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Meta-analyses of Colorectal Cancer Risk Factors

Constance M. Johnson¹, Caimiao Wei², Joe E. Ensor², Derek J. Smolenski³, Christopher I. Amos⁴, Bernard Levin⁵, and Donald A. Berry²

¹School of Nursing and Community and Family Medicine, Duke University, 307 Trent Drive, Durham, NC, 27710

²Department of Biostatistics, Division of Quantitative Sciences, The University of Texas MD Anderson Cancer Center, P. O. Box 301402, Houston, TX, 77230

³Research, Outcomes, Surveillance, Evaluations, National Center for Telehealth and Technology, Joint Base Lewis-McChord, WA 98431

⁴Department of Community and Family Medicine, Geisel School of Medicine, Dartmouth College, Lebanon, NH 03766

⁵Professor Emeritus, Division of Cancer Prevention and Population Sciences, The University of Texas MD Anderson Cancer Center, P.O. Box 301439, Houston, TX, 77230

Abstract

Purpose—Demographic, behavioral and environmental factors have been associated with increased risk of colorectal cancer (CRC). We reviewed the published evidence and explored associations between risk factors and CRC incidence.

Methods—We identified 12 established non-screening CRC risk factors and performed a comprehensive review and meta-analyses to quantify each factor's impact on CRC risk. We used random effects models of the logarithms of risks across studies: inverse variance weighted averages for dichotomous factors and generalized least squares for dose-response for multi-level factors.

Results—Significant risk factors include inflammatory bowel disease (RR = 2.93, 95% CI: 1.79–4.81); CRC history in first-degree relative (RR = 1.79, 95% CI: 1.60–2.02); body mass index (BMI) to overall population (RR = 1.10 per 8 kg/m² increase, 95% CI: 1.08–1.12); physical activity (RR = 0.88, 95% CI: 0.86–0.91 for 2 standard deviations increased physical activity score); cigarette smoking (RR = 1.06, 95% CI: 1.03–1.08 for 5 pack-years), and consumption of red meat (RR = 1.13, 95% CI: 1.09–1.16 for 5 servings/week), fruit (RR = 0.85, 95% CI: 0.75–0.96 for 3 servings/day), and vegetables (RR = 0.86, 95% CI: 0.78–0.94 for 5 servings/day).

Conclusions—We developed a comprehensive risk modeling strategy that incorporates multiple effects to predict an individual's risk of developing colorectal cancer. Inflammatory bowel disease

Corresponding author: Donald A. Berry, Department of Biostatistics, Unit 1409, The University of Texas MD Anderson Cancer Center, P O Box 301402, Houston TX 77230-1402, dberry@mdanderson.org, Telephone: 713-794-4141, Fax: 713-563-4243.

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and history of CRC in first-degree relatives are associated with much higher risk of CRC. Increased BMI, red meat intake, cigarette smoking, low physical activity, low vegetable consumption, and low fruit consumption were associated with moderately increased risk of CRC.

Keywords

Colorectal cancer; colon neoplasms; colonic neoplasms and colorectal neoplasms; colorectal risk factors; and colorectal cancer prevention; meta-analysis

INTRODUCTION

Colorectal cancer is the third most common cancer and cause of cancer death in the United States [1]. An estimated 142,820 new cases of colorectal cancer and an estimated 50,830 deaths will be attributable to colorectal cancer in 2013, accounting for 9% of all cancer deaths in the United States [1]. The lifetime risk of CRC for an average American man or woman is approximately 5% [2]. Approaches to reduce CRC incidence and mortality have included primary prevention strategies, such as dietary changes or increasing physical activity, and secondary prevention strategies, such as screening [3–16]. Modifiable factors associated with higher CRC risk include alcohol intake, obesity, smoking, and consumption of processed and red meat. Modifiable factors that have been associated with a decreased risk of colorectal cancer include increased physical activity, postmenopausal hormone therapy, non-steroidal anti-inflammatory drugs, and vegetable and fruit intake. However, studies showing the association of fruit and vegetable intake with decreased risk of colorectal cancer have been inconsistent [17]. Non-modifiable factors showing a positive association include inflammatory bowel disease, a family history of colorectal cancer, and age. Screening strategies beginning at age 50 have been shown to reduce CRC incidence and mortality through the removal of precancerous polyps [18], but screening itself may increase observed cancer rates due to early detection of cancers.

The objectives of this study are to assess and quantify the roles of the published risk factors of CRC in order to develop a CRC risk prediction model for use by the general public and clinicians. In particular, we present a comprehensive meta-analysis of each of the 12 published CRC risk factors as the first step in developing a CRC risk model. However, since the primary goal of this work was to develop a tool to measure risk, we restricted the studies to those that examined CRC incidence as the main outcome and assessed the specific dose-response relationship between multi-level risk factors and risk of CRC. Therefore, many of the studies that evaluated any of the 12 risk factors were not included herein because they lacked these criteria. We explored sex differences and study design differences when that information was available.

MATERIALS AND METHODS

Identification of CRC Risk Factors

To identify risk factors for CRC, we first reviewed the summary of evidence on colorectal cancer prevention from the Physician's Data Query of the National Cancer Institute [17, 18]. Then we conducted a comprehensive review of the literature using MEDLINE (1966–2010)

to identify articles using the following key terms: colon, colonic and colorectal neoplasms, colorectal risk factors, and colorectal cancer prevention. Risk and protective factor inclusion and exclusion were developed and refined over a period of time by experts in gastrointestinal preventive oncology, epidemiology, and biostatistics. The inclusion of a factor was based on the strength of the factor and the availability of at least three categories of dose/exposure and level of associated risk.

The 12 non-screening risk factors we identified are family history of CRC, inflammatory bowel disease, hormone therapy in postmenopausal women, aspirin/nonsteroidal anti-inflammatory drug use, cigarette smoking, body mass index, physical activity, and consumption of processed meat, red meat, fruit, vegetables, and alcohol. We did not include CRC screening; nor did we include supplemental and dietary calcium intake in our analysis because there is inadequate evidence to establish an association between CRC risk reduction and calcium intake, according to the Physician Data Query [18].

Although it is well established that screening with fecal (guaiac) occult blood testing or fecal immunochemical tests, flexible sigmoidoscopy, and colonoscopy reduces the CRC risk, there are no published studies as far as we know that present the relative risk (RR) associated with age at screening and years since screening.

We defined family history of CRC as having one first-degree relative with CRC. We classified inflammatory bowel disease (IBD) as having ulcerative colitis and/or Crohn's disease. Hormone therapy (HT) refers to the use of estrogen or estrogen plus progesterone therapy in women. We examined HT use in three categories, current, former and never, and considered duration in years of use in former and current HT users. We quantified aspirin/non-steroidal anti-inflammatory drug (NSAID) use as duration in years of regular use. We quantified cigarette smoking in pack-years. We quantified body mass index (BMI) as kilograms per meter squared. Different studies reported different types of physical activity (PA) (occupational, leisure, combinations of occupational and leisure, commuting, etc.) and used different units of measure (minutes walking/day, times/week, kilocalories, PA score, metabolic equivalent of task, hours/day, kJ/minute, sedentary/light/moderate/high, etc.). For the studies reporting multiple categories of physical activity measures such as occupational, household, etc., we used the measure reporting the most amount of activity. The number of activity categories within each study ranged from three to six. For all studies included in the analysis of PA, we assigned a PA score to each activity category. We scaled the activities measured in each study, assigning a value of 1 to the lowest activity category and 5 to the highest activity category, with activity categories assumed to be equally spaced. For example, the study of Kune et al. [19] divided activity into four categories. For the purpose of our analysis, the four categories of inactive, not very active, medium, and active/strenuous were numerically coded as 1, 2.33, 3.67, and 5, respectively. Processed meat refers to sausage, deli or sandwich meat, hot dogs, ham, bacon, smoked meats and any type of cured meat. We equated two ounces of processed meat to one serving [20] and quantified processed meat consumption as servings per week. One study reported processed meat as servings/time unit and 4 studies reported processed meat as grams/time unit or grams/kcal. We defined red meat as beef, pork, lamb and veal. We equated four ounces of red meat to one serving [20] and quantified red meat consumption as servings per week. A total of 7

studies reported red meat as servings or portions/time unit and 7 studies reported red meat as grams/time unit or grams/kcal. We included studies that measured servings of fruit consumed per day, and equated 150 grams to one serving [20] for studies that reported fruit intake in grams. We quantified vegetable consumption as servings per day and equated 75 grams to one serving of vegetables [20]. For studies reporting energy adjusted food intakes (intake/1000 kcal/day), we estimated the absolute intake by multiplying energy adjusted intakes by 2 for males, 1.5 for females, and 1.75 for a mixed population [21]. We quantified alcohol consumption as number of drinks per week. When alcohol was reported in grams, we used an average value of 12.0 grams per drink for U.S.-based studies and 9.8 grams per drink for studies based in Europe [22–24].

