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Does adherence to the WCRF/AICR cancer prevention guidelines reduce risk of colorectal cancer in the UK Women's Cohort Study?

WCRF/AICR cancer prevention and CRC in UKWCS

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WCRF/AICR guidelines

colonic neoplasms

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1 **Abstract**

2 Evidence on adherence to diet related cancer prevention guidelines and associations with
3 colorectal cancer (CRC) risk is limited and conflicting. The aim of this cohort analysis is to
4 evaluate associations between adherence to the World Cancer Research Fund / American
5 Institute of Cancer Research (WCRF/AICR) 2007 recommendations and incident CRC. The
6 UK Women's Cohort Study comprises over 35,372 women who filled in a food frequency
7 questionnaire at baseline in 1995. They were followed up for CRC incidence for a median of
8 17.4 years, an individual score linking adherence to eight of the WCRF/AICR
9 recommendations was constructed. Cox proportional hazards regression provided hazard
10 ratios (HRs) and 95% confidence intervals (CIs) for the estimation of CRC risk, adjusting for
11 confounders. Following exclusions, 444 CRC cases were identified. In the multivariate
12 adjusted model, women within the second and third (highest) categories of the WRCF/AICR
13 score had HRs (95% CIs) of 0.79 (0.62-1.00) and 0.73 (0.48-1.10) respectively for CRC
14 compared with those in the lowest, reference category. The overall linear trend across the
15 categories was not significant ($p=0.17$). No significant associations were observed between
16 the WCRF/AICR score and proximal colon, distal colon and rectal cancers separately. Of the
17 individual score components, a BMI within the normal weight range was borderline
18 significantly protective only for rectal cancer in the fully adjusted model. In view of the likely
19 different causes of CRC subtypes, further research is needed to identify the optimal dietary
20 patterns associated with reducing colon and rectal cancer risk respectively.

21

22 **Introduction**

23 Colorectal cancer (CRC) is the third most common cancer in men and the second in women,
24 with about 694 000 annual deaths estimated worldwide, accounting for 8.5% of deaths from
25 cancer. With respect to incidence, almost 55% of cases are reported in the more developed
26 countries and occurrence differs 10-fold in both men and women, between countries (1). This
27 wide geographical variation in incidence supports the theory that diet and nutrition may have
28 a role in the aetiology of CRC and are thus considered modifiable risk factors (2).

29

30 Although the role of diet in relation to CRC risk has been widely investigated, the synergistic
31 effect and complex interactions of food components make the analysis of dietary patterns
32 better at capturing disease risk than individual foods or nutrients (3). Furthermore, dietary
33 data combined with data on lifestyle choices represents a more complete picture. Guidelines

34 promoting lifestyles to reduce cancer risk have been issued by both the American Cancer
35 Society (ACS) (4) and the World Cancer Research Fund (WCRF) and the American Institute
36 of Cancer Research (AICR) (5). Both sets of guidelines include recommendations targeting a
37 healthy diet and body weight, low alcohol consumption, if any, and more physical activity for
38 cancer prevention whilst the WCRF/AICR also makes two special recommendations to
39 encourage breastfeeding where possible and for cancer survivors to follow guidelines for
40 cancer prevention (5). Several studies have operationalised a set of these guidelines to
41 explore the association between concordance to the guidelines and reduced risk of chronic
42 diseases, all-cause cancer and mortality (6-8).

43

44 With respect to reduced risk of incidence of cancers of the colon and rectum, studies have
45 mainly explored adherence to ACS guidelines (9-10) or the Dietary Guidelines for Americans
46 (11), and others have looked at incidence of total CRC rather than differentiated between the
47 colon and rectal cancer-sites (12-15). Furthermore, results of the latter studies are conflicting.
48 Further studies operationalising the WCRF/AICR guidelines and looking at the association
49 between CRC, and exploring colon and rectal cancer separately are needed. In fact, the 2017
50 WCRF/AICR Continuous Update Project report stated that due to the limited evidence on this
51 association, no conclusion can be made (16).

52

53 The aim of this study is to assess whether adherence to the WCRF/AICR cancer prevention
54 recommendations released in 2007, related to body fatness, physical activity, nutrition and
55 breastfeeding is associated with reduced incidence of cancer of the colorectum, colon and
56 rectum in a large UK cohort of women with a long follow up period.

57

58 **Methods**

59 **Study design and population**

60 The UK Women's Cohort Study (UKWCS) of 35 372 middle-aged women was formed from
61 participants of a WCRF 1995 direct mail survey, targeted towards women, with the aim of
62 exploring diet and chronic disease associations. Dietary information at baseline was obtained
63 using a postal questionnaire between 1995 and 1998, including a food frequency
64 questionnaire (FFQ) as well as information on lifestyle and health. Participants with varied
65 dietary patterns were chosen for inclusion in the cohort: namely large numbers of vegetarians,
66 fish (non-meat) eaters and meat eaters. This maximization in dietary variation increases the
67 explorative power of the cohort with respect to diet and disease outcomes. The cohort women

68 have a mean (standard deviation, s.d.) age of 52.3 (9.4) years at baseline, are mainly middle-
69 class and 86% have children. They are generally well-educated with 27% having a degree
70 and health conscious with only 8% reporting that they smoke daily and a mean BMI in the
71 normal range. Further details on the cohort profile have been reported in detail elsewhere (17-
72 18).

