	85 (68.0)	1.12 (0.59-2.15)	65 (72.2)	1.00 (0.50-2.02)
High (6-8)	111 (19.7)	1.00 (0.64-1.56)	39 (25.2)	1.10 (0.58-2.12)	28 (22.4)	1.27 (0.61-2.67)	15 (16.7)	0.76 (0.32-1.77)
p-Trend		0.983		0.531		0.494		0.435
Women								
Low (0-2)	17 (8.6)	1.00	4 (9.5)	1.00	2 (4.8)	1.00	1 (3.3)	1.00
Moderate (3-5)	138 (69.7)	1.69 (0.92-3.09)	32 (76.2)	1.30 (0.43-3.89)	27 (64.3)	2.45 (0.56-10.64)	23 (76.7)	4.42 (0.58-33.38)
High (6-8)	43 (21.7)	2.02 (1.01-4.06)	6 (14.3)	0.92 (0.25-3.40)	13 (31.0)	4.58 (0.98-21.39)	6 (20.0)	4.15 (0.48-35.56)
p-Trend		0.061		0.750		0.021		0.306
p-Interaction[2]		0.2152		0.3877		0.3253		0.1281
UDCA								
Low (0-2)	45 (12.0)	1.00	8 (11.8)	1.00	11 (13.4)	1.00	8 (11.9)	1.00
Moderate (3-5)	272 (72.3)	1.22 (0.81-1.84)	47 (69.1)	0.94 (0.42-2.11)	59 (72.0)	0.97 (0.49-1.94)	52 (77.6)	1.12 (0.51-2.45)

High (6-8)	59 (15.7)	1.08 (0.65-1.80)	13 (19.1)	1.11 (0.42-2.89)	12 (14.6)	0.84 (0.35-2.03)	7 (10.5)	0.59 (0.21-1.72)
p-Trend		0.846		0.781		0.689		0.299
WBF								
Low (0-2)	39 (10.1)	1.00	14 (10.9)	1.00	3 (3.5)	1.00	3 (5.6)	1.00
Moderate (3-5)	251 (65.2)	1.11 (0.69-1.80)	83 (64.3)	0.95 (0.50-1.80)	53 (62.4)	2.95 (0.89-9.73)	36 (67.9)	1.95 (0.58-6.50)
High (6-8)	95 (24.7)	1.38 (0.80-2.40)	32 (24.8)	1.09 (0.53-2.24)	29 (34.1)	4.94 (1.44-16.98)	14 (26.4)	2.15 (0.59-7.80)
p-Trend		0.192		0.707		0.003		0.318
p-Interaction[2]		0.3963		0.9864		0.0238		0.2581

[1] ORs adjusted for age, study (except for stratified analysis), baseline multiplicity (except villous histology analyses), and sex (except for stratified analysis)

[2] *P* for interaction calculated by likelihood ratio test

Table 5. Association of individual component scores for cancer prevention adherence and odds of new colorectal adenoma[1]

Adherence Score components	New Adenoma Occurrence, OR (95% CI)[1]
Diet	
0	1.00
1	1.03 (0.78-1.45)
2	0.96 (0.68-1.36)
BMI, kg/m^2	
≥30	1.00
≥25 and <30	0.96 (0.76-1.22)
≥18.5 and <25	0.82 (0.63-1.08)
Physical activity, MET-hours/week	
<8.75	1.00
≥8.75 and ≤17.5	1.03 (0.80-1.32)
>17.5	1.07 (0.84-1.35)
Alcohol	
Heavy	1.00
Moderate	1.01 (0.71-1.43)
Never	1.17 (0.81-1.69)

[1] OR (95% CI) obtained from multivariate logistic regression. Adjusted for age, sex, study, and other score components.