Study Selection

Our inclusion criteria included English language publications that provided estimates of risk for developing CRC. We included clinical trials, cohort studies, nested case-control studies, and population-based case-control studies that provided the number of cases, the number of controls/non-cases or total number of participants or total person-years, estimates of CRC relative risks, risk ratios, odds ratios, hazard ratios, standardized incidence ratios, or standardized morbidity ratios with 95% confidence intervals (CIs), or sufficient information to estimate these measures. If there were multiple articles from one study population, we used data from the article with the longest follow-up. To be included in our analysis, we required that each risk factor had been evaluated in at least three published studies. For a specific study to be included in the summary analysis for multi-level risk factors, data for each risk factor had to have been categorized with at least 3 levels within the original study. We excluded abstracts and unpublished reports, hospital-based case-control studies (due to the potential for bias) [25, 26], studies with mortality or adenoma as the endpoint, and studies that were not based on a broad population group. We reviewed 463 articles in our literature search and included data from 116 articles [19–21, 27–139]. In Table 1 we categorize the number and type of studies included in this analysis for each risk factor.

Data Extraction

From each publication we extracted the following information: the authors, year of publication, year of study, type of study (cohort, population-based case-control, clinical trial, or nested case-control), risk factor information (serving size, drug amount, etc.), gender, disease site, number of CRC or colon cancer cases, number of controls or non-cases or total sample size or total person-years, how risk was expressed (relative risk, odds ratio, rate ratio, hazard ratio, standardized incidence ratio, or standardized morbidity ratio), and the various risk estimates and their 95% CIs for colorectal cancer or for colon cancer if the risk estimate for colorectal cancer was not provided, and covariates. If multiple risk estimates were reported, we used the estimates that were adjusted for the most covariates. We also extracted separate risk estimates and the 95% CIs for women and men if they were provided.

Statistical Analyses

Using the abstracted risk estimate data, we conducted a meta-analysis for each CRC risk factor by applying a random-effects modeling approach. For the two dichotomous risk factors, family history and IBD, we used the “meta” R-package [140] to combine results

across studies weighted by the inverse variance. We used Cochran's Q test and/or the I^2 statistics [141] to examine heterogeneity among the studies. We first fitted a fixed effects model to the log risk. In the presence of significant heterogeneity ($p < 0.05$), as measured by Cochran's Q test, we then fitted a random-effects model based on the DerSimonian-Laird method [142]. We assessed the variations between gender (female vs. male vs. mixed population), study type (cohort vs. case-control), and site of cancer (colorectal vs. colon) when this information was available. We examined the probability of publication bias or small-study effect using Egger's test [143].

For the other 10 multi-level risk factors, as the all-risk estimates are relative to a reference group within each study, we first centered the exposure levels by the exposure of the referent group within each study (i.e., the referent group of all studies have 0 adjusted exposure) to account for differences in the referent group among studies. We then performed random-effects dose-response meta-regression (pool first) on the natural logarithmic risk estimate to examine a potential nonlinear relation between the exposure and CRC using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution [144]. We chose 3 knots mainly because the total number of observations was fewer than 100 for all the risk factors except for physical activity. For example, we have a total of 75 observations for red meat. When fitted with 3 knots using the default percentiles recommended by Harrell [144], the chi-squared statistic of the goodness of fit was 90; whereas it was 91 when 4 knots were used.

We then computed the trend of log RR estimates using the generalized least-squares regression method proposed by Greenland and Longnecker [145] and Orsini et al [146]. A P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. If there is no significant evidence of nonlinearity ($p > 0.05$), we reduced the model to include only the linear term of the exposure. The pooled relative risks and 95% CI for specific exposure values of the risk factors were estimated based on the final model using the STATA "lincom" command. We assessed the goodness of fit and heterogeneity using Q statistics [146]. In the presence of significant heterogeneity and a lack of goodness of fit, we assessed the variations between gender (female vs. male vs. mixed population), study type (cohort vs. case-control), and site of cancer (colorectal vs. colon) and adjusted for these variables when applicable. All analyses were conducted in with Stata software, version 11 (Stata Corp., College Station, TX, USA).

Prior to combining the multi-level risk factor findings using meta-regression techniques, we adjusted the exposure levels. In particular, when studies categorized risk factors into ranges, which were often inconsistent across studies, we represented each category range with the average value of the risk factor within the range, based on the distribution of the risk factor in the greater U.S. population according to national survey data. We used the National Health Interview Survey (1999 and 2005), National Health and Nutrition Examination Survey (1999–2002, 2001–2002, and 2003–2004), and the Continuing Survey of Food Intakes by Individuals (1994–96, 1998). We used different years and different datasets because all of the variables were not contained within a particular dataset. This allowed us to plot the risk factors in a form that was consistent across studies, and to determine the

appropriate form of the regression model. We combined relative risk, odds ratio, rate ratio, and hazard ratio based on the rare disease assumption.

RESULTS

The contribution of each risk factor to the overall estimation of CRC risk is described in detail below and summarized in Table 2 and Figure 1. Unless otherwise reported, there was no evidence of nonlinearity for the multilevel factors. In Table 3, we provide an example of the relative risk and confidence interval at one level of exposure for each risk factor.

Body Mass Index

We examined the relationship between BMI and the risk of CRC using data from 2309 colon cancer cases and 66199 CRC cases in 23 studies [19, 27–48]. There was no significant evidence of nonlinearity between BMI and CRC risk. Overall there was a significant association between BMI and CRC (RR = 1.10 per 8 kg/m², 95% CI: 1.08–1.12). Gender (male vs. female or mixed population) and cancer site were significant sources of variation. The association between BMI and CRC among males (for CRC, RR = 1.29 per 8 kg/m², 95% CI: 1.26–1.34; for colon cancer, RR = 1.53 per 8 kg/m², 95% CI: 1.32–1.77) was stronger than the association for females or the mixed population (for CRC, RR = 1.15 per 8 kg/m², 95% CI: 0.98–1.34; for colon cancer, RR = 1.27 per 8 kg/m², 95% CI: 1.07–1.51). Study type was not a significant source variation for the association between BMI and CRC risk. There was some evidence of publication bias toward excessively high risk estimates in small studies as determined by Egger's test ($p = 0.02$).

Physical Activity

We examined the relationship between PA and CRC using data from 5994 colon cancer cases and 5099 CRC cases in 21 studies [19, 32, 35, 46–63]. Without adjusting for any covariates, there was a significant negative correlation between CRC risk and PA (RR = 0.88 per 2 standard score, 95% CI: 0.86–0.91). There was significant heterogeneity ($Q=146$, $p<0.0001$). The heterogeneity was attributable to variations in study type (cohort vs. case-control), cancer site (colon vs. CRC), and gender (female vs. male or mixed population) when these covariates were examined one at a time. There was no significant lack of goodness of fit after we stratified the analyses by cancer site and study type. For cohort studies, the relative risk of CRC was 0.91 (95% CI: 0.88–0.96) and 0.84 (95% CI: 0.77–0.91) for an increase of 2 in the standardized PA score (Table 3 and Figure 1B). For case-control studies of colon cancer, an increase of 2 in the standardized PA score was associated with a relative risk of 0.73 (95% CI: 0.68–0.79). For case-control studies of CRC, the association between CRC risk and PA was not statistically significant ($p = 0.43$).

Tobacco (Cigarette Smoking)

We analyzed data from 1966 colon cancer cases and 7433 CRC cases in 15 studies [31, 38, 45, 47, 64–74] to examine the association between tobacco use and CRC. There was some evidence of nonlinearity between smoking and CRC ($p = 0.002$). Compared to non-smokers, the relative risks of CRC/colon cancer were 1.06 (95% CI: 1.03–1.08) for 5 pack-years, 1.11 (95% CI: 1.07–1.16) for 10 pack-years, 1.21 (95% CI: 1.13–1.29) for 20 pack-years, and

1.26 (95% CI: 1.17–1.36) for 30 pack-years (Table 3 and Figure 1C). There was no significant heterogeneity ($p = 0.20$).

Alcohol

We included data from 2469 colon cancer cases and 9717 CRC cases in 22 studies [31, 32, 34, 47, 68, 72, 75–90] to examine the role of alcohol in the development of CRC. Neither gender nor site of cancer was a significant source of variation. The overall linear trend between alcohol consumption and CRC was not significant ($RR = 1.06$ per 5 drinks/week, 95% CI: 0.91–1.23) and ($RR = 1.26$ per 20 drinks/week, 95% CI: 0.68–2.32) (Figure 1D). Egger's test ($p = 0.90$) suggested no evidence of a small-study effect or publication bias.

Family History

We studied the association between a history of CRC in first-degree relatives and CRC risk based on 8091 cases of CRC in 16 studies [30, 45–47, 63, 91–101] that included family history data. Six articles reported risk estimates for females only, and the other 10 articles reported risk estimates for a mixed population. We identified significant heterogeneity ($p = 0.001$). The overall random-effects inverse variance weighted average of the risk of CRC was higher for individuals with a family history of CRC compared to those with no family history of CRC ($RR = 1.80$, 95% CI: 1.61–2.02). The results are plotted in Figure 1E. The relative risk of CRC among the studies evaluating a male-female mixed population (1.90, 95% CI: 1.67–2.17) was slightly higher than the relative risk among the studies that evaluated only females (1.60, 95% CI: 1.33–1.92). However, the difference between the two groups was not significant ($p = 0.13$). The differences between the cohort studies and case-control studies were not significant ($p = 0.38$). Egger's test ($p = 0.14$) suggested no evidence of a small-study effect or publication bias.

