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**Adherence to WCRF/AICR Cancer Prevention Recommendations and Incident Sporadic Colorectal Adenoma Risk**

By

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Master of Public Health

Department of Epidemiology

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# Adherence to WCRF/AICR Cancer Prevention Recommendations and Incident Sporadic Colorectal Adenoma Risk

By

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Bachelor of Science

Shandong University

2014

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## Abstract

### Adherence to WCRF/AICR Cancer Prevention Recommendations and Incident Sporadic Colorectal Adenoma Risk

By Yongjia Song

Colorectal cancer is the second most common cause of cancer death in the United States. Though colorectal cancer incidence has been decreasing mainly due to advances in screening, there is need to develop comprehensive recommendations for cancer prevention with diet and lifestyle. The goal of this thesis is to investigate the association between adherence to the WCRF/AICR cancer prevention recommendations and incident, sporadic colorectal adenoma.

A case-control study was conducted by Minnesota Cancer Prevention Research Unit from 1991 to 1994, including 574 colorectal adenoma cases, 707 colonoscopy-negative controls, and 550 community-based controls. Data on demographics, diet, and lifestyle were collected to construct a 7-component score based on the WCRF/AICR cancer prevention recommendations. Logistic regression models were used to estimate associations between the computed score and its sub-components with incident, sporadic colorectal adenoma risk.

Higher adherence to the WCRF/AICR recommendations were associated with lower risk for incident, sporadic colorectal adenoma among men (OR = 0.66, 95% CI: 0.40, 0.98, $P_{trend}$ = 0.023), but not among women (OR = 0.72, 95% CI: 0.40, 1.31, $P_{trend}$ = 0.524; $P_{interaction}$ = 0.155). This inverse association was suggestively stronger among those who had multiple adenomas, or adenomas with a villous or tubulovillous component, or adenomas with large size.

In conclusion, the results of my thesis support the hypothesis that higher adherence to the WCRF/AICR recommendations were associated with lower risk for incident sporadic colorectal adenoma among men, but couldn't provide evidence to demonstrate this association among women. Further studies are needed to focus on association between genders on colorectal adenoma formation.

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# CHAPTER 1. INTRODUCTION AND BACKGROUND

## Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) is the second most common cause of death from cancer among both men and women in the United States(1). In 2016, there were estimated 134,490 new CRC cases and 49,190 deaths from CRC(2, 3). The incidence of CRC has decreased since the mid-1980s, with a rapid decline of incidence rates since 2008 as a result of the increasing popularization of colonoscopy. The incidence rates of CRC increase with age, while are approximately the same among males and females(1). The mortality rates of CRC also decreased 49% in overall from 1976 to 2012, presumably due to early detection and treatment(2). African Americans have the highest incident rates and mortality rates of CRC when compared to Caucasian, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native people(4). Since the mid-1970s, the survival rate after a CRC diagnosis has been steadily increasing from 51% to 65% for colon cancers and from 48% to 68% for rectal cancers (1, 2). The 5-year relative survival rates for local, regional, and distant CRC are 90%, 71%, and 13%, respectively, with an overall survival rate of 65% for CRC of all stages diagnosed between 2005 and 2011(3).

CRC has a high fatality rate and is the fourth leading cause of death from cancer worldwide(5). Previous international ecologic studies illustrated that there are large variations in incidence rates of CRC across countries. Compared to middle or low income countries, CRC is much more common in high income countries. From 1983-87 to 1998-2002, the Cancer Incidence in Five Continents database demonstrated a significant

increase in CRC incidence rates in developing countries, including most parts of Asia, Eastern European, and some countries of South America, while the United States was the only country where there was a decline in CRC incidence rates(6). For instance, the incidence rate of CRC is increasing dramatically in Japan, probably as a result of an increase in dietary intake of meat, milk, eggs, and fat/oil in Japan since 1940(7). Migrant studies showed the importance of the effect of environment, nutrition pattern, and ethnicity on the incidence rates of CRC(8).

CRC originates from the colon or rectum, which are parts of the digestive system of the human body. The vast majority of CRCs begin growth from a noncancerous polyp that develops on the inner lining of the colon or rectum. Most colorectal polyps are classified as hyperplastic polyps or dysplastic polyps (9). Hyperplastic polyps are thought to have no potential progression to CRC, and are generally considered to be benign growths. However, colorectal adenomas can develop into malignant tumors over time. Previous studies showed that the malignant potential of colorectal adenomas depends on the size and number of adenomas(10). A experiment conducted by St. Mark's Hospital found that the malignancy rates in adenomas under 1 cm, between 1 and 2 cm, and over 2 cm are 1.3%, 10%, and 46%(10). Persons who have 5 or more colorectal adenomas or 3 colorectal adenomas with at least one being greater than 1cm have the highest risk of developing CRC(11).

On average, adenomas are diagnosed 10 years before developing into CRC(11). This slow progression of growth from noncancerous polyps to invasive CRCs provides an opportunity for the prevention and early detection of CRC. Endoscopy screening can prevent CRC through removal of noncancerous polyps, as well as detect CRC at an early

stage(3). Fecal occult blood testing, colonoscopy and sigmoidoscopy are the most common methods for CRC screening, which can help detect the disease earlier and subsequently reduce the incidence and mortality rate of CRC(12). In the United States, colonoscopy is the most popular method for CRC screening. After adenomas are detected and removed, a surveillance is done to prevent reoccurrence at an interval of 1, 3 or 5 years depending on the number and size of adenomas (13).

## Molecular Basis of Colorectal Cancer

Several molecular events in the adenoma-carcinoma sequence, including mutations in the adenomas polyposis coli (APC) tumor suppressor gene, Mismatch repair genes (eg. MSH2, MLH1), K-ras protooncogene, and p53 tumor suppressor gene may lead to the development of adenoma or carcinoma from the normal colorectal epithelium (14, 15). The "APC-β catenin-Tcf" and the "Mismatch repair" are two main pathways that promote the progress of colorectal carcinogenesis. The "APC-β catenin-Tcf" pathway accounts for familial adenomatous polyposis(15). APC loses the function to destroy β catenin when mutated. If β catenin is not inhibited by APC, c-myc and cyclin D1 are up-regulated results in reducing apoptosis and promoting cell proliferation(16). The "Mismatch repair" pathway accounts for hereditary nonpolyposis colorectal cancer(15). Mutations in mismatch repair genes lead to the accumulation of mismatches in DNA replication, thereby promoting cell proliferation and inhibiting apoptosis(15).

## Risk Factors of Colorectal Cancer

Risk factors for CRC include diet, weight gain, alcohol consumption, smoking, lack of physical activity, family history of colon cancer and colon polyps, presence of colon polyps, and other chronic diseases and conditions including diabetes and inflammatory bowel disease. Based on the report of American Institute of Cancer Research (AICR)/World Cancer Research Fund (WCRF), 50% of US colorectal cancers - about 68,400 cases - can be prevented by eating healthy, being active and maintaining a healthy weight(17). Risk factors associated with CRC were listed in the following categories (adopted from (17)):

| Food, Nutrition, Physical Activity and Cancers of The Colon and The Rectum, 2011 | | |
|---|---|---|
| | **Decreases Risk** | **Increases Risk** |
| **Convincing** | Physical activity<br>Foods containing dietary fiber | Red meat<br>Processed meat<br>Alcoholic drinks (men)<br>Body fatness<br>Abdominal fatness<br>Adult attained height |
| **Probable** | Garlic<br>Milk<br>Calcium | Alcoholic drinks (women) |
| **Limited - suggestive** | Non-starchy vegetables<br>Fruits<br>Foods containing vitamin D | Foods containing iron<br>Cheese<br>Foods containing animal fats<br>Foods containing sugars |
| **Limited – no conclusion** | Fish; glycaemic index; folate; vitamin C; vitamin E; selenium; low fat; dietary pattern | |
| **Substantial effect on risk unlikely** | None identified | |
| *Source: AICR/WCRF Continuous Update Project Report: Colorectal Cancer, 2011* | | |

***Demographic risk factors***

In the United States, the incidence of CRC increases with age especially for people who are above 50 (1, 18). The probability of developing invasive CRC among individuals aged from birth to 49 years is 0.3% in males and 0.3% in females, compared with 4.8% and 4.5% among individuals aged from birth to death(1). Sex disparities in CRC incidence rates are greatest among men and women aged 65 and over (332.6 versus 237.3 per 100,000 respectively)(19). However, overall men and women have approximately equal incidence rates of CRC(1). Non-Hispanic blacks have the highest CRC incidence rate (61.9 in males and 45.6 in females per 100,000), compared to Non-Hispanic whites (49.2 in males and 37.4 in females per 100,000), Hispanic (45.9 in males and 31.6 in females per 100,000), American Indian/Alaska Native (50.9 in males and 41.1 in females per 100,000), and Asian/Pacific Islander (39.9 in males and 30.0 in females per 100,000)(1).

***Family history of colorectal cancer***

The incidence rate of CRC can be increased from twofold to threefold by having a first degree relative with CRC (20, 21). A meta-analysis of thirteen colonoscopy studies reported that the prevalence of colorectal adenoma was significantly higher in individuals who have a family history, compared to those who do not (OR = 1.7, 95% CI: 1.4-3.5)(22). Individuals who have two or more first degree relatives with CRC have a more than double risk for adenomas (OR = 2.3, 95% CI: 0.5, 8.2), compared to those with one first degree relative with CRC (OR = 0.8, 95% CI: 0.4, 1.5)(21). Few studies have investigated the association between family history of CRC and CRC risk among individuals younger than 50 years. Among persons who have a family history of CRC,

the prevalence of any size of advanced colorectal adenoma was higher in 45 – 49 years old patients compared to the 40 – 44 years old group (21.5% vs. 9.2%)(23). A case-control study conducted by Lee *et al* reported that advanced and multiple colorectal adenoma was associated with a family history of CRC among individuals aged 40 – 49 years (OR = 1.50, 95% CI: 1.05, 2.14) (20).

***Physical activity and body fatness***

Accumulating epidemiological evidence has consistently demonstrated an inverse association between physical activity and CRC, and a positive association between body weight and CRC (18, 24-27). Several meta-analyses and systematic reviews have been conducted. The association of physical activity and BMI with CRC risk by anatomical site was shown in a meta-analysis of 30 cohort studies, most of which were conducted in the United States(24). Physical activity was inversely associated with the risk of distal (RR = 0.77, 95% CI: 0.71-0.83) and proximal colon cancer (RR = 0.76, 95% CI: 1.02, 1.48) (24). BMI was positively associated with CRC overall and all colorectal sub-sites, with most significant for distal colon cancer (RR = 1.59, 95% CI: 1.34, 1.89)(24). In addition, a meta-analysis of 13 prospective cohort studies found that gain in body mass index was positively associated with CRC risk (HR = 1.16, 95% CI: 1.08, 1.24)(27). However, few studies investigated the association between body weight, physical activity, and steps in the colorectal adenoma-carcinoma sequence. A case-control study including 208 cases and 426 controls demonstrated that high frequency of physical activity is inversely associated with the risk of CRC (OR = 0.3, 95% CI: 0.2-0.5), but was not associated with colorectal adenomas (Small adenomas: OR = 1.3, 95% CI: 0.7, 2.5;

Large adenoma: OR = 0.8, 95% CI: 0.4, 1.5) (26). High BMI was positively associated with the risk of large (OR = 2.1, 95% CI: 1.2, 3.5) and small colorectal adenomas (OR = 1.7, 95% CI: 1.0, 3.1), but was not associated with CRC(26).

