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REVIEW

A systematic review and meta-analysis of the 2007 WCRF/AICR score in relation to cancer-related health outcomes

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Available online 8 January 2020

Background: We conducted a systematic literature review and meta-analysis of observational studies investigating adherence to the 2007 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) lifestyle recommendations for cancer prevention and health outcomes.

Patients and methods: We searched PubMed and the in-house database of the WCRF Continuous Update Project for publications up to June 2019. Cross-sectional studies were only narratively reviewed given their heterogeneity while findings of cohort/case-control studies were synthesized in umbrella reviews and meta-analyses. Summary relative risks (RRs) and 95% confidence intervals (CI) were estimated using a random-effects model when at least two studies reported results on a specific outcome.

Results: Thirty-eight articles (17 prospective, 8 case-control, and 13 cross-sectional studies) were included. The summary RR per each point increment in the 2007 WCRF/AICR score was 0.90 (95% CI: 0.87—0.93, $n = 11$) for breast cancer, regardless of hormone receptor and menopausal status, 0.86 (95% CI: 0.82—0.89, $n = 10$) for colorectal cancer, and 0.93 (95% CI: 0.89—0.96, $n = 2$) for lung cancer risk. No statistically significant associations were reported for prostate ($n = 6$) and pancreatic cancers ($n = 2$). Adherence to the recommendations was associated with lower overall mortality (RR = 0.90, 95% CI 0.84—0.96, $n = 3$) and cancer-specific mortality (RR = 0.91, 95% CI 0.89—0.92; $n = 3$) in healthy populations, as well as with higher survival in cancer patients ($n = 2$). In cross-sectional studies, a healthier plasma marker profile and lower cancer risk factors in the general population and a better health status and quality of life in cancer patients/survivors were reported.

Conclusions: Adhering to the 2007 WCRF/AICR recommendations is associated with lower risks of cancer incidence, namely breast and colorectal cancers, and mortality. Primary prevention of cancer should emphasize modification of multiple lifestyle factors. Upcoming studies examining the recently updated 2018 guidelines will further clarify such associations.

Key words: 2007 WCRF/AICR recommendations, diet, physical activity, cancer, mortality, meta-analysis

INTRODUCTION

Cancer prevalence is predicted to increase to over 29.5 million globally by 2040, with estimates showing that between 30% and 50% of the most common cancers might be preventable through diet, nutrition, and physical activity.[1,2] The combination of these factors in lifestyle patterns may influence cancer risk more than each factor in isolation. For this reason, evidence underpinning the association between multiple lifestyle factors and cancer must be rigorously reviewed in order to provide a robust understanding of the epidemiology of cancer as a sound basis for research, public education, and public policy.

In 2007, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) issued ten recommendations for cancer prevention based on the most comprehensive collection of scientific evidence available at that time.[3] Taken together, the recommendations aim to help people reduce their risk of cancer by having a healthy weight, being physically active throughout life, and having healthy patterns of diet and alcohol consumption (Box 1). In 2012, a score reflecting combined adherence to such guidelines (hereafter, the 2007 WCRF/AICR score) was constructed in a large prospective study conducted in ten European countries. This study found that higher adherence to such recommendations was inversely associated with

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Box 1. WCRF/AICR 2007 recommendations for cancer prevention[3]

General recommendations

1. **Body fatness** — Be as lean as possible within the normal range of body weight
2. **Physical activity** — Be physically active as part of everyday life
3. **Foods and drinks that promote weight gain** — Limit consumption of energy-dense foods and avoid sugary drinks
4. **Plant foods** — Eat mostly foods of plant origin
5. **Animal foods** — Limit intake of red meat and avoid processed meat
6. **Alcoholic drinks** — Limit alcoholic drinks
7. **Preservation, processing, and preparation** — Limit consumption of salt and avoid moldy cereals (grains) or pulses (legumes)
8. **Dietary supplements** — Aim to meet nutritional needs through diet alone

Special recommendations

9. **Breastfeeding** — Mothers to breastfeed; children to be breastfed
10. **Cancer survivors** — Follow the recommendations for cancer prevention

cancer risk.[4] Since then, numerous researchers have constructed similar scores in different settings and have studied their association with different health outcomes, mostly cancer incidence, but also mortality, cancer risk factors, plasma biomarkers, and health status and quality of life in cancer patients or survivors.

More evidence has accumulated since the publication of the WCRF/AICR Second Expert Report and the cancer prevention recommendations have been updated in the 2018 WCRF/AICR Third Expert Report.[5] The revised recommendations remain highly consistent with the previous report but further emphasize the importance of adopting an overall healthy lifestyle pattern for cancer prevention rather than focusing on individual factors. Following that publication, a collaborative group was formed to develop a standardized scoring system and provide guidance for its applications.[6] The analysis of previous findings, methodological challenges, and evidence gaps in the studies that implemented scores based on the 2007 WCRF/AICR recommendations will help to clarify future directions for upcoming studies. Therefore, the aim of our study is to systematically review and carry out a meta-analysis of the published literature reporting associations between adherence to the 2007 WCRF/AICR recommendations and health outcomes.

METHODS

Literature search

Two reviewers (MS and DR) searched PubMed and two reviewers (DC and TN) searched the in-house database of the WCRF Continuous Update Project (CUP) (http://www.wcrf.org/int/research-we-fund/continuous-update-project-cup) for observational studies on the 2007 WCRF/AICR score and health outcomes up to 5 June 2019. The PubMed search strategy contained the following words: 'World Cancer Research Fund' or 'WCRF' or 'American Institute for Cancer Research' or 'AICR' combined with 'cancer', 'neoplasm', 'mortality', or 'health'. The CUP search can be accessed online in the protocols for each cancer through https://www.wcrf.org/dietandcancer/cancers. We did not impose any language restriction in the search nor contact any author for additional information.