Inflammatory Bowel Disease

We examined the association between IBD and CRC risk using data from 44799 patients with IBD and findings of 582 CRC cases and 14 colon cancer cases in 13 cohort studies [102–114], 11 of which reported risk estimates for the male-female mixed population. Significant heterogeneity ($p < 0.0001$) was identified. The overall random-effects, inverse-variance, weighted-average of the relative risk of CRC due to IBD was 2.93 (95% CI: 1.79–4.81). Estimates of the relative risks are plotted in Figure 1F. Egger's test ($p = 0.09$) suggested no significant evidence of a small-study effect or publication bias.

Postmenopausal Hormone Therapy

To examine the association between duration of HT use and CRC, we calculated RR separately for women who were former HT users versus those who had never used HT, and for women who were current HT users versus those who had never used HT. We studied 765 colon cancer cases and 1441 CRC cases among current HT users and never users, as reported in 7 studies [34, 115–120]. The random-effects model suggested significant heterogeneity ($p = 0.04$) and nonlinearity ($p < 0.001$) between current HT use and CRC. Compared to no HT use, the relative risks of CRC were 0.89 (95% CI: 0.73–1.09) for 1 year,

0.80 (95% CI: 0.54–1.17) for 2 years, 0.65 (95% CI: 0.26–1.68) for 5 years, and 0.61 (95% CI: 0.10–3.96) for 10 years of HT use (Figure 1G).

The data included 705 colon cancer cases and 1489 CRC cases among former HT users and never users, as reported in the same 7 studies cited for data on current HT use [34, 115–120]. The linear trend between former HT use and CRC was not statistically significant. The relative risk was 0.96 (95% CI: 0.91–1.02) for 5 years, and 0.84 (95% CI: 0.70–1.02) for 10 years of HT use (Figure 1H). Egger's test ($p = 0.45$) suggested no evidence of a small-study effect or publication bias.

Aspirin/Non-steroidal Anti-inflammatory Drugs

We based our examination of the association between aspirin/NSAID use and the risk of developing CRC on 1967 colon cancer cases and 6684 CRC cases from 10 studies [30, 34, 45, 63, 81, 121–125]. Overall, the relative risk of CRC with 5 years of aspirin/NSAID use compared to no use was 0.76 (95% CI: 0.50–1.15). The correlation between CRC risk and aspirin/NSAID use was not statistically significant. The type of study was a significant source of variation. There was significant nonlinearity between aspirin/NSAIDs use and CRC. A restricted cubic spline model adjusted for the type of study suggested no lack of goodness of fit (Table 2). Compared to never users of aspirin/NSAIDs, the relative risk of CRC with 5 years of aspirin/NSAID use for case-control studies was 0.60 (95% CI: 0.45–0.80) and the relative risk of CRC with 5 years of aspirin/NSAID use for cohort studies was 0.83 (95% CI: 0.56–1.25) (see Table 3 and Figure 1G).

Processed Meat

We used data from 1197 colon cancer cases and 6766 CRC cases in 5 studies [21, 73, 126–128] to examine the association between processed meat consumption and CRC. The linear trend between processed consumption and CRC was not statistically significant ($p = 0.28$) (Table 2). The relative risk for 5 servings per week was 1.09 (95% CI: 0.93–1.25) (see Figure 1J and Table 3). The test of goodness of fit for the linear fit was not significant ($p = 0.26$). Egger's test ($p = 0.10$) suggested no evidence of a small-study effect or publication bias (Table 2).

Red Meat

To assess the association between red meat consumption and CRC we evaluated 2599 colon cancer cases and 10907 CRC cases from 14 studies [21, 32, 48, 73, 126–135]. There was an overall significant positive correlation between CRC and red meat consumption ($RR=1.13$ per 5 servings/wk, 95% CI: 1.09–1.16). The cancer site was a significant source of variation, which showed that there was a significant linear dose-response relationship between the risk of colon cancer and red meat consumption ($p=0.006$). Compared to very little red meat consumption, the relative risk for colorectal cancer was 1.12 (95% CI: 0.97–1.30) for consuming 5 servings per week, which was not significant ($p = 0.12$). However, the relative risk for colon cancer was 1.10 (95% CI: 1.03–1.17) for consuming 5 servings per week, which was statistically significant ($p = 0.006$). (Tables 2–3 and Figure 1K). The test of goodness of fit for the linear fit was not significant ($p=0.19$). Egger's test ($p = 0.97$) suggested no evidence of a small-study effect or publication bias.

Fruit

To assess the relationship between fruit consumption and CRC, we used data from 2006 colon cancer cases and 3504 CRC cases in 9 studies [20, 85, 129, 130, 132, 134, 136–138]. There was some evidence of a nonlinearity ($p=0.02$) association between fruit consumption and CRC. Compared to very little fruit consumption, the relative risks of CRC were 0.91 (95% CI: 0.85–0.96) for 1 serving per day, 0.85 (95% CI: 0.78–0.94) for 2 servings per day, and 0.84 (95% CI: 0.75–0.96) for 3 servings per day (Figure 1L). The test of lack of goodness of fit for the linear fit was not significant ($p=0.40$).

Vegetables

To assess the association between vegetable consumption and risk of developing CRC in our meta-analysis, we used data from 2910 colon cancer cases and 3275 CRC cases in 8 studies [20, 129, 130, 134, 136–139]. The random-effects meta-regression model with only a linear trend revealed a significant inverse association between vegetable consumption and CRC (RR = 0.94 per 2 servings/day, 95% CI: 0.91–0.98) and (RR = 0.86 per 5 servings/day, 95% CI: 0.78–0.94) (see Figure 1M). Egger's test suggested some evidence of a small-study effect or publication bias ($p=0.007$). The test of goodness of fit for the linear fit was not significant ($p=0.43$).

DISCUSSION

Evidence from the published literature suggests an association between the risk of developing colorectal cancer and being overweight or obese, drinking excessive alcohol, having a family history of colorectal cancer, having inflammatory bowel disease, smoking tobacco, and consuming processed and red meat. Conversely, there are several factors associated with a decreased risk of colorectal cancer: physical activity, hormone therapy in postmenopausal women, aspirin/NSAID use, fruit consumption, and vegetable consumption. Our meta-analysis showed mixed results with regard to these published factors. We found the following risk factors to be significantly associated with colorectal or colon cancer risk: BMI, smoking cigarettes, red meat consumption, family history of CRC, and IBD. Although we found an increase in CRC risk associated with alcohol and processed meat, these were not found to be statistically significant. Most studies have shown a positive association between an increase in BMI and risk of colorectal cancer [27, 28, 31–33, 53, 58, 147, 148]. A few studies have shown a stronger association in men than women [32, 149, 150]. Our random-effects dose-response meta-analysis showed a 29% greater risk of CRC per 8 kg/m² and a 53% greater risk of colon cancer per 8 kg/m² in men, but we did not find this greater risk in women with colorectal cancer. With the exception of the overall combined results for the cancer site, study design and gender, there was no significant heterogeneity for the studies where we examined gender and cancer site separately. Although the mechanism causing these differences between men and women remains poorly understood, the differences in fat proportions between men and women and abdominal adiposity are thought to influence the risk [149, 151].

Although the evidence associating the risk of CRC with tobacco smoking has not been reported consistently in the literature, our meta-analysis showed no significant

heterogeneity. The studies that showed an association also showed a dose- and time-dependent association. In a meta-analysis of prospective cohort studies from 1950 to 2008, Tsoi et al. showed a 20% increased risk of CRC in current smokers as compared to never smokers [152]. Huxley et al. showed a 16% greater risk in current smokers as compared to non-smokers [153], and Liang et al. showed a 50% greater risk for an increase of 60 pack-years [154]. Heterogeneity found within the studies reporting the risk of colorectal cancer associated with smoking may be due to the length of follow-up: studies with longer follow-up showed greater risk than studies with shorter follow-up [153]. Our results showed a nonlinear relationship between smoking and CRC with 11% greater risk for 10 pack-years and 21% greater risk for 20 pack-years as compared to non-smokers. Therefore, our results show a statistically significant association between cigarette smoking and CRC.

Overall we found a significant positive correlation between red meat consumption and CRC ($p < 0.001$), showing a 13% greater risk per 5 servings per week. Yet, there was a lack of goodness of fit showing the cancer site as a significant source of variation. Our results did not show a significant association between colorectal cancer and red meat consumption, but did show significance with colon cancer ($p = 0.006$). There were no gender or study design differences. Potential reasons why there were differences between associations with colon cancer vs. colorectal cancer was that we had data from more colorectal cancer studies than colon cancer studies and there were differences in how the results were reported, e.g., servings or grams or portions/time unit, vs. grams/kcal.