***Plant food***

It is biologically plausible that low consumption of vegetables and fruits are associated with high risk of CRC. However, this association is less established for colorectal adenoma, with multiple studies reporting inconsistent results, in part due to different dietary assessment methods(28, 29). A case-control study nested within the Nurses' Health Study (n=34,467) reported the women consuming five or more servings of fruits per day are at lower risk (OR = 0.60, 95% CI: 0.44, 0.81) for developing colorectal adenomas, compared to those who only consume one serving per day or less(30). In the same study, vegetable consumption was also inversely associated with colorectal adenoma risk (OR = 0.82, 95% CI: 0.65, 1.05)(30). In a meta-analysis of 16 case-control studies and 4 cohort studies including 10,948 cases of colorectal adenoma, and conducted in the US, Europe, and Asia, high dietary fiber intake was associated with lower colorectal adenoma risk (RR = 0.72, 95% CI: 0.63, 0.83), with a significant dose-response effect of 10 grams per day increase in fiber consumption (RR = 0.91, 95% CI: 0.87, 0.95)(31). The summary relative risks of colorectal adenoma were 0.93 for vegetable fiber (95% CI: 0.84, 1.04), 0.84 for fruit fiber (95% CI: 0.76, 0.94), and 0.76 for cereal fiber (95% CI: 0.62, 0.92)(31). A combined analysis of 13 case-control studies from the US (5287 cases, 10470 controls) found that the relative risks for colorectal adenoma were $RR_{Q5}$ = 0.79, $RR_{Q4}$ = 0.69, $RR_{Q3}$ =0.63, and $RR_{Q2}$ =0.53 compared to the

lowest quintile ($P_{trend} < 0.001$)(32).

### *Animal food*

High consumption of red meat or processed meat has been consistently associated with an increased risk of CRC. This relationship was potentially due to chemical carcinogens such as N-nitroso compounds, heterocyclic amines that are produced during the process of cooking meat and that may promote the development of CRC (33, 34). A meta-analysis including 15 studies on red meat and 14 studies on processed meat reported that the summary relative risks of CRC were 1.28 (95% CI: 1.15, 1.42) for red meat and 1.20 (95%CI: 1.11, 1.31) for processed meat(35). A meta-analysis of 12 case-control studies and 10 cohort studies found that the frequency of red meat intake rather than total amount of meat consumption was associated with a higher CRC risk(36). The summary relative risk for colon and rectal cancers were 1.37 (95% CI: 1.09, 1.71) and 1.43 (95% CI: 1.24, 1.64), respectively, among individuals who consumed red meat more than once per day compared to those who did not. (36). Furthermore, consuming over 50 grams of red meat per day was positively associated with risk for colon cancers (RR = 1.21, 95% CI: 1.07, 1.37), but not for rectal cancers (RR = 1.30, 95% CI: 0.90, 1.89)(36).

### *Calcium and vitamin D intake*

Calcium is an essential element for living organisms. It has been found to have an anti-proliferative effect by binding secondary bile acids, thereby inhibiting the development of CRC(37, 38). Secondary bile acids are formed by enzymatic

deconjugation and dehydroxylation of primary bile acids in the large bowel by anaerobic bacteria, and were found to have tumor-promoting capabilities(38). Previous analytic epidemiological studies have shown that high consumption of calcium may be associated with the lower risk of CRC. A pooled analysis of 10 prospective cohort studies found that CRC is inversely associated with dietary calcium (RR for highest quintile of intake compared to lower quintile of intake, Q5 vs. Q1: 0.86, 95% CI: 0.78, 0.95) and total calcium (RR Q5 vs. Q1 = 0.86, 95% CI: 0.69, 0.88) (39). A similar reduction was found in risk of recurrent colorectal adenomas in two clinical trials (40, 41). Vitamin D also may promote cell differentiation and reduce proliferation to inhibit the development of CRC (37). A meta-analysis of eight prospective studies suggested an inverse association of CRC (OR = 0.66, 95% CI: 0.54, 0.81), comparing top versus bottom quartiles of circulating 25(OH) D levels (42). The inverse association was stronger for rectal cancer (OR = 0.50 for top versus bottom quartiles, 95% CI: 0.28, 0.88) than colon cancer (OR = 0.77, 95% CI: 0.56, 1.07, P for difference between colon and rectal cancer = 0.20) (42).

***Alcohol and smoking***

Previous meta-analyses supported a positive association between CRC and alcohol consumption (43, 44). A meta-analysis of 27 cohort studies and 34 case-control studies provided evidence that risk of CRC was positively associated with heavy (RR: 1.52, 95% CI: 1.27, 1.81) and moderate alcohol drinking (RR:1.24, 95% CI: 1.13, 1.28)(43). Another meta-analysis of 9 cohort studies and 22 case-controls reported that any beer drinkers were associated with a higher CRC risk (RR = 1.20, 95% CI: 1.06, 1.37), compared to non-alcohol drinkers(44). A similar association was found on

smoking and CRC risk (45, 46). 26 cohort studies from a meta-analysis found that the adjusted RR of CRC was 1.18 (95% CI: 1.11, 1.25) for people who had smoked at some time in their lives versus people who had not (46). Cheng *et al.* reported in a meta-analysis of 24 prospective cohort studies that current smokers had a higher risk of rectal (RR = 1.24, 95% CI: 1.16, 1.39) than colon cancers (RR = 1.09, 95% CI: 1.01, 1.18), whereas former smokers had a similar risk of rectal (RR = 1.20, 95% CI: 1.11, 1.30) and colon cancers (RR = 1.16, 95% CI: 1.11, 1.28)(45).

## World Cancer Research Fund Recommendations

In 2007, WCRF and AICR published a report and issued eight general recommendations on body fatness, physical activities, foods and drinks that promote weight gain, plant foods, animal foods, alcohol drinks, preparation, dietary supplements, and two special recommendations on breast feeding and cancer survivors(47) (Table 1). The recommendations were based on their analysis of global research, which showed that about a third of most common cancers are preventable through a healthy diet, maintaining a healthy weight and regular physical activity.

Previous studies showed that adherence to the WCRF recommendation is associated with cancer risk. A case-control study conducted by Realdon *et al.* showed that meeting the WCRF cancer prevention guidelines was inversely associated with the Barrett's esophagus progression to esophageal adenocarcinoma (OR = 0.51, 95% CI: 0.37, 0.67)(48). The results from the Framingham cohort suggested that the adherence to the WCRF recommendations was not associated with obesity-related cancers (HR = 0.94,

95% CI: 0.86, 1.02) including gastrointestinal tract, reticuloendothelial system, genitourinary organs, and thyroid gland cancers. However, a plant-based diet and low alcohol consumption, in accordance with the WCRF recommendations, were associated with reduced risk of obesity-related cancers (HR = 0.71, 95% CI: 0.51, 0.99) (49). Arab *et al.* created a score based on the WCRF guidelines to illustrate that the high concordance with the WCRF recommendations was inversely associated with highly aggressive prostate cancer risk, with a 13% risk reduction for each additional point in the total adherence score (50). Risk of breast cancer was inversely associated with WCRF recommendations related to body fatness, plant foods, and alcohol. (HR = 0.38, 95% CI: 0.25, 0.58)(51). The EPIC study including 386,355 participants from 9 European countries reported significant inverse associations between adherence to the WCRF recommendations and cancers of the breast (HR $_{Q5\ vs\ Q1}$ = 0.84, 95% CI: 0.78, 0.90, $P_{trend}$ < 0.0001 ) , endometrium (HR $_{Q5\ vs\ Q1}$ = 0.77, 95% CI: 0.62, 0.94, $P_{trend}$ = 0.002), colon & rectum (HR $_{Q5\ vs\ Q1}$ = 0.73, 95% CI: 0.65, 0.81, $P_{trend}$ < 0.0001), lung (HR $_{Q5\ vs\ Q1}$ = 0.86, 95% CI: 0.74, 1.00, $P_{trend}$ = 0.001), kidney (HR $_{Q5\ vs\ Q1}$ = 0.71, 95% CI: 0.54, 0.93, P*trend* = 0.030), stomach (HR $_{Q5\ vs\ Q1}$ = 0.62, 95% CI: 0.46, 0.83, $P_{trend}$ < 0.0001), upper aerodigestive tract (HR $_{Q5\ vs\ Q1}$ = 0.69, 95% CI: 0.50, 0.95, $P_{trend}$ < 0.0001) , liver (HR $_{Q5\ vs\ Q1}$ = 0.85, 95% CI: 0.62, 1.16, $P_{trend}$ < 0.011), and esophagus (HR $_{Q5\ vs\ Q1}$ = 0.58, 95% CI: 0.38, 0.90, $P_{trend}$ < 0.008) (52).

Adherence to the WCRF cancer recommendations was also shown to be associated with improved survival after cancer diagnosis. Cancer survivors (including breast, colorectal, gynecologic, and other cancer) in the Iowa Women's Health Study who adhered to the WCRF recommendations were less likely to die from any cause

compared to women who did not adhere to the WCRF recommendations(HR = 0.67, 95% CI: 0.50, 0.94) (53). After stratifying on cancer type, survivors of breast cancers had the lowest risk of death rather than survivors of colorectal and gynecologic cancers. In the EPIC study, Romaguera *et al.* found that CRC patients had lower mortality compared to CRC patients comparing who adhered to the WCRF recommendations to those didn't (54). Therefore, the public health goals and personal recommendations are offered as significant contribution towards the prevention and control of cancer throughout the world.

# CHAPTER 2. MATERIALS AND METHODS

## Study Population

This case-control study was conducted from April 1991 to April 1994 by the Minnesota Cancer Prevention Research Unit and was approved by the institutional review boards of the University of Minnesota and nine hospitals serving the 10 endoscopy units utilized by Digestive Healthcare (55). The eligibility criteria of recruitment was patients who spoke English, were aged from 30 to 74 years, had no syndromes associated with colonic neoplasia or history of inflammatory bowel disease, colorectal adenoma, or cancer (except nonmelanoma skin cancer), and were residents in Minneapolis/St. Paul metropolitan area.

Colonoscopy appointments were scheduled to recruit cases and colonoscopy-negative controls by Digestive Healthcare staff. The participants received a compete colonoscopy and didn't have a new diagnosis of inflammatory bowel disease or invasive cancer. Before the colonoscopy visit, a package including an introductory letter, a consent form, and four questionnaires mailed to persons who met the eligibility criteria. During the colonoscopy visit, the blood was drawn and all the forms were collected. Among all participants receiving a colonoscopy, the participation rate was 68 percent, including 574 cases who had at least one colorectal adenoma (defined as either adenomatous or mixed pathology) and 707 controls were free of polyps at colonoscopy.

Since the colonoscopy-negative controls may have similar family histories or lifestyles as cases, a community-based control group was also recruited by the state of Minnesota Drivers' Registry. Community controls were matched to cases in the

distribution of age (intervals of 5 years), sex, and zip code, and were contacted by telephone calls to determine the eligibility of recruitment. The package sent to colonoscopy patients was also mailed to community controls and the participation rate was 65 percent (n=550). Since community controls didn't receive a colonoscopy, the current status of polyps of this group was unknown.

## Data Collection

Information about socio-demographic characteristics, lifestyle and dietary factors, personal medical history, family history of polyps and cancer, and reproductive history (women only) were collected for each participant. A semi-quantitative food frequency questionnaire (FFQ) developed by Walter Willett and his colleagues at Harvard University was used to collect the information about participants' dietary intake over the previous year. Calculations for nutrient intake were estimated via the nutrient database and analysis program developed at Harvard University (HarvardSSFQ.5/93). Body mass index was calculated after self-administrated measurements of height and weight. Physical activity was collected for moderate and strenuous activities separately, by asking participants concerning their levels of physical activity during the previous 12 months. For each activity, the number of months during the year the activity was performed, the average time per session, and the frequency the activity was performed were collected. Then, the total time of involving in physical activity in the past year was calculated. Alcohol intake was collected according to the usual number of drinks of beer, wine, and liquor on each day of the week.

