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Association between meeting the WCRF/AICR cancer prevention recommendations and colorectal cancer incidence: Results from the VITAL cohort

Theresa A. Hastert^{1,2,3,4} and Emily White^{3,4}

¹Department of Oncology, Wayne State University School of Medicine, Detroit, MI

²Population Studies and Disparities Research Program, Karmanos Cancer Institute, Detroit, MI

³Department of Epidemiology, University of Washington School of Public Health, Seattle, WA

⁴Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Purpose—In 2007 the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published eight recommendations regarding body weight, physical activity and dietary behaviors aimed at reducing cancer incidence worldwide. In this paper we assess whether meeting the WCRF/AICR recommendations is associated with lower CRC incidence; evaluate whether particular recommendations are most strongly associated with lower CRC incidence; and assess whether associations differ by sex.

Methods—We operationalized six of the recommendations (related to body weight, physical activity, energy density, plant foods, red and processed meat, and alcohol) and examined their association with CRC incidence over 7.6 years of follow-up in the prospective VITamins And Lifestyle (VITAL) Study cohort. Participants included 66,920 adults aged 50–76 years at baseline (2000–2002) with no history of CRC and with complete data for the recommendations evaluated. Incident colorectal cancers (n=546) were tracked through 2009.

Results—Compared with meeting no recommendations, meeting 1–3 recommendations was associated with 34–45% lower CRC incidence, and meeting 4–6 was associated with 58% lower incidence (95% CI: 34%, 74%) in fully-adjusted analyses. The recommendations most strongly associated with lower CRC risk for women were related to body fatness and red and processed meat, while for men these were alcohol intake and red and processed meat. Differences by sex were statistically significant ($p < 0.05$) for the recommendations related to body weight and to alcohol.

Author Addresses: Theresa A. Hastert (Corresponding Author), 4100 John R St. MM04EP, Detroit, MI 48201, Phone: (313) 578-4261, Fax: (313) 578-4306, hastertt@karmanos.org, Emily White, 1100 Fairview Ave. N, M4-B402, Seattle, WA 98109-1024.

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Authors' Contributions: TAH and EW designed the research, including project conception and development of the overall research plan. EW provided essential materials and study oversight. TAH analyzed the data, wrote the paper, and had primary responsibility for final content. All authors read and reviewed the final manuscript.

Conclusions—Meeting the WCRF/AICR recommendations, particularly those related to alcohol, body weight, and red and processed meat could substantially reduce CRC incidence; however, associations differ by sex.

Keywords

cancer prevention; colorectal cancer; recommendations; obesity; alcohol

In 2007 the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) released several cancer prevention recommendations related to body fatness, physical activity and diet aimed at reducing cancer incidence worldwide.[1] Meeting these recommendations has been associated with several outcomes, including lower total and site-specific cancer incidence [2–5] and all-cause and cancer mortality;[6–9] however, previous research into the association between meeting the WCRF/AICR and colorectal cancer (CRC) risk is limited,[2, 10] and has not examined whether observed associations differ by sex. Previous work has also not examined the associations between individual recommendations and CRC risk.

Results from a large European cohort study suggested that CRC incidence was 27% lower among adults with the highest adherence to the WCRF/AICR recommendations compared with the lowest.[2] Studies of other diet-specific [11, 12] and broader lifestyle indexes, including additional behaviors such as physical activity, body weight, smoking, and alcohol consumption have also found inverse associations between healthier behavior patterns and CRC risk.

The aims of this paper are to assess whether meeting the WCRF/AICR cancer prevention recommendations is associated with lower CRC incidence in a population of older adults in one region of the United States; to evaluate whether particular recommendations are most strongly associated with lower CRC incidence; and to assess whether these associations differ by sex.

SUBJECTS AND METHODS

Study Cohort

The VITamins And Lifestyle (VITAL) study is a prospective cohort study designed to investigate the associations between use of dietary supplements and cancer risk and has previously been described in detail.[17] Participants were eligible to join the cohort if they were between the ages of 50 and 76 and lived in one of the 13 counties in the Western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry at baseline.

We recruited participants into the VITAL cohort using names purchased from a commercial mailing list. Between October, 2000 and December, 2002, 77,719 men and women entered the cohort by completing a baseline questionnaire which passed quality control checks. We excluded participants with a history of CRC (n=971) or whose cancer history was unknown (n=214); those who were missing BMI at both baseline and at age 45 (n=2,478) or physical activity (n=1,093) data; and those whose food frequency questionnaires (FFQs) had <5 items completed on a single page (n=4,331) or whose estimated energy consumption was <600

calories for women or <800 calories per day for men (n=2,304), or >4,000 calories per day or women or >5,000 calories per day for men (n=547). Participants missing both pack-years and smoking history (N=788) were excluded, while those missing other covariate information were included in a separate category, as described below. Exclusions are not mutually exclusive, and resulted in 66,920 participants and 546 incident colorectal cancers in the analysis cohort.

The Institutional Review Board at the Fred Hutchinson Cancer Research Center approved this research.

Data Collection

Baseline questionnaires included items on medical history, self-reported height and weight, physical activity over the previous 10 years, individual and family medical history, medication use, and a 126-item FFQ covering diet in the year before baseline.

