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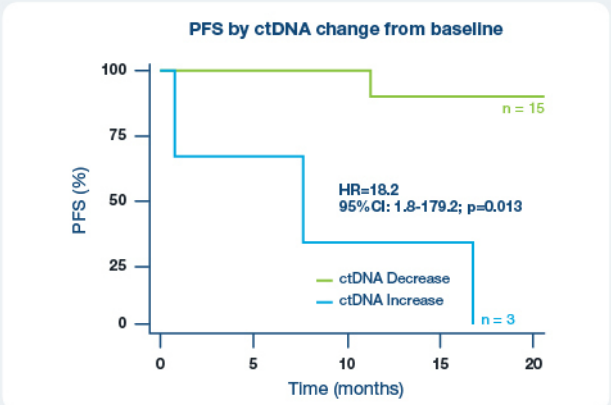

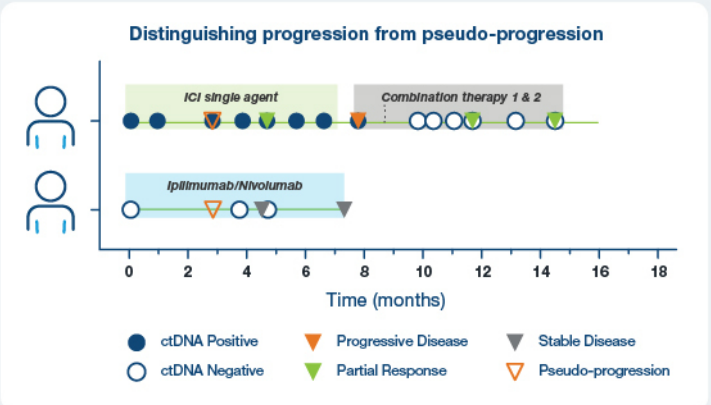

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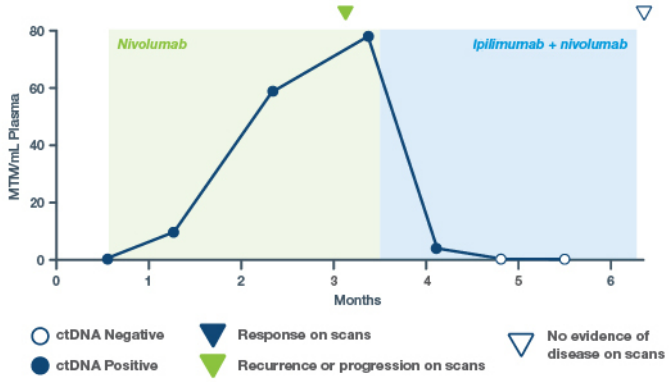
Should treatment be changed or escalated?

Early rise in ctDNA can help inform treatment escalation or change



60-year-old stage IV metastatic melanoma patient[2]

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PFS = Progression-free survival

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ORIGINAL ARTICLE

Adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations and cancer risk: A systematic review and meta-analysis

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Abstract

Background: The World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations are lifestyle-based guidelines that aim to reduce cancer risk. A systematic review and meta-analysis of studies investigating associations between a score for adherence to the 2018 Cancer Prevention Recommendations and cancer risk was conducted.

Methods: MEDLINE, Embase, Web of Science, and Scopus were searched for studies published to November 28, 2022. In meta-analysis, the estimated risk ratios and 95% CIs for adherence score as a continuous (per 1-point increment) and categorical (highest vs. lowest score category) variable using random-effects models were estimated.

Results: Eighteen studies (11 cohort; seven case-control) were included investigating incidence of breast (n = 7), colorectal (n = 5), prostate (n = 2), lung (n = 2), pancreatic (n = 1), endometrial (n = 1), unknown primary cancer (n = 1), chronic lymphocytic leukemia (n = 1), and overall (any) cancer (n = 1). The summary risk ratio per 1-point increment in adherence score was 0.89 (95% CI, 0.85–0.93; I^2 = 76.5%; n = 7) for breast cancer, 0.88 (95% CI, 0.84–0.91; I^2 = 26.2%; n = 4) for colorectal cancer, and 0.92 (95% CI, 0.86–0.98, I^2 = 66.0%; n = 2) for lung cancer. There were no significant associations with prostate or other cancers. Meta-analysis results using categorical adherence score variables were consistent with these findings.

Conclusions: Greater adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations was

The first two authors contributed equally to this article.

associated with lower risk of breast, colorectal, and lung cancers. Future studies investigating associations with risk of other forms of cancer are warranted.

PROSPERO registration number: CRD42022313327.

KEYWORDS

2018 WCRF/AICR Cancer Prevention Recommendations, cancer risk, diet, lifestyle, lifestyle score, meta-analysis, physical activity

BACKGROUND

It has been estimated that 30% to 50% of all cancers are linked with modifiable lifestyle and environmental factors, such as physical inactivity, tobacco use, obesity, poor diet, and alcohol intake, suggesting that a large proportion of cancer cases are potentially preventable.[1] Furthermore, recent estimates suggest that more than 40% of global cancer deaths and disability-adjusted life-years were attributable to such lifestyle factors in 2019.[2]

In their Second Expert Report published in 2007,[3] the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) produced a set of 10 lifestyle-based guidelines (Cancer Prevention Recommendations) that aim to reduce the risk of cancer worldwide at the individual, as well as population-wide, level. These lifestyle recommendations focused on dietary advice ("eat a diet rich in wholegrains, vegetables, fruits and beans," "limit consumption of fast foods and other processed foods high in fat, starches or sugars," "limit consumption of red and processed meat," and "limit consumption of sugar-sweetened drinks") as well as recommendations to maintain a healthy body weight, undertake physical activity, and limit alcohol consumption. In 2020, Solans and colleagues conducted a systematic review and meta-analysis of observational studies investigating adherence to the 2007 Cancer Prevention Recommendations and health outcomes including cancer incidence and survival, mortality, markers of cancer risk, and cancer aggressiveness in patients or survivors.[4] They found that greater adherence to these recommendations was associated with lower risk of breast and colorectal cancer incidence as well as of overall and cancer-specific mortality. The findings of that study were in line with those from an earlier systematic review of prospective cohort studies that reported consistent reductions in the risk of cancer overall as well as of several site-specific cancers including breast, colorectal, and endometrial cancer with greater adherence to the recommendations.[5]

In the 2018 WCRF/AICR Third Expert Report,[6] these Cancer Prevention Recommendations were updated to reflect the latest scientific evidence. The main changes include the removal of the 2007 recommendation to "eat less salt" because the evidence was no longer sufficiently conclusive, and the addition of a recommendation to "limit consumption of sugar-sweetened drinks" (previously incorporated into the recommendation to "avoid foods and drinks that promote weight gain").[6] Following this updated publication, researchers at the National Institutes of Health National Cancer Institute, WCRF, and AICR created a standardized scoring system (the 2018 WCRF/AICR Score) to assess adherence to eight of the 10 recommendations (with the eighth component of the score (breastfeeding) being optional).[7,8] The range in adherence score is 0 to 7 (or 0–8) points, with a higher score representing greater adherence (healthier lifestyle) and a lower score showing less adherence (unhealthier lifestyle). The main aim of the 2018 WCRF/AICR Score is to provide a framework for greater consistency in studies of associations between adherence to the Cancer Prevention Recommendations and cancer risk and mortality[7,8] and to facilitate comparisons between studies. Since publication of the score, researchers worldwide have applied the 2018 WCRF/AICR Score to investigate relationships with cancer-related outcomes, including incidence and mortality, recurrence,[9] plasma metabolite concentrations,[10] and quality of life in colorectal cancer survivors,[11] as well as other health-related outcomes such as cardiovascular disease mortality.[12] However, to date, there are no systematic reviews or meta-analyses that have investigated associations between the 2018 WCRF/AICR Score and cancer risk or other health-related outcomes.

The aim of this study is to perform a systematic review and meta-analysis of the published literature to date that has reported associations between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and risk of developing cancer. A secondary aim is to review the application and operationalization of the standardized scoring system devised by Shams-White and colleagues[7] as used in the identified studies.