Participants were excluded from analyses if more than 10 percent of the items on the FFQ were missing, or they reported an implausible energy intake (<600 or >6000 kcal/day). Under these criteria, 48 participants, including 10 cases, 23 colonoscopy-negative controls, and 15 community controls, were excluded from the analyses.

## WCRF/AICR Score Construction

An index score was constructed to reflect the adherence to the WCRF/AICR cancer prevention recommendations (**Table 2**). The recommendations on body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, alcoholic drinks, and food preservation, processing, and preparation were used to construct the score. The recommendation "dietary supplements are not recommended for cancer prevention" was excluded in this score, since this recommendation was under the premise that people met their daily intake of dietary elements. Dietary supplements consumption may exert a protective effect on people who cannot meet their daily need of nutrients. The special recommendation related to breastfeeding was not included, since it was not applicable to the study population. Because the score was derived from recommendations on cancer prevention, the recommendation on cancer survivors was also excluded. Participants were excluded from analyses if any information of the included recommendations were missing. Under these criteria, 38 participants (13 cases, 19 colonoscopy-negative controls, 6 community controls) were excluded from the analyses.

All individuals received 1 point for each component when recommendation was met. A score 0.5 was assigned as intermediate category to adjust the variability of the

population. The score assigned for all other individuals was 0. Under the recommendation of animal foods, the component score was the average of the sub-recommendation scores. A single score with a range from 0 to 7 was calculated for each participant by adding up all scores obtained for each component. Greater adherence to the WCRF/AICR recommendations were represented by higher scores. Since analyses were conducted separately by gender, the score was also categorized into quartiles for male and female separately, only based on the distribution of community controls: quartile 1 (0-3 point in male; 0-3.75 points in female), quartile 2 (3-3.75 points in male; 3.75-4.5 points in female), quartile 3 (3.75-4.5 points in male; 4.5-5.25 points in female), and quartile 4 (4.5-7 points in male; 5.25-7 points in female).

## Colorectal Adenoma

Participants who had an adenoma removed during colonoscopy and verified by an index study pathologist using diagnostic criteria established in the National Polyp Study were considered cases. Participants who had no adenomatous or hyperplastic polyps upon colonoscopy were considered controls. Among the cases, polyp size was determined in vivo by comparison of the polyp with fully opened standard-sized flexible colonoscopy forceps. Polyps were removed and examined by the study pathologist using diagnostic criteria established for the National Polyp Study.

## Statistical Methods

Analyses were conducted for male and female separately and combined. The associations between the sporadic colorectal adenoma incidence and the WCRF/AICR score were assessed using unconditional and multivariable logistic regressions. WCRF/AICR score was considered to be both a continuous variable and a categorical variable. WCRF/AICR was categorized as sex-specific quartiles based on the distribution of community controls. Age, education, race, total energy intake, family history of colorectal cancer, smoking status, and Aspirin and non-steroidal anti-inflammatory drug (NSAID) use were checked as potential confounders. Confounders will be considered present when the crude and adjusted measures differ by at least 10%. Stratified analyses were conducted to examine the interactions in the association of sporadic colorectal adenoma incidence with WCRF/AICR score according to different categories of age, education, total energy intake, family history of colorectal cancer, smoking status, and Aspirin and NSAID use. Interactions were also assessed statistically by conducting maximum likelihood ratio tests comparing statistics between crude and adjusted model. These associations were also assessed by number of adenoma (1 vs. more than 1), shape of worst adenoma (pedunculated vs. sessile), type of worst adenoma (mild vs. moderate/sever), location of worst adenoma (left vs. right side of colon), subtype of worst adenoma (tubular vs. villous/tubulovillous), and size of worst adenoma (1-3cm vs. 4-8cm vs. larger than 8cm). Separate analyses were performed for comparisons of the cases versus the colonoscopy-negative controls and for the cases versus the community controls. For all models, tests for linear trend were performed using a score variable with values from 1 to 4, consistent with the quartile grouping (or with category-specific median values).

All statistical calculations were performed using SAS (version 9.4; SAS Institute Inc.; Cary, NC). All statistical analyses were two-sided and the significance levels for all tests are 0.05.

# CHAPTER 3. RESULTS AND DISCUSSION

## Demographic and Baseline Characteristics

Our study included 1745 subjects including 551 colorectal adenoma cases (CAC), 665 endoscopy controls (EC), and 529 community controls (CC). Selected demographic, lifestyle and dietary characteristics of study participants by case-control status are presented in **Table 3**. Most participants were White and had at least high school degree. Compared with controls, cases had higher BMI, lower consumption of fruits and vegetables, and higher intakes of alcohol, red meat, processed meat, sodium intake, and total fat.

## Adherence to WCRF/AICR Recommendations

The age- and sex-adjusted results for the association between WCRF/AICR score and risk of colorectal adenoma are shown in **Table 4**. When treating WCRF/AICR score as a continuous variable, a 1-point increment in the score was associated with lower risk for colorectal adenoma (OR = 0.82, 95% CI: 0.73, 0.91 when comparing CAC to EC; OR = 0.85, 95% CI: 0.76, 0.95 when comparing CAC to CC). When treating WCRF/AICR score as a categorical variable, the age- and sex- adjusted odds ratios comparing persons in the highest quartile of the WCRF/AICR score relative to the lowest quartile were, 0.77 (95% CI: 0.54, 1.09, $P_{trend}$ = 0.203) when comparing CAC with EC, and 0.67 (95% CI: 0.47, 0.96, $P_{trend}$ = 0.010) when comparing CAC with CC.

Since a potential effect modification by sex ($P_{interaction} < 0.001$ in the age- and sex-adjusted analyses involving CAC and EC; $P_{interaction} < 0.195$ involving CAC and CC) was identified, the association between the colorectal adenoma risk and adherence to WCRF/AICR recommendations was analyzed for men and women separately. After stratifying on sex, 1-point increase in the score was statistically significantly associated with lower risk of colorectal adenoma (OR = 0.76, 95% CI: 0.64, 0.90 when comparing CAC to EC; OR=0.83, 95% CI: 0.72, 0.97 when comparing CAC to CC) among men, but not among women (OR = 1.17, 95% CI: 0.98, 1.39 among when comparing CAC to EC; OR= 0.96, 95% CI: 0.79, 1.16 when comparing CAC to CC). Among men, the age-adjusted odds ratios comparing persons in the highest quartile of the WCRF/AICR score relative to the lowest quartile were, 0.46 (95% CI: 0.28, 0.75, $P_{trend} = 0.002$) when comparing CAC with EC, and 0.64 (95% CI: 0.40, 1.02, $P_{trend} = 0.010$) when comparing CAC with CC. Among women, the age-adjusted odds ratios comparing persons in the highest quartile of the WCRF/AICR score relative to the lowest quartile were, 1.20 (95% CI: 0.71, 2.02, $P_{trend} = 0.238$) when comparing CAC with EC, and 0.73 (95% CI: 0.42, 1.28, $P_{trend} = 0.498$) when comparing CAC with CC. In overall sample (men and women combined), all the components of the score were not associated with colorectal adenoma risk, except for the components of body fatness and plant foods. In sex-specific analyses, all the components of the score were not associated with colorectal adenoma risk in men and women separately.

The multivariable associations of the WCRF/AICR score and its individual components with colorectal adenoma are presented in **Table 5**. In the multivariable-adjusted analyses, when the WCRF score was treated as continuous variable, 1-point

increase in the score was associated with lower risk for colorectal adenoma (OR = 0.85, 95% CI: 0.76, 0.97 when comparing CAC to EC; OR = 0.88, 95% CI: 0.77, 0.98 when comparing CAC to CC). When the score was treated as categorical variable, the multivariate adjusted odds ratios comparing persons in the highest quartile of the WCRF/AICR score relative to the lowest quartile were, 0.83 (95% CI: 0.57, 1.21, $P_{trend}$ = 0.611) when comparing CAC with EC, and 0.69 (95% CI: 0.47, 1.01, $P_{trend}$ = 0.027) when comparing CAC with CC.

Since we identified a potential effect modification by sex ($P_{interaction} < 0.001$ in the multivariate adjusted analyses involving CAC and EC; $P_{interaction} = 0.155$ involving CAC and CC), we repeated analyses for men and women separately. After stratifying on sex, 1-point increment for the score was significantly associated with lower risk of colorectal adenoma (OR = 0.78, 95% CI: 0.65, 0.93 when comparing CAC to EC; OR = 0.85, 95% CI: 0.71, 1.01 when comparing CAC to CC) among men, but not among women (OR = 1.14, 95% CI: 0.94, 1.38 when comparing CAC to EC; OR = 0.95, 95% CI: 0.77, 1.16 when comparing CAC to CC). Among men, the multivariate adjusted odds ratios comparing persons in the highest quartile of the WCRF/AICR score relative to the lowest quartile were, 0.50 (95% CI: 0.30, 0.85, $P_{trend}$ =0.012) when comparing CAC with EC, and 0.66 (95% CI: 0.40, 0.98, $P_{trend}$ = 0.023) when comparing CAC with CC. Among women, the multivariate adjusted ORs comparing persons in the highest quartile of the WCRF/AICR score relative to the lowest quartile were, 1.03 (95% CI: 0.58, 1.81, $P_{trend}$ = 0.476) when comparing CAC with EC, and 0.72 (95% CI: 0.40, 1.31, $P_{trend}$ = 0.524) when comparing CAC with CC. In overall sample (men and women combined), all the components of the score were not associated with colorectal adenoma risk, except for the

components of body fatness and plant foods. In sex-specific analyses, colorectal adenoma risk was inversely associated with plant foods in females, but not any components in males.

We detected no evidence of effect modification by age ($P_{interaction}$ = 0.934 in men and 0.296 in women), education ($P_{interaction}$ = 0.648 in men and 0.860 in women), family history of CRC ($P_{interaction}$ = 0.366 in men and 0.164 in women), smoking status ($P_{interaction}$ = 0.879 in men and 0.882 in women), aspirin and NSAID use ($P_{interaction}$ = 0.130 in men and 0.053 in women), and total energy ($P_{interaction}$ = 0.867 in men and 0.302 in women) (**Table 6**).

## Colorectal Adenoma Characteristics

**Table 7** showed the results of the risk analyses of colorectal adenoma for the separate shape, degree of atypia, location, subtype, size of the worst adenoma and the number of adenoma polyps. In overall participants, the risks of colorectal adenoma with all shape, degree of atypia, location of the worst adenoma were associated with WCRF/AICR recommendations. 1-point increment for the score was associated with lower risk of colorectal adenoma among people who have 1 adenoma polyp (OR = 0.73, 95% CI: 0.60, 0.88 when comparing CAC to EC; OR=0.74, 95% CI: 0.62, 0.90 when comparing CAC to CC), who have villous or tubulovillous colorectal adenoma (OR = 0.76, 95% CI: 0.63, 0.91 when comparing CAC to EC; OR = 0.77, 95% CI: 0.65, 0.93 when comparing CAC to CC), or who have the worst adenoma larger than 9 cm (OR = 0.77, 95% CI: 0.64, 0.92 when comparing CAC to EC; OR = 0.78, 95%CI: 0.65, 0.94

when comparing CAC to CC). In sex-specific analyses, 1-point increment for the score was associated with lower risk of colorectal adenoma among males who have 1 adenoma polyp (OR = 0.61, 95% CI: 0.47, 0.80 when comparing CAC to EC; OR = 0.69, 95% CI: 0.54, 0.88 when comparing CAC to CC), who have pedunculated adenoma (OR = 0.65, 95% CI: 0.49, 0.87 when comparing CAC to EC; OR = 0.69, 95%CI: 0.53, 0.91 when comparing CAC to CC), who have mild adenoma (OR = 0.72, 95% CI: 0.57, 0.91 when comparing CAC to EC; OR = 0.79, 95% CI: 0.63, 0.99 when comparing CAC to CC), whose worst adenoma located in the right colon (OR = 0.62, 95% CI: 0.47, 0.82 when comparing CAC to EC; OR = 0.71, 95% CI: 0.54, 0.93 when comparing CAC to CC), who have villous or tubulovillous colorectal adenoma (OR = 0.72, 95% CI: 0.55, 0.93 when comparing CAC to EC; OR=0.78, 95%CI: 0.61, 1.00 when comparing CAC to CC), or who have the worst adenoma larger than 9 cm (OR = 0.65, 95% CI: 0.49, 0.84 when comparing CAC to EC; OR = 0.70, 95% CI: 0.54, 0.92 when comparing CAC to CC). However, 1-point increment for the score was not associated with risk of colorectal adenoma among males in any separate shape, degree pf atypia, location, subtype, size of the worst adenoma or the number of adenoma polyps.