73

74 **Baseline characteristics and dietary information**

75 Values for age, weight, height and waist circumference were self-reported. Additional
76 information on medical history, smoking habit, supplement use and breastfeeding was also
77 self-described, as was socio-demographic information such as marital status. Participants
78 were asked about the time spent on vigorous activities to collect information on physical
79 activity whilst their socio-economic status was classified based on their occupation. Women
80 were grouped as either (a) professional / managerial; (b) intermediate; (c) routine / manual as
81 defined by the UK National Statistics – Socio-Economic Classification (NS-SEC) (19).
82 Although collected, ethnicity data was not used since over 99% of cohort participants were
83 Caucasian.

84

85 The FFQ sent to participants at baseline was developed from one used by the Oxford arm of
86 the European Prospective Study Investigation into Cancer & Nutrition (EPIC) (20), and
87 adapted to better suit the high proportion of vegetarians in the UKWCS. A total of 217 food
88 items made up the questionnaire; participants were asked to tick one of 10 pre-coded
89 categories, indicating average consumption frequency of the specific item over a 12 month
90 period and ranging from never to 6 portions/day or more. The estimated number of portions
91 were assigned a standard portion weight and the energy intake from macronutrients and
92 alcohol was derived using McCance & Widdowson's The Composition of Foods (5th Edition)
93 (21). In the case of missing data on food consumption, non-response was assumed to imply
94 non-consumption.

95

96 **Ethical approval**

97 Ethical approval was granted at the initiation of the UKWCS in 1995 from 174 individual
98 relevant research ethics committees (REC) and from participants consenting to the
99 confidential use of collected data at baseline, in follow-up stages and from cancer registries
100 for research purposes. The REC reference number is 15/YH/0027.

101

102 **Cancer case definition**

103 The cancer outcomes used in the analyses are incident malignant neoplasms of the colon (as
104 identified by codes 153.0-153.9 or C18) and of the rectosigmoid junction and of the rectum
105 (as identified by codes 154.0-154.1 or C19 and C20) of the International Statistical
106 Classification of Diseases (ICD, 9th and 10th revisions) (22-23). Registrations of cancer
107 diagnosis for women in the UKWCS were made via record linkage of identification codes to
108 the central register of the NHS Digital. This data is available from baseline in 1995 until the
109 01st April 2014 for 98% of the cohort women. Cases were defined as patients who were
110 cancer free, except for non-melanoma skin cancer, at the time of FFQ completion and who
111 developed CRC, as reported through the NHS Digital, a minimum of 12 months after the
112 dietary assessment to ensure the absence of latent disease that may otherwise have influenced
113 the women's dietary habits. In cases where no self-reported data of prior medical history was
114 available (n=2585), women were assumed to be free from disease.

115

116

117 **WCRF/AICR score construction**

118 An adherence score to WCRF/AICR recommendations for cancer prevention was generated
119 from the UKWCS database for each cohort participant. The approach taken in constructing
120 the score was to operationalise eight out of ten WCRF/AICR recommendations, namely body
121 fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal
122 foods, alcoholic drinks, consumption of salty foods and breastfeeding. All recommendations
123 for which data was available were operationalized in an attempt to allow the evaluation of
124 adherence to the dietary pattern formed as a whole, in relation to CRC risk. The
125 recommendation to avoid the use of dietary supplements for cancer protection was explored
126 in sensitivity analyses since data in the cohort related only to whether supplements were
127 taken or not, and no information was available on whether supplements were taken to reduce
128 cancer risk. The recommendation for cancer survivors was not applicable to this population.

129

130 A maximum adherence score of 8 was therefore possible for the UKWCS, with higher values
131 indicating greater concordance with the recommendations. If the recommendation was met,
132 the woman was assigned a score of 1, if not met a 0 was assigned and an intermediate
133 category for partially met, resulting in a score of 0.5 was also created. Each major
134 recommendation contributed equally to the final single score for each participant since
135 WCRF/AICR recommendations were not ranked according to priority. For guidelines with

136 more than one sub recommendation, namely energy density and plant foods, each sub
137 recommendation was scored separately and an average of the allocated scores was derived.
138 Where quantitative criteria were described in the WCRF/AICR recommendations, these were
139 used as cut-offs. This was the case for body fatness, physical activity, energy density,
140 consumption of fruit and vegetables, dietary fibre intake, consumption of animal food,
141 alcohol intake, sodium intake and breastfeeding. With respect to the consumption of sugary
142 drinks, the recommendation is avoidance of drinks with added sugars; for this study subjects
143 were considered non-adherent if they reported consuming more than one sugary drink a day
144 (>250g/day) in the FFQ. Participants with missing data on Body Mass Index (BMI) were
145 dropped from the analysis, those with missing information on physical activity (n=1928) and
146 breastfeeding (n=9533) were assumed to not have undertaken physical activity or breastfed
147 respectively, whilst missing data on food and drinks was assumed to imply non-consumption.
148 Details of the score operationalisation are given in Table I. The WCRF/AICR scores for
149 participants were categorised into three groups, to indicate low, medium and high adherence
150 to the recommendations (i.e. 0 to ≤ 3, >3 to ≤ 5, > 5 to 8).