Study selection

The inclusion criteria for the studies were (i) cohort, case-control, and cross-sectional studies without restriction of study population; (ii) studies that investigated the associations between adherence to a 2007 WCRF/AICR score and any health outcome, and (iii) studies reporting estimates of relative risk (RR) [e.g. hazard ratio (HR), risk ratio, or odds ratio] with the corresponding measure of variability [95% confidence intervals (CI) or *P* value]. Studies using the 2007 WCRF/AICR score but only including dietary recommendations were not selected[7–10] given that a strength and novelty of the score is that it models an overall lifestyle pattern including diet together with physical activity and weight management. In addition, we excluded a birth cohort in which the score was measured at mid-pregnancy and micronucleus frequency (a biomarker of early genetic effects) in mothers and newborns at birth.[11]

Data extraction

Study characteristics, operationalization of the 2007 WCRF/AICR score, and study results were extracted by two reviewers (DR and MS) including the name of the first author, publication year, country or region, study design, sample size and number of cases and deaths, gender, age, type of outcome, WCRF/AICR score categories, RR estimates and their corresponding 95% CI or *P* values, and confounder adjustments used in the studies. The data on cancer outcomes were extracted from the CUP database.

Displaying of findings

The results of all cohort and case-control studies were included in an umbrella review that encompassed all the relevant health outcomes identified. Categorical and dose-response results were further summarized by health outcome when at least two studies reported results and the required information for conducting a meta-analysis. Cross-sectional studies were only narratively reviewed given the heterogeneity of the study designs and outcomes examined. For all sections, only results with the most comprehensive adjustment for confounders were considered.

Statistical analyses

We calculated the summary RRs and 95% CIs using random-effects models that account for possible heterogeneity between studies.[12] Both categorical (comparing the highest

versus the lowest level of the score) and linear dose-response (per unit increment in the score) meta-analyses were performed.

For the dose-response meta-analyses, we calculated the RR estimates in the studies that reported results for a different increment (e.g. per 0.5-point increase or 1-point decrease) or from the categorical data using generalized least-squares for trend estimation[13] before pooling these with other studies that reported results per 1 point increase. To estimate dose-response trends from categorical data, at least three levels of exposure, number of cases and non-cases or population at risk, and exposure values per category had to be available or estimated using standard methods.[14,15] All studies reported close-ended categories (starting from 0 points), apart from one[16] in which we assumed 0 as the lowest boundary.

The Cochran Q test and I^2 test statistic were used to assess heterogeneity between studies.[17] I^2 <30%, 30% to <50%, and ≥50% were considered low, moderate, and high proportions of heterogeneity, respectively. Sources of heterogeneity were explored in subgroups defined by study design and geographical region. We also stratified results by menopausal status and hormone receptor status for breast cancer risk and by site for colorectal cancer. Small-study bias such as publication bias was assessed by Egger's test and visual inspection of the funnel plots.[18] Each study was omitted in turn to examine its influence on the summary RR.

A two-tailed P value of <0.05 was considered as statistically significant in the analyses, except for the generally low-powered Egger's test, where a P value of <0.10 was used as the cut-off point. All analyses were conducted using Stata version 14.0 (StataCorp, College Station, TX).

RESULTS

A total of 339 publications were identified. Of these, 272 were excluded on the basis of title and abstract, and 67 full-text publications were retrieved and assessed for inclusion. Twenty-nine publications were excluded for not fulfilling the inclusion criteria (8 publications based on the 1997 WCRF/AICR recommendations, 14 descriptive studies, 4 publications only operationalizing dietary recommendations, 1 birth cohort, 1 overlapping study, and 1 review). Hence, 38 publications were finally included in the systematic review: 13 cross-sectional studies,[19–31] 17 cohort studies,[4,32–47] and 8 case-control studies.[16,48–54] Twenty cohort and case-control studies assessed cancer incidence,[4,16,32–34,40–54] which, with the exception of one study that did not provide enough information for dose-response estimates,[49] were all included in the cancer incidence umbrella review. Among them 11 publications on breast cancer,[4,32,40–46,50,53] 10 on colorectal cancer,[4,16,32–34,40,41,47,53,54] 6 on prostate cancer,[4,32,40,41,48,53] and 2 of each on lung[4,41] and pancreatic[4,51] cancers were included in their respective meta-analyses. Finally, five cohort studies assessed overall mortality, two studied cancer survivors[38,39] and three studied the general population,[35–37] which were included in the mortality umbrella review. Those conducted on the general population were also included in meta-analyses of all-cause,[35,37] cancer,[35–37] and cardiovascular disease[35,37] mortality (see supplementary Flow Chart, available at *Annals of Oncology* online).

In all selected studies, adherence to or concordance with the 2007 WCRF/AICR recommendations was operationalized based on the available data in the studies and the individual cut-off points indicated in the recommendations (or the population distribution of the data). No standard scoring approach had been previously developed and thus, each study used different versions of the score that varied considerably both in the number of recommendations included (Table 1) and the cut-off points used in their operationalization (supplementary Table S1, available at *Annals of Oncology* online).

Most of the publications reported the distribution of sociodemographic characteristics according to the level of adherence to the 2007 WCRF/AICR score in their study populations. The largest study, the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort that included over half a million European participants, observed that those with higher scores tended to be younger, more highly educated, and less likely to be smokers or suffer from chronic diseases (e.g. hyperlipidemia, hypertension).[4,35] These patterns were also seen in populations of cancer survivors, in which higher scores were reported in those individuals with high educational level, non-smokers, fewer comorbid conditions, and greater perceived health status.[38,39]

Association with cancer risk

A total of 12 cohort and 8 case-control studies explored the association between the WCRF/AICR score and cancer risk (Table 2). Breast and colorectal cancers were the cancer sites most often investigated.