## Discussion

Our results suggest that individuals, and especially men, adhering to the WCRF/AICR recommendations for cancer prevention are less likely to develop colorectal adenoma. A 1-point increase in the WCRF/AICR score was associated with a 15% lower risk of colorectal adenoma among men, and with a 5% lower risk of colorectal

adenoma among women in the comparisons involving the community controls. In addition, men within the highest category of the WCRF/AICR score (4.5 - 7 points) were 34% less likely to develop colorectal adenoma compared with those in the first category of the score (0 - 3 points), while women within the highest category of the WCRF/AICR score (5.25 - 7 points) were 28% less likely to develop colorectal adenoma compared with those in the first category of the score (0 - 3.75 points). Since the endoscopy controls may have similar family histories or lifestyles as cases, the community-based control group recruited in this study may be better generalizable to the whole US population.

This study found limited but marked differences between endoscopy controls and community-based controls: endoscopy controls were younger, more likely to be females, and had less physical activities, higher consumption of red meat, and had a larger proportion of men rather than women compared to community-based controls. Although age and sex are known risk factors for colorectal adenomas and were controlled for in the analyses, the degree to which the endoscopy controls were, on average, younger and more likely to be female raises the possibility of some selection bias. In sex-specific analyses, this association was assessed similar between using cases and endoscopy controls, and cases and community-based controls. However, cases and community-based controls, but not cases and endoscopy controls, showed a significant inversely association of risk of colorectal adenoma with adherence to WCRF/AICR cancer prevention recommendations.

The associations between individual components of the WCRF/AICR score and colorectal adenoma risk were investigated in men and women separately and combined, in order to identify any specific components are contributing to the observed associations.

Overall analyses reported 2 individual recommendations were associated with the risk of colorectal adenoma including body fatness and plant foods. However, in sex-specific analyses, the analyses identified only 1 individual recommendation on plant foods consumption that was associated with colorectal adenoma risk among men, while no individual recommendation was associated with colorectal adenoma risk among women.

The non-significant ORs and large confidence intervals among women may be explained by small samples sizes in each category of both overall and components of the WCRF/AICR score. Small sample sizes also limited the stratified analyses on the association of sporadic colorectal adenoma risk with WCRF/AICR score. When conducting the risk analyses for colorectal adenoma characteristics, colorectal adenoma cases among women were limited, especially sub-analyses for adenomas which were pedunculated, located in the right side of colon, and multiple adenomas. Other possible explanation for these associations may include the role of endogenous and exogenous sex hormones in colorectal adenoma formation. A previous meta-analysis showed that pre-menopausal women have a stronger susceptibility to colorectal adenoma formation, although this association disappeared for post-menopausal females(56). It may indicate that endogenous estrogens might have an important role in colorectal adenoma formation. This is supported by mechanistic studies demonstrating an increase in gene transcription and cancer proliferation following the activation of estrogen receptor-α(57). As a result, further mechanistic studies of colorectal adenoma initiation and progression are required to better understand the association between genders on adenoma formation.

Stronger associations between incident sporadic colorectal adenoma risk and adherence to WCRF/AICR cancer prevention recommendations were reported among

participants with multiple adenomas, adenoma with a villous or tubulovillous component, and adenoma with large size. Although previous epidemiologic studies investigated these associations for multiple adenomas, adenoma with a villous or tubulovillous component, and adenoma with larger size, but the exact mechanisms are not clear(58-60). A colonoscopy-based cross-sectional study in Koreans reported an inverse association of colorectal adenoma risk and physical activity for the adenomas with multiple locations (OR = 0.39, 95 % CI: 0.21, 0.72)(60). A protective association of colorectal adenoma risk and fruits and vegetables intakes was observed for multiple adenomas(58). Another large colonoscopy-based case-control study built a risk score based on lifestyle and diet information collected and demonstrated stronger associations of colorectal adenoma risk and risk score for advanced adenomas than for non-advanced adenomas, for multiple adenomas than for a single adenoma, and for large adenomas (diameter ≥ 1 cm) than for small adenomas (diameter <1 cm)(59).

Two studies previously evaluated the association between the adherence to WCRF/AICR cancer prevention recommendations and risk of colorectal cancer (49, 52). Consistent with our results, a prospective European cohort found that higher adherence to WCRF/AICR guidelines was associated with reduced risk of colorectal cancer (52). The findings from the Framingham cohort also suggested an inverse association between the score and colorectal cancer risk, but it was not statistically significant (multivariable HR = 0.87, 95% CI: 0.68, 1.12) (49). In the latter study, significant associations were observed between colorectal cancer risk and several score components including alcohol intake (HR = 0.24, 95% CI: 0.12–0.45 for age-adjusted model; HR = 0.29, 95%CI: 0.15, 0.56 for multivariate-adjusted model), preservation, processing, and preparation (HR =

2.56, 95% CI: 1.02, 6.40 for multivariate-adjusted model), intake of non-starchy and starchy plant foods (HR = 0.44, 95% CI: 0.22, 0.88 for age-adjusted model) (49). Overall, these results are consistent with findings of our study, where modest significant associations between the overall score and colorectal adenoma risk were observed among all participants. However, no significant associations were observed between the other score components and colorectal adenoma risk except for body fatness and plant foods.

The similarity between our study and the previous two was all of these studies provided a score for participants who partially met the recommendations and used tertiles or median cutoffs to operationalize the recommendations that didn't provide quantitative cutoffs (49, 52). The discrepancy between the present study findings and the Framingham study may be contributed to differences in different operationalization of WCRF/AICR recommendations. The Framingham study used definitions and quantitative cutoffs for body fatness, sugar beverages, fruits and vegetables, alcohol consumption and sodium intake that were consistent with the present study. However, definitions varied for the physical activity, energy-dense foods, and intake of red meat and processed meat. Starchy vegetables and non-starchy vegetables, fruits, and legumes, energy-dense foods, refined grains, and salty foods were only considered in the Framingham study (49).

Strengths of this study included reducing recall bias by assessing exposure information prior to colonoscopy; reducing misclassification of outcome by conducting pathological verification of colorectal adenomas; collecting detailed information on potentially confounding variables; using 2 control groups with its own strengths and limitations; and constructing an index score to reflect the adherence to WCRF/AICR cancer prevention recommendations. The main limitation of this study was its small

sample size, which provided less power to study the association of the adherence to WCRF/AICR score with sporadic colorectal adenoma risk, especially for men and women separately. Race were not analyzed as a potential effect modifier, since there were less than 50 subjects in this study. Even though education and smoking status were analyzed, the small sample sizes of people who didn't graduate from high school and who are current smokers reduce the reliability of the estimating results. The other limitation of this study was that the actual diet pattern and lifestyle of the participants could not be reflected as strongly consistent with constructing WCRF/AICR recommendations. Some WCRF/AICR recommendations related to body fatness, physical activities, or dietary intake that may associate with colorectal adenoma risk were not included in constructing the WCRF/AICR score. For example, abdominal adiposity measurements, such as waist circumference, and consumption of fast foods or energy-density foods that promote weight gain were not included because of data were not available. This suggested our findings may underestimate the potential of adherence to WCRF/AICR cancer prevention recommendations for reducing colorectal adenoma risk. Furthermore, since study participants were predominantly White, our results might not be generalizable to nonwhite populations. Even though dietary intake and lifestyle information were collected by detailed questionnaires, recall bias, misclassification and error in measurements may occur.

In conclusion, the results of this study suggest that adherence to the WCRF/AICR recommendations was associated with lower risk for incident sporadic colorectal adenoma among men in the US populations, but couldn't provide evidence to demonstrate this association among women. Further studies are needed to investigate the

differences of gender in association of colorectal adenoma risk with adherence to WCRF/AICR cancer prevention recommendations and the association between genders on colorectal adenoma formation.

# CHAPTER 4. PUBLIC HEALTH IMPLICATIONS

The primary goal of this study was to investigate the associations between adherence to WCRF/AICR cancer prevention recommendations and incident sporadic colorectal adenoma risk. We found that adherence to the WCRF/AICR recommendations was associated with lower risk for incident, sporadic colorectal adenoma among men, but not among women. This inverse association was suggestively stronger among those who had multiple adenomas, adenomas with a villous or tubulovillous component, and adenomas with large size.

There were several reasons for the observed insignificant association between adherence to WCRF/AICR cancer prevention recommendations and incident sporadic colorectal adenoma risk among women. The small sample size of women may result in insignificant statistical estimates and large confidence intervals. Future larger studies are needed to investigate whether the associations may differ by sex. The other possible explanation may include the role of endogenous and exogenous sex hormones in colorectal adenoma formation. Further mechanistic studies of colorectal adenoma initiation and progression are required to better understand the association between genders on adenoma formation.

Since we found stronger associations among persons who had multiple adenomas, adenomas with a villous or tubulovillous component, and adenomas with large size, further studies could examine the mechanisms of components of WCRF/AICR cancer prevention recommendations on adenoma characteristics.

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# LIST OF TABLES

## Table 1. WCRF Goals and Recommendations on Food, Nutrition, Physical Activity

| | Public Health Goals | Personal Recommendations |
|---|---|---|
| **Body Fatness** | Median adult body mass index (BMI) to be between 21 and 23, depending on the normal range for different populations;<br><br>The proportion of the population that is overweight or obese to be no more than the current level, or preferably lower, in 10 years. | Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at age 21;<br><br>Maintain body weight within the normal range from age 21;<br><br>Avoid weight gain and increases in waist circumference throughout adulthood. |
| **Physical Activity** | The proportion of the population that is sedentary to be halved every 10 years;<br><br>Average physical activity levels (PALs) to be above 1.6. | Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day;<br><br>As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day;<br><br>Limit sedentary habits such as watching television. |
| **Food and Drinks that Promote Health** | Average energy density of diets to be lowered towards 125 kcal per 100 g;<br><br>Population average consumption of sugary drinks to be halved every 10 years. | Consume energy-dense foods sparingly;<br><br>Avoid sugary drink;<br><br>Consume 'fast foods' sparingly, if at all. |
| **Plant Food** | Population average consumption of non-starchy vegetables and of fruits to be at least 600 g (21 oz.) daily;<br><br>Relatively unprocessed cereals (grains) and/or pulses (legumes), and other foods that are a natural source of dietary fiber, to contribute to a population average of at least 25 g non-starch polysaccharide daily. | Eat at least five portions/servings (at least 400 g or 14 oz.) of a variety of non-starchy vegetables and of fruits every day;<br><br>Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal;<br><br>Limit refined starchy foods; |

| | | |
|---|---|---|
| | | People who consume starchy roots or tubers as staples also to ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes). |
| **Animal Food** | Population average consumption of red meat to be no more than 300 g (11 oz.) a week, very little if any of which to be processed. | People who eat red meat to consume less than 500 g (18 oz.) a week, very little if any to be processed. |
| **Alcoholic Drinks** | Proportion of the population drinking more than the recommended limits to be reduced by one third every 10 years | If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women. |
| **Preservation, Processing, Preparation** | Population average consumption of salt from all sources to be less than 5 g (2 g of sodium) a day;<br><br>Proportion of the population consuming more than 6 g of salt (2.4 g of sodium) a day to be halved every 10 years;<br><br>Minimize exposure to aflatoxins from mouldy cereals (grains) or pulses (legumes). | Avoid salt-preserved, salted, or salty foods; preserve foods without using salt;<br><br>Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) a day;<br><br>Do not eat mouldy cereals (grains) or pulses (legumes). |
| **Dietary Supplements** | Maximize the proportion of the population achieving nutritional adequacy without dietary supplements. | Dietary supplements are not recommended for cancer prevention. |