The non-modifiable risk factors of family history of CRC and IBD were both confirmed to have a positive association with CRC, as reported in the literature [155, 156]. Our results ($RR = 1.80$) for the association with a family history of CRC in a first-degree relative are similar but less extreme compared to those of Butterworth et al. (2006), which showed a pooled risk estimate of 2.24 for one first-degree relative diagnosed with colorectal cancer [155]. Our pooled analysis showed no statistically significant differences by gender or study design. For IBD, our results ($RR = 2.93$) are different from those of Eaden et al. ($RR = 3.7$) [156], perhaps because they evaluated only ulcerative colitis in their meta-analysis; whereas we evaluated both ulcerative colitis and Crohn's disease. Modern treatments for IBD greatly decrease the severity of the disease, which may also decrease CRC risk.

For alcohol consumption, our pooled estimate for colorectal cancer risk showed a trend toward a positive association with a relative risk of 1.06 (95% CI: 0.91–1.23) for an increase of 5 drinks/week. Although our results are dose-dependent, the association is not statistically significant. We found no evidence of significant heterogeneity and Egger's test showed no evidence of a small study effect. Although we did not find a statistically significant relationship, our relative risk results are similar to those of other published meta-analyses [157–160]. For example, Fedirko et al. [158] evaluated data from 27 cohort studies and 34 case-control studies, and found estimated RRs of 1.07 (95% CI: 1.04–1.10), 1.38 (95% CI: 1.28–1.50), and 1.82 (95% CI: 1.41–2.35) for the consumption of 10, 50, and 100 g/day of alcohol, respectively. Moskal et al. [159] found a 19% increase in the risk of colorectal cancer associated with an increase of 100 g of alcohol per week ($RR = 1.19$; 95% CI: 1.14–1.27) in a meta-analysis of 14 cohort studies. We further did not find any statistically significant differences by cancer site or study design for alcohol intake and CRC risk.

Based on all the studies, we found an estimated 9% greater risk of CRC for every 5 servings of processed meat consumed per week, however the association was not statistically significant. There was also not a statistically significant linear trend between processed meat and CRC. Although this factor is not statistically significant, there was a trend of some effect on CRC risk. A proposed explanation for not finding a statistically significant result for processed meat may be due to the various ways the consumption of processed meat was measured, e.g., differences in dietary questionnaires used or reporting consumption in terms of servings or grams or portions/time unit, vs. grams/kcal.

Significant factors found to be inversely associated with CRC risk included physical activity, fruit consumption and vegetable consumption. Aspirin/NSAIDs and hormone therapy were not found to be significantly inversely associated with CRC risk but showed a trend of some effect.

In our meta-analysis, we found an overall reduction of risk of 12% ($p<0.001$) for an increase of 2 in the standardized physical activity score. However, there was significant heterogeneity in our overall results. This was due to differences in both study design (cohort vs. case-control) and cancer site (colorectal and colon). Both the cohort studies and case-control studies (colon cancer only) showed statistically significant results ($p<0.001$) with a reduction of risk of 9% and 27%, respectively, for an increase of 2 in the standardized PA scores. This difference was not found with the case-control CRC studies, which showed only a 6% reduction in risk. This may be due to the differences in how the studies report physical activity, e.g., total PA vs. occupational PA or leisure PA.

Consumption of fruit showed a statistically significant ($p=0.02$) decreased CRC risk of 15% for 3 servings or more per day. Additionally, there was no heterogeneity for fruit consumption. The overall results were similar for a statistically significant ($p=0.001$) association with vegetable consumption ($RR = 0.86$ per 5 servings/day). No evidence of a significant association between fruit or vegetable intake and risk of colorectal cancer was shown in a recent meta-analysis conducted by Huxley et al. [153], nor was it shown in the WCRF/AICR Systematic Literature Review [161]. Our restriction to studies that used cancer incidence as the endpoint, rather than mortality, may explain these variations in findings among different meta-analyses.

Our meta-analysis of hormone therapy for current and former users showed an inverse association, but no statistical significance. There was significant heterogeneity for current HT users, but not for former users. For current users, the decrease in risk at 10 years is 39% compared to 16% at 10 years for former users. Clearly, the effect is greater in current HT users than former HT users. In a meta-analysis of postmenopausal hormone therapy, Grodstein et al. showed that the reduction in risk for CRC is limited mainly to current users [162]. Our results show that HT shows a trend of some effect.

Although we showed a trend of inverse association between aspirin/NSAIDs and CRC risk, the association was not statistically significant. A meta-analysis of 52 randomized double-blind placebo controlled trials that evaluated the use of aspirin as chemoprevention for colorectal adenomas found a risk ratio of 0.83 (95% CI: 0.72–0.96) in the aspirin group (at

any dose), as compared to the placebo group [163]. A recent international consensus statement showed a similar relative risk (0.85) with aspirin/NSAIDs. However, because questions yet remain concerning the risk/benefit profile, no recommendations were made regarding the use of aspirin or other NSAIDs [164]. As we have concluded that the restricted cubic spline fit is a good fit, there is no evidence of heterogeneity (i.e. there is no significant difference between NSAIDs and aspirin), yet there is a trend of some effect.

Our study has a few limitations. First, we included case-control studies, which are not considered as reliable as cohort studies. However, we did exclude hospital-based case-control studies, which are considered the least reliable of case-control studies. Second, since we used the incidence of CRC as our endpoint and excluded studies that used mortality as an endpoint, this limited the number of studies included in this analysis. Third, we did not include screening for colorectal cancer as an endpoint because, to our knowledge, there are no studies that present relative risk with age at screening and years since screening. Lastly, since our data relied upon published studies and the studies presented these data at different levels of exposure, we had to deduce comparable units from the published data. For example, with fruit, vegetables, red and processed meat, we had to create a common denominator of serving size after accounting for a standardized serving size. Additionally, since the physical activity data were published with different activity categories, we ranked these by study, making the assumption that the lowest level of activity and the highest level of activity per study were equally spaced. Ranking these results as such may have decreased the accuracy of our results and therefore may not make these results generalizable to the general population. There are, of course, general concerns related to combining studies that differ with regard to design, conduct, participants, interventions, exposures, measures of risk, and other aspects that are unknown. But such heterogeneity is a virtue if the appropriate level of uncertainty is considered in the analysis. Meta-analyses address reproducibility and generalizability of the results. The strength of this study compared to other studies such as Huxley et al. [153] is that we report a dose-response level instead of a categorical response of highest vs. lowest levels.

In summary, we found a statistically significantly higher risk of CRC for both inflammatory bowel disease and history of CRC in a first-degree relative. Statistically significant increases in risk were also associated with higher BMI, tobacco smoking, and red meat intake. Although the relative risks for alcohol and processed meat showed a trend of some effect, no statistical significance was found for these risk factors. Statistically significant decreases in risk were associated with physical activity, and fruit and vegetable consumption. The relative risk for colorectal cancer additionally showed a trend of a positive effect with HT use and aspirin/NSAID use, but no statistical significance was found with these factors.

These results may be useful for counseling patients about modifiable risk factors and for helping to establish health policies. But they must be considered in the context of other possible health risks, including other cancers and cardiovascular disease.

Our analysis of 12 potential CRC risk factors is a first step in building a statistical risk model of CRC. The risk model will allow individuals and their clinicians to estimate the ten-

year and lifetime risks of developing CRC based on population-level cancer incidence and mortality rates, as well as peer-reviewed epidemiologic and clinical data.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *Ca-a Cancer Journal for Clinicians*. 2013; 63:11–30. [PubMed: 23335087]
2. Howlader, N.; Noone, AM.; Krapcho, M., et al. SEER cancer statistics review, 1975–2008. BKE, editor. Rockville, MD: National Cancer Institute; 2011.
3. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst*. 1992; 84:1572–5. [PubMed: 1404450]
4. Sellers TA, Kushi LH, Potter JD, et al. Effect of family history, body fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. *N Engl J Med*. 1992; 326:1323–9. [PubMed: 1565145]
5. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut*. 2002; 50:29–32. [PubMed: 11772963]
6. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996; 348:1467–71. [PubMed: 8942774]
7. Hardcastle JD, Chamberlain JO, Robinson MHE, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996; 348:1472–7. [PubMed: 8942775]
8. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med*. 1993; 328:1365–71. [PubMed: 8474513]
9. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med*. 2000; 343:1603–7. [PubMed: 11096167]
10. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med*. 1993; 329:1977–81. [PubMed: 8247072]
11. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. *Epidemiol Rev*. 1993; 15:499–545. [PubMed: 8174669]
12. Tomeo CA, Colditz GA, Willett WC, et al. Harvard report on cancer prevention. Volume 3: prevention of colon cancer in the United States. *Cancer Causes Control*. 1999; 10:167–80. [PubMed: 10454062]
13. Wilmink ABM. Overview of the epidemiology of colorectal cancer. *Dis Colon Rectum*. 1997; 40:483–93. [PubMed: 9106701]
14. Pinto BM, Eakin E, Maruyama NC. Health behavior changes after a cancer diagnosis: what do we know and where do we go from here? *Ann Behav Med*. 2000; 22:38–52. [PubMed: 10892527]
15. Lieberman DA, Prindiville S, Weiss DG, Willett W, 380 VCSG. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA*. 2003; 290:2959–67. [PubMed: 14665657]
16. Boyle P, Leon ME. Epidemiology of colorectal cancer. *Br Med Bull*. 2002; 64:1–25. [PubMed: 12421722]
17. NCI. Colorectal Cancer Screening (PDQ®). Rockville, MD: National Cancer Institute; <http://www.cancer.gov/cancertopics/pdq/screening/colorectal/HealthProfessional> [Accessed 11 March 2013]
18. NCI. Colorectal Cancer Prevention (PDQ®). Rockville, MD: National Cancer Institute; http://www.cancer.gov/cancertopics/pdq/prevention/colorectal/HealthProfessional/page2#Section_995 [Accessed 15 February 2013]

19. Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. *Nutr Cancer*. 1990; 13:9–17. [PubMed: 2300499]
20. Slattery ML, Sorenson AW, Mahoney AW, French TK, Kritchevsky D, Street JC. Diet and colon cancer - assessment of risk by fiber type and food source. *J Natl Cancer Inst*. 1988; 80:1474–80. [PubMed: 2846855]
21. Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. *Plos Medicine*. 2007; 4:1973–84.
22. Dufour M. What is moderate drinking? Defining “drinks” and drinking levels. *Alcohol Res Health*. 1999; 23:5–14. [PubMed: 10890793]
23. Turner C. How much alcohol is in a ‘standard drink’? An analysis of 125 studies. *Br J Addict*. 1990; 85:1171–5. [PubMed: 2224197]
24. Miller WR, Heather N, Hall W. Calculating standard drink units: international comparisons. *Br J Addict*. 1991; 86:43–7. [PubMed: 2009396]
25. Kopec JA, Esdaile JM. Bias in case-control studies. A review. *J Epidemiol Community Health*. 1990; 44:179–86. [PubMed: 2273353]
26. Hess DR. Retrospective studies and chart reviews. *Respir Care*. 2004; 49:1171–4. [PubMed: 15447798]
27. Gerhardsson de Verdier M, Hagman U, Steineck G, Rieger A, Norell SE. Diet, body mass and colorectal cancer: a case-referent study in Stockholm. *Int J Cancer*. 1990; 46:832–8. [PubMed: 2172171]
28. Lee IM, Paffenbarger RS. Quetelet index and risk of colon cancer in college alumni. *J Natl Cancer Inst*. 1992; 84:1326–31. [PubMed: 1495102]
29. Olsen J, Kronborg O, Lynggaard J, Ewertz M. Dietary risk factors for cancer and adenomas of the large intestine. A case-control study within a screening trial in Denmark. *Eur J Cancer*. 1994; 30A: 53–60. [PubMed: 8142166]
30. Reeves MJ, Newcomb PA, TrenthamDietz A, Storer BE, Remington PL. Nonsteroidal anti-inflammatory drug use and protection against colorectal cancer in women. *Cancer Epidemiology Biomarkers & Prevention*. 1996; 5:955–60.
31. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of colon and rectal cancer among Hawaii Japanese men. *Ann Epidemiol*. 1996; 6:276–82. [PubMed: 8876837]
32. Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol*. 1998; 148:761–74. [PubMed: 9786231]
33. Ford ES. Body mass index and colon cancer in a national sample of adult US men and women. *Am J Epidemiol*. 1999; 150:390–8. [PubMed: 10453815]
34. Rodriguez LAG, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. *Epidemiology*. 2001; 12:88–93. [PubMed: 11138826]
35. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br J Cancer*. 2001; 84:417–22. [PubMed: 11161410]
36. Lin J, Zhang SM, Cook NR, Rexrode KM, Lee IM, Buring JE. Body mass index and risk of colorectal cancer in women (United States). *Cancer Causes Control*. 2004; 15:581–9. [PubMed: 15280637]
37. Engeland A, Tretli S, Austad G, Bjorge T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. *Cancer Causes Control*. 2005; 16:987–96. [PubMed: 16132807]
38. Yeh CC, You SL, Chen CJ, Sung FC. Peanut consumption and reduced risk of colorectal cancer in women: a prospective study in Taiwan. *World J Gastroenterol*. 2006; 12:222–7. [PubMed: 16482621]
39. Hou LF, Ji BT, Blair A, et al. Body mass index and colon cancer risk in Chinese people: menopause as an effect modifier. *Eur J Cancer*. 2006; 42:84–90. [PubMed: 16321519]
40. Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: nested case-control study. *Gastroenterology*. 2007; 133:393–402. [PubMed: 17681160]

41. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *Br Med J*. 2007; 335:1134–9. [PubMed: 17986716]
42. Hoffmeister M, Raum E, Winter J, Chang-Claude J, Brenner H. Hormone replacement therapy, body mass, and the risk of colorectal cancer among postmenopausal women from Germany. *Br J Cancer*. 2007; 97:1486–92. [PubMed: 17987040]
43. Adams KF, Leltzmann MF, Albanes D, et al. Body mass and colorectal cancer risk in the NIH-AARP cohort. *Am J Epidemiol*. 2007; 166:36–45. [PubMed: 17449892]
44. Wang Y, Jacobs EJ, Patel AV, et al. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer Causes Control*. 2008; 19:783–92. [PubMed: 18322811]
45. Shadman M, Newcomb PA, Hampton JM, Wernli K, Trentham-Dietz A. Non-steroidal anti-inflammatory drugs and statins in relation to colorectal cancer risk. *World J Gastroenterol*. 2009; 15:2336–9. [PubMed: 19452574]
46. Lee SA, Shu XO, Yang G, Li HL, Gao YT, Zheng W. Animal origin foods and colorectal cancer risk: A report from the Shanghai Women's Health Study. *Nutr Cancer*. 2009; 61:194–205. [PubMed: 19235035]
47. Hoffmeister M, Raum E, Krtischil A, Chang-Claude J, Brenner H. No evidence for variation in colorectal cancer risk associated with different types of postmenopausal hormone therapy. *Clin Pharmacol Ther*. 2009; 86:416–24. [PubMed: 19606090]
48. Campbell PT, Jacobs ET, Ulrich CM, et al. Case-control study of overweight, obesity, and colorectal cancer risk, overall and by tumor microsatellite instability status. *J Natl Cancer Inst*. 2010; 102:391–400. [PubMed: 20208017]
49. Severson RK, Nomura AMY, Grove JS, Stemmermann GN. A prospective analysis of physical activity and cancer. *Am J Epidemiol*. 1989; 130:522–9. [PubMed: 2763997]
50. Slattery ML, Abd-Elghany N, Kerber R, Schumacher MC. Physical activity and colon cancer: a comparison of various indicators of physical activity to evaluate the association. *Epidemiology*. 1990; 1:481–5. [PubMed: 2090287]
51. Ballard-Barbash R, Schatzkin A, Albanes D, et al. Physical activity and risk of large bowel cancer in the Framingham Study. *Cancer Res*. 1990; 50:3610–3. [PubMed: 2340509]
52. Lee IM, Paffenbarger RS, Hsieh CC. Physical activity and risk of developing colorectal cancer among college alumni. *J Natl Cancer Inst*. 1991; 83:1324–9. [PubMed: 1886158]
53. Bostick RM, Potter JD, Kushi LH, et al. Sugar, meat, and fat intake, and nondietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control*. 1994; 5:38–52. [PubMed: 8123778]
54. White E, Jacobs EJ, Daling JR. Physical activity in relation to colon cancer in middle-aged men and women. *Am J Epidemiol*. 1996; 144:42–50. [PubMed: 8659484]
55. Lee IM, Manson JE, Ajani U, Paffenbarger RS, Hennekens CH, Buring JE. Physical activity and risk of colon cancer: the Physicians' Health Study (United States). *Cancer Causes Control*. 1997; 8:568–74. [PubMed: 9242472]
56. Slattery ML, Edwards SL, Boucher KM, Anderson K, Caan BJ. Lifestyle and colon cancer: an assessment of factors associated with risk. *Am J Epidemiol*. 1999; 150:869–77. [PubMed: 10522658]
57. Boutron-Ruault MC, Senesse P, Meance S, Belghiti C, Faivre J. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. *Nutr Cancer*. 2001; 39:50–7. [PubMed: 11588902]
58. Wei EK, Giovannucci E, Wu K, et al. Comparison of risk factors for colon and rectal cancer. *Int J Cancer*. 2004; 108:433–42. [PubMed: 14648711]
59. Hou L, Ji BT, Blair A, Dai Q, Gao YT, Chow WH. Commuting physical activity and risk of colon cancer in Shanghai, China. *Am J Epidemiol*. 2004; 160:860–7. [PubMed: 15496538]
60. Chao A, Connell CJ, Jacobs EJ, et al. Amount, type, and timing of recreational physical activity in relation to colon and rectal cancer in older adults: the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:2187–95. [PubMed: 15598779]