The FFQ was adapted from the questionnaire developed for use in the Women's Health Initiative and other studies. The University of Minnesota's Nutrition Coordinating Center database was used to convert food frequency information into nutrients.[18] Number of servings was calculated based on frequency of intake and whether respondents indicated their usual portion size was small, medium or large compared with a provided sex-specific medium portion size of each food and beverage. Validity studies of similar FFQs have reported correlation coefficients of 0.41 for servings of fruits and vegetables compared with food records and 0.57–0.61 compared with dietary recalls,[19, 20] 0.50–0.59 for measures of red and processed meat intake compared with diet records,[21] and 0.89 for alcohol consumption compared with a combination of diet recalls and food records.[22]

Physical activity was assessed by a one-page questionnaire that asked about walking (including usual pace) and other moderate and strenuous recreational activities done at least once per week in the previous 10 years. The questionnaire included categorical questions on minutes per day, days per week, and number of years participating in each activity. Estimates of metabolic equivalent task (MET)-hours per week were validated against a detailed in-person interview on 10-year recreational physical activity among a subsample of VITAL respondents (age- and sex-adjusted correlation coefficient: 0.68).[23]

Body fatness was assessed using self-reported height and weight at baseline. Estimates of overweight status based on self-reported height and weight have been found to have 84–95% sensitivity and 84–99% specificity among adults ages 50–79.[24]

Operationalization of the WCRF/AICR Recommendations

The main exposures of this study were whether or not respondents met each individual WCRF/AICR cancer prevention recommendation and the number of recommendations met. The recommendations include 8 broad guidelines, with 1–4 more-specific personal recommendations and public health goals for each. An expert panel of four nutritional epidemiologists (including EW) with knowledge of the VITAL cohort data made recommendations on the operationalization of 6 of the 8 recommendations. Additional information about this panel and its methodology is provided in the Appendix. The key

components of each recommendation were identified (noted in italics in Table 1) and cutoffs for meeting the key components were selected based on information provided in the recommendations or from external sources (e.g. the World Health Organization)[25] (Table 1). The recommendation to limit salt-preserved foods and moldy cereals and legumes was not operationalized because those exposures are not common in the United States food supply and data were not available in VITAL. The recommendation to meet nutritional needs through diet alone was not operationalized because while it did not recommend using dietary supplements, it also did not recommend against supplement use. Detail about the operationalization of the remaining recommendations is below.

Body fatness—The recommendation to be as lean as possible within the normal range of body weight was operationalized as having a body mass index (BMI) of at least 18.5 but less than 25 kg/m² based on height and weight reported at baseline. This range was based on that set by the World Health Organization [25] as normal weight, as suggested in the recommendation.[1]

For participants missing weight at baseline but reporting BMI at age 45 (n=1,383), BMI at baseline was imputed by calculating the average annual change in BMI within age-, sex-, and race/ethnicity-specific strata (<60, 60–69, and 70+ for age; sex; white, Hispanic, African-American, American Indian/Alaska Native, Asian or Pacific Islander, and other for race/ethnicity), multiplying that value by the difference between respondents' baseline age and 45 and adding the product to their BMI at age 45.

Physical activity—The recommendation to be physically active as a part of everyday life (equivalent to brisk walking for at least 30 minutes every day) was operationalized as engaging in moderate or fast walking and/or other moderate or strenuous activity for an average of at least 30 minutes per day, at least 5 days per week, and in at least 7 of the past 10 years. Respondents who were missing data for this constructed variable but whose physical activity responses were complete enough to estimate MET-hours per week of walking and/or moderate/strenuous activity (n=1,272) were categorized as meeting this recommendation if they engaged in an average of at least 10 MET-hours of walking and/or moderate/strenuous physical activity per week (based on an estimate of 4.0 METs/hour x 0.5 hours/day x 5 days/week) over the previous 10 years.

Energy density—The recommendation to limit consumption of energy-dense foods and to avoid sugary drinks was operationalized as consuming a diet where the energy density of foods consumed was less than 125 kcal per 100 g based on responses to the FFQ, and also consuming less than one serving of regular (not diet) soda, fruit drinks and/or cranberry juice with added sugar per week and also no more than three servings of other fruit juices which typically do not have added sugar (e.g., orange juice) per week. The energy density cutoff was based on a public health goal included in the WCRF/AICR recommendation that the average energy density of diets should be lowered towards 125 kcal per 100 g.

Plant foods—The recommendation to eat mostly foods of plant origin, specifically the personal recommendations to eat at least five servings of a variety of non-starchy vegetables and fruits every day and to eat relatively unprocessed grains and/or legumes with every

meal, were operationalized as consuming at least 5 servings of fruits and/or non-starchy vegetables and also at least one serving of whole grains and/or legumes per day. Servings of fruits and non-starchy vegetables included 25 foods or food groups, adjusted by portion size and by summary questions on total numbers of fruits and vegetables eaten to reduce over-estimation by participants. It excluded fruit juices and potatoes. Because the VITAL FFQ only included 5 items on whole grains (covering breads and breakfast cereals) and therefore failed to fully separate whole grains from other grains (e.g., brown rice from white rice), we used a cutoff of one serving per day rather than per meal to represent those who habitually eat whole grains and/or legumes. Legume servings included 3 items on bean dishes and one item on tofu and tempeh.

Red meat—The recommendation to limit intake of red meat and to avoid processed meat was operationalized as consuming fewer than 18 total ounces of red and/or processed meat, including no more than one serving of processed meat per week. Red and processed meat from mixed dishes in the FFQ were also included by assuming that red or processed meat accounted for one-quarter of their weight.

Alcohol—The recommendation to limit alcoholic drinks was operationalized as consuming no more than one alcoholic beverage per day on average for women, and no more than two per day for men. A drink was classified as 12 ounces of beer, 4 ounces of wine, or one shot (1.5 ounces) of liquor or one mixed drink.

Case Ascertainment and Censoring

Incident primary colorectal cancers (ICD-10-CM Codes 153 – 154.1)[26] were ascertained through December 31, 2009 by annual linkage with the Western Washington SEER cancer registry. All incident cancers diagnosed in the 13 counties of the Western Washington SEER registry (except for nonmelanoma skin cancers) are reported to SEER by all area hospitals and by offices of pathologists, oncologists and radiotherapists. Linkage between VITAL and SEER is largely automated and based on ranking agreement between items common to both datasets, such as Social Security number, name, and date of birth. Matches with high concordance are linked automatically. Visual inspection is used to adjudicate incomplete matches.