151

152 **Statistical analysis**

153 Descriptive statistics were used to describe baseline characteristics of participants. Survival
154 analysis was conducted using the Cox proportional hazards regression model to estimate
155 cancer risk in the form of hazard ratios (HRs) and 95% confidence intervals (CI). The
156 relationship between adherence to WCRF/AICR guidelines and colorectal cancer was
157 explored as the primary outcome, whilst some exploratory analysis was carried out on distal
158 and proximal colon cancers and on rectal cancer as secondary outcomes. Probability
159 weighting was used to account for the large proportion of vegetarians and fish eaters in the
160 cohort and to reflect the inverse probability of being sampled, thus increasing the cohort's
161 external validity. The time variable used in the models was time in the study (person years),
162 calculated from the date of questionnaire receipt until either cancer diagnosis, death or censor
163 date (01 April 2014). Assumptions for proportional hazards were tested graphically for all
164 terms in the model.

165

166 The risk of cancer as adherence to the WCRF/AICR score increased was determined by
167 comparing each of the four groups of participants, to the lowest adherence, reference group.
168 Risk estimates were calculated per one-point increment in the continuous WCRF/AICR score
169 and by the score quartiles; linear trend was also calculated. Risk factors for CRC previously

170 identified in the literature were taken into consideration. Potential confounders that were
171 either included in the score derivation, such as BMI and physical activity, or were closely
172 related to a score component, such as energy (kcal) to energy density were excluded from the
173 adjusted analyses, as were those that had considerable missing observations, particularly if a
174 strongly related variable was available. Associations were estimated for CRC, and then for
175 colon, proximal colon, distal colon and rectal cancer separately. Results are presented for an
176 age-adjusted model, and then for a full model adjusting for age (years), smoking status
177 (never, current or former smoker), family history in a first degree relative and socio-
178 economic status (professional/ managerial, intermediate or routine and manual). Sensitivity
179 analyses were carried out operationalising a 9th recommendation relating to supplement use in
180 the WCRF/AICR score (data not shown).

181

182 Stata version 13.0 statistical software was used for all analyses and a 2-sided p-value ≤ 0.05
183 was considered statistically significant.

184

185 **Results**

186 During a mean (s.d.) follow up time of 18.7 (0.8) years, 527 incident CRC cases were
187 documented for women in the UKWCS. From the total cohort (n=35 372), participants who
188 did not provide sufficient data at baseline to allow flagging on NHS Digital (n=695), women
189 self-reporting history of any previous malignant cancer at baseline, except for non-melanoma
190 of the skin (n=2391), women who were diagnosed with CRC within one year of baseline
191 (n=53), women with energy intakes outside the plausible range of 500 to 6000kcal/day
192 (n=79), and women with missing data for BMI (n=1191) were excluded. Following
193 exclusions, a total of 30 963 cohort participants, followed for a median of 17.4 years
194 (IQR=1.7) were eligible for inclusion in the analysis with 444 CRC cases, of which 322 were
195 located in the colon (164 in the proximal colon and 115 cases in the distal colon) and 146
196 cases were of rectal cancer.

197

198 The baseline characteristics of total study participants, women diagnosed with CRC and
199 according to the level of adherence to the WCRF/AICR recommendations are reported in
200 Table II. Women who were in the highest adherence category of the score were likely to be
201 younger and less likely to smoke or eat meat when compared to those in low and medium
202 adherence categories. Lower adherers were less likely to possess a degree qualification or to
203 hold a managerial position.

204 The HRs (95% CIs) for incidence of colorectal, colon and rectal cancer according to the three
205 different adherence categories of the WCRF/AICR score are shown in Table III. In the age-
206 adjusted model, those within the second and third adherence categories had HRs (95% CI) for
207 CRC of 0.76 (0.61, 0.95) and 0.66 (0.45, 0.99) ($p=0.05$) respectively, compared with those in
208 the lowest adherence category, with a 1-unit increment in the WCRF/AICR score
209 corresponding to a 10% decrease in risk of CRC (HR=0.90, 95% CI 0.81-1.00). However,
210 further adjustment for smoking, socioeconomic status and family history of CRC in a first
211 degree relative rendered the overall linear trend across the categories for the association non-
212 statistically significant ($p=0.17$). Although HRs suggested an inverse relationship between
213 the WCRF/AICR score and cancers of the colon and rectum respectively, no significant
214 associations were observed in multivariate adjusted models. Sensitivity analyses
215 operationalising the recommendation for dietary supplements did not significantly change the
216 results (data not shown).

217

218 Table IV shows the results for the independent association between the separate components
219 of the WCRF/AICR score and risk of colorectal, colon and rectal cancer. In the age-adjusted
220 models, women who met the recommendation for body fatness had a statistically significant
221 reduced risk of colorectal and rectal cancer (HR (95% CI) of 0.69 (0.53, 0.91; $p=0.03$) and
222 0.53 (0.33, 0.83; $p=0.004$)) respectively, compared to those who did not. Women who met
223 the recommendation for animal foods had a statistically significant 32% reduced risk of colon
224 cancer incidence when compared to the non-adherent (HR (95% CI) 0.68 (0.48, 0.96;
225 $p=0.03$)). These associations were however attenuated; the association between body fatness
226 and rectal cancer did not reach statistical significance ($p=0.07$), associations were not
227 statistically significant for any of the other components in the fully adjusted multivariate
228 models.