Breast cancer. Nine cohort[4,32,40–46] and three case-control studies[49,50,53] assessed adherence to the WCRF/AICR recommendations and risk of breast cancer (Table 2). In linear dose-response meta-analysis, including 21 753 breast cancer cases in 11 studies,[4,32,40–46,50,53] each one-point increment in the 2007 WCRF/AICR score resulted in a 10% (95% CI, 13% to 6%) lower risk of breast cancer (Figure 1). Substantial heterogeneity across the studies was detected (I^2 69.8%; P for heterogeneity <0.001), which is partly explained by differences in study design [i.e. case-control studies tend to observe stronger associations (Figure 1)], and study size [i.e. there was evidence of small-study effect/publication bias according to the funnel plot (data not shown)]. Results were similar in the meta-analysis stratified by geographical location, menopausal status, and hormone receptor tumor subtype (Table 3). Influence analyses did not suggest a strong influence from any of the individual studies on the summary estimates (data not shown). The highest versus lowest meta-analysis, including 11 studies[4,40–43,45,47,49,50,53] and 22 609 cases, yielded consistent results overall ($RR_{highestvslowest}$ = 0.74, 95% CI 0.65–0.83, I^2 = 67.6%, P for heterogeneity <0.001) and by subgroups (Table 3).

Table 1. Recommendations included in the 2007 WCRF/AICR score

Author, year	BW	PA	FPWG	PF	AF	A	S	SU	BF	CS	Other	Range
Cohort studies												
Romaguera, 2012	Y	Y	Y	Y	Y	Y			Y			0–7 (0–6 ♂)
Vergnaud, 2013	Y	Y	Y	Y	Y	Y			Y			0–7 (0–6 ♂)
Hastert, 2013	Y	Y	Y	Y	Y	Y						0–6
Inoue-Choi, 2013	Y	Y	Y	Y	Y	Y	Y					0–7
Catsburg, 2014	Y	Y	Y	Y	Y	Y	Y					0–7
Hastert, 2014	Y	Y	Y	Y	Y	Y						0–6
Makarem, 2015	Y	Y	Y	Y	Y	Y	Y					0–7
Romaguera, 2015	Y	Y	Y	Y	Y	Y			Y			0–7 (0–6 ♂)
Nomura, 2016 (IWHS)	Y	Y	Y	Y	Y	Y	Y					0–8
Harris, 2016	Y	Y	Y	Y	Y	Y		Y				0–7
Nomura, 2016 (BWHS, BC)	Y	Y	Y	Y	Y	Y	Y					0–7
Nomura, 2016 (BWHS, CRC)	Y	Y	Y	Y	Y	Y	Y					0–7
Lohse, 2016	Y	Y	Y	Y	Y	Y	Y					0–9
Hastert, 2016	Y	Y	Y	Y	Y	Y						0–6
Jones, 2018	Y	Y	Y	Y	Y	Y	Y		Y			0–8
Lavalette, 2018	Y	Y	Y	Y	Y	Y	Y	Y				0–8
Xu, 2019	Y	Y		Y	Y	Y		Y				0–6
Case-control studies												
Er, 2014	Y	Y	Y	Y	Y	Y						0–6
Castelló, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y			0–9 (0–8 ♂)
Fanidi, 2015	Y	Y	Y	Y	Y	Y			Y			0–7
Lucas, 2016	Y	Y	Y	Y	Y	Y	Y					0–7
Romaguera, 2017	Y	Y	Y	Y	Y	Y						0–6
Turati, 2017	Y	Y	Y	Y	Y	Y	Y					0–7
Bravi, 2017	Y	Y	Y	Y	Y	Y	Y					0–7
El Kinany, 2019	Y	Y	Y	Y	Y	Y						0–6
Cross-sectional studies												
Inoue-Choi, 2013	Y	Y		Y	Y	Y	Y					0–7
Arab, 2013	Y	Y	Y	Y	Y	Y	Y					0–9
Smith, 2014	Y	Y		Y	Y	Y	Y					0–7
Morimoto, 2015	Y	Y	Y	Y	Y	Y	Y				Y (Smoking)	0–8
Castelló, 2015	Y	Y	Y	Y	Y	Y	Y	Y				0–8
Song, 2015	Y	Y	Y	Y	Y		Y					0–12
Realdon, 2016		Y	Y	Y	Y	Y						0–6
Bruno, 2016		Y	Y	Y	Y	Y						0–5
Tabung, 2016	Y	Y	Y	Y	Y	Y						0–6
Lei, 2018	Y	Y	Y	Y	Y	Y						0–6
Breedveld-Peters, 2018	Y	Y	Y	Y	Y	Y		Y				0–10
Malcomson, 2018	Y	Y		Y	Y	Y	Y	Y			Y (Smoking)	0–8
Van Veen, 2019	Y	Y	Y	Y	Y	Y	Y	Y				0–8

A, alcohol; AF, animal foods; BF, breastfeeding; BW, body weight; CS, cancer survivors; FPWG, foods that promote weight gain; PA, physical activity; PF, plant foods; S, salt; SU, dietary supplements; Y, yes.