Participants who did not develop colorectal cancer were right-censored at the earliest of the following events: date they requested removal from the study (n=18), date they moved out of the Western Washington SEER catchment area (n=4,639), date of death (n=4,860) or December 31, 2009 (n=56,857). Moves out of the SEER catchment area were identified through linkage with the National Change of Address System. Deaths occurring in Washington State were ascertained via linkage with the Washington State death file using linkage procedures similar to that for linkage to SEER.

Statistical Analyses

Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident CRC associated with meeting (vs. not meeting) each individual recommendation and for the number of recommendations met (vs. meeting none) were estimated using Cox proportional hazards

models. We used participant age as the time scale, with participants entering the analysis at the age they completed the baseline questionnaire and exiting at age at CRC diagnosis or censoring event. Mean follow-up was 7.6 years. Proportional hazards assumptions were examined using scaled Schoenfeld residuals. No significant ($p < 0.05$) deviations from proportionality were observed. *P*-values for trend were calculated using the Wald test associated with modeling the number of recommendations met as a continuous variable. All statistical tests were two-sided with 5% alpha error used as the threshold for statistical significance.

Multivariate analyses included adjustment for potential confounders selected *a priori*, including known CRC risk factors. These analyses included categorical variable adjustment for sex (except in sex-specific models), education, race, receipt of a colonoscopy or sigmoidoscopy in the 10 years before baseline, history of CRC in a first-degree relative, history of cancer other than colorectal cancer, smoking status, and use of non-steroidal anti-inflammatory (NSAID) medications using the categories in Table 2, as well as adjustment for kilocalories of average daily energy intake (continuous). Participants missing information for a potential confounder were included in a “missing” category.

In additional sex-stratified analyses, binary variables indicating whether respondents met each of the 6 recommendations were included in one model with the potential confounders. The recommendation with the largest HR was subsequently removed, the model was run again and the process was repeated until only the recommendation associated with the lowest CRC risk remained. Each subset of recommendations identified through this process was evaluated in relation to CRC risk, and each model controlled for previously-eliminated recommendations.

Analyses were conducted using Stata 14.0 (StataCorp LP, College Station, TX).

RESULTS

Table 1 gives the proportion of all VITAL participants and those diagnosed with CRC during follow-up who met each of the recommendations. More than 85% of participants met the recommendation to limit alcohol intake and approximately one-third met the recommendations related to red and processed meats and to body fatness. Fewer than 20% met the recommendations related to physical activity, energy density, and plant foods. Overall, recommendation adherence was lower in CRC cases than in the cohort as a whole.

Table 2 gives baseline characteristics of all VITAL participants and of those diagnosed with CRC during follow-up. The average age at baseline was 61.1 years for all members of the cohort and 65.3 for those diagnosed with CRC. The majority of both groups were white, and a lower proportion of CRC cases completed college or professional degrees, had a colonoscopy or sigmoidoscopy in the previous 10 years or reported regular NSAID use than the cohort as a whole. Smoking was more common among cases. Family history of CRC was equally common in the two groups; however, a higher proportion of cases had a prior history of cancer other than colorectal cancer compared with the cohort as a whole.

Table 3 gives HRs and 95% CIs associated with meeting (vs. not meeting) each individual recommendation, overall and by sex. In fully-adjusted analyses, meeting the recommendation to limit alcohol consumption was associated with a 31% lower CRC risk compared with not meeting the recommendation (HR: 0.69; 95% CI: 0.56, 0.86), meeting the recommendation related to red and processed meat was associated with 19% lower CRC risk (HR: 0.81, 95% CI: 0.66, 0.99), and meeting the recommendation related to body fatness was marginally associated with 15% lower risk (HR: 0.85; 95% CI: 0.70, 1.03). Additional analyses suggest that these associations differ by sex, with the recommendation related to body fatness being most strongly associated with lower HR risk among women (HR: 0.70, 95% CI: 0.53, 0.92) but not men (HR: 1.03, 95% CI: 0.79, 1.33; $P_{\text{interaction}}=0.023$) and the alcohol recommendation being most strongly associated with lower CRC risk in men (HR: 0.56, 95% CI: 0.42, 0.73) but not in women (HR: 0.96, 95% CI: 0.66, 1.39; $P_{\text{interaction}}=0.032$).

CRC risk was 10% lower in participants meeting the recommendation related to physical activity, although the association was not statistically significant, and no effect modification was observed by sex. Hazard ratios associated with meeting the energy density and plant foods recommendations were greater than one, but also not significant (HR_{energy density}: 1.02; 95% CI: 0.77, 1.35; HR_{plant foods}: 1.10, 95% CI: 0.82, 1.48).

Table 4 gives HRs and 95% CIs associated with the number of recommendations met. In adjusted analyses, compared with meeting no recommendations, meeting 1–3 recommendations was significantly associated with 34–45% lower CRC risk, and meeting 4–6 recommendations was associated with 58% lower risk (HR: 0.42; 95% CI: 0.26, 0.66). After adjusting for potential confounders, each additional recommendation met was associated with 13% lower CRC risk on average (HR: 0.87; 95% CI: 0.80, 0.95, $P_{\text{trend}}=0.001$).

Results were similar in sex-specific analyses (Table 5). On average, each additional recommendation met was associated with 14% lower CRC risk in women (HR: 0.86, 95% CI: 0.76, 0.97) and with 12% lower risk in men (HR: 0.88, 95% CI: 0.78, 1.00). No statistically significant effect modification was observed ($P_{\text{interaction}}=0.60$).