**Table 2. WCRF/ACIR dietary and lifestyle recommendations and corresponding score construction in CPRU study, 1991-1994.**

| WCRF/ACIR personal recommendations | Criteria | Scoring | Percentage (%) [a] |
|---|---|---|---|
| **1) Body fatness** | | | |
| 1a) Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at age 21 | Not applicable to this population | NA | |
| 1b) Maintain body weight within the normal range from age 21 | BMI (kg/m$^2$): | 1 | 36.3 |
| | ≥18.5 and <25 | 0.5 | 39.1 |
| | ≥25 and <30 | 0 | 24.5 |
| | <18.5 or ≥30 | | |
| 1c) Avoid weight gain and increases in waist circumference throughout adulthood | Insufficient data available | NA | |
| **2) Physical activities** | | | |
| 2a) Be moderately physical active, equivalent to brisk walking, for at least 30 minutes every day; | Moderate and vigorous physical activities (MET-minutes/day): | | |
| 2b) As fitness improve, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day; | ≥268 | 1 | 33.0 |
| | <268 and ≥113 | 0.5 | 33.8 |
| | <113 | 0 | 33.2 |
| 2c) Limit sedentary habits such as watching television. | Insufficient data available | NA | |
| **3) Foods and drinks that promote weight gain** | | | |
| 3a) Consume energy-dense foods sparingly | Insufficient data available | NA | |
| 3b) Avoid sugary drinks | Sugar beverage (serving): | | |
| | =0 | 1 | 35.0 |
| | >0 and ≤0.4 | 0.5 | 33.5 |
| | >0.4 | 0 | 31.5 |
| 3c) Consume fast food sparingly, if at all | Insufficient data available | NA | |
| **4) Plant foods [a]** | | | |
| 4a)Eat at least five portions/servings(at least 400g or 14oz) of a variety of non-starchy vegetables or fruits every day | Fruits and vegetables (serving): | | |
| | ≥5 | | |
| | <5 and ≥3.4 | 1 | 58.8 |
| | <3.4 | 0.5 | 21.0 |
| | | 0 | 20.2 |

| | | | |
|---|---|---|---|
| 4b) Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal | Insufficient data available | NA | |
| 4c) Limit refined starchy foods | Insufficient data available | NA | |
| 4d) People who consume starchy roots or tubers as staples also to ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes) | Insufficient data available | NA | |
| **5) Animal foods** [b] | | | |
| 5a) People who eat red meat to consume less than 500g (18oz) a week, very little if any to be processed | Red meat (g/week): | | |
| | <18 | 1 | 83.0 |
| | ≥18 and <23.8 | 0.5 | 9.9 |
| | ≥23.8 | 0 | 7.1 |
| | Processed meat (g/week): | | |
| | =0 | 1 | 17.9 |
| | >0 and ≤3.8 | 0.5 | 44.9 |
| | >3.8 | 0 | 37.2 |
| **6) Alcoholic drinks** | | | |
| 6a) If alcohol drinks are consumed, limit consumption to no more than two drinks a day, for **men** and one drink a day of **women** | Men (drink): | | |
| | =0 | 1 | 32.8 |
| | >0 and ≤2 | 0.5 | 51.3 |
| | >2 | 0 | 15.9 |
| | Women: | | |
| | 0 | 1 | 50.3 |
| | >0 and ≤1 | 0.5 | 39.8 |
| | >1 | 0 | 9.9 |
| **7) Preservation, processing, preparation.** | | | |
| 7a) Avoid salt-preserved, salted, or salted foods; preserve foods without using salt | Insufficient data available | NA | |
| 7b) Limit consumption of processed foods with added salt to ensure an intake of less than 6g (2.4g sodium) a day | Sodium intake (g/day): | | |
| | <2.4 | 1 | 51.9 |
| | ≥2.4 and <3.0 | 0.5 | 23.2 |
| | ≥3.0 | 0 | 24.9 |
| 7c) Do not eat mouldy cereals (grains) or pulses (legumes) | Insufficient data available | | |
| **8) Dietary supplements.** | | | |

| | | |
|---|---|---|
| Dietary supplements are not recommended for cancer prevention | Not applicable to this population | NA |
| **9) Breastfeeding** | | |
| Aim to breastfeed infants exclusively up to six months and continue with complementary feeding thereafter | Not applicable to this population | NA |
| **10) Cancer survivors** | | |
| 10a) All cancer survivors to receive nutritional care from an appropriately trained professional | Not applicable to this population | NA |
| 10b) If able to do so, and unless otherwise advised, aim to follow the recommendations for diet, healthy weight, and physical activity | Not applicable to this population | NA |

Abbreviations: WCRF/ACIR: World Cancer Research Fund/American Institute for Cancer Research; CPRU, Cancer Prevention Research Unit; BMI, body mass index; MET, metabolic equivalent.

[a] Percentage was shown the distribution of study population by each recommendation categorization of the WCRF/ACIR score.

[b] The score of recommendation 5 was the average of the scores of each sub-recommendation.

**Table 3. Demographic and dietary characteristics of study participant by case-control status, CPRU study, 1991-1994.**

| Characteristic | CPRU Study | | | | | |
|---|---|---|---|---|---|---|
| | Cases(n=551) | | Endoscopy Controls(n=665) | | Community Controls(n=529) | |
| | Mean (SD) | Frequency (%) | Mean (SD) | Frequency (%) | Mean (SD) | Frequency (%) |
| **Age, years** | 58.3 (9.5) | | 52.8 (11.0) | | 57.7 (10.4) | |
| **Sex** | | | | | | |
| Male | | 340 (61.7) | | 252 (37.9) | | 291 (55.0) |
| Female | | 211 (38.3) | | 413 (62.1) | | 238 (45.0) |
| **Race** [a] | | | | | | |
| White | | 538 (97.6) | | 647 (97.3) | | 514 (97.2) |
| Black/Other | | 12 (2.2) | | 18 (2.7) | | 15 (2.8) |
| **Education** | | | | | | |
| Didn't graduate high school | | 58 (10.5) | | 50 (7.5) | | 37 (7.0) |
| High school degree | | 326 (59.2) | | 417 (62.7) | | 338 (63.9) |
| College degree or higher | | 167 (30.3) | | 198 (29.8) | | 154 (29.1) |
| **BMI** [b] | 27.4 (4.7) | | 26.9(5.0) | | 26.8 (4.5) | |
| **Physical activity, hours/week** | | | | | | |
| Total | 9.5 (9.5) | | 8.8 (8.1) | | 9.9 (9.8) | |
| Moderate | 7.6 (7.7) | | 7.2 (7.0) | | 7.9 (7.8) | |
| Vigorous | 1.9 (4.2) | | 1.6 (3.0) | | 2.0 (3.9) | |
| **Physical activity, MET-hours/week** | | | | | | |
| Total | 37.3 (39.0) | | 33.6 (31.1) | | 38.4 (39.3) | |
| Moderate | 25.6 (25.5) | | 23.8 (22.3) | | 26.6 (25.7) | |
| Vigorous | 11.6 (25.5) | | 9.8(18.0) | | 11.8 (23.3) | |
| **Alcohol status** [a] | | | | | | |
| Never | | 26 (4.7) | | 56 (8.4) | | 49 (9.3) |
| Former | | 125 (22.7) | | 132 (19.9) | | 88 (16.6) |
| Current | | 400 (72.6) | | 476 (71.7) | | 392 (74.1) |
| **Alcohol, drinks/day** [c] | | | | | | |

| | | | | |
|---|---|---|---|---|
| Male | 1.1 (1.5) | 0.9 (1.5) | 0.9 (1.5) | |
| Female | 0.4 (0.9) | 0.3 (0.6) | 0.4 (0.8) | |
| **Fruits and Vegetables, serving/day [d]** | 6.1 (3.4) | 6.3 (3.8) | 6.3 (3.3) | |
| **Red meat, g/wk** | 335.0 (251.7) | 331.3 (256.4) | 308.0 (225.7) | |
| **Processed meat, g/wk** | 181.6 (269.9) | 145.1 (207.8) | 172.5 (251.6) | |
| **Sugar beverage, serving/day [e]** | 0.4 (0.9) | 0.5 (1.0) | 0.5 (0.9) | |
| **Sodium, g/day** | 2.6 (1.0) | 2.5 (1.0) | 2.5 (0.9) | |
| **Multivitamin use** | | | | |
| No | 425 (77.1) | 456 (68.6) | 366 (69.2) | |
| Yes | 126 (22.9) | 209 (31.4) | 163 (30.8) | |
| **Family history of colorectal cancer** | | | | |
| No | 462 (83.9) | 483 (72.6) | 492 (93.0) | |
| Yes | 89 (16.1) | 182 (27.4) | 37 (7.0) | |
| **Smoking status** | | | | |
| Never | 178 (32.3) | 311 (46.8) | 233 (44.1) | |
| Former | 260 (47.2) | 255 (38.4) | 215 (40.6) | |
| Current | 113 (20.5) | 99 (14.8) | 81 (15.3) | |
| **Aspirin use** | | | | |
| No | 439 (79.7) | 521 (78.4) | 430 (81.3) | |
| Yes | 112 (20.3) | 144 (21.6) | 99 (18.7) | |
| **NSAID use** | | | | |
| No | 487 (88.4) | 522 (78.5) | 438 (82.8) | |
| Yes | 64 (11.6) | 143 (21.5) | 91 (17.2) | |
| **Total fat, g/day** | 72.9 (33.9) | 69.3 (30.8) | 70.1 (30.9) | |
| **Total fat, kcal/day** | 31.0 (6.4) | 30.5 (6.6) | 30.4 (6.6) | |
| **Total folate intake, µg/day [f]** | 402.4 (238.0) | 414.6 (241.1) | 429.5 (250.0) | |
| **Total calcium intake, mg/day [f]** | 964.4 (532.1) | 988.9(528.8) | 984.4 (545.8) | |
| **Total vitamin D intake, IU/day [f]** | 329.1 (259.0) | 329.7 (244.1) | 354.5 (264.6) | |
| **Total vitamin E intake, mg-TE/day [f]** | 63.6 (143.8) | 69.4 (156.0) | 75.2 (170.1) | |
| **Total vitamin C intake, mg/day [f]** | 247.8 (297.5) | 277.4 (309.6) | 260.6 (290.9) | |
| **Total energy intake, kcal/day** | 2091.4 (774.9) | 2023.8 (717.0) | 2050.9 (714.2) | |
| **Dietary fiber intake, g/day** | 21.9 (9.6) | 21.8 (9.8) | 22.2 (9.6) | |

Abbreviations: CPRU, Cancer Prevention Research Unit; BMI, body mass index; MET, metabolic equivalent; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

[a] There was 1 missing observations in race and alcohol information.

[b] Weight (kg)/height (m) [2].