Colorectal cancer. Ten studies (six cohort[4,32–34,40,41,47] and three case-control studies[16,53,54]) evaluated adherence to the 2007 WCRF/AICR recommendations and colorectal cancer (Table 2). In the dose-response meta-analyses of all studies, including 11 017 cases, each point increment in the WCRF/AICR score resulted in a 14% (95% CI, 18% to 11%) lower risk of colorectal cancer (Figure 2). Heterogeneity across the studies was detected (I^2 53.2%; P for heterogeneity = 0.02) and is mainly explained by differences in study design (Figure 2). Indeed, case-control studies tend to find stronger inverse associations, while summary estimates from prospective studies are far more consistent (I^2 0.0%, P for heterogeneity = 0.97). Further sources of heterogeneity were explored in a meta-analysis stratified by geographical location and site, which showed similar associations across subgroups (Table 3). Overall, there was no evidence of small-study bias/publication bias and the influence analysis did not suggest a strong influence from any of the individual studies on the summary estimates (data not shown). The highest versus lowest meta-analysis, based on nine studies[4,16,33,34,40,41,47,53,54] and 10 954 cases, yielded similar results [$RR_{highestvslowest}$ = 0.62, 95% CI 0.56–0.70, I^2 = 49.7%, P for heterogeneity = 0.04)] (Table 3).

Other cancers. An umbrella review was conducted to display the dose-response results of other studies evaluating adherence to the 2007 WCRF/AICR recommendations and cancer risk (Figure 3). A total of 19 studies including data on 14 different cancer sites were displayed. For several cancer sites (i.e. bladder, endometrial, kidney, liver, lung, esophageal, ovarian, stomach, and upper aerodigestive cancer), data came from a single cohort study, the EPIC study. Dose-response meta-analyses revealed no associations for prostate (RR 0.99, 95% CI 0.97–1.02, I^2 0.0%, P for heterogeneity = 0.43, n = 6, 7444 cases) and pancreatic (RR 0.86, 95% CI 0.62–1.18, I^2 90.1%, P for heterogeneity <0.001, n = 2, 1082 cases) cancers. There was an inverse association for lung cancer (RR 0.93, 95% CI 0.89–0.96, I^2 0.0%, P for heterogeneity = 0.43, n = 2, 2648 cases).

https://doi.org/10.1016/j.annonc.2020.01.001

Table 2. Summary of studies

Author, year Country	Study name Study design Sex, age (years)	Cases/total *N* (years follow-up) or cases/controls *Cases of secondary outcomes*	Outcome *Secondary outcomes*	Components of the WCRF/AICR score *Score range*	Comparison	RR (95% CI) *RR (95% CI) for secondary outcomes*	Adjustment factors
A. Cancer incidence							
Multiple cancer sites							
Romaguera, 2012 Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, UK	EPIC Cohort M/W (25—70 y)	36 994/386 355 (11 y) *(a) 9358* *(b) 1148* *(c) 906* *(d) 4039* *(e) 3880* *(f) 2462* *(g) 1514* *(h) 783* *(i) 745* *(j) 696* *(k) 602* *(l) 522* *(m) 312*	Total cancer *(a) Breast* *(b) Endometrial* *(c) Ovarian* *(d) Prostate* *(e) Colorectal* *(f) Lung* *(g) Bladder* *(h) Pancreas* *(i) Kidney* *(j) Stomach* *(k) UADT* *(l) Liver* *(m) Esophageal*	7 recommendations (BW, PA, FPWG, PF, AF, A, BF) *0—7 points women* *0—6 points men*	High (5—6 M/6—7 W) versus Low (0—2 M/0—3 W) *For specific cancers, High (4—6 M/5—7 W) versus Low (0—2 M/0—3 W)* 1-unit increase	0.82 (0.75—0.90) *(a) 0.84 (0.78—0.90)* *(b) 0.77 (0.62—0.94)* *(c) 0.99 (0.79—1.25)* *(d) 1.02 (0.91—1.14)* *(e) 0.73 (0.65—0.81)* *(f) 0.86 (0.74—1.00)* *(g) 0.84 (0.69—1.02)* *(h)1.00 (0.78—1.28)* *(i) 0.71 (0.54—0.93)* *(j) 0.62 (0.46—0.83)* *(k) 0.69 (0.50—0.95)* *(l) 0.85 (0.62—1.16)* *(m) 0.58 (0.38—0.90)* 0.95 (0.93—0.97) *(a) 0.95 (0.93—0.97)* *(b) 0.88 (0.83—0.94)* *(c) 0.95 (0.89—1.02)* *(d) 1.00 (0.96—1.04)* *(e) 0.88 (0.84—0.91)* *(f) 0.92 (0.89—0.96)* *(g) 0.94 (0.89—1.00)* *(h) 1.00 (0.92—1.08)* *(i) 0.91 (0.85—0.99)* *(j) 0.84 (0.78—0.91)* *(k) 0.82 (0.74—0.90)* *(l) 0.90 (0.81—0.99)* *(m) 0.84 (0.73—0.96)*	Center, age, sex, energy intake, education, smoking, chronic disease at baseline. For women also contraceptive pill use, hormone replacement therapy use, age first menarche, age first pregnancy, menopausal status
Makarem, 2015 USA	Framingham offspring cohort Cohort M/W (66 y)	480/2983 (11.5 y) *(a) 124* *(b) 153* *(c) 63*	Obesity-related cancers *(a) Breast* *(b) Prostate* *(c) Colorectal*	7 recommendations (BW, PA, FPWG, PF, AF, A, S) *0—7 points*	1-unit increase	0.94 (0.86—1.02) *(a) 0.87 (0.74—1.03)* *(b) 1.08 (0.92—1.27)* *(c) 0.87 (0.68—1.12)*	Age, sex, smoking
Romaguera, 2017 Spain	Multi-case-control Spain (MCC-Spain) study Case control M/W (20—85 y)	3925/3431 *(a) 1718* *(b) 1169* *(c) 533* *(d) 1343* *(e) 483* *(f) 860* *(g) 902* *(h) 231* *(i) 94* *(j) 864*	Colorectal, breast, and prostate cancer *(a) Colorectal* *(b) Colon* *(c) Rectal* *(d) Breast* *(e) Premenopausal* *(f) Postmenopausal* *(g) HR+* *(h) HER2+* *(i) TN* *(j) Prostate*	6 recommendations (BW, PA, FPWG, PF, AF, A) *0—6 points*	T3 (4.25—6 M/4.5—6 W) versus T1 (0.25—3 M/0.5—3.5 W)	(a) 0.54 (0.45—0.63) (b) 0.52 (0.43—0.63) (c) 0.54 (0.41—0.71) (d) 0.76 (0.63—0.92) (e) 0.97 (0.68—1.40) (f) 0.64 (0.51—0.81) (g) 0.81 (0.65—1.00) (h) 0.53 (0.36—0.78) (i) 0.89 (0.51—1.54) (j) 0.93 (0.72—1.20) (k) 0.73 (0.52—1.01) (l) 1.27 (0.92—1.76)	Sex, age, education, region, family history of cancer (colorectal, breast, or prostate, depending on the analysis), smoking, and energy intake. For breast cancer, also hormone replacement therapy use, oral contraceptive use, age at menarche, age first pregnancy, number of children, menopausal status