To identify specific subsets of recommendations most associated with lower CRC incidence, additional analyses were performed in which the fully-adjusted models presented in Table 3 were repeated with the recommendation least associated with lower CRC risk sequentially removed. Because of the effect modification observed by sex for specific recommendations (Table 3), these analyses were conducted among women and men separately. Additional results given in Table 5 suggest that the recommendations most strongly associated with lower risk of CRC differ by sex. Compared with meeting no recommendations, CRC incidence is 44% lower in women who meet the recommendations related to body fatness and red and processed meat (HR: 0.56, 95% CI: 0.37, 0.83). CRC incidence is approximately 56% lower in men who meet the recommendations related to red and processed meat and alcohol (HR: 0.44, 95% CI: 0.29, 0.67).

DISCUSSION

The results of this study suggest that meeting the WCRF/AICR cancer prevention recommendations is associated with substantially lower CRC incidence; however, associations between specific recommendations and CRC risk differ by sex, such that the recommendation related to body fatness is most strongly associated with lower CRC risk among women while the recommendations related to alcohol is most strongly associated among men.

We are aware of only two previous studies examining adherence to the WCRF/AICR recommendations and CRC incidence. Utilizing data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, Romaguera et al. reported a hazard ratio of 0.88 (95% CI: 0.84, 0.91) associated with a 1-point increase in WCRF/AICR score, nearly identical to our covariate-adjusted hazard ratio of 0.89 (95% CI: 0.81, 0.97).[2] They also reported a hazard ratio of 0.73 (95% CI: 0.65, 0.81) associated with being in the highest-adherence group compared with the lowest, which represents a much weaker association than our hazard ratio of 0.27 (95% CI: 0.11, 0.70) for meeting 5–6 recommendations vs. none.

Several differences in the operationalization of the WCRF/AICR recommendations between the two studies could account for the much stronger association we observed between high adherence and CRC risk. Romaguera et al. included the special recommendation that mothers breastfeed for six months, which we did not include in the VITAL study. The inclusion of this recommendation is likely to weaken the observed association between the recommendations and CRC, which is not linked with breastfeeding behaviors. Additionally, the lowest WCRF/AICR score category used by Romaguera et al. included men who met up to two recommendations and women who met up to three, while our lowest-adherence category included only participants who met no recommendations.

Nomura et al. also examined the association between the WCRF/AICR recommendations and CRC risk among African American women, but found no association.[10] In this study they created a three-level adherence score with low adherence women meeting <3 recommendations and high adherence women meeting >4 recommendations. Similar to Romaguera, the large low-adherence category of 0–2.5 recommendations likely limited the ability to detect associations between the high and low adherence and CRC risk. In sensitivity analyses using a three-level adherence variable (0–2, 3–4, and 5–6 recommendations), roughly consistent with Romaguera and Nomura, higher adherence was no longer significantly associated with lower CRC risk (HR for meeting 3–4 recommendations: 0.91, 95% CI: 0.74, 1.12; HR for meeting 5–6 recommendations: 0.53, 95% CI: 0.24, 1.19 compared with meeting 0–2 recommendations). Consistent with the results we present in Table 4, these findings suggest that there are important differences in CRC risk for participants meeting no recommendations compared with even 1–2 recommendations. Combining participants who meet between 0–2.5 recommendations may limit the ability to detect associations between low and high adherence and CRC risk.

A handful of additional studies have examined the association between other indexes and CRC risk. Kirkegaard et al. reported a similar association (incidence rate ratio: 0.89; 95% CI: 0.82, 0.96) between each additional point on a healthy lifestyle index including measures of physical activity, waist circumference, smoking, alcohol use, and diet in a Danish cohort. [13] Wei et al. used the Nurses' Health Study to develop a risk score including smoking, body weight, physical activity, red and processed meat, and folate consumption and estimate its association with colon cancer risk by the age of 70.[16] The relative risk of colon cancer among women in the highest-risk group was nearly four times that of women in the lowest-risk group (RR: 3.84, 95% CI: 1.61, 9.16), similar to our results for the highest- vs. lowest-adherence to the WCRF/AICR recommendations. When examining the association between the same lifestyle factors and colon cancer in the Health Professionals Follow-up Study, Platz et al. reported an 8% increase in risk for each additional 1-point increase in risk score. [15] Driver et al. developed a risk score for CRC among men in the Physicians' Health Study and identified alcohol use, body mass index, and smoking as the modifiable risk factors independently associated with CRC risk,[14], somewhat consistent with our finding that the WCRF/AICR recommendation related to alcohol was most strongly associated with CRC risk in men.

Our finding of a particularly strong inverse association between meeting the alcohol recommendation and CRC incidence in men is also consistent with evidence cited in the WCRF/AICR Continuous Update Project Colorectal Cancer 2011 Report in which the evidence for an increase in CRC risk associated with alcohol consumption in men was rated as "convincing" while the evidence in women was rated as only "probable".[27] This difference by sex may be due to differences in total alcohol consumption among men compared with women. Among VITAL participants, men who met the recommendation related to alcohol consumption consumed an average of 5.2 g of alcohol per day compared with 46.5 g/day for men who did not meet the recommendation while women who met the recommendation consumed an average of 2.0 g/day and those who did not consumed 25.7 g/day. This additional exposure among men who did not meet the alcohol recommendation could account for the stronger association observed between meeting the alcohol recommendation and CRC risk among men. Men and women may also prefer different alcoholic drinks, and hormonal differences in alcohol metabolism may exist.[1]

Although substantial prior literature exists linking body weight to colorectal cancer risk,[1, 28] less evidence exists to support the stronger association we observed among women compared with men. To the extent that previous work has reported differences by sex, inverse associations between body weight and CRC risk have been stronger among men, although evidence consistently links body weight and CRC risk in women.[28, 29] Reasons for our observed association among women but not men are not clear.