229

230 **Discussion**

231 This study evaluated adherence to the WCRF/AICR cancer prevention recommendations in
232 relation to risk of CRC in a UK cohort of middle-aged women. The overall score related to
233 operationalisation of eight recommendations was not significantly associated with incidence
234 of colorectal, colon or rectal cancer in multivariate adjusted analyses. Investigation of the
235 separate score components showed adherence to the body fatness and animal foods
236 recommendations to potentially offer a degree of protection against risk of cancers of the
237 colorectum and rectum and of the colon, respectively.

238 Few studies have looked at the WCRF/AICR recommendations and CRC incidence. Findings
239 from this study are consistent with those from the Framingham Offspring cohort (12) and in
240 the Black Women's Health Study (15) where the overall WCRF/AICR score was not
241 significantly associated with CRC incidence. Conversely, a one-point increment in the
242 WCRF/AICR score was significantly associated with a 12% (95% CI: 9% to 16%) decreased
243 CRC risk in the EPIC cohort (13) and a 13% (95% CI: 5% to 20%) decreased risk of CRC in
244 the VITAL cohort (14). However, the EPIC and VITAL cohorts (13, 14) operationalized a
245 total of 7 and 6 recommendations respectively, rather than 8 score components as
246 operationalized in this cohort. Notwithstanding, an evaluation of our results using a similar
247 composite to the EPIC and VITAL cohorts (13, 14) to facilitate comparison, by dropping first
248 the recommendation in relation to salt-preserved food, and secondly dropping two
249 recommendations – those related to salt-preserved food and to breastfeeding, did not
250 significantly change the results (data not shown). Thomson and colleagues (9) also reported a
251 statistically significant decreased risk of CRC in the Women's Health Initiative (WHI)
252 Observational Study but the ACS cancer prevention guidelines were operationalized for the
253 study and associations were weakest amongst whites, which may partly explain the
254 inconsistency in findings when compared to this study where most women are white.
255 Associations for colon and rectal cancers were not investigated separately in any of the
256 previous cohort studies operationalising the WCRF/AICR guidelines. Two studies evaluating
257 associations for risk of colon and rectal cancer separately looked at adherence to the Dietary
258 Guidelines for Americans (11) and to the ACS recommendations (4) respectively. A
259 statistically significant decrease in colon cancer risk was reported with greater adherence in
260 both studies (10-11). In agreement with results from this cohort, data from the Iowa Women's
261 Health Study, a population-based cohort of postmenopausal women reported inverse, but not
262 significant decreased rectal cancer incidence with increased adherence to cancer prevention
263 guidelines (11).

264

265 The different strengths of associations for the colon and for the rectal cancer sites may be due
266 to the different biological characteristics of the mucosa in that part of the colorectum or to the
267 different mechanisms in oncogenesis (25). Notwithstanding this plausible explanation, the
268 estimation of the association between the WCRF/AICR recommendations and cancer
269 incidence by site should be considered as being of an exploratory nature due to the smaller
270 sample size. The cohort comprises relatively health conscious women when compared to the
271 general population. Furthermore, the source of diet assessment was a single FFQ measured at

272 baseline that is not only prone to recall bias and under-reporting, but also may not be fully
273 representative of eating patterns long term. Nevertheless, dietary patterns in the UKWCS
274 have been previously shown to be relatively stable over time and using groupings of dietary
275 patterns in contrast to energy and nutrient intake, reduces bias caused by such measurement
276 error (26). Although women who died within one year of dietary assessment were excluded
277 to reduce reverse causation, anthropometric and lifestyle factors were self-reported, there is
278 no data on their validity and thus potentially contributed to measurement error. No data was
279 available on whether women were previously screened for CRC; this would have been an
280 important confounding factor. These factors may have led to an attenuation of results
281 suggesting that the association between risk of cancer at different sites of the colorectum and
282 some dietary factors is probably stronger than stated in this cohort. Further discrepancies in
283 results between different studies may be explained by differences in the treatment of the
284 individual recommendations, the cut-offs chosen and the number of components used during
285 the WCRF/AICR score operationalization. The main limitation

286

287 An assessment of the contribution of the individual components to the overall score showed
288 body fatness, assessed by BMI to be the strongest predictor of cancer of both the colon and
289 rectum, as well as animal foods being a predictor of colon cancer. This is in line with findings
290 from the VITAL cohort (14) who also reported body fatness and red and processed meat
291 intake to be the recommendations most strongly associated with higher CRC risk for women.
292 Despite inverse associations of these components with cancer incidence in this cohort,
293 associations after adjusting for confounders were not significant although borderline
294 significance was noted for BMI and rectal cancer. BMI was similarly reported to be the
295 strongest predictor of all cancer incidence in the NIH_AARP cohort (10) whilst almost all
296 components of the WCRF/AICR score were associated with total cancer incidence in the
297 EPIC study (13). The lack of statistical significance in this study with respect to BMI and
298 animal foods could be explained by insufficient statistical power of the sample, or in the case
299 of BMI, closely related measurements such as that of visceral fat may have been a better
300 indicator of body fatness and a better predictor of colorectal cancer (27). The association may
301 also be stronger in men than in women, which could potentially explain the stronger links
302 reported in other cohorts including both sexes (10, 13). Men have higher rates of CRC than
303 women, with rectal cancer being higher in men and proximal colon cancer higher in women.
304 Hormonal factors could protect women from distal cancers (28). Other score components –
305 such as breastfeeding, are unlikely to be on the direct causal pathway for cancer of the

306 colorectum and thus, the fact that the scoring system used gives equal weighting to every
307 recommendation is considered a limitation of this study.