61. Takahashi H, Kuriyama S, Tsubono Y, et al. Time spent walking and risk of colorectal cancer in Japan: the Miyagi Cohort Study. *Eur J Cancer Prev.* 2007; 16:403–8. [PubMed: 17923810]
62. Lee KJ, Inoue M, Otani T, et al. Physical activity and risk of colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective study. *Cancer Causes Control.* 2007; 18:199–209. [PubMed: 17206529]
63. Hoffmeister M, Brenner H, Chang-Claude J. Individual and joint use of statins and low-dose aspirin and risk of colorectal cancer: a population-based case-control study. *Int J Cancer.* 2007; 121:1325–30. [PubMed: 17487832]
64. Giovannucci E, Rimm EB, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in US men. *J Natl Cancer Inst.* 1994; 86:183–91. [PubMed: 8283490]
65. Baron JA, Gerhardsson de Verdier M, Ekblom A. Coffee, tea, tobacco, and cancer of the large bowel. *Cancer Epidemiol Biomarkers Prev.* 1994; 3:565–70. [PubMed: 7827586]
66. Sturmer T, Glynn RJ, Lee IM, Christen WG, Hennekens CH. Lifetime cigarette smoking and colorectal cancer incidence in the Physicians' Health Study I. *J Natl Cancer Inst.* 2000; 92:1178–81. [PubMed: 10904092]
67. Chiu BCH, Lynch CF, Cerhan JR, Cantor KP. Cigarette smoking and risk of bladder, pancreas, kidney, and colorectal cancers in Iowa. *Ann Epidemiol.* 2001; 11:28–37. [PubMed: 11164117]
68. Otani T, Iwasaki M, Yamamoto S, et al. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. *Cancer Epidemiol Biomarkers Prev.* 2003; 12:1492–500. [PubMed: 14693743]
69. Slattery ML, Samowitz W, Ma K, et al. CYP1A1, cigarette smoking, and colon and rectal cancer. *Am J Epidemiol.* 2004; 160:842–52. [PubMed: 15496536]
70. Lilla C, Verla-Tebit E, Risch A, et al. Effect of NAT1 and NAT2 genetic polymorphisms on colorectal cancer risk associated with exposure to tobacco smoke and meat consumption. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:99–107. [PubMed: 16434594]
71. Weijenberg MP, Aardening PW, de Kok TM, de Goeij AF, van den Brandt PA. Cigarette smoking and KRAS oncogene mutations in sporadic colorectal cancer: results from the Netherlands Cohort Study. *Mutat Res.* 2008; 652:54–64. [PubMed: 18296105]
72. Poynter JN, Haile RW, Siegmund KD, et al. Associations between smoking, alcohol consumption, and colorectal cancer, overall and by tumor microsatellite instability status. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:2745–50. [PubMed: 19755657]
73. Nothlings U, Yamamoto JF, Wilkens LR, et al. Meat and heterocyclic amine intake, smoking, NAT1 and NAT2 polymorphisms, and colorectal cancer risk in the Multiethnic Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:2098–106. [PubMed: 19549810]
74. Gram IT, Braaten T, Lund E, Le Marchand L, Weiderpass E. Cigarette smoking and risk of colorectal cancer among Norwegian women. *Cancer Causes Control.* 2009; 20:895–903. [PubMed: 19274482]
75. Klatsky AL, Armstrong MA, Friedman GD, Hiatt RA. The relations of alcoholic beverage use to colon and rectal cancer. *Am J Epidemiol.* 1988; 128:1007–15. [PubMed: 3189277]
76. Slattery M, West D, Robison L, et al. Tobacco, alcohol, coffee, and caffeine as risk factors for colon cancer in a low-risk population. *Epidemiology.* 1990; 1:141–5. [PubMed: 2073501]
77. Newcomb PA, Storer BE, Marcus PM. Cancer of the large bowel in women in relation to alcohol consumption: a case-control study in Wisconsin (United States). *Cancer Causes Control.* 1993; 4:405–11. [PubMed: 8218871]
78. Gerhardsson de Verdier M, Romelsjö A, Lundberg M. Alcohol and cancer of the colon and rectum. *Eur J Cancer Prev.* 1993; 2:401–8. [PubMed: 8401175]
79. Goldbohm RA, van den Brandt PA, Van't Veer P, Dorant E, Sturmans F, Hermus RJ. Prospective study on alcohol consumption and the risk of cancer of the colon and rectum in the Netherlands. *Cancer Causes Control.* 1994; 5:95–104. [PubMed: 8167268]
80. Gapstur SM, Potter JD, Folsom AR. Alcohol consumption and colon and rectal cancer in postmenopausal women. *Int J Epidemiol.* 1994; 23:50–7. [PubMed: 8194924]

81. Rosenberg L, Louik C, Shapiro S. Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. *Cancer*. 1998; 82:2326–33. [PubMed: 9635524]
82. Chen J, Ma J, Stampfer MJ, Hines LM, Selhub J, Hunter DJ. Alcohol dehydrogenase 3 genotype is not predictive for risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:1303–4. [PubMed: 11751450]
83. Flood A, Caprario L, Chatterjee N, Lacey JV, Schairer C, Schatzkin A. Folate, methionine, alcohol, and colorectal cancer in a prospective study of women in the United States. *Cancer Causes Control*. 2002; 13:551–61. [PubMed: 12195645]
84. Pedersen A, Johansen C, Grønbaek M. Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study. *Gut*. 2003; 52:861–7. [PubMed: 12740343]
85. Sanjoaquin MA, Appleby PN, Thorogood M, Mann JI, Key TJ. Nutrition, lifestyle and colorectal cancer incidence: a prospective investigation of 10 998 vegetarians and non-vegetarians in the United Kingdom. *Br J Cancer*. 2004; 90:118–21. [PubMed: 14710217]
86. Wakai K, Kojima M, Tamakoshi K, et al. Alcohol consumption and colorectal cancer risk: findings from the JACC study. *J Epidemiol*. 2005; 15:S173–9. [PubMed: 16127230]
87. Tsong WH, Koh WP, Yuan JM, Wang R, Sun CL, Yu MC. Cigarettes and alcohol in relation to colorectal cancer: the Singapore Chinese Health Study. *Br J Cancer*. 2007; 96:821–7. [PubMed: 17311023]
88. Ferrari P, Jenab M, Norat T, et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2007; 121:2065–72. [PubMed: 17640039]
89. Akhter M, Kuriyama S, Nakaya N, et al. Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: the Miyagi Cohort Study. *Eur J Cancer*. 2007; 43:383–90. [PubMed: 17150353]
90. Toriola AT, Kurl S, Laukanen JA, Mazengo C, Kauhanen J. Alcohol consumption and risk of colorectal cancer: the Findrink study. *Eur J Epidemiol*. 2008; 23:395–401. [PubMed: 18409007]
91. Kune GA, Kune S, Watson LF. The role of heredity in the etiology of large bowel cancer: data from the Melbourne Colorectal Cancer Study. *World J Surg*. 1989; 13:124–31. [PubMed: 2728462]
92. Centonze S, Boeing H, Leoci C, Bonfiglio C, Guerra V, Misciagna G. Familial risk of colo-rectal cancer in a low incidence area in southern Italy. *Eur J Epidemiol*. 1993; 9:26–32. [PubMed: 8472798]
93. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med*. 1994; 331:1669–74. [PubMed: 7969357]
94. Boutron MC, Faivre J, Quipourt V, Senesse P, Michiels C. Family history of colorectal tumours and implications for the adenoma-carcinoma sequence: a case control study. *Gut*. 1995; 37:830–4. [PubMed: 8537056]
95. Le Marchand L, Zhao LP, Quiaoit F, Wilkens LR, Laurence N, Kolonel LN. Family history and risk of colorectal cancer in the multiethnic population of Hawaii. *Am J Epidemiol*. 1996; 144:1122–8. [PubMed: 8956624]
96. Newcomb P, Taylor J, Trentham-Dietz A. Interactions of familial and hormonal risk factors for large bowel cancer in women. *Int J Epidemiol*. 1999; 28:603–8. [PubMed: 10480684]
97. Carstensen B, Soll-Johanning H, Villadsen E, Søndergaard JO, Lynge E. Familial aggregation of colorectal cancer in the general population. *Int J Cancer*. 1996; 68:428–35. [PubMed: 8945611]
98. Slaterry M, Levin T, Ma K, Goldgar D, Holubkov R, Edwards S. Family history and colorectal cancer: predictors of risk. *Cancer Causes Control*. 2003; 14:879–87. [PubMed: 14682445]
99. Hemminki K, Chen B. Familial risks for colorectal cancer show evidence on recessive inheritance. *Int J Cancer*. 2005; 115:835–8. [PubMed: 15704173]
100. Boardman LA, Morlan BW, Rabe KG, et al. Colorectal cancer risks in relatives of young-onset cases: is risk the same across all first-degree relatives? *Clin Gastroenterol Hepatol*. 2007; 5:1195–8. [PubMed: 17702662]