The findings presented here should be considered within the context of several potential limitations. VITAL participants may have more positive health behaviors than the general population. However, selection bias is unlikely to impact results of a prospective study where future disease status is not known at baseline. Although VITAL is a large cohort study and the analyses presented here include 546 incident CRC cases, the sample size was not large enough to conduct more detailed analyses for colon and rectal cancer separately or by

tumor site (e.g. left colon vs. right colon). VITAL's large size and detailed data collection allowed for control for several potential confounders; however, residual confounding may remain due to missing or misspecified confounders. Measurement error in the assessment of whether participants met each recommendation and the combined adherence score would bias results toward the null.[30]

Strengths of this study include its prospective design, large sample size, and detailed information collected at baseline that allowed for the operationalization of the six of the WCRF/AICR cancer prevention recommendations and control for several important potential confounding factors. Accurate and near-complete assessment of CRC and other outcomes is provided by linkage with SEER, the Washington State death file, and the National Change of Address System.

This is the first study to report the association between the WCRF/AICR recommendations and CRC incidence in the United States, to examine associations for individual recommendations, and to examine whether these associations differ by sex. Overall we found a strong inverse association between meeting the WCRF/AICR recommendations and CRC incidence, driven by different recommendations among men and women.

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Appendix 1

In the Fall of 2011 we convened an expert panel of nutritional epidemiologists (Emily White, Alan Kristal, Ruth Patterson, Shirley Beresford) with knowledge of the VITAL cohort and the WCRF/AICR recommendations to determine the approach and appropriate cutoffs to be used when operationalizing these recommendations in the VITAL cohort. Decisions on how to operationalize each recommendation were made by first attempting to define adherence using the “Personal Recommendations,” with additional information from the “Public Health Goals” and included references used to determine cutoffs when the personal recommendations were not specific. When the personal recommendations included clear targets, those values were used. The expert panel also decided that the overall analysis approach would treat each recommendation as either being met or not met and that we would not include partial adherence points for the recommendations.

Recommendation 1: Body Fatness - We set cutoffs of body mass index at baseline of between 18.5 and $<25.0 \text{ kg/m}^2$ to be consistent with the personal recommendation to “maintain body weight within the normal range from age 21” with a reference to ranges issued by national governments or the World Health Organization (whose cutoffs we used). We opted not to incorporate the additional personal recommendations related to childhood and adolescent body weight and about avoiding weight gain and increases in waist circumference throughout adulthood because the child and adolescent body weight and waist circumference data were not available and, although participant reports of body weight at ages 18, 30, and 45 were available, there were several missing responses and we were concerned about the accuracy of the provided estimates.

Recommendation 2: Physical Activity - We utilized the detailed physical activity questionnaire in VITAL, incorporating walking and other moderate and strenuous activities and their frequency and duration over the previous 10 years, to set cutoffs to identify participants meeting the personal recommendation to “be moderately physically active, equivalent to brisk walking for at least 30 minutes every day.” We ultimately counted participants reporting walking at a moderate or fast (but not casual) pace and/or participating in moderate or strenuous activities (such as running, aerobics, dancing, swimming, cycling, or sports) but not mild exercise (such as golf, slow dancing, or bowling) for an average of at least 30 minutes per day on an average of at least 5 days per week over at least 7 of the previous 10 years. The personal recommendation to aim for 60 minutes of moderate or 30 minutes of vigorous activity every day as fitness improves was not incorporated because data on changes in fitness and activity over time were not available; however, we did capture long-term physical activity patterns by incorporating data from the previous 10 years. The personal recommendation to limit sedentary habits such as watching television was not incorporated because data on sedentary time were not available.

Recommendation 3: Foods and Drinks that Promote Weight Gain – The personal recommendations to “consume energy-dense foods sparingly”, “avoid sugary drinks”, and “consume ‘fast foods’ sparingly, if at all” did not provide clear cut-points for what

constituted meeting this recommendation. The VITAL food frequency questionnaire (FFQ) captures detailed information on beverages, and also captures total calories consumed and the average weight in grams of each of the included individual foods and mixed dishes, but does not specifically ask about “fast foods”. We utilized additional information from the associated public health goals that the average energy density of the diets should be lowered to 125 kcal per 100 g to establish our cutoff for dietary energy density of foods consumed. This cutoff excluded beverages, so we further required that participants also consume less than one serving of regular (not diet) soda, fruit drinks, or cranberry juice with added sugar each week. The additional requirement that participants consume fewer than 3 servings of other fruit juices (e.g. orange juice) per week was added in response to suggestions received through peer review of these recommendations.

Recommendation 4: Plant Foods – The personal recommendations related to plant foods included eating at least 5 portions of fruits and non-starchy vegetables every day, relatively unprocessed grains and/or legumes with every meal, and limiting refined starches. The expert panel decided that participants would be counted as meeting this recommendation if they consumed at least 5 servings per day of fruits and non-starchy vegetables (fruit juices and white potatoes did not count toward meeting the recommendation) and also consumed at least one serving per day of whole grains or legumes. The VITAL FFQ was not developed to capture whole grains separately from refined grains, so this lower threshold was selected to capture regular consumption of these foods rather than requiring the consumption of at least one serving per meal. An additional personal recommendation that individuals who consume starchy roots or tubers as staples also ensure sufficient intake of non-starchy vegetables, fruits, and legumes was not addressed because this dietary pattern is not common in the United States.

Recommendation 5: Animal Foods – The expert panel decided to follow the personal recommendation that “people who eat red meat to consume less than 500 g (18 oz) a week, very little, if any to be processed” and count participants as meeting this recommendation if they consumed fewer than 18 oz of red or processed meat (reported as individual foods or mixed dishes such as pasta with meat sauce) per week. The additional requirement that participants consume no more than one serving per week of processed meat was added in response to suggestions received through peer review of these recommendations.