308

309 Although the exact mechanisms linking body fatness to CRC are yet unclear, some
310 possibilities have been put forward. Insulin / insulin-like growth factor (IGF) and the
311 adipokines, adiponectin and leptin are two hormonal systems that have been hypothesized to
312 mediate the association (29). Adipose tissue is metabolically active and could produce
313 inflammatory molecules that modulate carcinogenesis – cytokines, sex steroids and
314 adipokines (30). Thus, as adiposity increases, concentrations of IGF-binding protein-1
315 (IGFBP-1) and adiponectin decrease, resulting in elevated levels of free IGF-1 and serum
316 leptin that have been associated with increased CRC risk (27).

317

318 Strengths of this prospective cohort include its design, the long follow-up period, the
319 potential to adjust for several confounding variables and the size of the study population. The
320 latter enabled for the first time, a separate investigation of the colon and rectal sites in
321 relation to the score derived from the WCRF/AICR cancer prevention guidelines and its
322 individual components.

323

324 In conclusion, there were no statistically significant trends shown between adherence to the
325 WCRF/AICR cancer prevention guidelines and risk of CRC. Of the individual score
326 components, a BMI within the normal weight range was borderline significantly protective in
327 the fully adjusted model, emphasising the importance of this for cancer prevention. A better
328 understanding of different dietary components on this health outcome may permit higher or
329 lower WCRF/AICR score component weighting. In view of the likely different causes of
330 CRC subtypes, further research is needed to identify the optimal dietary patterns associated
331 with reducing colon and rectal cancer risk respectively.

332

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335

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340 **Conflict of Interest**

341 JC is the director of a University company, Dietary Assessment Ltd.

342

343 **Authorship**

344 JC conceived and designed the UKWCS, which was at its conception funded by the World
345 Cancer Research Fund. PJ conducted the analysis for this report, wrote the first version and
346 contributed to all other versions. DG provided statistical advice. All authors contributed to
347 the interpretation of the data and review of the manuscript.

348

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Tables

Table I: Classification and operationalization of the WCRF/AICR cancer prevention recommendations and the percentage adherence in the UKWCS¹

WCRF/AICR recommendation	Personal recommendations	Operationalisation	Scoring	UKWCS adherents (%)	CRC cases adherents (%)
1. Body fatness <i>Be as lean as possible within the normal range of body weight.</i>	(a) Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at 21	Insufficient data available	NA	NA	NA
	(b) Maintain body weight within the normal range from age 21	BMI (kg/m^2): 18.5-24.9 BMI: 25-29.9 BMI: <18.5 or ≥ 30	1 0.5 0	62.4 25.6 12.0	55.6 26.8 17.6
	(c) Avoid weight gain and increases in waist circumference throughout adulthood	Insufficient data available	NA	NA	NA
2. Physical activity <i>Be physically active as part of everyday life.</i>	(a) Be moderately physically active, equivalent to brisk walking, for ≥ 30 min every day.	>30 min/d of vigorous PA 15-30 min/d of vigorous PA <15 min/d of vigorous PA	1 0.5 0	13.8 19.4 66.8	12.6 17.1 70.3
	(b) As fitness improves, aim for ≥ 60 min of moderate or for ≥ 30 min of vigorous physical activity every day.	Insufficient data available	NA	NA	NA
	(c) Limit sedentary habits such as watching television.	Insufficient data available	NA	NA	NA
3. Foods and beverages that promote weight gain <i>Limit consumption of</i>	(a) Consume energy-dense foods sparingly	ED: ≤ 125 kcal/100 g/d ED: >125 to <175 kcal/100 g/d ED: >175 kcal/100 g/d	1 0.5 0	32.8 57.9 9.3	33.3 59.0 7.7