[c] One "drink" contains about 10-15 grams of ethanol. (WCRF)

[d] One serving fruits and vegetables: 1 cup of raw leafy vegetables (about the size of a small fist), 1/2 cup of other vegetables or 1/2 cup of vegetable juice; 1 medium fruit (medium is defined as the size of a baseball); 1/2 cup chopped, cooked or canned fruit; or 1/2 cup juice. (American Heart Association)

[e] One serving of sugar beverage: 1 glass, bottle or can.

[f] Diet plus supplements.

**Table 4. The association of sporadic colorectal adenoma incidence with categories of the WCRF/AICR score and each component in CPRU study for all participants and men and women separately, adjusted for age and sex (all participants analysis only).**

| | All participants (n=1745) | | | | | Men (n=883) | | | | | Women (n=862) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Endoscopy Controls | | Community Controls | | Cases | Endoscopy Controls | | Community Controls | | Cases | Endoscopy Controls | | Community Controls | |
| **WCRF score** | **n** | **n** | **OR (95% CI)** | **n** | **OR (95% CI)** | **n** | **n** | **OR (95% CI)** | **n** | **OR (95% CI)** | **n** | **n** | **OR (95% CI)** | **n** | **OR (95% CI)** |
| Per 1 unit | 551 | 665 | 0.82 (0.73, 0.91) | 529 | 0.85 (0.76, 0.95) | 340 | 252 | 0.76 (0.64, 0.90) | 291 | 0.83 (0.72, 0.97) | 221 | 413 | 1.17 (0.98, 1.39) | 238 | 0.96 (0.79, 1.16) |
| **Score category** [a] | | | | | | | | | | | | | | | |
| Quartile 1 | 143 | 184 | 1.00 (ref) | 122 | 1.00 (ref) | 93 | 61 | 1.00 (ref) | 66 | 1.00 (ref) | 50 | 123 | 1.00 (ref) | 56 | 1.00 (ref) |
| Quartile 2 | 151 | 161 | 1.04 (0.75, 1.44) | 121 | 1.05 (0.75, 1.48) | 102 | 63 | 0.92 (0.58, 1.48) | 64 | 1.13 (0.73, 1.77) | 49 | 98 | 1.04 (0.64, 1.70) | 57 | 0.91 (0.53, 1.57) |
| Quartile 3 | 152 | 174 | 1.04 (0.75, 1.43) | 156 | 0.82 (0.59, 1.13) | 81 | 55 | 0.84 (0.52, 1.37) | 90 | 0.64 (0.41, 0.99) | 71 | 119 | 1.41 (0.89, 2.23) | 66 | 1.15 (0.69 (1.92) |
| Quartile 4 | 105 | 146 | 0.77 (0.54, 1.09) | 130 | 0.67 (0.47, 0.96) | 64 | 73 | 0.46 (0.28, 0.75) | 71 | 0.64 (0.40, 1.02) | 41 | 73 | 1.20 (0.71, 2.02) | 59 | 0.73 (0.42, 1.28) |
| $P_{trend}$ b | | | 0.2028 | | 0.0102 | | | 0.0021 | | 0.0095 | | | 0.2378 | | 0.4982 |
| **WCRF score components** | | | | | | | | | | | | | | | |
| **Body fatness** | | | | | | | | | | | | | | | |
| 0 | 147 | 161 | 1.00 (ref) | 120 | 1.00 (ref) | 96 | 57 | 1.00 (ref) | 69 | 1.00 (ref) | 51 | 104 | 1.00 (ref) | 51 | 1.00 (ref) |
| 0.5 | 231 | 242 | 1.04 (0.77, 1.39) | 210 | 0.89 (0.66, 1.21) | 160 | 110 | 0.87 (0.57, 1.32) | 146 | 0.79 (0.54, 1.16) | 71 | 132 | 1.08 (0.68, 1.70) | 64 | 1.07 (0.64, 1.80) |
| 1 | 173 | 262 | 0.74 (0.55, 1.00) | 199 | 0.71 (0.52, 0.97) | 84 | 85 | 0.58 (0.36, 0.91) | 76 | 0.80 (0.51, 1.23) | 89 | 177 | 1.10 (0.71, 1.70) | 123 | 0.72 (0.45, 1.16) |
| $P_{trend}$ | | | 0.0357 | | 0.0284 | | | 0.0168 | | 0.3039 | | | 0.6929 | | 0.1114 |
| **Physical activity** | | | | | | | | | | | | | | | |
| 0 | 187 | 223 | 1.00 (ref) | 170 | 1.00 (ref) | 119 | 76 | 1.00 (ref) | 105 | 1.00 (ref) | 68 | 147 | 1.00 (ref) | 65 | 1.00 (ref) |
| 0.5 | 179 | 241 | 0.92 (0.69, 1.22) | 169 | 0.96 (0.72, 1.29) | 100 | 92 | 0.71 (0.47, 1.07) | 82 | 1.08 (0.73, 1.60) | 79 | 149 | 1.22 (0.81, 1.84) | 87 | 0.86 (0.55, 1.37) |
| 1 | 185 | 201 | 1.06 (0.79, 1.41) | 190 | 0.88 (0.66, 1.18) | 121 | 84 | 0.88 (0.58, 1.33) | 104 | 1.04 (0.71, 1.50) | 64 | 117 | 1.15 (0.75, 1.78) | 86 | 0.72 (0.45, 1.15) |
| $P_{trend}$ | | | 0.7299 | | 0.3827 | | | 0.5613 | | 0.8510 | | | 0.5064 | | 0.1663 |
| **Foods and drinks that promote weight gain** | | | | | | | | | | | | | | | |
| 0 | 175 | 212 | 1.00 (ref) | 163 | 1.00 (ref) | 134 | 93 | 1.00 (ref) | 103 | 1.00 (ref) | 41 | 119 | 1.00 (ref) | 60 | 1.00 (ref) |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.80 | | 0.89 | | | 0.69 | | 0.81 | | | 1.27 | | 1.23 |
| 0.5 | 176 | 227 | (0.60, 1.08) | 181 | (0.66, 1.20) | 108 | 91 | (0.46, 1.03) | 104 | (0.55, 1.17) | 68 | 136 | (0.79, 2.05) | 77 | (0.73, 2.07) |
| | | | 0.93 | | 0.99 | | | 0.88 | | 0.90 | | | 1.60 | | 1.38 |
| 1 | 200 | 226 | (0.70, 1.24) | 185 | (0.73, 1.33) | 98 | 68 | (0.57, 1.33) | 84 | (0.61, 1.34) | 102 | 158 | (1.02, 2.51) | 101 | (0.85, 2.26) |
| $P_{trend}$ | | | 0.6507 | | 0.9583 | | | 0.4561 | | 0.5660 | | | 0.0359 | | 0.1996 |
| **Plant foods** | | | | | | | | | | | | | | | |
| | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 |
| 0 | 124 | 135 | (ref) | 93 | (ref) | 83 | 65 | (ref) | 55 | (ref) | 41 | 70 | (ref) | 38 | (ref) |
| | | | 0.83 | | 0.75 | | | 1.00 | | 0.76 | | | 0.63 | | 0.70 |
| 0.5 | 115 | 139 | (0.58, 1.18) | 113 | (0.52, 1.10) | 84 | 59 | (0.62, 1.61) | 73 | (0.48, 1.22) | 31 | 80 | (0.35, 1.13) | 40 | (0.36, 1.33) |
| | | | 0.73 | | 0.70 | | | 0.89 | | 0.71 | | | 0.77 | | 0.75 |
| 1 | 312 | 391 | (0.54, 0.99) | 323 | (0.51, 0.96) | 173 | 128 | (0.59, 1.35) | 163 | (0.47, 1.07) | 139 | 263 | (0.49, 1.21) | 160 | (0.45, 1.24) |
| $P_{trend}$ | | | 0.0422 | | 0.0342 | | | 0.5546 | | 0.1126 | | | 0.4345 | | 0.3343 |
| **Animal foods** | | | | | | | | | | | | | | | |
| | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 |
| 0 | 75 | 58 | (ref) | | (ref) | 63 | 43 | (ref) | 47 | (ref) | 12 | 39 | (ref) | 11 | (ref) |
| | | | 1.07 | | 0.84 | | | 1.20 | | 0.90 | | | 1.30 | | 0.74 |
| 0.5 | 187 | 173 | (0.73, 1.58) | | (0.56, 1.25) | 143 | 77 | (0.73, 1.96) | 118 | (0.58, 1.42) | 44 | 105 | (0.61, 2.76) | 55 | (0.30, 1.84) |
| | | | 0.78 | | 0.75 | | | 0.68 | | 0.79 | | | 1.85 | | 0.83 |
| 1 | 289 | 298 | (0.54, 1.12) | | (0.52, 1.10) | 134 | 132 | (0.43, 1.09) | 126 | (0.50, 1.24) | 155 | 269 | (0.92, 3.70) | 172 | (0.35, 1.94) |
| $P_{trend}$ | | | 0.0342 | | 0.1360 | | | 0.0244 | | 0.2680 | | | 0.0261 | | 0.9897 |
| **Alcoholic drinks** | | | | | | | | | | | | | | | |
| | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 |
| 0 | 89 | 70 | (ref) | 66 | (ref) | 65 | 35 | (ref) | 40 | (ref) | 24 | 35 | (ref) | 26 | (ref) |
| | | | 0.72 | | 0.73 | | | 0.68 | | 0.63 | | | 0.89 | | 0.97 |
| 0.5 | 248 | 295 | (0.50, 1.04) | 253 | (0.51, 1.05) | 162 | 134 | (0.42, 1.10) | 157 | (0.40, 0.99) | 86 | 161 | (0.49, 1.62) | 96 | (0.52, 1.81) |
| | | | 0.56 | | 0.76 | | | 0.72 | | 0.74 | | | 0.69 | | 0.93 |
| 1 | 214 | 300 | (0.39, 0.81) | 210 | (0.52, 1.10) | 113 | 83 | (0.43, 1.20) | 94 | (0.46, 1.19) | 101 | 217 | (0.38, 1.24) | 116 | (0.50, 1.73) |
| $P_{trend}$ | | | 0.0013 | | 0.2791 | | | 0.3147 | | 0.4155 | | | 0.1115 | | 0.8078 |
| **Preservation, processing, preparation** | | | | | | | | | | | | | | | |
| | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 | | | 1.00 | | 1.00 |
| 0 | 152 | 154 | (ref) | 129 | (ref) | 117 | 70 | (ref) | 81 | (ref) | 35 | 84 | (ref) | 48 | (ref) |
| | | | 0.82 | | 0.80 | | | 0.80 | | 0.71 | | | 1.15 | | 1.135 |
| 0.5 | 123 | 151 | (0.58, 1.15) | 130 | (0.57, 1.13) | 79 | 57 | (0.51, 1.28) | 77 | (0.47, 1.08) | 44 | 94 | (0.66, 2.00) | 53 | (0.63, 2.06) |
| | | | 0.76 | | 0.87 | | | 0.64 | | 0.75 | | | 1.43 | | 1.35 |
| 1 | 276 | 360 | (0.57, 1.01) | 270 | (0.65, 1.16) | 144 | 125 | (0.43, 0.94) | 133 | (0.52, 1.09) | 132 | 235 | (0.90, 2.29) | 137 | (0.82, 2.23) |
| $P_{trend}$ | | | 0.0668 | | 0.4285 | | | 0.0234 | | 0.1499 | | | 0.1006 | | 0.2056 |

Abbreviations: WCRF/ACIR: World Cancer Research Fund/American Institute for Cancer Research; CPRU, Cancer Prevention Research Unit; OR: Odds Ratio; CI: Confidence Interval.