Recommendation 6: Alcohol – The expert panel followed the personal recommendation that alcohol consumption should be limited to no more than one drink per day for women and no more than two per day for men, where a drink contains between 10–15 g of ethanol.

Recommendation 7: Preservation, Processing, Preparation – The expert panel chose not to operationalize the personal recommendations to avoid salt-preserved foods and to not eat moldy grains or legumes because these practices are not common in the United States and appropriate data are not captured in the VITAL FFQ. The panel further decided not to include the recommendation to limit consumption of processed foods and limit intake to less than 2.4 g sodium per day because the validity of sodium measurement using FFQs has not been established.

Recommendation 8: Dietary Supplements – The personal recommendation that “dietary supplements are not recommended for cancer prevention” was not operationalized. While the public health goal is to increase the proportion of the population meeting nutritional needs through diet, rather than supplements, the WCRF/AICR also cites studies that have suggested that supplements may reduce cancer risk in certain high-risk groups and declines to make a population-wide recommendation on whether to take or avoid supplements

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Table 1 WCRF/AICR cancer prevention recommendations, their operationalization in this study, and percent who met each recommendation

WCRF/AICR recommendation	Associated personal recommendations	Met/did not meet recommendation in this study if:		Colorectal cancer cases (N=546)		Non-cases (N=66,374)		VITAL cohort (N=66,920)	
		N	%	N	%	N	%	N	%
1. Body fatness Be as lean as possible within the normal range of body weight	<ul style="list-style-type: none"> Ensure that weight through childhood and adolescent growth projects toward the lower end of the normal BMI range at age 21 Maintain body weight within the normal range from age 21 Avoid weight gain and increases in waist circumference throughout adulthood 	Met: 18.5 kg/m ²	BMI < 25	160	29.3	22,121	33.3	22,281	33.3
		Did not meet: BMI < 18.5 kg/m ² or BMI ≥ 25 kg/m ²		386	70.7	44,253	66.7	44,639	66.7
2. Physical activity Be physically active as part of everyday life	<ul style="list-style-type: none"> Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day Limit sedentary habits such as watching television 	Met: 30 minutes per day of moderate or fast walking and/or moderate or strenuous activity on at least 5 days per week in at least 7 of the past 10 years		88	16.1	12,268	18.5	12,356	18.5
		Did not meet: < 30 minutes per day or < 5 days per week or < 7 moderate or fast walking and/or moderate or strenuous activity		458	83.9	54,106	81.5	54,564	81.5
3. Energy density Limit consumption of energy dense foods; avoid sugary drinks	<ul style="list-style-type: none"> Consume energy-dense foods sparingly Avoid sugary drinks. (This principally refers to drinks with added sugars. Fruit juices should also be limited.) Consume 'fast foods' sparingly, if at all 	Met: Energy density of diet < 125 kcal per 100 g and < 1 sugary drink and 3 servings of fruit juice per week		58	10.6	7,595	11.4	7,653	11.4
		Did not meet: Energy density of diet ≥ 125 kcal per 100 g or 1 sugary drink or > 3 servings of fruit juice per week		488	89.4	58,779	88.6	59,267	88.6
4. Plant foods Eat mostly foods of plant origin	<ul style="list-style-type: none"> 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 Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal 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) 	Met: 5 servings of fruits and vegetables and 1 serving of whole grains and/or legumes per day		57	10.4	7,606	11.5	7,663	11.5
		Did not meet: < 5 servings of fruits and vegetables and/or < 1 serving of whole grains and/or legumes per day		489	89.6	58,768	88.5	59,257	88.6

WCRF/AICR recommendation	Associated personal recommendations	Met/did not meet recommendation in this study if:		Colorectal cancer cases (N=546)		Non-cases (N=66,374)		VITAL cohort (N=66,920)	
		N	%	N	%	N	%	N	%
5. Red meat Limit intake of red meat and avoid processed meat	<ul style="list-style-type: none"> People who eat red meat to consume less than 500 g (18 oz) a week, very little if any to be processed 	159	29.1	23,158	34.9	23,317	34.8	43,216	65.2
	<ul style="list-style-type: none"> Met: < 18 oz total red and processed meat, including no more than 1 serving processed meat, per week Did not meet: 18 oz red and/or processed meat or > 1 serving processed meat per week 	441	80.8	56,767	85.5	57,208	85.5	9,607	14.5
6. Alcohol Limit alcoholic drinks	<ul style="list-style-type: none"> If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women 	105	19.2	9,607	14.5	9,712	14.5		
	<ul style="list-style-type: none"> Met: 1 drink per day for women, 2 drinks per day for men Did not meet: > 1 drink per day for women, > 2 drinks per day for men 								
7. Salt-preserved foods Limit consumption of salt; avoid moldy grains or legumes	<ul style="list-style-type: none"> Avoid salt-preserved, salted, or salty foods; preserve foods without using salt Limit consumption of processed foods with added salt to ensure an intake of less than 6 g (2.4 g sodium) a day Do not eat moldy cereals (grains) or pulses (legumes) 								
	<ul style="list-style-type: none"> Not operationalized 								
8. Supplements Aim to meet nutritional needs through diet alone	<ul style="list-style-type: none"> Dietary supplements are not recommended for cancer prevention 								
	<ul style="list-style-type: none"> Not operationalized 								

Italicized text indicates portions of the WCRF/AICR recommendations operationalized in this study. These represent the key components of the recommendations selected by an expert panel.