Continued

Table 2. Continued

Author, year Country	Study name Study design Sex, age (years)	Cases/total *N* (years follow-up) or cases/controls *Cases of secondary outcomes*	Outcome *Secondary outcomes*	Components of the WCRF/AICR score *Score range*	Comparison	RR (95% CI) *RR (95% CI) for secondary outcomes*	Adjustment factors
		(k) 445 *(l) 405*	*(k) Prostate undifferentiated* *(l) Prostate moderately/well differentiated*		1-unit increase	(a) 0.75 (0.70—0.81) (b) 0.75 (0.69—0.81) (c) 0.76 (0.68—0.84) (d) 0.85 (0.78—0.93) (e) 0.99 (0.84—1.16) (f) 0.78 (0.70—0.87) (g) 0.87 (0.79—0.96) (h) 0.79 (0.67—0.94) (i) 0.87 (0.68—1.12) (j) 0.98 (0.88—1.08) (k) 0.87 (0.76—0.99) (l) 1.13 (0.99—1.29)	
Lavalette, 2018 France	NutriNet-Santé Study Cohort M/W (61.6 y)	1489/40 054 (2009—2017) *(a)* 488 *(b) 222* *(c) 118*	Total cancer *(a)* Breast *(b) Prostate* *(c) Colorectal*	8 recommendations (BW, PA, FPWG, PF, AF, A, S, SU) *0—8 points*	Q5 (5.75—8 M/6—8 W) versus Q1 (0.75—3.5 M/ 0.75—3.75 W) 1-unit increase	0.66 (0.55—0.79) *(a) 0.64 (0.46—0.89)* *(b) 0.54 (0.34—0.86)* *(c) 0.58 (0.30—1.12)* 0.88 (0.84—0.92) *(a) 0.86 (0.79—0.94)* *(b) 0.88 (0.78—1.00)* *(c) 0.86 (0.72—1.03)*	Age, sex, education, smoking, number of 24-h dietary records, height, and family history of cancer. For women also, number of biological children, menopausal status, hormonal treatment of menopause, and oral contraception use
Xu, 2019 Canada	Alberta's Tomorrow Project (ATP) Study Cohort M/W (50.5 y)	2066/25 100 (11.7 y) *(a)* 454 *(b) 360* *(c) 221* *(d) 186* *(e) 611* *(f) 1209*	Total cancer *(a)* Breast *(b) Prostate* *(c) Colorectal* *(d) Lung* *(e) Smoking related* *(f) Obesity related*	6 recommendations (BW, PA, PF, AF, A, SU) *0—6 points*	High (4—6) versus Low (0—2)	0.87 (0.78—0.98) *(a)* 0.86 (0.68—1.09) *(b) 0.99 (0.76—1.29)* *(c) 0.67 (0.48—0.95)* *(d) 0.84 (0.58—1.22)* *(e) 0.79 (0.65—0.97)* *(f) 0.86 (0.75—0.99)*	Age, sex, marital status, education, employment status, annual household income, smoking, first-degree family history of cancer, history of chronic disease (high blood pressure, angina, high cholesterol in blood, heart attack, stroke), and hormone replacement for women
Breast cancer							
Hastert, 2013 USA	Vitamins and lifestyle (VITAL) Study Cohort M/W (50—76 y)	899/30 797 (6.7 y)	Postmenopausal breast cancer (a) *ER+* (b) *ER—*	6 recommendations (BW, PA, FPWG, PF, AF, A) *0—6 points*	High (5—6) versus Low (0) 1-unit increase	0.40 (0.25—0.65) 0.89 (0.84—0.95) *(a) 0.90 (0.85—0.96)* *(b) 0.84 (0.72—0.99)*	Age, education, race, mammography, family history, age at menarche, age at first birth, age at menopause, years of hormone therapy, energy intake
Catsburg, 2014 Canada	Canadian National Breast Screening Study Cohort W (40—59 y)	1970/47 130 (16.6 y)	Breast cancer	7 recommendations (BW, PA, FPWG, PF, AF, A, S) *0—7 points*	High (6—7) versus Low (0—1) 1-unit increase	0.79 (0.57—1.10) 0.95 (0.91—0.98)	Age, reproductive factors, family history, benign breast disease, menopausal status, study center
Fanidi, 2015 Mexico	Cancer de Mama (CAMA) Study	980/1074 *(a) 405* *(b) 575*	Breast cancer *(a) Premenopausal* *(b) Postmenopausal*	7 recommendations (BW, PA, FPWG, PF, AF, A, BF)	Q4 versus Q1 (0—3.25)	1.04 (0.78—1.41) *(a) 1.17 (0.75—1.82)* *(b) 0.97 (0.64—1.46)*	Age, region, health care institution, age first pregnancy, number