METHODS

Literature search

This systematic review was prepared in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist and was registered with the International Prospective Register of Systematic Reviews (registration number: CRD42022313327).

The search was conducted in MEDLINE (Ovid interface), Embase, SCOPUS, and Web of Science for observational studies investigating associations between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and incident cancer published up to November 28, 2022. The reference lists of included articles were scanned to identify any other studies that may be eligible, and the gray literature was searched using Index to Theses.

The following search terms were included: (WCRF OR AICR OR World Cancer Research Fund OR American Institute for Cancer Research) AND ((Neoplasms [MeSH] OR Cancer or Health [MeSH] OR Mortality [MeSH])) AND (Adherence OR Compliance OR Concordance).

Citation titles and abstracts were first screened to remove studies that clearly did not meet the eligibility criteria. Subsequently, a more detailed screening was performed by reviewing full articles to select eligible studies to be included in the review. Screening, data extraction, and quality assessment were performed independently by two reviewers (F.C.M. and C.W.). Discrepancies were resolved by discussion or by conferring with the senior investigator (J.C.M.).

Study selection

Eligibility criteria for this review were based on the Population, Exposure, Comparator, Outcomes, Study framework for systematic reviews.[13] The inclusion criteria for studies were: (1) case-control, prospective cohort, or cross-sectional studies in adult humans; (2) studies that investigated associations between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and cancer incidence/risk, using the 2018 WCRF/AICR Score (details of this standardized scoring system are shown in Table S1) or their own scoring system; (3) studies reporting estimates of relative risk (RR), or related effect estimates (e.g., hazard ratio, odds ratio) with an associated confidence interval for incident cancer at one or more sites; and (4) full articles available in English. Conference abstracts were not eligible because these generally do not report sufficient detail to permit quality appraisal. If full-text articles were not easily available, we requested them from the study authors.

Data extraction

Data extraction was performed independently by two reviewers (F.C.M. and C.W.) with discrepancies discussed and resolved. The following data were extracted: (1) study information (including first author, publication year, country, study design, eligibility criteria); (2) participant demographics (including age, sex, ethnicity, sample size, number of cases, study setting, comorbidities, recruitment year, and median follow-up time); (3) study methods (including data collection method, assessment of adherence to the 2018 Cancer Prevention Recommendations and information on how they operationalized the 2018 WCRF/AICR Score (Table S1) or their own scoring system, outcome ascertainment, statistical analyses, confounder adjustments, and score categories); and (4) results (including risk estimates, corresponding 95% CIs for both categorical and continuous score data, and p values). We extracted reported crude estimates, minimally adjusted estimates and fully adjusted estimates for each study, if applicable.

If articles reported different "variants" of the score, we extracted the one that included most of the components of the recommendations. For example, in their main analysis, Petimar and colleagues reported the findings for a score based on three components of the recommendations (diet, adiposity, and physical activity), which ranged between 0 and 3 points.[14] Scores for subcomponents were averaged to allocate a maximum score of 1 point to each component, giving equal weighting to the diet, adiposity, and physical activity components. As a sensitivity analysis, the authors also produced an alternative lifestyle score that summed scores for all seven individual dietary subcomponents of the score, adiposity scores, and physical activity score, with all nine score components having equal weight in the score calculation (range, 0–9 points). This "alternative" lifestyle score included more of the components of the recommendations and so was used in our analysis.

Statistical analyses

To assess associations between adherence score and cancer risk, categorical (comparing the highest vs lowest adherence score categories) meta-analyses and continuous (per 1-point increment in score) meta-analyses were performed, using a random-effects model, which accounts for heterogeneity between studies. Fully adjusted estimates from each study were used for all meta-analyses.

In the primary analysis, the studies were grouped by cancer site (breast, colorectal, lung, prostate, other). Additional prespecified subgroup analyses were conducted according to study design (case-control and prospective cohort), and by menopausal status for breast cancer and by subsite (colon and rectal) for colorectal cancer. Furthermore, we conducted sensitivity analyses removing the two studies that included a component on smoking within their scoring systems, which investigated breast cancer[15] and lung cancer.[16]

Forest plots were used to visualize effect sizes and included 95% CIs. All analyses were conducted using Stata version 17.0 (StataCorp, College Station, Texas, USA). We considered a p value of $< .05$ (two-sided test) as statistically significant.

Assessment of heterogeneity, study bias, and study quality

The I^2 test statistic and tau-squared (τ^2) were used to assess heterogeneity between studies[17]; tests of heterogeneity between subgroups were also conducted where appropriate. Study quality was evaluated independently by two reviewers (F.C.M. and C.W.) using the Newcastle-Ottawa Scale.[18] Each study was assessed based on nine items across three categories: (1) study selection (four items); (2) comparability of the groups (two items); and (3) exposure or outcome ascertainment (three items) and given a total score between 0 and 9 stars. Total scores were used to categorize studies as follows: poor (zero–three stars), fair (four–six stars), and good (seven–nine stars). Bias was assessed by visual inspection of funnel plots.

RESULTS

Literature search and study characteristics

The results of the literature search are summarized in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow chart (Figure S1). After removal of duplicate records, the literature search identified 235 publications. Of these, 174 were excluded during the first screening of titles and abstracts according to the inclusion criteria. After reviewing full texts ($n = 61$) during the second screening, a further 44 studies were excluded. Consequently, 17 studies were identified as eligible.[14,19–31] We identified one additional article outside of the literature search.[15]

Finally, a total of 18 independent studies were included in the systematic review and meta-analysis. The details of the included studies are summarized in Table S2. Of these studies, 11 were prospective cohort studies[14,15,19,20,22,24–26,28,31,32] and seven used a case-control design.[16,21,23,27,29,30,33] Only one study assessed associations with risk of "total cancer," defined as International Classification of Diseases, 10th Revision, codes: C00-D48[24], and another with 17 cancer types with evidence suggesting causal links to body weight, physical activity, dietary intake, and alcohol consumption according to the WCRF/AICR Third Expert Report.[32] In addition, Korn and colleagues investigated associations with the three most common cancers in the United States in 2021 for males (lung, prostate, and colorectal) and females (lung, breast, and colorectal), both combined and at each site individually.[32] Seventeen studies investigated the associations between adherence score and the risk of site-specific cancers, mainly breast cancer ($n = 7$) and colorectal cancer ($n = 5$), but also cancer of unknown primary ($n = 1$),[22] pancreatic cancer ($n = 1$),[31] prostate cancer ($n = 2$),[27,32] lung cancer ($n = 2$),[16,32] endometrial cancer ($n = 1$),[33] and chronic lymphocytic leukemia ($n = 1$).[29]

Most of the studies ($n = 12$) were undertaken in Europe, namely Spain,[19,20,27,29] The Netherlands,[22] Sweden,[24] the United Kingdom,[15,26] Poland,[16] Italy,[30,33] and Switzerland,[30] and the EPIC cohort included participants from Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdeom.[25] Four studies were in the United States[14,28,31,32] and two in Africa (Morocco and South Africa).[20,23] The largest study sample sizes were 260,151 participants and 12,693 cancer cases[25] among the prospective cohort studies, and 6426 participants and 3034 cancer cases[30] among the case-control studies. Seven studies were conducted in women only[15,19,23,25,26,30,33] and two in men only.[16,27] The median follow-up duration across the cohort studies ranged from 6 years[20] to 24 years.[14]

All 18 studies analyzed associations between score as a categorical variable (comparing the highest vs. the lowest score category) and 16 studies presented data per 1-point increment in score (score as a continuous variable). When creating score categories, most studies used cut-points predefined by the authors ($n = 9$)[16,19,22–26,30,32] or tertiles ($n = 6$).[15,21,27–29,31] Barrubes et al.[20] and Esposito et al.[33] categorized participants according to score quartiles, and Petimar et al.[14] according to quintiles. All studies used the lowest score category (worst adherence, unhealthier lifestyle) as the reference group for statistical analyses.