<i>energy dense foods; avoid sugary drinks.</i>		Sugary drinks: 0 g/d	1	4.8	5.2
		Sugary drinks: ≤250 g/d	0.5	83.5	84.0
		Sugary drinks: >250 g/d	0	11.7	10.8
	(c) Consume fast foods sparingly, if at all.	Insufficient data available	NA	NA	NA
4. Plant foods <i>Eat mostly foods of plant origin.</i>	(a) Eat ≥ 5 portions/servings (≥400 g) of a variety of nonstarchy vegetables and of fruit every day.	F&V: ≥400 g/d F&V: 200 to <400 g/d F&V: <200 g/d	1 0.5 0	24.5 41.1 34.4	23.4 42.8 33.8
	(b) Eat relatively unprocessed cereals (grains) and / or pulses (legumes) with every meal.	Dietary fibre: ≥25 g Dietary fibre: 12.5 to <25 g/d Dietary fibre: <12.5 g/d	1 0.5 0	7.5 50.4 42.1	7.0 50.2 42.8
	(c) Limit refined starchy foods.	Insufficient data available	NA	NA	NA
	(d) People who consume starchy roots or tubers as staples should also ensure sufficient intake of nonstarchy vegetables, fruit and pulses (legumes).	Not applicable to this population	NA	NA	NA
5. Animal foods <i>Limit intake of red meat and avoid processed meat.</i>	People who eat red meat should consume <500 g / wk and very few, if any, processed meats	RPM <500 g/wk and PM <3 g/d RPM <500 g/wk and PM 3 to <50 g/d RPM ≥500 g or PM ≥50 g/d	1 0.5 0	36.0 48.8 15.2	27.3 53.8 18.9
6. Alcohol <i>Limit alcoholic drinks.</i>	If alcoholic drinks are consumed, limit consumption to ≤2 drinks/d for men and 1 drink/d for women.	Ethanol: ≤10 g/d Ethanol: >10-20 g/d Ethanol: >20 g/d	1 0.5 0	66.3 21.1 12.6	68.2 19.4 12.4
7. Preservation, processing, preparation <i>Limit consumption of salt; avoid mouldy cereals (grains) or pulses (legumes).</i>	(a) Avoid salt-preserved, salted or salty foods; preserve foods without using salt.	Insufficient data available	NA	NA	NA
	(b) Limit consumption of processed foods with added salt to ensure an intake of <6g (2.4g sodium) every day.	Sodium: ≤ 1.5 g/d Sodium: >1.5 to 2.4 g/d Sodium: >2.4 g/d	1 0.5 0	3.5 23.3 73.2	3.36 23.2 73.2
	(c) Do not eat mouldy cereals (grains) or pulses (legumes).	Insufficient data available	NA	NA	NA

8. Dietary supplements <i>Aim to meet nutritional needs through diet alone.</i>	Dietary supplements are not recommended for cancer prevention.	Not applicable to this population	NA	NA	NA
<i>WCRF/AICR special recommendations</i>					
S1. Breastfeeding (BF) <i>Mothers to breastfeed; children need to be breastfed.</i>	Aim to breastfeed infants exclusively up to 6 months and continue with supplementary feeding thereafter.	Cumulative BF: ≥6 months Cumulative BF: >0 to <6 months No breastfeeding	1 0.5 0	38.2 26.4 35.4	37.6 28.8 33.6
S2. Cancer survivors <i>Follow the recommendations for cancer prevention.</i>	(a) All cancer survivors should receive nutritional care from an appropriately trained professional. (b) If able to do so, and unless otherwise advised, aim to follow the recommendations for diet, healthy weight, and physical activity.	Not applicable to this population	NA	NA	NA
		Not applicable to this population	NA	NA	NA

¹BMI, body mass index; NA, not applicable; PA, physical activity; ED, energy density; F&V, fruit and vegetables; wk, week; d, day; RPM, red and processed meat; PM, processed meat

Table II: Characteristics of colorectal cancer cases, non-cases and across WCRF/AICR quartiles for participants in the UKWCS¹

Variable	Total	CRC cases	WCRF/AICR score categories		
			1	2	3
Observations N (%)	30963	444 (1.4)	6319 (20.4)	20978 (67.7)	3671 (11.9)
WCRF / AICR score range	0-8		0-3	3.25-5	5.25-8.0
Age (years)					
Mean	52.0	57.7	52.8	52	50.6
95% CI	(51.9, 52.1)	(56.9, 58.6)	(52.6, 53.0)	(51.9, 52.1)	(50.3, 50.9)
BMI (kg/m ²)					
Mean	24.4	25.1	26.9	24	22.5
95% CI	(24.4, 24.5)	(24.6, 25.5)	(26.8, 27.0)	(24.0, 24.1)	(22.4, 22.5)
Energy intake (kcal/day)					
Mean	2342	2355	2450	2326	2247
95% CI	(2334, 2350)	(2285, 2425)	(2433, 2468)	(2317, 2335)	(2222, 2272)
Ethanol (g/day)					
Median	5.54	4.73	11.88	5.23	2.21
IQR	11.8	11.74	20.23	10.8	6.64
Physical activity (hr/day)					
Mean	0.24	0.22	0.1	0.23	0.56
95% CI	(0.24, 0.25)	(0.18, 0.26)	(0.09, 0.11)	(0.22, 0.24)	(0.54, 0.58)
Smoking status					
Current smoker N (%)	3361 (11.2)	42 (9.8)	985 (16.0)	2106 (10.3)	270 (7.6)
Former smoker N (%)	9240 (30.7)	136 (31.6)	2006 (32.5)	6146 (30.2)	1088 (30.6)
Never smoker N (%)	17501 (58.14)	252 (58.6)	3177 (51.5)	12129 (59.5)	2195 (61.8)
Socio-economic status					
Professional / Managerial N (%)	19298 (63.6)	247 (57.0)	3688 (59.6)	13039 (63.5)	2571 (71.5)
Intermediate N (%)	8298 (27.4)	139 (32.1)	1825 (29.5)	5734 (27.9)	739 (20.5)