101. Rennert G, Rennert HS, Pinchev M, Lavie O, Gruber SB. Use of hormone replacement therapy and the risk of colorectal cancer. *J Clin Oncol*. 2009; 27:4542–7. [PubMed: 19704062]
102. Greenstein AJ, Sachar DB, Smith H, Janowitz HD, Aufses AHJ. A comparison of cancer risk in Crohn's disease and ulcerative colitis. *Cancer*. 1981; 48:2742–5. [PubMed: 7306930]
103. Mellemkjaer L, Olsen JH, Frisch M, Johansen C, Gridley G, McLaughlin JK. Cancer in patients with ulcerative colitis. *Int J Cancer*. 1995; 60:330–3. [PubMed: 7829239]
104. Gyde SN, Prior P, Allan RN, et al. Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. *Gut*. 1988; 29:206–17. [PubMed: 3345932]
105. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology*. 1992; 103:1444–51. [PubMed: 1358741]
106. Gillen D, Andrews HA, Prior P, Allan RN. Crohn's disease and colorectal cancer. *Gut*. 1994; 35:651–5. [PubMed: 8200559]
107. Stewénus J, Adnerhill I, Anderson H, et al. Incidence of colorectal cancer and all cause mortality in non-selected patients with ulcerative colitis and indeterminate colitis in Malmo, Sweden. *Int J Colorectal Dis*. 1995; 10:117–22. [PubMed: 7636371]
108. Persson PG, Karlén P, Bernell O, et al. Crohn's disease and cancer: a population-based cohort study. *Gastroenterology*. 1994; 107:1675–9. [PubMed: 7958678]
109. Karlén P, Löfberg R, Broström O, Leijonmarck CE, Hellers G, Persson PG. Increased risk of cancer in ulcerative colitis: a population-based cohort study. *Am J Gastroenterol*. 1999; 94:1047–52. [PubMed: 10201481]
110. Askling J, Dickman PW, Karlén P, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. *Gastroenterology*. 2001; 120:1356–62. [PubMed: 11313305]
111. Kvist N, Jacobsen O, Kvist HK, et al. Malignancy in ulcerative colitis. *Scand J Gastroenterol*. 1989; 24:497–506. [PubMed: 2781242]
112. Ekblom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. a population-based study. *N Engl J Med*. 1990; 323:1228–33. [PubMed: 2215606]
113. Ekblom A, Helmick C, Zack M, Adami HO. Increased risk of large bowel cancer in Crohn's disease with colonic involvement. *Lancet*. 1990; 336:357–9. [PubMed: 1975343]
114. Söderlund S, Granath F, Broström O, et al. Inflammatory bowel disease confers a lower risk of colorectal cancer to females than to males. *Gastroenterology*. 2010; 138:1697–703. [PubMed: 20167217]
115. Troisi R, Schairer C, Chow WH, Schatzkin A, Brinton LA, Fraumeni JF. A prospective study of menopausal hormones and risk of colorectal cancer (United States). *Cancer Causes Control*. 1997; 8:130–8. [PubMed: 9134236]
116. Grodstein F, Martinez ME, Platz EA, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med*. 1998; 128:705–12. [PubMed: 9556463]
117. Paganini-Hill A. Estrogen replacement therapy and colorectal cancer risk in elderly women. *Dis Colon Rectum*. 1999; 42:1300–5. [PubMed: 10528768]
118. Jacobs EJ, White E, Weiss NS, Heckbert SR, LaCroix A, Barlow WE. Hormone replacement therapy and colon cancer among members of a health maintenance organization. *Epidemiology*. 1999; 10:445–51. [PubMed: 10401882]
119. Prihartono N, Palmer JR, Louik C, Shapiro S, Rosenberg L. A case-control study of use of postmenopausal female hormone supplements in relation to the risk of large bowel cancer. *Cancer Epidemiol Biomarkers Prev*. 2000; 9:443–7. [PubMed: 10794491]
120. DeLellis Henderson K, Duan L, Sullivan-Halley J, et al. Menopausal hormone therapy use and risk of invasive colon cancer: the California Teachers Study. *Am J Epidemiol*. 2010; 171:415–25. [PubMed: 20067917]
121. Friedman GD, Coates AO, Potter JD, Slattery ML. Drugs and colon cancer. *Pharmacoepidemiol Drug Saf*. 1998; 7:99–106. [PubMed: 15073733]
122. McGreavey LE, Turner F, Smith G, et al. No evidence that polymorphisms in CYP2C8, CYP2C9, UGT1A6, PPAR delta and PPAR gamma act as modifiers of the protective effect of regular NSAID use on the risk of colorectal carcinoma. *Pharmacogenet Genomics*. 2005; 15:713–21. [PubMed: 16141797]

123. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA*. 2005; 294:914–23. [PubMed: 16118381]
124. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J Natl Cancer Inst*. 2007; 99:608–15. [PubMed: 17440162]
125. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. *Gastroenterology*. 2008; 134:21–8. [PubMed: 18005960]
126. Lin J, Zhang SM, Cook NR, Lee IM, Buring JE. Dietary fat and fatty acids and risk of colorectal cancer in women. *Am J Epidemiol*. 2004; 160:1011–22. [PubMed: 15522858]
127. English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, Giles GG. Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:1509–14. [PubMed: 15342453]
128. Chao A, Thun MJ, Connell CJ, et al. Meat consumption and risk of colorectal cancer. *JAMA*. 2005; 293:172–82. [PubMed: 15644544]
129. Kampman E, Verhoeven D, Sloots L, Van't Veer P. Vegetable and animal products as determinants of colon cancer risk in Dutch men and women. *Cancer Causes Control*. 1995; 6:225–34. [PubMed: 7612802]
130. Shannon J, White E, Shattuck AL, Potter JD. Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiology Biomarkers & Prevention*. 1996; 5:495–502.
131. Le Marchand L, Hankin JH, Wilkens LR, et al. Combined effects of well-done red meat, smoking, and rapid N-acetyltransferase 2 and CYP1A2 phenotypes in increasing colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:1259–66. [PubMed: 11751443]
132. Seow A, Quah SR, Nyam D, Straughan PT, Chua T, Aw TC. Food groups and the risk of colorectal carcinoma in an Asian population. *Cancer*. 2002; 95:2390–6. [PubMed: 12436447]
133. Butler LM, Sinha R, Millikan RC, et al. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Am J Epidemiol*. 2003; 157:434–45. [PubMed: 12615608]
134. Turner F, Smith G, Sachse C, et al. Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer. *Int J Cancer*. 2004; 112:259–64. [PubMed: 15352038]
135. Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2008; 17:3098–107. [PubMed: 18990750]
136. Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: the Netherlands Cohort Study on Diet and Cancer. *Am J Epidemiol*. 2000; 152:1081–92. [PubMed: 11117618]
137. McCullough ML, Robertson AS, Chao A, et al. A prospective study of whole grains, fruits, vegetables and colon cancer risk. *Cancer Causes Control*. 2003; 14:959–70. [PubMed: 14750535]
138. van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P, et al. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*. 2009; 89:1441–52. [PubMed: 19339391]
139. Michels KB, Giovannucci E, Joshipura KJ, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst*. 2000; 92:1740–52. [PubMed: 11058617]
140. Schwarzer, G. [Accessed 2010–10–28] meta: Meta-Analysis with R. <http://cran.r-project.org/web/packages/meta/index.html>
141. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21:1539–58. [PubMed: 12111919]
142. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177–88. [PubMed: 3802833]

143. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol*. 2000; 53:1119–29. [PubMed: 11106885]
144. Harrell FE, Lee KL, Pollock BG. Regression-Models in Clinical-Studies - Determining Relationships between Predictors and Response. *J Natl Cancer Inst*. 1988; 80:1198–202. [PubMed: 3047407]
145. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *American Journal of Epidemiology*. 1992; 135:1301–9.
146. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J*. 2006; 6:40–57.
147. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med*. 2003; 348:1625–38. [PubMed: 12711737]
148. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. *J Natl Cancer Inst*. 1997; 89:948–55. [PubMed: 9214674]
149. Giovannucci E. Obesity, gender, and colon cancer. *Gut*. 2002; 51:147. [PubMed: 12117867]
150. Ning Y, Wang L, Giovannucci EL. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. *Obes Rev*. 2010; 11:19–30. [PubMed: 19538439]
151. Heymsfield SB, Gallagher D, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr*. 2000; 72:694–701. [PubMed: 10966886]
152. Tsoi KK, Pau YY, Wu WK, Chan FKL, Griffiths SM, Sung JJ. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol*. 2009; 7:682–8. [PubMed: 19245853]
153. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer*. 2009; 125:171–80. [PubMed: 19350627]
154. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer*. 2009; 124:2406–15. [PubMed: 19142968]
155. Butterworth AS, Higgins JPT, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis. *Eur J Cancer*. 2006; 42:216–27. [PubMed: 16338133]
156. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001; 48:526–35. [PubMed: 11247898]
157. Cho EY, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: A pooled analysis of 8 cohort studies. *Ann Intern Med*. 2004; 140:603–13. [PubMed: 15096331]
158. Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. *Ann Oncol*. 2011; 22:1958–72. [PubMed: 21307158]
159. Moskal A, Norat T, Ferrari P, Riboli E. Alcohol intake and colorectal cancer risk: A dose-response meta-analysis of published cohort studies. *Int J Cancer*. 2007; 120:664–71. [PubMed: 17096321]
160. Longnecker MP, Orza MJ, Adams ME, Vioque J, Chalmers TC. A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. *Cancer Causes Control*. 1990; 1:59–68. [PubMed: 2151680]
161. Norat T.; Chan, D.; Lau, R.; Aune, D.; Vieira, R. The associations between food nutrition and physical activity and the risk of colorectal cancer WCRF/AICR. London, UK: Imperial College; 2010. WCRF/AICR systematic literature review continuous Update Project Report.
162. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med*. 1999; 106:574–82. [PubMed: 10335731]