Associations between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and Cancer Risk

We performed categorical and continuous meta-analyses of associations between adherence score cancer risk by cancer site (breast cancer, colorectal cancer, prostate cancer, lung cancer, and other cancers). This showed significant reductions in risk of breast, colorectal cancer, and lung cancers, but not prostate or other cancers combined, with higher adherence to the Cancer Prevention Recommendations (Figures 1 and 2).

Across all studies (with subgroups by cancer site), in the categorical meta-analysis, comparing participants in the highest with the lowest score category, cancer risk was 27% (95% CI, 21–33) lower in participants with greatest adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations (Figure 1). Similarly, in the continuous meta-analysis, across all studies, cancer risk was reduced by 10% (95% CI, 7–12) for each 1-point increment in adherence score (Figure 2). There was no evidence of significant heterogeneity in the pooled effect estimates by cancer site in either categorical ($p_{heterogeneity} = .245$) or continuous ($p_{heterogeneity} = .458$) meta-analyses (Figures 1 and 2).

Finally, there was no effect of removing the two studies that included a smoking component within their scoring system (Arthur et al.[15] and Hawrysz et al.[16]) on cancer risk in the pooled analysis (Figure S3 and Figure S4).

Breast cancer risk

Seven studies (five prospective cohort[15,19,25,26,32] and two case-control[23,30]) investigated adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and risk of breast cancer. All except one study (Korn et al.[32]) included a mix of pre- and postmenopausal women. Because Arthur et al.[15] only presented their findings stratified according to menopause status, the results from this study for pre- and postmenopausal breast cancer are presented separately in forest plots (Figures 1 and 2). Korn et al.[32] also stratified analyses according to smoking status.

In the categorical meta-analysis, there was a 26% (95% CI, 18–34) lower risk of breast cancer in the highest adherence score category compared with the lowest (Figure 1). In the continuous meta-analysis, each 1-point increment in adherence score was associated with an 11% (95% CI, 7–15) reduction in risk of breast cancer (Figure 2). Levels of heterogeneity between studies were significant ($I^2 = 53.1\%$; $\tau^2 = .016$; $p = .024$; and $I^2 = 76.5\%$; $\tau^2 = .003$; $p < .001$ for categorical and continuous analyses, respectively).

Of the seven studies that investigated breast cancer incidence as an outcome, four[15,19,23,30] reported findings for pre- and

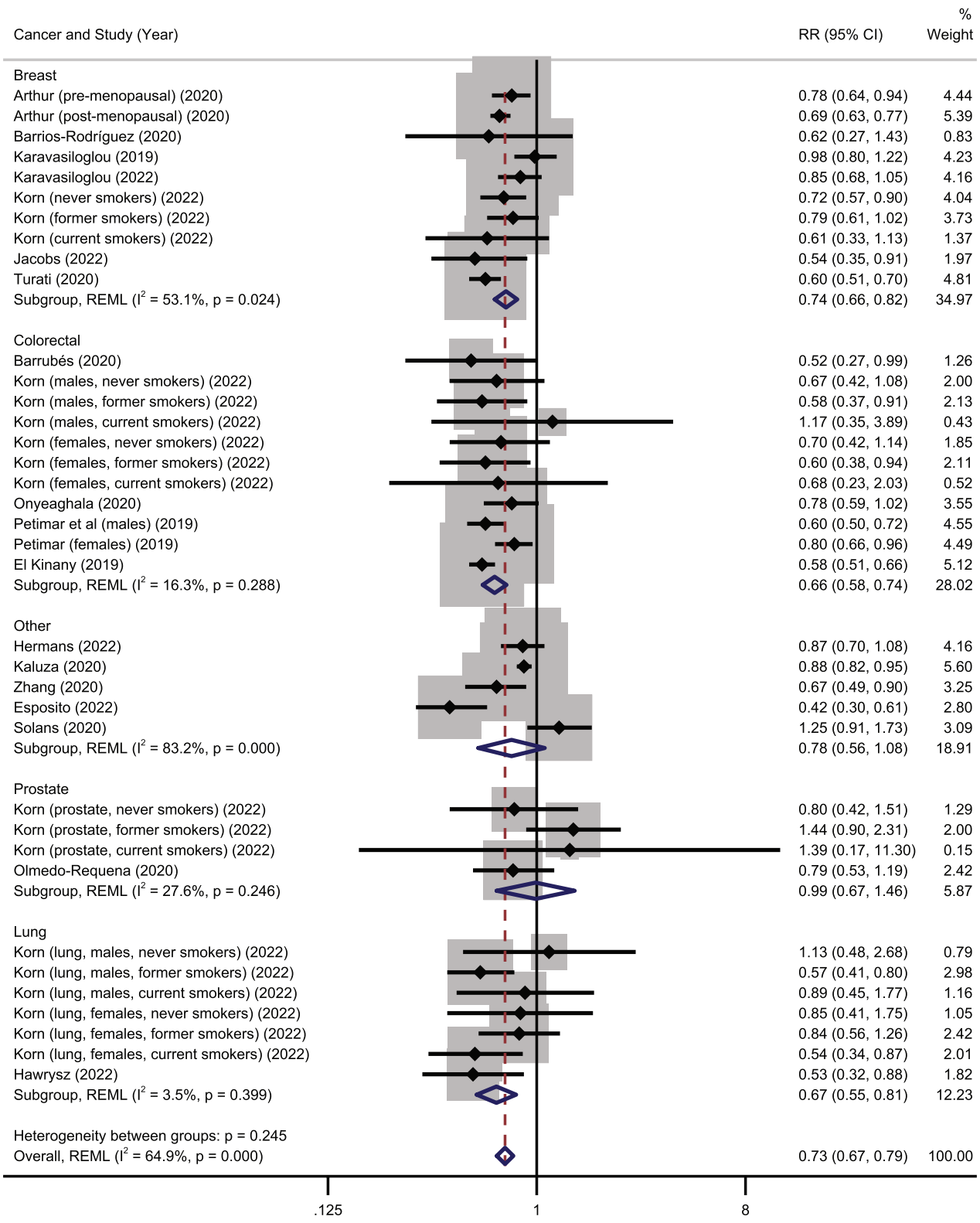

FIGURE 1 Categorical meta-analysis of studies examining the association between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and cancer risk by cancer site. Categorical meta-analyses were performed by comparing the highest vs lowest adherence score categories reported in each study. The data for Korn et al. (2022) represent those specifically for breast, prostate, colorectal, and lung cancers (each stratified by sex and by smoking status). AICR indicates American Institute for Cancer Research; WCRF, World Cancer Research Fund.