Routine and manual N (%)	2736 (9.0)	47 (10.9)	675 (10.9)	1773 (8.6)	288 (8.0)
Education level					
No qualifications N (%)	4656 (16.4)	98 (24.8)	1215 (21.2)	3020 (15.7)	421 (12.2)
Non-degree qualifications N (%)	15983 (56.2)	205 (51.8)	3209 (55.9)	10920 (56.8)	1854 (53.6)
Degree N (%)	7789 (27.4)	93 (23.5)	1312 (22.9)	5293 (27.5)	1184 (34.2)
Diet group					
Meat-eaters N (%)	19919 (70.3)	317 (78.5)	5162 (92.2)	13408 (69.8)	1349 (38.3)
Fish-eaters N (%)	3860 (13.6)	39 (9.7)	181 (3.2)	2699 (14.1)	980 (27.8)
Vegetarians N (%)	4543 (16.0)	48 (11.9)	254 (4.5)	3095 (16.1)	1194 (33.9)
Supplement users N (%)	16244 (57.6)	236 (58.3)	2972 (51.2)	11129 (58.3)	2143 (65.3)
Family history of colorectal cancer N (%)	1755 (6.0)	35 (8.3)	326 (5.5)	1238 (6.3)	191 (5.6)

¹WCRF/AICR, World Cancer Research Fund/ American Institute of Cancer Research; BMI, body mass index; CRC, colorectal cancer

Table III: Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incidence of colorectal, colon and rectal cancer according to quartiles of the WCRF/AICR score

Cancer site	WCRF/AICR score categories	Cases ^a	Age-adjusted HR (95% CI)	Multivariable-adjusted ^b HR (95% CI)
Colorectal		444		
	1		1.0	1.0
	2		0.76 (0.61, 0.95)	0.79 (0.62, 1.00)
	3		0.66 (0.45, 0.99)	0.73 (0.48, 1.10)
	Per 1 unit increment		0.90 (0.81, 1.00)	0.92 (0.82, 1.03)
	<i>P</i> _{trend}		0.046	0.169
Colon		322		
	1		1.0	1.0
	2		0.79 (0.61, 1.02)	0.82 (0.62, 1.09)
	3		0.61 (0.38, 0.99)	0.72 (0.44, 1.19)
	Per 1 unit increment		0.89 (0.79, 1.01)	0.93 (0.82, 1.07)
	<i>P</i> _{trend}		0.065	0.308
Proximal colon		164		
	1		1.0	1.0
	2		0.71 (0.50, 1.02)	0.75 (0.51, 1.10)
	3		0.69 (0.36, 1.31)	0.83 (0.43, 1.60)
	Per 1 unit increment		0.90 (0.76, 1.06)	0.93 (0.77, 1.12)
	<i>P</i> _{trend}		0.212	0.441
Distal colon		115		
	1		1.0	1.0
	2		1.01 (0.65, 1.59)	0.96 (0.58, 1.58)
	3		0.41 (0.17, 0.99)	0.41 (0.16, 1.07)
	Per 1 unit increment		0.91 (0.76, 1.09)	0.93 (0.76, 1.14)
	<i>P</i> _{trend}		0.290	0.504
Rectal		146		
	1		1.0	1.0
	2		0.72 (0.49, 1.06)	0.72 (0.48, 1.08)
	3		0.65 (0.33, 1.28)	0.61 (0.29, 1.26)
	Per 1 unit increment		0.90 (0.75, 1.09)	0.88 (0.72, 1.08)
	<i>P</i> _{trend}		0.291	0.239

^aCase numbers apply to multivariable adjusted models. ^bAdjusted for age, smoking status, socioeconomic status and family history of colorectal cancer.

Table IV: Age and fully-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for colorectal, colon and rectal cancers per component of the WCRF/AICR score¹