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Table 2. Continued

Author, year Country	Study name Study design Sex, age (years)	Cases/total *N* (years follow-up) or cases/controls *Cases of secondary outcomes*	Outcome *Secondary outcomes*	Components of the WCRF/AICR score *Score range*	Comparison	RR (95% CI) *RR (95% CI) for secondary outcomes*	Adjustment factors
	Case control W (35—69 y)			*0—7 points*			pregnancies, socioeconomic status, age menarche, hormone therapy, family history
Castelló, 2015 Spain	EpiGEICAM Case control W (22—71 y)	973/973 *(a) 513* *(b) 460* *(c) 653* *(d) 199* *(e) 119*	Breast cancer *(a) Premenopausal* *(b) Postmenopausal* *(c) ER+/PR+ & HER2—* *(d) HER2+* *(e) ER— & PR— & HER2—*	9 recommendations (BW, PA, FPWG, PF, AF, A, S, SU, BF) *0—9 points*	Low (0—<3) versus High (6—9) 1-unit decrease	2.98 (1.59—5.59) *(a) 2.66 (1.23—5.76)* *(b) 3.60 (1.24—10.47)* *(c) 3.60 (1.84—7.05)* *(d) 4.23 (1.66—10.78)* *(e) 2.32 (1.20—4.46)* 1.22 (1.11—1.34) *(a) 1.20 (1.06—1.36)* *(b) 1.24 (1.10—1.41)* *(c) 1.26 (1.14—1.40)* *(d) 1.20 (1.03—1.40)* *(e) 1.20 (0.99—1.46)*	Age, hospital, energy intake, smoking, age at first delivery, education, history of breast problems, family history of breast cancer, and menopausal status
Nomura, 2016 USA	Iowa Women's Health Study (IWHS) Cohort W (61.7 y)	3189/36 626 (1986—2010)	Postmenopausal breast cancer	7 recommendations (BW, PA, SD, PF, AF, A, S) *0—8 points*	High (6—8) versus Low (0—3.5) 0.5-unit increase	0.76 (0.67—0.87) 0.94 (0.90—0.97)	Age, smoking, education, hormone replacement therapy, family history of breast cancer, menarche age, menopause age, and parity
Harris, 2016 Sweden	Swedish Mammography Cohort (SMC) Cohort W (61.4 y)	1388/31 514 (15 y) *(a) 746* *(b) 118*	Postmenopausal breast cancer *(a) ER+/PR+* *(b) ER—/ER—*	7 recommendations (BW, PA, FPWG, PF, AF, A, SU) *0—7 points*	High (6—7) versus Low (0—2) 1-unit increase	0.49 (0.35—0.70) *(a) 0.44 (0.27—0.70)* *(b) 0.90 (0.33—2.42)* 0.89 (0.83—0.95) *(a) 0.86 (0.79—0.94)* *(b) 1.01 (0.79—1.29)*	Age, height, education, oral contraceptive use, hormone replacement therapy use, age at menarche, age at menopause, family history of breast cancer, history of benign breast disease, smoking
Nomura, 2016 USA	Black Women's Health Study (BWHS) Cohort W (21—69 y)	1567/42 792 (13.86 y) *(a) 678* *(b) 826* *(c) 686* *(d) 196* *(e) 399*	Breast cancer *(a) Premenopausal* *(b) Postmenopausal* *(c) ER+ and PR+* *(d) ER+ or PR+* *(e) ER— and PR—*	7 recommendations (BW, PA, SD, PF, AF, A, S) 'time-varying score' *0—7 points*	High (>4—7) versus Low (<3) 0.5-unit increase	0.84 (0.65—1.08) *(a) 0.67 (0.44—1.03)* *(b) 1.00 (0.72—1.40)* *(c) 0.97 (0.67—1.42)* *(d) 1.33 (0.70—2.53)* *(e) 0.32 (0.14—0.74)* 0.89 (0.84—0.96) *(a) 0.90 (0.82—1.00)* *(b) 0.90 (0.81—0.99)* *(c) 0.93 (0.83—1.03)* *(d) 1.02 (0.84—1.24)* *(e) 0.85 (0.74—0.98)*	Age, region, energy intake, smoking, family history of breast cancer, education, menopausal status, oral contraceptive use, parity, menopausal hormone use
Colorectal cancer Nomura, 2016 USA	Black Women's Health Study (BWHS) Cohort W (21—69 y)	328/42 792 (15.1 y) *(a) 259*	Colorectal cancer *(a) Colon*	7 recommendations (BW, PA, SD, PF, AF, A, S)	High (>4—7) versus Low (<3) 0.5-units increase	0.51 (0.23—1.10) *(a) 0.54 (0.23—1.26)* 0.98 (0.84—1.15) *(a) 1.00 (0.83—1.19)*	Age, region, energy intake, smoking, family history of colorectal cancer, education, menopausal status, diabetes,