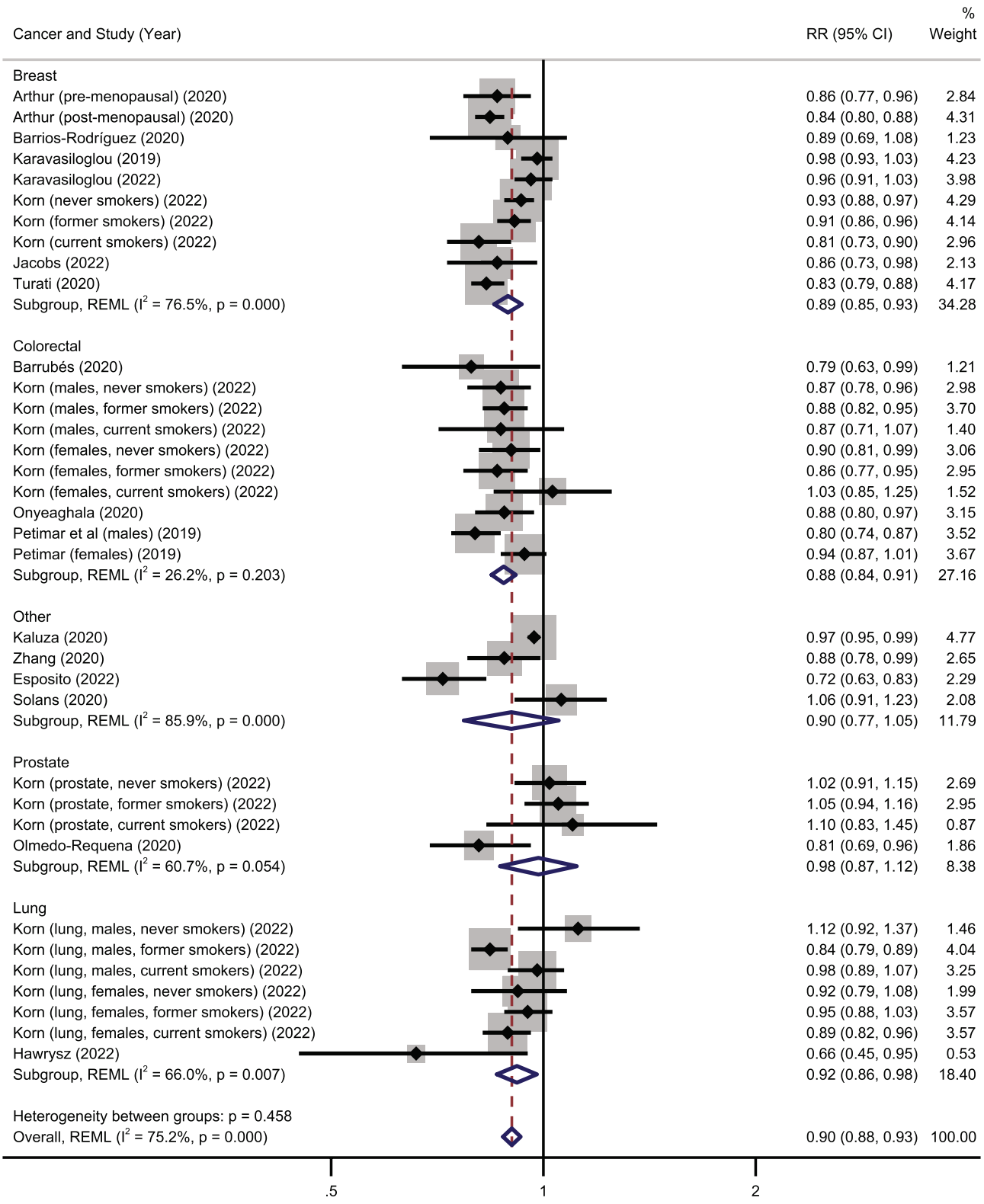

FIGURE 2 Continuous meta-analysis of studies examining the association between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and overall cancer risk per 1-point increment in score by cancer site. The data for Korn et al. (2022) represent those specifically for breast, prostate, colorectal, and lung cancers (each stratified by sex and by smoking status). AICR indicates American Institute for Cancer Research; WCRF, World Cancer Research Fund.

postmenopausal women separately. In addition, because of the age of participants, all breast cancer cases in the National Institutes of Health–AARP Diet and Health Study were postmenopausal.[32] In categorical analysis, risk reduction estimates were slightly stronger for premenopausal (RR, 0.62; 95% CI, 0.46–0.83) compared with postmenopausal (RR, 0.69; 95% CI, 0.64–0.75)) breast cancers, and there was no heterogeneity in pooled effect sizes for pre- and postmenopausal breast cancer studies ($p_{heterogeneity}$ = 0.472) (Figure 3). There was evidence for heterogeneity within the premenopausal subgroup (p = .004), but not for postmenopausal studies (p = .693). In continuous analysis, risk estimates for premenopausal (RR, 0.87; 95% CI, 0.79–0.96) and postmenopausal (RR, 0.87; 95% CI, 0.83–0.92) breast cancers were comparable, and there was no evidence for heterogeneity in effect sizes between subgroups (p = .923) (Figure 4). There was significant heterogeneity within studies of postmenopausal breast cancer (I^2 = 62.4%; τ^2 = .002; p = .021).

More pronounced associations were observed for case-control studies (RR highest vs lowest 0.59 [95% CI, 0.51–0.69]) compared with prospective cohort studies (RR, 0.78; 95% CI, 0.70–0.86) (Figure S4). Similar findings were observed in the continuous meta-analysis; breast cancer risk was 17% (95% CI, 12–21) lower per 1-point score increment in case-control studies, compared with 10% (95% CI, 5–14) reduction in risk per 1-point increment in prospective cohort studies (Figure S5). There was significant heterogeneity in pooled effect sizes for prospective cohort and case-control studies in categorical (p = .005) and continuous (p = .026) analyses. Furthermore, in the continuous analysis, there was heterogeneity in effect size estimates within prospective cohort studies (I^2 = 75.3%; τ^2 = = .003; p < .001).

In a sensitivity analysis, we removed the study by Arthur et al.,[15] which included smoking status as one of its scoring system components, and observed a slight attenuation of the estimate of breast cancer risk reduction but this remained statistically significant (RR, 0.74; 95% CI, 0.63–0.86) for the categorial meta-analysis and (RR, 0.90; 95% CI, 0.86–0.95) for the continuous meta-analysis (Figures S2 and S3). In subgroup analyses according to menopausal status, after removing the study by Arthur et al. (2020), effect sizes for premenopausal breast cancers were strengthened in the categorical meta-analysis (RR, 0.51; 95% CI, 0.40–0.65) vs. RR, 0.62; 95% CI, 0.46–0.83 in the original analysis), and there was significant heterogeneity in pooled effect sizes for pre- and postmenopausal breast cancer studies ($p_{heterogeneity}$ = 0.021). In contrast, in the continuous meta-analysis, the risk reduction was no longer significant (RR, 0.90; 95% CI, 0.74–1.10). For postmenopausal breast cancer, risk reductions remained significant, but were slightly attenuated (RR, 0.70;

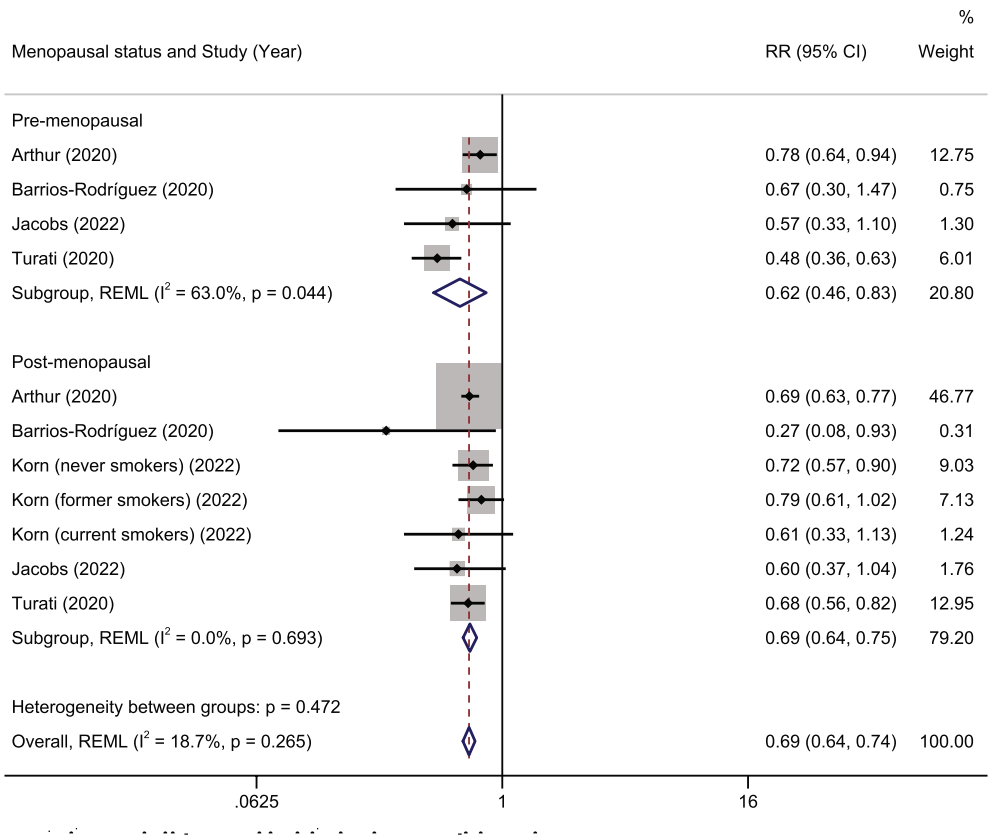

FIGURE 3 Categorical meta-analysis of studies examining the association between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and breast cancer risk by menopausal status. Categorical meta-analyses were performed by comparing the highest vs lowest adherence score categories reported in each study. AICR indicates American Institute for Cancer Research; WCRF, World Cancer Research Fund.