	Colorectal Cancer				Colon Cancer				Rectal Cancer			
	Age-adjusted HR (95% CI)	<i>P</i> _{trend}	Multivariate-adjusted HR (95% CI)	<i>P</i> _{trend}	Age-adjusted HR (95% CI)	<i>P</i> _{trend}	Multivariate-adjusted HR (95% CI)	<i>P</i> _{trend}	Age-adjusted HR (95% CI)	<i>P</i> _{trend}	Multivariate-adjusted HR (95% CI)	<i>P</i> _{trend}
1. Body fatness (BMI)												
0 ²	1.0	0.032	1.0	0.102	1.0	0.390	1.0	0.391	1.0	0.004	1.0	0.070
0.5	0.69 (0.51, 0.93)		0.70 (0.51, 0.97)		0.69 (0.48, 0.99)		0.66 (0.45, 0.96)		0.75 (0.46, 1.22)		0.85 (0.50, 1.46)	
1	0.69 (0.53, 0.91)		0.72 (0.54, 0.97)		0.78 (0.57, 1.07)		0.76 (0.55, 1.07)		0.53 (0.33, 0.83)		0.66 (0.40, 1.09)	
2. Physical activity												
0	1.0	0.859	1.0	0.886	1.0	0.721	1.0	0.965	1.0	0.677	1.0	0.815
0.5	0.97 (0.74, 1.26)		0.97 (0.73, 1.28)		1.00 (0.74, 1.37)		1.07 (0.77, 1.48)		0.63 (0.51, 1.36)		0.62 (0.36, 1.08)	
1	0.99 (0.73, 1.34)		0.99 (0.72, 1.36)		0.92 (0.64, 1.33)		0.97 (0.66, 1.43)		1.22 (0.75, 1.98)		1.12 (0.67, 1.87)	
3. Foods that promote weight gain												
0	1.0	0.492	1.0	0.644	1.0	0.656	1.0	0.860	1.0	0.487	1.0	0.563
0.25	0.85 (0.31, 2.34)		0.76 (0.28, 2.11)		1.18 (0.28, 4.90)		1.01 (0.24, 4.21)		0.60 (0.14, 2.57)		0.58 (0.14, 2.46)	
0.5	0.74 (0.27, 1.98)		0.67 (0.25, 1.80)		1.07 (0.26, 4.33)		0.98 (0.24, 3.97)		0.49 (0.12, 2.00)		0.44 (0.11, 1.79)	
0.75	0.79 (0.34, 2.13)		0.75 (0.28, 2.03)		1.10 (0.27, 4.47)		1.03 (0.25, 4.23)		0.56 (0.14, 2.30)		0.54 (0.13, 2.20)	
1	0.52 (0.17, 1.79)		0.42 (0.11, 1.55)		0.83 (0.17, 4.15)		0.62 (0.11, 3.35)		0.19 (0.02, 2.07)		0.20 (0.02, 2.21)	
4. Plant foods												
0	1.0	0.529	1.0	0.891	1.0	0.727	1.0	0.787	1.0	0.551	1.0	0.532
0.25	0.88 (0.66, 1.17)		0.88 (0.64, 1.20)		0.93 (0.66, 1.31)		0.96 (0.66, 1.39)		0.71 (0.42, 1.18)		0.69 (0.40, 1.17)	
0.5	1.02 (0.78, 1.35)		1.05 (0.78, 1.41)		1.02 (0.73, 1.41)		1.10 (0.77, 1.58)		1.09 (0.69, 1.74)		0.97 (0.59, 1.60)	
0.75	0.79 (0.56, 1.11)		0.84 (0.58, 1.21)		0.81 (0.54, 1.22)		0.88 (0.57, 1.36)		0.64 (0.34, 1.19)		0.67 (0.36, 1.27)	
1	0.92 (0.43, 1.97)		1.08 (0.50, 2.33)		1.23 (0.56, 2.75)		1.51 (0.68, 3.39)		0.50 (0.10, 2.59)		0.55 (0.11, 2.85)	

5. Animal foods													
0	1.0	0.065	1.0	0.236	1.0	0.030	1.0	0.167	1.0	0.477	1.0	0.433	
0.5	0.87 (0.68, 1.11)		0.94 (0.72, 1.22)		0.83 (0.62, 1.10)		0.89 (0.66, 1.21)		0.82 (0.53, 1.26)		0.89 (0.56, 1.41)		
1	0.75 (0.56, 1.01)		0.82 (0.59, 1.13)		0.68 (0.48, 0.96)		0.76 (0.52, 1.11)		0.83 (0.50, 1.39)		0.80 (0.45, 1.40)		
6. Alcohol													
0	1.0	0.561	1.0	0.360	1.0	0.685	1.0	0.703	1.0	0.827	1.0	0.702	
0.5	0.91 (0.64, 1.30)		0.92 (0.63, 1.34)		1.10 (0.72, 1.67)		1.11 (0.71, 1.74)		0.69 (0.37, 1.31)		0.72 (0.38, 1.36)		
1	0.90 (0.67, 1.22)		0.86 (0.63, 1.19)		0.98 (0.68, 1.42)		0.99 (0.66, 1.47)		0.92 (0.55, 1.55)		0.82 (0.47, 1.41)		
7. Preservation, processing and preparation													
0	1.0	0.769	1.0	0.821	1.0	0.814	1.0	0.940	1.0	0.824	1.0	0.833	
0.5	0.99 (0.79, 1.26)		0.96 (0.75, 1.24)		0.94 (0.71, 1.24)		0.89 (0.66, 1.20)		1.11 (0.75, 1.64)		1.13 (0.75, 1.71)		
1	1.16 (0.69, 1.96)		0.99 (0.55, 1.80)		1.32 (0.75, 2.35)		1.30 (0.71, 2.40)		0.86 (0.29, 2.50)		0.38 (0.08, 1.91)		
8. Breastfeeding													
0	1.0	0.730	1.0	0.719	1.0	0.317	1.0	0.780	1.0	0.694	1.0	0.627	
0.5	0.99 (0.77, 1.27)		0.96 (0.74, 1.25)		0.90 (0.68, 1.20)		0.90 (0.66, 1.49)		1.18 (0.76, 1.82)		1.04 (0.65, 1.65)		
1	0.96 (0.76, 1.21)		1.04 (0.90, 1.33)		0.87 (0.66, 1.14)		0.96 (0.72, 1.28)		1.09 (0.72, 1.65)		1.11 (0.73, 1.69)		

¹WCRF/AICR, World Cancer Research Fund/ American Institute of Cancer Research; BMI, body mass index.

²0 is assigned if the recommendation is not met, 0.5 is assigned for partly met recommendations and 1 is assigned for met recommendations.