[a] The WCRF/AICR score was categorized into quartiles for male and female separately, based on the distribution of community controls: Quartile 1 (0-3 point in male; 0-3.75 points in female), Quartile 2 (3-3.75 points in male; 3.75-4.5 points in female), Quartile 3 (3.75-4.5 points in male; 4.5-5.25 points in female), and Quartile 4 (4.5-7 points in male; 5.25-7 points in female).

[b] P trend was assessed by calculating the median score of each quartile as a continuous regression.

# Table 5. Multivariable-adjusted associations of the WCRF/AICR score and its individual components with incident sporadic colorectal adenoma risk in CPRU study, 1991-1994.

| | All participants (n=1745) | | | | | Men (n=883) | | | | | Women (n=862) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Endoscopy Controls | | Community Controls | | Cases | Endoscopy Controls | | Community Controls | | Cases | Endoscopy Controls | | Community Controls | |
| WCRF score | n | n | OR [a] (95% CI) | n | OR (95% CI) | n | n | OR (95% CI) | n | OR (95% CI) | n | n | OR (95% CI) | n | OR (95% CI) |
| Per 1 unit | 551 | 665 | 0.85 (0.76, 0.97) | 529 | 0.88 (0.77, 0.98) | 340 | 252 | 0.78 (0.65, 0.93) | 291 | 0.85 (0.71, 1.01) | 221 | 413 | 1.14 (0.94, 1.38) | 238 | 0.95 (0.77, 1.16) |
| **Score category [b]** | | | | | | | | | | | | | | | |
| Quartile 1 | 143 | 184 | 1.00 (ref) | 122 | 1.00 (ref) | 93 | 61 | 1.00 (ref) | 66 | 1.00 (ref) | 50 | 123 | 1.00 (ref) | 56 | 1.00 (ref) |
| Quartile 2 | 151 | 161 | 1.12 (0.80, 1.56) | 121 | 1.05 (0.74, 1.49) | 102 | 63 | 1.02 (0.63, 1.65) | 64 | 1.13 (0.71, 1.79) | 49 | 98 | 1.00 (0.60, 1.66) | 57 | 0.90 (0.51, 1.60) |
| Quartile 3 | 152 | 174 | 1.23 (0.88, 1.74) | 156 | 0.83 (0.59, 1.17) | 81 | 55 | 0.96 (0.57, 1.61) | 90 | 0.64 (0.41, 1.02) | 71 | 119 | 1.43 (0.88, 2.31) | 66 | 1.18 (0.69, 2.02) |
| Quartile 4 | 105 | 146 | 0.83 (0.57, 1.21) | 130 | 0.69 (0.47, 1.01) | 64 | 73 | 0.50 (0.30, 0.85) | 71 | 0.66 (0.40, 0.98) | 41 | 73 | 1.03 (0.58, 1.81) | 59 | 0.72 (0.40, 1.31) |
| P trend [c] | | | 0.6105 | | 0.0271 | | | 0.0120 | | 0.0227 | | | 0.4764 | | 0.5241 |
| **WCRF score components** | | | | | | | | | | | | | | | |
| **Body fatness** | | | | | | | | | | | | | | | |
| 0 | 147 | 161 | 1.00 (ref) | 120 | 1.00 (ref) | 96 | 57 | 1.00 (ref) | 69 | 1.00 (ref) | 51 | 104 | 1.00 (ref) | 51 | 1.00 (ref) |
| 0.5 | 231 | 242 | 0.99 (0.73, 1.34) | 210 | 0.81 (0.59, 1.11) | 160 | 110 | 0.83 (0.54, 1.29) | 146 | 0.73 (0.49, 1.13) | 71 | 132 | 1.05 (0.65, 1.69) | 64 | 0.99 (0.58, 1.70) |
| 1 | 173 | 262 | 0.71 (0.52, 0.97) | 199 | 0.69 (0.50, 0.96) | 84 | 85 | 0.52 (0.32, 0.83) | 76 | 0.72 (0.45, 1.13) | 89 | 177 | 1.04 (0.66, 1.64) | 123 | 0.75 (0.46, 1.24) |
| P trend | | | 0.0297 | | 0.0297 | | | 0.0061 | | 0.1508 | | | 0.8753 | | 0.2119 |
| **Physical activity** | | | | | | | | | | | | | | | |
| 0 | 187 | 223 | 1.00 (ref) | 170 | 1.00 (ref) | 119 | 76 | 1.00 (ref) | 105 | 1.00 (ref) | 68 | 147 | 1.00 (ref) | 65 | 1.00 (ref) |
| 0.5 | 179 | 241 | 0.94 (0.70, 1.26) | 169 | 0.98 (0.72, 1.33) | 100 | 92 | 0.73 (0.48, 1.12) | 82 | 1.06 (0.71, 1.59) | 79 | 149 | 1.22 (0.80, 1.86) | 87 | 0.91 (0.56, 1.47) |
| 1 | 185 | 201 | 1.03 (0.77, 1.39) | 190 | 0.87 (0.64, 1.17) | 121 | 84 | 0.86 (0.57, 1.32) | 104 | 1.03 (0.70, 1.51) | 64 | 117 | 1.18 (0.75, 1.84) | 86 | 0.68 (0.42, 1.12) |
| P trend | | | 0.8349 | | 0.3400 | | | 0.5066 | | 0.8694 | | | 0.4551 | | 0.1255 |
| **Foods and drinks that promote weight gain** | | | | | | | | | | | | | | | |
| 0 | 175 | 212 | 1.00 (ref) | 163 | 1.00 (ref) | 134 | 93 | 1.00 (ref) | 103 | 1.00 (ref) | 41 | 119 | 1.00 (ref) | 60 | 1.00 (ref) |
| 0.5 | 176 | 227 | 0.87 (0.64, 1.18) | 181 | 0.94 (0.69, 1.29) | 108 | 91 | 0.74 (0.49, 1.14) | 104 | 0.84 (0.56, 1.24) | 68 | 136 | 1.30 (0.79, 2.13) | 77 | 1.38 (0.80, 2.40) |
| 1 | 200 | 226 | 1.02 (0.74, 1.39) | 185 | 1.05 (0.77, 1.44) | 98 | 68 | 0.95 (0.60, 1.49) | 84 | 0.96 (0.64, 1.45) | 102 | 158 | 1.55 (0.95, 2.52) | 101 | 1.47 (0.87, 2.51) |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P trend | | | 0.8601 | | 0.7325 | | | 0.7748 | | 0.8138 | | | 0.0769 | | 0.1835 |
| **Plant foods** | | | | | | | | | | | | | | | |
| 0 | 124 | 135 | 1.00 (ref) | 93 | 1.00 (ref) | 83 | 65 | 1.00 (ref) | 55 | 1.00 (ref) | 41 | 70 | 1.00 (ref) | 38 | 1.00 (ref) |
| 0.5 | 115 | 139 | 0.80 (0.55, 1.16) | 113 | 0.69 (0.47, 1.02) | 84 | 59 | 0.98 (0.60, 1.61) | 73 | 0.72 (0.44, 1.16) | 31 | 80 | 0.68 (0.37, 1.26) | 40 | 0.64 (0.32, 1.27) |
| 1 | 312 | 391 | 0.70 (0.50, 0.97) | 323 | 0.66 (0.47, 0.94) | 173 | 128 | 0.78 (0.49, 1.26) | 163 | 0.63 (0.40, 1.00) | 139 | 263 | 1.06 (0.63, 1.80) | 160 | 0.81 (0.46, 1.43) |
| P trend | | | 0.0356 | | 0.0314 | | | 0.2801 | | 0.0544 | | | 0.5354 | | 0.6330 |
| **Animal foods** | | | | | | | | | | | | | | | |
| 0 | 75 | 82 | 1.00 (ref) | 58 | 1.00 (ref) | 63 | 43 | 1.00 (ref) | 47 | 1.00 (ref) | 12 | 39 | 1.00 (ref) | 11 | 1.00 (ref) |
| 0.5 | 187 | 182 | 1.17 (0.78, 1.78) | 173 | 0.85 (0.56, 1.31) | 143 | 77 | 1.40 (0.82, 2.38) | 118 | 0.97 (0.59, 1.57) | 44 | 105 | 1.10 (0.50, 2.40) | 55 | 0.60 (0.23, 1.59) |
| 1 | 289 | 401 | 0.94 (0.62, 1.44) | 298 | 0.81 (0.52, 1.27) | 134 | 132 | 0.82 (0.47, 1.43) | 126 | 0.87 (0.51, 1.48) | 155 | 269 | 1.54 (0.72, 3.29) | 172 | 0.69 (0.27, 1.76) |
| P trend | | | 0.4089 | | 0.4062 | | | 0.1559 | | 0.5562 | | | 0.1142 | | 0.8574 |
| **Alcoholic drinks** | | | | | | | | | | | | | | | |
| 0 | 89 | 70 | 1.00 (ref) | 66 | 1.00 (ref) | 65 | 35 | 1.00 (ref) | 40 | 1.00 (ref) | 24 | 35 | 1.00 (ref) | 26 | 1.00 (ref) |
| 0.5 | 248 | 295 | 0.85 (0.58, 1.26) | 253 | 0.81 (0.56, 1.18) | 162 | 134 | 0.74 (0.45, 1.22) | 157 | 0.67 (0.42, 1.06) | 86 | 161 | 1.01 (0.54, 1.91) | 96 | 1.17 (0.61, 2.26) |
| 1 | 214 | 300 | 0.68 (0.68, 1.00) | 210 | 0.86 (0.58, 1.27) | 113 | 83 | 0.77 (0.46, 1.31) | 94 | 0.81 (0.49, 1.33) | 101 | 217 | 0.77 (0.41, 1.44) | 116 | 1.09 (0.57, 2.09) |
| P trend | | | 0.0270 | | 0.6393 | | | 0.4564 | | 0.6584 | | | 0.1919 | | 0.9851 |
| **Preservation, processing, preparation** | | | | | | | | | | | | | | | |
| 0 | 152 | 154 | 1.00 (ref) | 129 | 1.00 (ref) | 117 | 70 | 1.00 (ref) | 81 | 1.00 (ref) | 35 | 84 | 1.00 (ref) | 48 | 1.00 (ref) |
| 0.5 | 123 | 151 | 0.89 (0.60, 1.31) | 130 | 0.82 (0.56, 1.21) | 79 | 57 | 0.81 (0.47, 1.38) | 77 | 0.71 (0.44, 1.14) | 44 | 94 | 0.90 (0.48, 1.68) | 53 | 1.06 (0.54, 2.07) |
| 1 | 276 | 360 | 0.85 (0.55, 1.31) | 270 | 0.95 (0.62, 1.02) | 144 | 125 | 0.60 (0.33, 1.09) | 133 | 0.78 (0.45, 1.35) | 132 | 235 | 0.91 (0.45, 1.82) | 137 | 1.21 (0.58, 2.51) |
| P trend | | | 0.4762 | | 0.9108 | | | 0.0894 | | 0.4287 | | | 0.8439 | | 0.5835 |

Abbreviations: WCRF/ACIR: World Cancer Research Fund/American Institute for Cancer Research; CPRU, Cancer Prevention Research Unit; OR: Odds Ratio; CI: Confidence Interval.

[a] Adjusted for age, sex (where applicable), education, race, family history of colorectal cancer, smoking status, total energy intake, and Aspirin and NSAID use.

[b] The WCRF/AICR score was categorized into quartiles for male and female separately, based on the distribution of community controls: Quartile 1 (0-3 point in male; 0-3.75 points in female), Quartile 2 (3-3.75 points in male; 3.75-4.5 points in female), Quartile 3 (3.75-4.5 points in male; 4.5-5.25 points in female), and Quartile 4 (4.5-7 points in male; 5.25-7 points in female).

[c] P trend was assessed by calculating the median score of each quartile as a continuous regression.