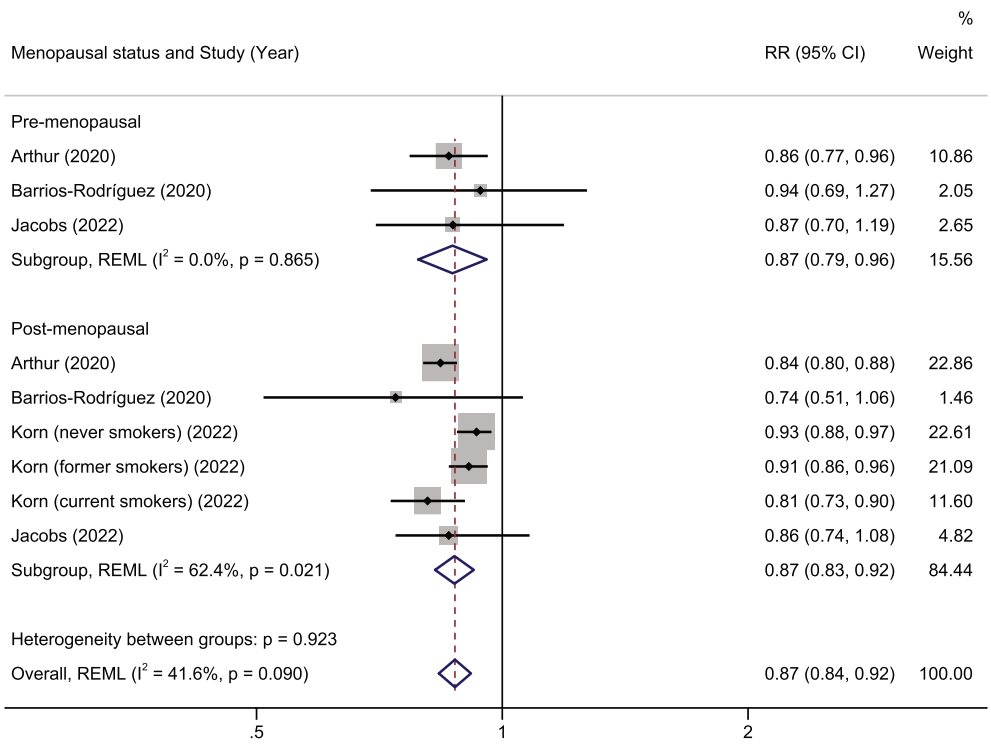

FIGURE 4 Continuous meta-analysis of studies examining the association between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and breast cancer risk per 1-point increment in score, stratified by menopausal status. AICR indicates American Institute for Cancer Research; WCRF, World Cancer Research Fund.

95% CI, 0.62-0.79, for categorical meta-analysis and RR, 0.89; 95% CI, 0.83–0.94, for continuous meta-analysis). When performing subgroup analyses according to study design, removal of this study also attenuated the risk reduction in prospective cohort studies (RR, 0.82; 95% CI, 0.72–0.93, for the highest score category and RR, 0.90; 95% CI, 0.86–0.95, per 1-point increment in score).

Colorectal cancer risk

Five studies (four prospective cohort[14,20,28,32] and one case-control[21]) investigated adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and risk of colorectal cancer. When assessing associations between adherence score and colorectal cancer risk both as a continuous variable and categorical variable comparing score categories, there was a consistent inverse association. In the categorical meta-analysis, participants in the highest adherence score category had a significantly lower risk of developing colorectal cancer compared with those in the lowest score category (RR, 0.66; 95% CI, 0.58–0.74) (Figure 1). In the continuous meta-analysis, a 12% (95% CI, 9–16) reduction in colorectal cancer risk per 1-point increment in score was observed (Figure 2). The one case-control study[21] presented data for categorical analysis of the adherence score only (and not per 1-point increment in score); therefore, only the four prospective cohort studies were included in this meta-analysis.

Three of the five studies that investigated colorectal cancer incidence as the outcome reported their findings for colorectal subsites (colon and rectal cancers) separately.[14,21,28] When performing subgroup analyses according to colorectal cancer subsite, the pooled risk estimates were similar for colon and rectal cancers in categorical (RR, 0.68; 95% CI, 0.58–0.79, and RR 0.66; 95% CI, 0.50–0.88, respectively) (Figure 5) and continuous (RR, 0.86; 95% CI, 0.77-0.97, and RR, 0.91; 95% CI, 0.82–1.02, respectively) (Figure 6) meta-analyses. There was no evidence for heterogeneity in pooled effect sizes for colon and rectal cancers ($p = .910$) or within subgroups in categorical analysis ($p = .910$). There was no significant heterogeneity between subgroups (sites) in the continuous analysis ($p = .501$); however, there was significant heterogeneity within colon cancer studies ($I^2 = 78.3\%$, $p = .010$).

Assessment of adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and operationalization of the 2018 WCRF/AICR Score

All of the included articles assessed adherence to at least five of the 2018 WCRF/AICR Cancer Prevention Recommendations, and six studies assessed adherence to all eight recommendations (although not necessarily using the 2018 WCRF/AICR Score). Table 1 summarizes the assessment methods and scores applied by the studies. The recommendation that was most frequently not assessed was "For

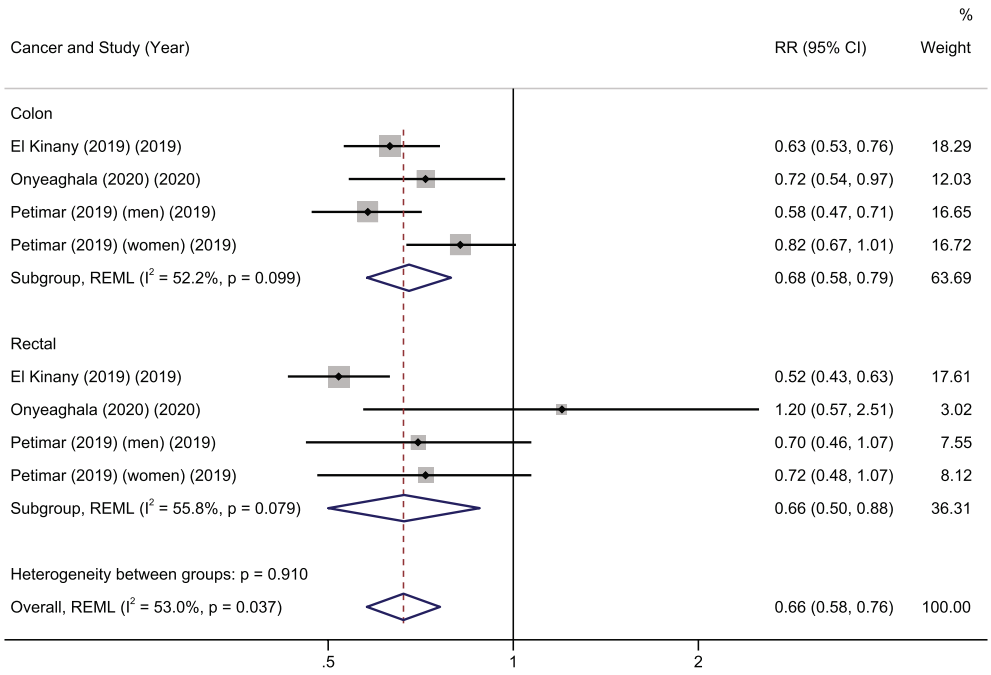

FIGURE 5 Categorical meta-analysis of prospective cohort studies examining the association between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and colorectal cancer risk by cancer subsite. Categorical meta-analyses were performed by comparing the highest vs lowest adherence score categories reported in each study. AICR indicates American Institute for Cancer Research; WCRF, World Cancer Research Fund.