Continued

Table 2. Continued

Author, year Country	Study name Study design Sex, age (years)	Cases/total *N* (years follow-up) or cases/controls *Cases of secondary outcomes*	Outcome *Secondary outcomes*	Components of the WCRF/AICR score *Score range*	Comparison	RR (95% CI) *RR (95% CI) for secondary outcomes*	Adjustment factors
				'time-varying score' *0—7 points*			insulin usage, aspirin usage, colonoscopy, sigmoidoscopy
Hastert, 2016 USA	VITAL Study Cohort M/W (50—76 y)	546/66 920 (7.6 y)	Colorectal cancer	6 recommendations (BW, PA, FPWG, PF, AF, A) *0—6 points*	High (4—6) versus Low (0) 1-unit increase	0.42 (0.26—0.66) 0.87 (0.80—0.95)	Age, sex, education, race, colonoscopy/sigmoidoscopy in 10 years before baseline, family history of colorectal cancer, NSAID use, other cancer diagnosis, energy intake
Turati, 2017 Italy	Two case control M/W (19—74; 31—80 y)	2246/4463 *(a) 1420* *(b) 818*	Colorectal cancer *(a) Colon* *(b) Rectum*	7 recommendations (BW, PA, FPWG, FP, AF, A, S) *0—7 points*	High (5—7) versus Low (<3.5) 1-unit increase	0.67 (0.56—0.80) *(a) 0.67 (0.54—0.82)* *(b) 0.67 (0.52—0.87)* 0.83 (0.78—0.89)	Age, sex, study, center, education, family history of colorectal cancer, and non-alcoholic energy intake
Jones, 2018 UK	UK Women's Cohort Study Cohort W (52.3 y)	444/30 963 (17.4 y) *(a) 322* *(b) 146*	Colorectal cancer *(a) Colon* *(b) Rectum*	8 recommendations (BW, PA, FPWG, PF, AF, A, S, BF) *0—8 points*	High (>5—8) versus Low (0—3) 1-unit increase	0.73 (0·48—1·10) *(a) 0.72 (0.44—1.19)* *(b) 0.61 (0.29—1.26)* 0.92 (0.82—1.03) *(a) 0.93 (0.82—1.07)* *(b) 0.88 (0.72—1.08)*	Age, smoking, socioeconomic status and family history of colorectal cancer
El Kinany, 2019 Morocco	Case control M/W (56 y)	1453/1453 *(a) 729* *(b) 724*	Colorectal cancer *(a) Colon* *(b) Rectum*	6 recommendations (BW, PA, FPWG, PF, AF, A) *0—6 points*	T3 (>4—6) versus T1 (<3.5)	0.58 (0.51—0.66) *(a) 0.63 (0.53—0.76)* *(b) 0.52 (0.43—0.63)*	Age, area of residence, education, monthly income, family history of colorectal cancer, smoking, energy intake
Head and neck							
Bravi, 2017 Italy	Two case control M/W (19—82; 21—80 y)	1495/3458 *(a) 871* *(b) 624*	Head and neck cancer *(a) Oral cavity and pharynx* *(b) Larynx*	7 recommendations (BW, PA, FPWG, FP, FA, A, S) *0—7 points*	High (5—7) versus Low (<3) 1-unit increase	0.27 (0.20—0.37) *(a) 0.32 (0.22—0.49)* *(b) 0.24 (0.15—0.38)* 0.60 (0.55—0.66) *(a) 0.61 (0.54—0.69)* *(b) 0.59 (0.51—0.68)*	Age, sex, center, year of interview, education, smoking, body mass index, non-alcohol energy intake
Prostate cancer							
Er, 2014 UK	PSA-tested cohort ProtecT trial Case control M (50—69 y)	1806/12 005 *(a) 1612* *(b) 184* *(c) 1204* *(d) 596*	PSA-detected prostate cancer *(a) Localized* *(b) Locally advanced* *(c) Low grade* *(d) High grade*	6 recommendations (BW, PA, FPWG, PF, AF, A) *0—6 points*	High (4—6) versus Low (0—2) 1-unit increase	1.01 (0.85—1.19) *(a) 0.99 (0.83—1.19)* *(b) 1.16 (0.72—1.84)* *(c) 1.00 (0.81—1.24)* *(d) 1.00 (0.76—1.31)* 0.99 (0.94—1.05) *(a) 0.99 (0.93—1.05)* *(b) 1.00 (0.85—1.18)* *(c) 1.00 (0.93—1.07)* *(d) 0.97 (0.89—1.07)*	Age, center, family history of prostate cancer, smoking, total energy intake
Pancreatic cancer							
Lucas, 2016 Italy	Case control M/F (63 y)	299/596	Pancreatic cancer	7 recommendations (BW, PA, FPWG, PF, AF, A, S) *0—7 points*	High (5—7) versus Low (<3.5) 1-unit increase	0.41 (0.24—0.68) 0.72 (0.60—0.87)	Sex, study center, year of interview, age, education, smoking, and history of diabetes

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https://doi.org/10.1016/j.annonc.2020.01.001