163. Cole BF, Logan RF, Halabi S, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *J Natl Cancer Inst.* 2009; 101:256–66. [PubMed: 19211452]
164. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol.* 2009; 10:501–7. [PubMed: 19410194]

Figure 1. Colorectal cancer (CRC) relative risk estimates by risk factor

Dose was modeled with both linear and restricted cubic splines random effects meta-regression model. All exposure levels were reference subtracted in model fitting. For the purpose of graphical illustration, 22 kg/m² was used as the reference for BMI, the value of 1 for the standardized PA score was used as the reference for PA, and the lowest value of 0 was used as the reference for all other multi-level risk factors. CC=case-control studies, CRC=colorectal cancer, F=Female, B=mixed genders, M=Male.

A. body mass index (BMI in kg/m²);

B. physical activity (PA);

- C. cigarette smoking;
- D. alcohol;
- E. CRC family history;
- F. inflammatory bowel disease (IBD);
- G. current postmenopausal hormone therapy (HT);
- H. former postmenopausal hormone therapy (HT);
- I. aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs);
- J. processed meat;
- K. red meat;
- L. fruit;
- M. vegetables

Table 1

Summary of study type, disease cases and gender of studies included in the meta-analysis for each risk factor.

Number of studies reporting risk estimate by cancer site												
Study type				Disease cases				Number of studies reporting risk estimate by gender ^b			Number of studies reporting risk estimate by cancer site	
Risk Factors	Total studies ^a	Cohort	Pop. Case-Control	Nested Case-Control	Total	Colon	CRC	Combined	Female	Male	Colon	CRC
BMI	23	12	8	3	68,508	2309	66199	4	17	13	7	16
Physical activity	21	12	9	0	11,093	5994	5099	3	14	15	12	9
Smoking	15	7	7	1	9,399	1966	7433	6	4	6	3	12
Alcohol	22	15	5	2	12,186	2469	9717	12	6	6	9	13
Family history	16	5	10	1	8091	8091	0	10	6	16	0	16
IBD ^c	13	13	0	0	596	582	14	11	2	2	3	13
HT												
Current use	7	4	2	1	2,206	765	1441	NA	7	NA	3	4
Former use	7	4	2	1	2,194	705	1489	NA	7	NA	3	4
Aspirin/NSAIDs	10	3	6	1	8,651	1967	6684	7	2	1	1	9
Processed meat	5	4	0	1	7,963	1197	6766	3	2	1	1	4
Red meat	14	5	8	1	13,506	2599	10907	9	5	4	5	9
Fruit	9	5	4	0	5510	2006	3504	4	5	5	5	4
Vegetables	8	4	4	0	6,185	2910	3275	4	4	4	4	4

^aSome studies evaluated more than one risk factor

^bSome articles provided risk estimates for both males and females separately.

^cIBD (inflammatory bowel disease) includes Crohn's disease and/or ulcerative colitis

Note: Pop. = population; BMI = body mass index; HT = postmenopausal hormone therapy; NSAIDs = nonsteroidal anti-inflammatory drugs

Table 2

Estimate of linear trend and nonlinear relationship between the multi-level risk factors and CRC.

Risk Factor	Final Model ^a	P-value for coefficients	P-value for goodness of fit	P-value of Egger's test
BMI				0.02
Overall	RR = exp (0.012*BMI)	<0.001	<0.001	
Male, CRC	RR = exp (0.032*BMI)	<0.001	0.78	
Male, colon cancer	RR = exp (0.053*BMI)	<0.001	0.64	
Female or mixed, CRC	RR = exp (0.017*BMI)	0.087	0.08	
Female or mixed, colon cancer	RR = exp (0.030*BMI)	0.01	0.64	
Physical Activity				0.80
Overall	RR = exp (-0.061*PA)	<0.001	<0.001	
Cohort	RR = exp (-0.045*PA)	<0.001	0.20	
CC, CRC	RR = exp (-0.029*PA)	0.43	0.19	
CC, colon cancer	RR = exp (-0.155*PA)	<0.001	0.40	
Smoking	RR = exp(0.011 * pack-yrs - 0.017 * rcs) knots=(0, 14.4, 57.7)	Linear: <0.001 rcs: 0.002	0.20	NA
Alcohol	RR = exp(0.011 × drinks/wk)	0.46	0.09	0.9
HT (Current)^c	RR = exp(-0.120 * yrs + 0.415 * rcs) knots=(0, 1.7, 14.4)	Linear: 0.23 rcs: <0.001	0.04	NA
HT (Former)^c	RR = exp(-0.008 * yrs)	0.20	0.73	0.45
Aspirin/NSAIDs^c				NA
Overall	RR = exp(-0.069 * yrs + 0.146* rcs)	Linear: 0.11 rcs: 0.001	0.012	
Adjusted for type of study	RR = exp(-0.155 * yrs + 0.487* rcs + 0.113 * yrs *I(cohort) - 0.431* yrs*I(cohort)) knots=(0, 2.0, 13.2)	Linear: <0.001 rcs: <0.001 Linear*I(cohort): 0.04 rcs*I(cohort): <0.001	0.22	

Risk Factor	Final Model ^a	P-value for coefficients	P-value for goodness of fit	P-value of Egger's test
Processed Meat	RR = exp(0.017 * serv/wk)	0.28	0.26	0.1
Red Meat				0.97
Overall	RR = exp(0.024 * serv/wk)	<0.001	<0.001	
CRC	RR = exp(0.023 * serv/wk)	0.12	0.19	
Colon cancer	RR = exp(0.018 * serv/wk)	0.006	0.19	
Fruit	RR = exp(-0.104 * serv/d + 0.128 * rcs) knots=(0, 1.08, 3.95)	Linear: 0.003 rcs: 0.02	0.40	NA
Vegetables	RR = exp(-0.030 * serv/d)	0.001	0.43	0.007

^a All exposure levels (dose) in the final model are referent exposure subtracted;
^b

$$rcs = \frac{(dose - knot_1)^3 + \frac{(knot_3 - knot_1)(dose - knot_2)^3 - (knot_2 - knot_1)(dose - knot_3)^3}{knot_3 - knot_2}}{(knot_3 - knot_1)^2}$$

Note:
^c some studies report risk estimate for males and females separately

RR = relative risk; CC = case-control; res = restricted cubic spline; HT = menopausal hormone therapy; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 3

Relative Risks for Each Risk Factor

Risk Factor	Level	RR (95%CI)
BMI	30 vs. 22 kg/m ²	
	Overall	1.10 (1.08–1.12)
	Male, CRC	1.29 (1.26–1.34)
	Male, colon cancer	1.53 (1.32–1.77)
	Female or mixed, CRC	1.15 (0.98–1.34)
	Female or mixed, colon cancer	1.27 (1.07–1.51)
Physical Activity	An increase of 2 in standardized PA score	
	Overall	0.88 (0.86–0.91)
	Cohort studies	0.91 (0.88–0.96)
	CC studies, CRC	0.94 (0.81–1.09)
Smoking	5 vs. 0 pack-years	1.06 (1.03–1.08)
	30 vs. 0 pack-years	1.26 (1.17–1.36)
Alcohol	5 vs. 0 drinks/wk	1.06 (0.91–1.23)
	20 vs. 0 drinks/wk	1.26 (0.68–2.32)
CRC Family History	Yes vs. no	1.80 (1.61–2.02)
IBD	Yes vs. no	2.93 (1.79–4.81)
HT (Current)*	5 vs. 0 year	0.65 (0.26–1.68)
	10 vs. 0 year	0.61 (0.10–3.96)
HT (Former)*	5 vs. 0 year	0.96 (0.91–1.02)
	10 vs. 0 year	0.84 (0.70–1.02)
Aspirin/NSAIDs*	5 vs. 0 year	
	Overall	0.76 (0.50–1.15)
	CC studies	0.60 (0.45–0.80)
	Cohort studies	0.83 (0.56–1.25)
Processed Meat	5 vs. 0 servings/wk	1.09 (0.93–1.25)
Red Meat	5 vs. 0 servings/wk	
	Overall	1.13 (1.09–1.16)
	CRC	1.12 (0.97–1.30)
	Colon	1.10 (1.03–1.17)
Fruit	3 vs. 0 servings/d	0.84 (0.75–0.96)
Vegetables	5 vs. 0 servings/d	0.86 (0.78–0.94)