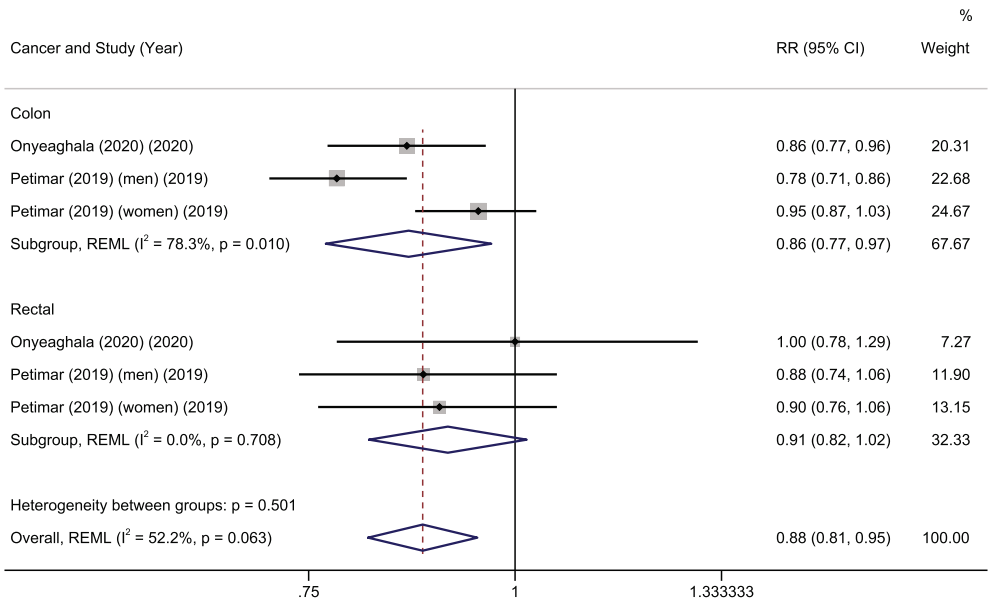

FIGURE 6 Continuous meta-analysis of prospective cohort studies examining the association between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and colorectal cancer risk per 1-point increment in score by cancer subsite. AICR indicates American Institute for Cancer Research; WCRF, World Cancer Research Fund.

mothers; breastfeed, if you can," which is an optional component of the standardized scoring system.[7]

Four[23,24,27,31] studies fully operationalized the 2018 WCRF/AICR Score (score range, 0–7 points), of which Zhang et al.[31] and Jacobs et al.[23] also included the optional eighth recommendation "For Mothers; Breastfeed, if you can" (score range, 0–8 points). Barrios-Rodriguez and colleagues[19] and Korn and colleagues[32] fully operationalized all score components with the exception of the waist circumference subcomponent because of lack of data. To compensate for this data limitation, the authors doubled the score for the body

TABLE 1 Recommendations included in scoring system used to assess adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations.

Study (year)	Exposure ascertainment	BMI	WC	PA	F&V	Fiber	UPFs	Red and processed meat	SSB	Alcohol	Breast-feeding (optional)	Score range (points)
Arthur (2020)[a]	Measurements by trained staff, self-administered touchscreen questionnaires	Y	Y	Y	Y	Y		Y		Y		0–5 or 0–6
Barrios-Rodriguez (2020)	Self-reported weight and height, FFQ, PA questionnaire	Y		Y	Y	Y	Y	Y	Y	Y	Y	0–8
Barrubes (2020)	Measurements by trained staff, FFQ, PA questionnaire	Y		Y	Y	Y	Y	Y	Y	Y		0–7
El Kinany (2019)	Interviewed by trained interviewers including FFQ and PA questionnaire. Self-reported weight and height	Y		Y	Y	Y		Y	Y	Y		0–6
Esposito (2022)	Interviews including FFQ and occupational and leisure time physical activity. Self-reported weight and height	Y		Y	Y	Y	Y	Y	Y	Y		0–7
Hawrysz (2022)	Measurements by trained staff. Face-to-face survey and FFQ by trained interviewer.	[b]		Y	Y	Y	Y	Y	Y	Y		0–8[b]
Hermans (2022)	Self-reported weight and height, FFQ, PA questionnaire	Y		Y	Y	Y		Y		Y		0–5
Jacobs (2021)	Measurements by trained staff, self-reported FFQ, face-to-face interviews for physical activity	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0–8
Kaluza (2020)	Self-reported weight and height and WC, FFQ, PA questionnaire	Y	Y	Y	Y	Y	Y	Y	Y	Y		0–7
Karavasiloglou (2019)	Interviews and via questionnaires	Y		Y	Y	Y	Y	Y	Y	Y	Y	0–8
Karavasiloglou (2022)	Measurements by trained staff, self-administered touchscreen questionnaires	Y	Y	Y	Y	Y		Y	Y	Y		0–6
Korn (2022)	Self-reported weight and height, FFQ, PA questionnaire	Y		Y	Y	Y	Y	Y	Y	Y		0–7
Olmedo-Requena (2020)	Face-to-face interviews including questionnaires for diet and physical activity. WC measured at the interview. Self-reported weight and height	Y	Y	Y	Y	Y	Y	Y	Y	Y		0–7
Onyeaghala (2020)	Interviews and via questionnaires	Y		Y	Y	Y		Y	Y	Y		0–7
Petimar (2019)	Self-reported weight and height and WC, FFQ, PA questionnaire	Y	Y	Y	Y	Y	Y	Y	Y	Y		0–3 or 0–9
Solans (2020)	Interviews and via questionnaires. WC measured at the interview. Self-reported weight and height	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0–7 0–8 (women)

TABLE 1 (Continued)

Study (year)	Exposure ascertainment	BMI	WC	PA	F&V	Fiber	UPFs	Red and processed meat	SSB	Alcohol	Breast-feeding (optional)	Score range (points)
Turati (2020)	Interviews and via questionnaires. WC measured at the interview. Self-reported weight and height	Y		Y	Y	Y	Y	Y	Y	Y	Y	0–8
Zhang (2020)	Collected via self-reported questionnaire	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	0–8

Note: Y indicates that study assessed adherence to that recommendation/subrecommendation.

Abbreviations: BMI, body mass index; F&V, fruits and vegetables; PA, physical activity; SSB, sugar-sweetened beverages; UPFs, ultra-processed foods; WC, waist circumference.

■ = applied same cut-points as 2018 WCRF/AICR Score.

■ = applied different cut-points to those in 2018 WCRF/AICR Score.

[a]Arthur et al. used equivalent METs as cut-points to assess adherence to physical activity recommendation. They assessed adherence to the dietary fiber subrecommendation using intake of whole grains. An additional score component to limit smoking was added.

[b]Hawrysz et al. used body fat percentage to assess adherence to the body weight recommendation. They assessed adherence to the dietary fiber subrecommendation using intake of whole grains and beans. An additional score component to limit smoking was added.

mass index (BMI) subcomponent to yield a total score range of 0 to 7 points.

Although a number of studies made reference to the standardized 2018 WCRF/AICR Score, not all operationalized it fully because of lack of data availability or because they applied alternative cut-points to assess adherence. For example, Arthur and colleagues[15] created a modified version of the 2018 WCRF/AICR Score (which they named the Healthy Lifestyle Index) because of a lack of available data to operationalize all score components (score range, 0–6 points). Because of inverse associations between obesity and breast cancer risk among premenopausal women, the "healthy body weight" recommendation was not included in the score when assessing associations with premenopausal breast cancer (score range, 0–5 points).