Table 2

Baseline characteristics of the study population and of colorectal cancer cases

Characteristic	Colorectal cancer cases (N=546)						Non-cases (N=66,374)						VITAL cohort (N=66,920)					
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%		
Age																		
50–54	54	9.9	16,121	24.3	16,175	24.2												
55–59	70	12.8	15,519	23.4	15,589	23.3												
60–64	99	18.1	12,213	18.4	12,312	18.4												
65–69	145	26.6	10,649	16.0	10,794	16.1												
70 or older	178	32.6	11,872	17.9	12,050	18.0												
Sex																		
Female	250	45.8	33,855	51.0	34,105	51.0												
Male	296	54.2	32,519	49.0	32,815	49.0												
Education																		
High school graduate/GED or below	162	29.7	12,321	18.5	12,483	18.7												
Some college/technical school	205	37.6	25,219	38.0	25,424	38.0												
College graduate	109	20.0	16,799	25.3	16,908	25.3												
Advanced degree	66	12.1	11,840	17.8	11,906	17.8												
Missing	4	0.7	195	0.3	199	0.3												
Race																		
White	502	93.2	62,079	93.5	62,581	93.5												
Hispanic	3	0.4	542	0.8	545	0.8												
African-American	12	2.1	700	1.1	712	1.1												
American Indian/Alaska Native	13	2.1	974	1.5	987	1.5												
Asian/Pacific Islander	10	1.8	1,455	2.2	1,465	2.2												
Other	2	0.4	389	0.6	391	0.6												
Missing	4	0.7	235	0.4	239	0.4												
Colonoscopy or sigmoidoscopy in 10 years prior to baseline																		
No	284	52.0	28,383	42.8	28,667	42.8												

Characteristic	Colorectal cancer cases (N=546)		Non-cases (N=66,374)		VITAL cohort (N=66,920)	
	N	%	N	%	N	%
Yes	256	46.9	37,513	56.5	37,769	56.4
Missing	6	1.1	478	0.7	484	0.7
Family history of colorectal cancer (first degree)						
No	459	84.1	58,065	87.5	58,524	87.5
Yes	77	14.1	7,513	11.3	7,590	11.3
Missing	10	1.8	478	1.2	806	1.2
Previous (non-colorectal) cancer diagnosis						
No	449	82.2	57,701	86.9	58,150	86.9
Yes	97	17.8	8,673	13.1	8,770	13.1
Smoking status						
Never smoker	220	40.3	31,708	47.8	31,928	47.7
Current smoker	56	10.3	5,415	8.2	5,471	8.2
Former smoker	270	49.5	29,251	44.1	29,521	44.1
NSAID use						
<4 times/week or <4 of past 10 years	413	75.6	47,724	71.9	48,137	71.9
4+ times/week, at least 4 of past 10 years	120	22.0	17,397	26.2	17,517	26.2
Missing	13	2.4	1,253	1.9	1,266	1.9

Table 3

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for colorectal cancer associated with meeting (vs. not meeting) each WCRF/AICR recommendation

Recommendation	Age-adjusted HR (95% CI)	Covariate-adjusted [†] HR (95% CI)	Fully-adjusted [‡] HR (95% CI)	<i>P</i> _{interaction} By sex [*]
Body fatness				
Cohort	0.80 (0.67, 0.97)	0.84 (0.70, 1.01)	0.85 (0.70, 1.03)	0.023
Women	0.64 (0.49, 0.85)	0.68 (0.52, 0.90)	0.70 (0.53, 0.92)	
Men	0.99 (0.77, 1.28)	1.02 (0.79, 1.32)	1.03 (0.79, 1.33)	
Physical activity				
Cohort	0.78 (0.62, 0.98)	0.88 (0.70, 1.11)	0.90 (0.71, 1.14)	0.91
Women	0.82 (0.58, 1.16)	0.89 (0.63, 1.27)	0.98 (0.69, 1.39)	
Men	0.75 (0.55, 1.01)	0.86 (0.63, 1.18)	0.85 (0.62, 1.17)	
Energy density				
Cohort	0.94 (0.72, 1.24)	0.99 (0.75, 1.31)	1.02 (0.77, 1.35)	0.41
Women	0.86 (0.60, 1.24)	0.91 (0.63, 1.32)	0.95 (0.65, 1.38)	
Men	1.06 (0.70, 1.61)	1.12 (0.74, 1.72)	1.12 (0.72, 1.73)	
Plant foods				
Cohort	0.89 (0.67, 1.17)	1.03 (0.77, 1.37)	1.10 (0.82, 1.48)	0.16
Women	0.77 (0.53, 1.12)	0.86 (0.58, 1.28)	0.92 (0.61, 1.38)	
Men	1.06 (0.71, 1.59)	1.29 (0.85, 1.96)	1.40 (0.91, 2.15)	
Red meat				
Cohort	0.78 (0.65, 0.95)	0.79 (0.65, 0.97)	0.81 (0.66, 0.99)	0.93
Women	0.78 (0.61, 1.00)	0.79 (0.60, 1.03)	0.83 (0.63, 1.09)	
Men	0.79 (0.59, 1.07)	0.80 (0.58, 1.09)	0.78 (0.57, 1.08)	
Alcohol				
Cohort	0.73 (0.59, 0.90)	0.70 (0.57, 0.87)	0.69 (0.56, 0.86)	0.032
Women	1.01 (0.70, 1.45)	1.00 (0.69, 1.44)	0.96 (0.66, 1.39)	
Men	0.59 (0.45, 0.77)	0.56 (0.43, 0.74)	0.56 (0.42, 0.73)	

Age is used as the timeline in the Cox proportional hazards models. Models of the full cohort included 66,920 participants and 546 incident colorectal cancers. Sex-specific models included 34,105 women and 250 incident colorectal cancers, and 32,815 men and 296 incident colorectal cancers, respectively.

[†]Adjusted for age (as the timeline in the Cox model), education, race/ethnicity, receipt of colonoscopy or sigmoidoscopy in 10 years before baseline, family history of colon or rectal cancer, NSAID use, history of cancer other than colorectal cancer, and total energy intake (kcal/day). Models among the whole cohort also adjusted for sex.