**Table 6. The association of sporadic colorectal adenoma incidence per 1 unit increase in the WCRF/AICR score by categories of potential effect modifiers, CPRU study, 1991-1994.**

| | Men (n=886) | | | | | Women (n=862) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | Endoscopy Controls | | Community Controls | | Cases | Endoscopy Controls | | Community Controls | |
| **WCRF score** | **n** | **n** | **OR (95% CI)** | **n** | **OR (95% CI)** | **n** | **n** | **OR (95% CI)** | **n** | **OR (95% CI)** |
| **Sex** | 340 | 252 | 0.78 (0.65, 0.93) | 291 | 0.85 (0.71, 1.01) | 211 | 413 | 1.14 (0.94, 1.38) | 238 | 0.95 (0.77, 1.16) |
| **Age** [a] | | | | | | | | | | |
| Tertile 1 | 78 | 105 | 0.88 (0.63, 1.23) | 142 | 0.97 (0.67, 1.39) | 45 | 172 | 1.23 (0.84, 1.79) | 62 | 1.03 (0.67, 1.57) |
| Tertile 2 | 120 | 86 | 0.79 (0.59, 1.05) | 61 | 0.75 (0.55, 1.02) | 71 | 134 | 1.32 (0.94, 1.86) | 85 | 1.14 (0.79, 1.63) |
| Tertile 3 | 142 | 113 | 0.70 (0.50, 0.98) | 118 | 0.79 (0.60, 1.03) | 95 | 107 | 1.08 (0.78, 1.50) | 91 | 0.70 (0.48, 1.02) |
| P value [d] | | | 0.7817 | | 0.9339 | | | 0.8477 | | 0.2957 |
| **Education** | | | | | | | | | | |
| Didn't graduate | 34 | 20 | 0.58 (0.30, 1.14) | 24 | 0.61 (0.29, 1.26) | 24 | 30 | 1.82 (0.81, 4.10) | 13 | 0.90 (0.40, 2.00) |
| High school degree | 193 | 144 | 0.78 (0.61, 0.99) | 172 | 0.88 (0.70, 1.11) | 133 | 273 | 1.29 (1.02, 1.64) | 166 | 0.98 (0.77, 1.26) |
| College degree or greater | 113 | 88 | 0.86 (0.62, 1.18) | 95 | 0.85 (0.63, 1.15) | 54 | 110 | 0.75 (0.50, 1.14) | 59 | 0.79 (0.50, 1.25) |
| P value | | | 0.9896 | | 0.6481 | | | 0.1282 | | 0.8601 |
| **Family history of CRC** | | | | | | | | | | |
| No | 288 | 191 | 0.81 (0.66, 0.98) | 270 | 0.86 (0.73, 1.04) | 174 | 292 | 1.16 (0.90, 1.41) | 222 | 0.89 (0.71, 1.11) |
| Yes | 52 | 61 | 0.69 (0.42, 1.12) | 21 | 0.62 (0.33, 1.18) | 37 | 121 | 1.18 (0.79, 1.77) | 16 | 1.18 (0.51, 2.73) |
| P value | | | 0.4669 | | 0.3662 | | | 0.9913 | | 0.1635 |
| **Smoking status** | | | | | | | | | | |
| Current | 66 | 35 | 0.88 (0.57, 1.34) | 38 | 0.90 (0.59, 1.38) | 47 | 64 | 1.26 (0.76, 2.08) | 43 | 0.93 (0.56, 1.56) |
| Former | 182 | 127 | 0.78 (0.60, 1.00) | 152 | 0.84 (0.66, 1.06) | 78 | 128 | 1.15 (0.84, 1.56) | 63 | 0.97 (0.67, 1.40) |
| Never | 92 | 90 | 0.67 (0.47, 0.95) | 101 | 0.83 (0.60, 1.16) | 86 | 221 | 1.09 (0.80, 1.48) | 132 | 0.94 (0.69, 1.27) |
| P value | | | 0.6042 | | 0.8789 | | | 0.8082 | | 0.8815 |
| **Aspirin and NSAID usage** | | | | | | | | | | |
| No | 242 | 165 | 0.84 (0.68, 1.05) | 212 | 0.89 (0.73, 1.09) | 148 | 248 | 1.10 (0.87, 1.40) | 153 | 0.83 (0.64, 1.07) |
| Yes | 98 | 87 | 0.64 (0.46, 0.89) | 79 | 0.72 (0.51, 1.03) | 63 | 165 | 1.21 (0.87, 1.70) | 85 | 1.28 (0.88, 1.86) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| P value | | | 0.1141 | | 0.1296 | | | 0.7089 | | 0.0533 |
| **Total energy** [c] | | | | | | | | | | |
| Tertile 1 | 71 | 59 | 0.71 (0.47, 1.08) | 72 | 0.70 (0.47, 1.05) | 106 | 167 | 1.02 (0.76, 1.36) | 99 | 0.81 (0.58, 1.13) |
| Tertile 2 | 114 | 93 | 0.85 (0.63, 1.16) | 87 | 0.86 (0.63, 1.18) | 71 | 142 | 1.25 (0.86, 1.83) | 87 | 1.10 (0.75, 1.60) |
| Tertile 3 | 155 | 100 | 0.73 (0.55, 0.97) | 132 | 0.86 (0.67, 1.10) | 34 | 104 | 1.33 (0.85, 2.06) | 52 | 0.74 (0.46, 1.21) |
| P value | | | 0.8669 | | 0.8667 | | | 0.5786 | | 0.3023 |

Abbreviations: WCRF/ACIR: World Cancer Research Fund/American Institute for Cancer Research; CPRU, Cancer Prevention Research Unit; OR: Odds Ratio; CI: Confidence Interval; NSAID: non-steroidal anti-inflammatory drug.

[a] Age was categorized as tertiles: tertile 1 (30-50 years), tertile 2 (51-61 years), tertile 3 (62-77 years).

[b] Age was categorized as 50 percent.

[c] Total energy intake was categorized as tertiles: tertile 1 (less than 1680 kcal/day), tertile 2 (1680 – 2262.9 kcal/day), tertile 3 (2263 kcal/day or more).

[d] P values were statistics of assessing interaction, conducting maximum likelihood ratio tests by comparing crude and adjusted model included the interaction term.

# Table 7 The association of the WCRF/AICR score (per 1 unit increase) with incident, sporadic colorectal adenoma by colorectal adenoma characteristics[a], CPRU study, 1991-1994.

| | All participants (n=1745) | | | Men (n=886) | | | Women (n=862) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases | Endoscopy Controls (n=665) | Community Controls (n=529) | Cases | Endoscopy Controls (n=665) | Community Controls (n=529) | Cases | Endoscopy Controls (n=665) | Community Controls (n=529) |
| **WCRF score** | **n** | **OR [a] (95% CI)** | **OR (95% CI)** | **n** | **OR (95% CI)** | **OR (95% CI)** | **n** | **OR (95% CI)** | **OR (95% CI)** |
| **Per 1 unit** | 551 | 0.85 (0.76, 0.97) | 0.88 (0.77, 0.98) | 340 | 0.78 (0.65, 0.93) | 0.85 (0.71, 1.01) | 211 | 1.14 (0.94, 1.38) | 0.95 (0.77, 1.16) |
| **Number of adenoma polyps** | | | | | | | | | |
| 1 | 380 | 0.91 (0.79, 1.04) | 0.93 (0.81, 1.06) | 220 | 0.86 (0.71, 1.04) | 0.93 (0.77, 1.12) | 160 | 1.10 (0.89, 1.36) | 0.93 (0.74, 1.15) |
| more than 1 | 171 | 0.73 (0.60, 0.88) | 0.74 (0.62, 0.90) | 120 | 0.61 (0.47, 0.80) | 0.69 (0.54, 0.88) | 51 | 1.22 (0.87, 1.71) | 1.02 (0.72, 1.43) |
| **Shape of the worst adenoma [b]** | | | | | | | | | |
| Pedunculated | 134 | 0.72 (0.59, 0.89) | 0.72 (0.59, 0.88) | 90 | 0.65 (0.49, 0.87) | 0.69 (0.53, 0.91) | 44 | 1.01 (0.70, 1.44) | 0.83 (0.57, 1.19) |
| Sessile | 290 | 0.85 (0.74, 0.99) | 0.87 (0.75, 1.00) | 175 | 0.76 (0.61, 0.94) | 0.83 (0.67, 1.02) | 115 | 1.13 (0.90, 1.43) | 0.96 (0.75, 1.21) |
| **Degree of atypia of the worst adenoma** | | | | | | | | | |
| Mild | 241 | 0.83 (0.71, 0.97) | 0.86 (0.73, 1.00) | 142 | 0.72 (0.57, 0.91) | 0.79 (0.63, 0.99) | 99 | 1.10 (0.86, 1.42) | 0.95 (0.74, 1.22) |
| Moderate/Severe | 310 | 0.87 (0.75, 1.00) | 0.87 (0.75, 1.01) | 198 | 0.80 (0.65, 0.98) | 0.87 (0.71, 1.06) | 112 | 1.18 (0.92, 1.50) | 0.96 (0.74, 1.24) |
| **Location of the worst adenoma [b]** | | | | | | | | | |
| Right | 139 | 0.79 (0.65, 0.96) | 0.82 (0.67, 1.00) | 92 | 0.62 (0.47, 0.82) | 0.71 (0.54, 0.93) | 47 | 1.38 (0.97, 1.95) | 1.16 (0.82, 1.66) |
| Left | 406 | 0.87 (0.76, 0.99) | 0.88 (0.76, 1.00) | 244 | 0.81 (0.67, 0.99) | 0.87 (0.72, 1.05) | 162 | 1.09 (0.88, 1.34) | 0.91 (0.73, 1.14) |
| **Subtype of the worst adenoma [b]** | | | | | | | | | |
| Tubular | 362 | 0.91 (0.79, 1.04) | 0.92 (0.80, 1.06) | 217 | 0.81 (0.67, 0.99) | 0.89 (0.73, 1.08) | 145 | 1.21 (0.97, 1.50) | 1.00 (0.80, 1.26) |
| Villous/Tubulovillous | 188 | 0.76 (0.63, 0.91) | 0.77 (0.65, 0.93) | 123 | 0.72 (0.55, 0.93) | 0.78 (0.61, 1.00) | 65 | 0.99 (0.74, 1.33) | 0.83 (0.61, 1.13) |
| **Size of the worst adenoma** | | | | | | | | | |
| 0-3 | 171 | 0.95 (0.79, 1.15) | 0.97 (0.81, 1.17) | 98 | 0.91 (0.70, 1.19) | 0.99 (0.76, 1.28) | 73 | 1.13 (0.85, 1.50) | 1.00 (0.74, 1.35) |
| 4-8 | 210 | 0.85 (0.72, 1.00) | 0.87 (0.73, 1.02) | 138 | 0.78 (0.62, 0.98) | 0.84 (0.68, 1.05) | 72 | 1.17 (0.88, 1.57) | 0.98 (0.73, 1.31) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0.77 | 0.78 | | 0.65 | 0.70 | | 1.17 | 0.94 |
| more than 9 | 170 | (0.64, 0.92) | (0.65, 0.94) | 104 | (0.49, 0.84) | (0.54, 0.92) | 66 | (0.86, 1.58) | (0.70, 1.27) |

Abbreviations: WCRF/ACIR: World Cancer Research Fund/American Institute for Cancer Research; CPRU, Cancer Prevention Research Unit; OR: Odds Ratio; CI: Confidence Interval.

[a] Adjusted for age, education, race, family history of colorectal cancer, smoking status, total energy intake, and Aspirin and NSAID use.

[b] Among cases, there was 127 missing information on shape of worst adenoma, 6 missing on location of the worst adenoma, and 1 missing on size of the worst adenoma.