Several studies, including that by Barrubes et al.,[20] did not refer to the standardized 2018 WCRF/AICR Score but created their own scoring system to assess adherence to the Cancer Prevention Recommendations. Nonetheless, the cut-points that they applied for most of the recommendations (BMI, physical activity, fruits and vegetables, dietary fiber, and sugar-sweetened beverages) matched those proposed by Shams-White and colleagues.[7] For the alcohol component of the score, the authors used national guidelines as cut-points, as advised by Shams-White and colleagues.[8] Because most of the Netherlands Cohort Study participants clustered in the highest adherence group for the plant foods recommendation and the lowest for the recommendation on red and processed meat, Hermans et al.[22] used a tertile-based approach to assess adherence to these two recommendations, similar to that advised by Shams-White and colleagues and applied in the 2018 WCRF/AICR Score to assess adherence to the "Limit consumption of 'fast foods' and other processed foods high in fat, starches, or sugars" as ultra-processed food consumption.[7,8] Similarly, in addition to the 2018 WCRF/AICR Score, Jacobs et al. also calculated a data-driven tertile-based score (referred to as the adapted WCRF/AICR score) because the authors argued that their data for adherence distributions to some of the recommendations were highly skewed and, therefore, could limit their statistical power.[23]

Hawrysz and colleagues created an adapted version with respect to lung cancer (Ad-LC WCRF/AICR Score).[16] Assessment of adherence to the recommendation on ultra-processed food consumption and alcohol was in line with that in the 2018 WCRF/AICR Score, and the authors used a tertile-based approach to assess adherence to the recommendations regarding (1) fruits and vegetables, (2) red and processed meat, and (3) sugar-sweetened drinks. They also used this approach to allocate points for the intake of whole grains and beans (instead of the original dietary fiber score subcomponent). The recommendation to "be a healthy body weight" was changed to "have a healthy body fat," and the authors used body fat percentage to allocate points for this recommendation. In addition, they added an eighth recommendation to limit smoking (score range, 0–8 points),[16] an additional component that was also added to Arthur et al.'s Healthy Lifestyle Index.[15]

Other studies also added additional subcomponents to their scoring systems, outside of those included in the 2018 WCRF/AICR

TABLE 2 Risk of bias assessment of included articles evaluated by the Newcastle-Ottawa Scale (NOS).

		Selection ****				Comparability **		Outcome/exposure ***				
Study (Year)	Study type	1	2	3	4	5	6	7	8	9	Total	Outcome[a]
Arthur (2020)	Prospective cohort	*	*	0	0	*	*	*	*	*	7	Good
Barrios-Rodriguez (2020)	Prospective cohort	*	*	0	*	*	*	*	*	*	8	Good
Barrubes (2020)	Prospective cohort	0	*	0	*	*	0	*	*	*	6	Fair
El Kinany (2019)	Case-control	*	*	*	*	*	*	*	*	0	8	Good
Esposito (2022)	Case-control	*	*	0	*	*	*	0	*	*	7	Good
Hawrysz (2022)	Cancer control	*	*	0	*	*	*	0	*	*	7	Good
Hermans (2022)	Prospective cohort	*	*	0	*	*	0	*	*	0	6	Fair
Jacobs (2021)	Case-control	*	*	*	*	*	*	0	*	*	8	Good
Kaluza (2020)	Prospective cohort	*	*	0	*	*	*	*	*	0	7	Good
Karavasiloglou (2019)	Prospective cohort	*	*	0	*	*	*	*	*	*	8	Good
Karavasiloglou (2022)	Prospective cohort	*	*	0	*	*	*	*	*	*	8	Good
Korn (2022)	Prospective cohort	0	*	0	*	*	*	*	*	*	7	Good
Olmedo-Requena (2020)	Case-control	*	*	*	*	*	*	0	*	*	8	Good
Onyeaghala (2020)	Prospective cohort	*	*	*	*	*	*	*	*	*	9	Good
Petimar (2019)	Prospective cohort	0	*	0	*	*	*	*	*	0	6	Fair
Solans (2020)	Case-control	*	*	*	0	*	*	*	*	*	8	Good
Turati (2020)	Case-control	*	*	0	*	*	*	0	*	0	6	Fair
Zhang (2020)	Prospective cohort	*	*	0	*	*	*	0	*	0	6	Fair

[a]Outcomes classified as poor (zero to three stars), fair (four to six stars), or good (seven to nine stars).

Score. For example, Barrubes and colleagues added a third subcomponent to the recommendation to "Eat a diet rich in whole grains, vegetables, fruits, and beans" by assessing the intake of legumes such as beans and lentils.[20] Another example was the addition by Petimar and colleagues of a subcomponent to the recommendation to "Be physically active and limit sedentary behaviors," in which data on television watching as a proxy for sedentary habits.[14]

Study quality

The majority of the included studies (n = 13) were rated as good quality (seven–nine stars)[4,15,16,19,21,23–28,32,33] and five studies were rated as fair (four to six stars)[14,20,22,30,31] (Table 2). Study bias was assessed by visual inspection of the funnel plot (Figure S6) that showed a symmetrical spread with only a minority of studies falling outside the funnel. This suggests that this systematic review and meta-analysis is unlikely to be affected by significant publication or small-study bias.[34]

DISCUSSION

This systematic review and meta-analysis summarize the latest evidence for associations between adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations and the risk of cancer, including risk of breast, lung, and colorectal cancer. These are the first, second, and third most common cancers worldwide, respectively, and are among those cancers in which risk is most affected by lifestyle factors.[6] Across all studies, we found that risk of any cancer was 27% lower in individuals with greater adherence to the 2018 Cancer Prevention Recommendations in the highest versus the lowest score category. These findings are similar to a previous study that reported a 29% lower risk of incident total cancer with the healthiest lifestyle scores compared with the least healthy.[35] In addition, in the current meta-analysis, across all studies, each 1-point increment in adherence score, equivalent to fully adhering to one additional recommendation, was associated with a 10% reduction in cancer risk.

To date, the risk of pancreatic cancer,[31] chronic lymphocytic leukemia,[29] endometrial,[33] and cancer of unknown primary[22] associated with adherence to the 2018 Cancer Prevention Recommendations has been investigated by only one study each. Nonetheless, all of these individual studies showed an inverse association between adherence score and cancer risk, with the exception of chronic lymphocytic leukemia, in which there was no evidence of a significant association.[29] There is limited evidence to suggest associations between lifestyle and chronic lymphocytic leukemia and other types of leukemia, and most studies have assessed single lifestyle factors, such as individual nutrients, and yielded contradictory results.[36] In

contrast, the assessment of overall lifestyle or dietary patterns may be more meaningful. For example, a Western dietary pattern (high intake of processed meat, refined grains, confectionery, high-fat dairy products, and calorific drinks) was associated with increased risk of chronic lymphocytic leukemia.[37] In contrast, there were no associations between Mediterranean or Prudent dietary patterns,[37] or dietary inflammatory index and chronic lymphocytic leukemia.[38] Two studies investigated associations between score and risk of prostate[27,32] and lung[16,32] cancer. Greater adherence scores were associated with a 33% lower risk of lung cancer compared with those in the lowest score categories, and an 8% reduction in risk per 1-point increment in score. There were no associations with prostate cancer risk, or when individual studies for other cancer sites (i.e., pancreatic, chronic lymphocytic leukemia, endometrial, and cancer of unknown primary) were combined.