[‡]Adjusted for the factors in the covariate-adjusted model, as well as for whether respondents met each of the other recommendations.

^{*}*P*_{interaction} from fully-adjusted models

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for colorectal cancer associated with number of WCRF/AICR recommendations met at baseline

Table 4

Recommendations met	VITAL cohort N = 66,920		Colorectal cancer cases N = 546		Age- and sex-adjusted	Covariate-adjusted [‡]
	N (%)	N (%)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
None	3,474 (5.2)	47 (8.6)	1.00	1.00	1.00	
1	23,392 (35.0)	207 (37.9)	0.67 (0.49–0.92)	0.66 (0.48–0.90)		
2	21,236 (31.7)	160 (29.3)	0.55 (0.40–0.76)	0.55 (0.40–0.77)		
3	12,399 (18.5)	99 (18.1)	0.58 (0.41–0.83)	0.61 (0.43–0.88)		
4–6	6,419 (9.6)	33 (6.0)	0.37 (0.24–0.58)	0.42 (0.26–0.66)		
Per recommendation			0.84 (0.78–0.91)	0.87 (0.80–0.95)		
<i>P</i> _{trend} [‡]			<0.001	<0.001		0.001

Age is used as the timeline in the Cox proportional hazards models. All models included 66,920 observations and 546 incident colorectal cancers.

[‡]Adjusted for age (as the timeline in the Cox model), sex, education, race/ethnicity, receipt of colonoscopy or sigmoidoscopy in 10 years before baseline, family history of colon or rectal cancer, NSAID use, history of cancer other than colorectal cancer, and total energy intake (kcal/day).

[†]HRs, 95% CIs and *P* values were calculated using a two-sided test for linear trend modeling categories as a continuous variable (0–6).

Table 5

Sex-specific hazard ratios and 95% confidence intervals for colorectal cancer associated with subsets of WCRF/AICR cancer prevention recommendations met at baseline after sequentially eliminating the recommendation least associated with a reduction in colorectal cancer risk

WOMEN Recs included:	All recommendations			Alcohol, energy density, plant foods, meat, body fatness (Removed PA)			Energy density, plant foods, meat, body fatness (Removed alcohol)			Plant foods, meat, body fatness (Removed energy density)			Meat, body fatness (Removed plant foods)					
	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	
None	12	1.00	None	12	1.00	None	82	1.00	None	89	1.00	None	104	1.00	None	104	1.00	
1	77	0.74 (0.40, 1.37)	1	85	0.83 (0.45–1.52)	1	103	0.93 (0.69–1.25)	1	112	0.94 (0.71–1.26)	1	110	0.88 (0.66–1.16)	1	110	0.88 (0.66–1.16)	
2	84	0.63 (0.34, 1.17)	2	94	0.75 (0.41–1.37)	2	51	0.68 (0.47–0.98)	2	49	0.63 (0.44–0.91)	2	36	0.56 (0.37–0.83)	2	36	0.56 (0.37–0.83)	
3	55	0.61 (0.32, 1.14)	3	46	0.58 (0.31–1.12)	3–4	14	0.55 (0.31–0.99)	3–4									
4–6	22	0.45 (0.22, 0.92)	4–5	13	0.50 (0.23–1.11)													
Per rec.		0.86 (0.76, 0.97)			0.84 (0.74–0.96)			0.82 (0.71–0.95)			0.81 (0.68–0.95)			0.77 (0.64–0.93)			0.77 (0.64–0.93)	
<i>P</i> _{trend} [‡]		0.012			0.011			0.007			0.011			0.006			0.006	

MEN Recs included:	All recommendations			Energy density, body fatness, PA, meat, alcohol (Removed plant foods)			Body fatness, PA, meat, alcohol (Removed energy density)			PA, meat, alcohol (Removed body fatness)			Meat, alcohol (Removed physical activity)				
	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]	Recs met	N Cases	HR (95% CI) [‡]
None	35	1.00	None	36	1.00	None	41	1.00	None	57	1.00	None	63	1.00	None	63	1.00
1	130	0.61 (0.42, 0.89)	1	141	0.64 (0.44–0.93)	1	140	0.56 (0.39–0.79)	1	161	0.50 (0.37–0.68)	1	189	0.55 (0.41–0.74)	1	189	0.55 (0.41–0.74)
2	76	0.50 (0.33, 0.75)	2	70	0.45 (0.30–0.68)	2	77	0.45 (0.30–0.66)	2	78	0.44 (0.31–0.64)	2	44	0.44 (0.29–0.67)	2	44	0.44 (0.29–0.67)
3	44	0.68 (0.43, 1.07)	3	42	0.65 (0.41–1.04)	3–4	38	0.50 (0.31–0.79)	3–4								
4–6	11	0.41 (0.21, 0.82)	4–5	7	0.41 (0.15–0.77)												
Per rec.		0.88 (0.78, 1.00)			0.83 (0.73–0.95)			0.81 (0.70–0.93)			0.71 (0.59–0.85)			0.65 (0.52–0.80)			0.65 (0.52–0.80)
<i>P</i> _{trend} [‡]		0.047			0.008			0.003			<0.001			<0.001			<0.001

Adjusted for age (as the timeline in the Cox model), education, race/ethnicity, receipt of colonoscopy or sigmoidoscopy in 10 years before baseline, family history of colon or rectal cancer, NSAID use, history of cancer other than colorectal cancer, and total energy intake (kcal/day). Models are further controlled for the eliminated recommendations.

[‡]HRs, 95% CIs and *P* values were calculated using a two-sided test for linear trend modeling categories as a continuous variable.

Abbreviations: CI – confidence interval; HR – hazard ratio; PA – physical activity