Meta-analysis of seven studies that evaluated associations between adherence score and breast cancer risk revealed a 26% lower risk of breast cancer in the highest adherence score category compared with the lowest, with an 11% reduction in risk for each 1-point increment in adherence score. These findings are comparable with those from a systematic review and meta-analysis that evaluated associations between adherence to the earlier (2007) version of the WCRF/AICR Cancer Prevention Recommendations in 11 studies; that review reported a 26% lower risk in the highest adherence score group versus the lowest and a 10% lower risk of breast cancer per each point increment in the 2007 WCRF/AICR Score.[4] In an updated meta-analysis of 13 studies, Turati and colleagues reported a 27% lower risk of breast cancer in the highest versus the lowest category of adherence to the 2007 WCRF/AICR Cancer Prevention Recommendations, and a 9% reduction in risk per 1-point increment in score.[30]

For colorectal cancer incidence, assessed in five studies, we observed a 34% lower risk in participants with the greatest versus the lowest adherence to the 2018 Cancer Prevention Recommendations, and a 12% reduction in risk per 1-point increment in adherence score. Again, our findings are similar to those reported in the systematic review and meta-analysis of 10 studies assessing adherence to the 2007 Cancer Prevention Recommendations, in which a 14% reduction in the risk of colorectal cancer per 1-point increment in score was found.[4] However, it must be noted that there are several differences between the 2007 and updated 2018 versions of the recommendations. These include the foci of the recommendations per se; for example, the 2007 recommendation to "Eat less salt" has been removed because the evidence was no longer sufficiently conclusive. In addition, the cut-points used to assess adherence to some of the recommendations have changed; for example, to fully adhere to the subrecommendation on dietary fiber intake, consumption of at least 30g of fiber per day is required (25 g/d in the 2007 version).[7]

Given the recent publication of a standardized scoring system[7] used to assess adherence to the 2018 update of the Cancer Prevention Recommendations, which the creators encourage researchers to apply to facilitate comparability across studies, we also evaluated the scoring systems applied and, where applicable, evaluated operationalization of the 2018 WCRF/AICR Score. Fewer than one quarter of the included studies in this meta-analysis (n = 4, breast n = 1,[23] total cancers n = 1,[24] prostate n = 1,[27] pancreatic n = 1[31]) fully operationalized this standardized scoring system, limiting the comparability across studies. The differences in assessment of adherence and in operationalization of the Score, including the number of included score components and total score range, likely contributed to the heterogeneity observed in our meta-analysis, heterogeneity that could not be explained by differences in study designs or cancers considered. Of course, some studies, particularly prospective cohort studies, may not have available all the data for all score components to fully operationalize the score. In particular, lack of available data to assess adherence to the subrecommendation regarding waist circumference (within the "healthy body weight" recommendation), was common. Another factor limiting the comparability of the studies and contributing to heterogeneity is the categorization of scores. For the categorical analyses, all studies compared the highest score category with the lowest score category (reference group), but studies used a mix of predefined cut-points,[16,19,22–26,30,32] tertiles,[15,21,27–29,31] quartiles,[20,33] and quintiles[14] for categorization. Our findings emphasize the need for transparency in describing the methodology used for ascertainment of exposure data and for scoring adherence to the Cancer Prevention Recommendations, including the cut-points applied and categorization of participants according to scores.

We conducted a comprehensive search strategy including four databases and applied robust methodology to systematically review and meta-analyze the evidence. The 2018 WCRF/AICR Score allocates equal weightings to the seven (or eight) score components that may be a limitation for certain cancers in which there is greater evidence for effect of particular dietary, or other lifestyle-related, components. For example, the strong associations between greater consumption of red and processed meats and colorectal cancer risk may suggest that adherence to this recommendation should be given a greater weighting when investigating this cancer site.[39] Alternative score weightings should be explored further in future studies. For example, in their main analysis, Petimar and colleagues used a score that ranged from 0 to 3 points, allocating a maximum of 1 point each to diet, adiposity, and physical activity by averaging the scores for individual subcomponents, and thus giving these three lifestyle components equal weightings.[14] Because their alternative lifestyle score, included as a sensitivity analysis, was most comparable to the other scoring systems from our included articles (range, 0–9 points), we used the data for this alternative score. However, in our meta-analysis, we found similar findings regardless of which version of the score was included (data not shown). Another strength is that we have focused solely on cancer incidence as our outcome. However, because healthier lifestyles and greater adherence to the Cancer Prevention Recommendations may be associated with lower risk of other noncommunicable diseases, such as cardiovascular disease, and mortality,[12] as more studies become available, the evidence for

associations with adherence to the Cancer Prevention Recommendations should be reviewed.

A limitation relating to the evidence-base is that, to date, a relatively small number (n = 18) of studies have evaluated associations between adherence to the 2018 version of the WCRF/AICR Cancer Prevention Recommendations and cancer risk. Nonetheless, this was sufficient to undertake the meta-analysis and to allow us to examine associations with breast, colorectal, lung, and prostate cancers separately. We undertook the analyses of all cancer combined because the recommendations relate to cancer as a whole. Interpretation of findings for any analyses of all cancers combined always requires some care because they are influenced by the mix of cancers included. However, our finding of 27% lower risk of cancer compared with the earlier estimate of 29% lower risk of incident total cancer with the healthiest lifestyle scores compared with the least healthy[35] provides confidence in the size of the health benefit. Furthermore, caution should be exercised in interpretation of estimates from some of the subgroups where numbers of studies were small (e.g., case-control studies of breast cancer). Although we were able to stratify our analyses according to menopausal status for breast cancer and to colorectal cancer subsite, the limited number of studies restricted our ability to explore the influence of other factors such as geographical location or hormone receptor status for breast cancer. Furthermore, only a few of the more common cancer sites were investigated; for example, only two studies investigated prostate cancer risk.[27,32] This highlights the need for additional epidemiological studies assessing associations between adherence to the current Cancer Prevention Recommendations and the risk of other cancers, particularly those where there is convincing evidence for the role of lifestyle factors (e.g., liver and stomach cancers).

Overall, the quality of the included studies, assessed using the Newcastle-Ottawa Scale, was good. The observed heterogeneity could result from methodological differences, including exposure ascertainment and scoring system used (discussed previously). For example, some studies collected body weight and anthropometric measurements by trained staff,[15,20,23] whereas others used self-reported data,[14,19,22,24] which is likely to influence the precision and accuracy of the collected data. We addressed this issue using a random effects model.[40] Furthermore, to limit the potential effects of confounders, we used risk estimates from the fully adjusted statistical models, which included covariates such as age, family history of cancer, ethnicity, and presence of comorbidities. The specific covariates included in individual studies differed which may have influenced the extent of residual confounding. All studies included smoking as a covariate with the exception of Jacobs and colleagues who reported that smoking status did not alter the crude odds ratio by more than 10%,[23] Korn et al., who stratified all analyses by smoking status,[32] and two studies that created their own lifestyle scores and included smoking as a score component.[15,16] When we performed sensitivity analyses removing these two studies, pooled effect estimates for any cancer, as well as for breast and lung cancers specifically, were largely unchanged. Interestingly, in subgroup analyses according to menopausal status, when the study by Arthur et al. (2020) was removed, the association between score and premenopausal cancer was strengthened in the categorical analysis, equating to a 49% lower risk of breast cancer in those in the highest score category.

In conclusion, the findings from this systematic review and meta-analysis provide strong evidence that adherence to the 2018 WCRF/AICR Cancer Prevention Recommendations reduces the risk of any cancer as well as the risk of breast, colorectal, and lung cancers. Because high levels of heterogeneity were observed, the pooled effect estimates should be interpreted with caution. Further studies investigating associations between adherence to the 2018 Cancer Prevention Recommendations and the risk of cancer at additional sites, particularly lifestyle-related cancers and the less common cancers, are warranted. Furthermore, additional cancer-related outcomes, such as cancer survival, as well as wider health-related outcomes, such as all-cause mortality, should be explored. Last, given the inconsistencies in operationalization of the standardized scoring system, which limits comparability between studies, we further encourage researchers to operationalize the published 2018 WCRF/AICR Score[7] as fully as possible.

AUTHOR CONTRIBUTIONS

Fiona C. Malcomson: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, visualization, writing - original draft, and writing - review and editing. **Christopher Wiggins:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing - original draft, and writing - review and editing. **Solange Parra-Soto:** Methodology, resources, and writing - review and editing. **Linda Sharp:** Funding acquisition, project administration, writing - original draft, and writing - review and editing. **Fred K. Ho:** Writing - review and editing. **Carlos Celis-Morales:** Writing - review and editing. **John C. Mathers:** Conceptualization, methodology, funding acquisition, project administration, supervision, writing - original draft, and writing - review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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