Table 2. Continued

Author, year Country	Study name Study design Sex, age (years)	Cases/total *N* (years follow-up) or cases/controls *Cases of secondary outcomes*	Outcome *Secondary outcomes*	Components of the WCRF/AICR score *Score range*	Comparison	RR (95% CI) *RR (95% CI) for secondary outcomes*	Adjustment factors
B. Mortality							
General population							
Vergnaud, 2013 Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, UK	EPIC Cohort M/W (25—70 y)	23 828/378 864 (12.8 y) *(a) 9388* *(b) 5229* *(c) 1004* *(d) 4228*	All-cause mortality *Death due to:* *(a) Cancer* *(b) Circulatory disease* *(c) Respiratory disease* *(d) Other causes*	7 recommendations (BW, PA, FPWG, PF, AF, A, BF) *0—7 points women* *0—6 points men*	High (5—6 M/6—7 W) versus Low (0—2 M/0—3 W) 1-unit increase	0.66 (0.60—0.73) *(a) 0.80 (0.69—0.93)* *(b) 0.56 (0.46—0.69)* *(c) 0.50 (0.31—0.80)* *(d) 0.55 (0.43—0.70)* 0.87 (0.86;0.88) *(a) 0.91 (0.89—0.93)* *(b) 0.83 (0.81—0.86)* *(c) 0.79 (0.74—0.85)* *(d) 0.83 (0.80—0.86)*	Sex, age, center, education, smoking, menopausal status
Hastert, 2014 USA	VITAL Study Cohort M/F (50—76 y)	1595/57 841 (7.7 y)	Cancer-specific mortality	6 recommendations (BW, PA, FPWG, PF, AF, A) *0—6 points*	High (5—6) versus Low (0) 1-unit increase	0.39 (0.24—0.62) 0.89 (0.84—0.95)	Age, sex, education, race/ethnicity, screenings, NSAI/aspirin use, smoking, energy intake, reproductive factors
Lohse, 2016 Switzerland	MONItoring the trends and determinants in Cardiovascular disease (MONICA) & National Research Program 1A (NRP1A) Cohort M/W (25—74 y)	2715/16 722 (21.7 y) *(a) 992* *(b) 187* *(c) 57* *(d) 21* *(e) 79* *(f) 40* *(g) 55* *(h) 39* *(i) 115* *(j) 71* *(k) 73* *(l) 60* *(m) 828*	All-cause mortality *(a) Total cancer death* *(b) Lung* *(c) Upper aerodigestive tract* *(d) Stomach* *(e) Colorectal* *(f) Liver* *(g) Pancreatic* *(h) Urinary tract* *(i) Blood* *(j) Prostate* *(k) Breast* *(l) Female genital tract* *(m) Cardiovascular disease death*	7 recommendations, 9 sub-recommendations (BW, PA, SB, ED, FV, G, AF, A, S) *0—9 points*	High (5—9) versus Low (0—3.5) 1-unit increase	0.82 (0.75—0.89) *(a) 0.74 (0.64—0.86)* *(b) 0.72 (0.51—0.99)* *(c) 0.49 (0.26—0.92)* *(d) 0.34 (0.14;0.83)* *(e) 0.84 (.050—1.42)* *(f) 1.07 (0.54—2.11)* *(g) 0.65 (0.35—1.20)* *(h) 0.63 (0.31—1.28)* *(i) 1.04 (0.65—1.67)* *(j) 0.48 (0.28—0.82)* *(k) 0.76 (0.45—1.30)* *(l) 0.66 (0.35—1.25)* *(m) 0.96 (0.82—1.13)* 0.93 (0.90—0.95) *(a) 0.90 (0.86—0.94)* *(b) 0.90 (0.81—1.00)* *(c) 0.82 (0.67—1.00)* *(d) 0.71 (0.54—0.95)* *(e) 0.86 (0.73—1.02)* *(f) 0.98 (0.77—1.24)* *(g) 0.88 (0.72—1.07)* *(h) 0.99 (0.78—1.26)* *(i) 0.98 (0.85—1.13)* *(j) 0.79 (0.66—0.95)* *(k) 0.91 (0.77—1.08)* *(l) 0.90 (0.73—1.09)* *(m) 0.97 (0.92—1.02)*	Age, sex, education, marital status, study, language region, nationality, smoking

Continued

Table 2. Continued

Author, year Country	Study name Study design Sex, age (years)	Cases/total *N* (years follow-up) or cases/controls *Cases of secondary outcomes*	Outcome *Secondary outcomes*	Components of the WCRF/AICR score *Score range*	Comparison	RR (95% CI) *RR (95% CI) for secondary outcomes*	Adjustment factors
Cancer survivors							
Inoue-Choi, 2013 USA	Iowa Women's Health Study Cohort W (78.9 y)	461/2017 (5.4 y) *(a) 184* *(b) 145*	All-cause mortality among older female cancer survivors *(a) Cancer-specific mortality* *(b) Cardiovascular disease-specific mortality* Note that it also provided results according to primary cancer site, not included here.	7 recommendations (BW, PA, SD, PF, AF, A, S) *0—7 points*	Q4 (6—8) versus Q1 (1.5—4)	0.67 (0.49—0.90) *(a) 0.63 (0.39—1.04)* *(b) 0.92 (0.57—1.47)*	Age, number of comorbid conditions, perceived health, smoking, cancer stage, type, treatment, other cancer diagnosis, person-years since diagnosis
Romaguera, 2015 Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, UK	EPIC Cohort M/W (25—70 y)	872/3292 (4.2 y) *1113*	Colorectal cancer-specific mortality among colorectal cancer cases *Overall mortality among colorectal cancer cases*	7 recommendations (BW, PA, FPWG, PF, AF, A, BF) *0—7 points women* *0—6 points men*	High (4—6 M/5—7 W) versus Low (0—2 M/0—3 W) 1-unit increase	0.70 (0.56—0.89) *0.79 (0.65—0.98)* 0.90 (0.83—0.97) *0.93 (0.87—0.99)*	Age, country, sex, education, smoking, year of colorectal cancer diagnosis, tumor stage, grade, and site

M, men; NSAID, nonsteroidal anti-inflammatory drug; Q, quantile; T, tertile; UADT, upper aerodigestive track; W, women.
Components of the 2007 WCRF/AICR score: A, alcohol; AF, animal foods; BW, body weight; FPWG, foods that promote weight gain; PA, physical activity; PF, plant foods; S, salt; SU, dietary supplements.
Sub-recommendations of the 2007 WCRF/AICR score: ED, energy-dense foods (excluding sweet drinks); F, fiber; FV, fruits and vegetables; G, grains; SB, sedentary behavior; SD, sweet drinks.
In Xu et al., 2019. Smoking-related cancers include bladder, colon, esophagus, kidney, larynx, liver, lung and bronchus, ovary (mucinous tumors), pancreas, rectum, stomach, and uterine cervical cancers. Obesity-related cancers include breast, prostate, colon, rectum, endometrial, kidney, and ovarian cancers.

https://doi.org/10.1016/j.annonc.2020.01.001

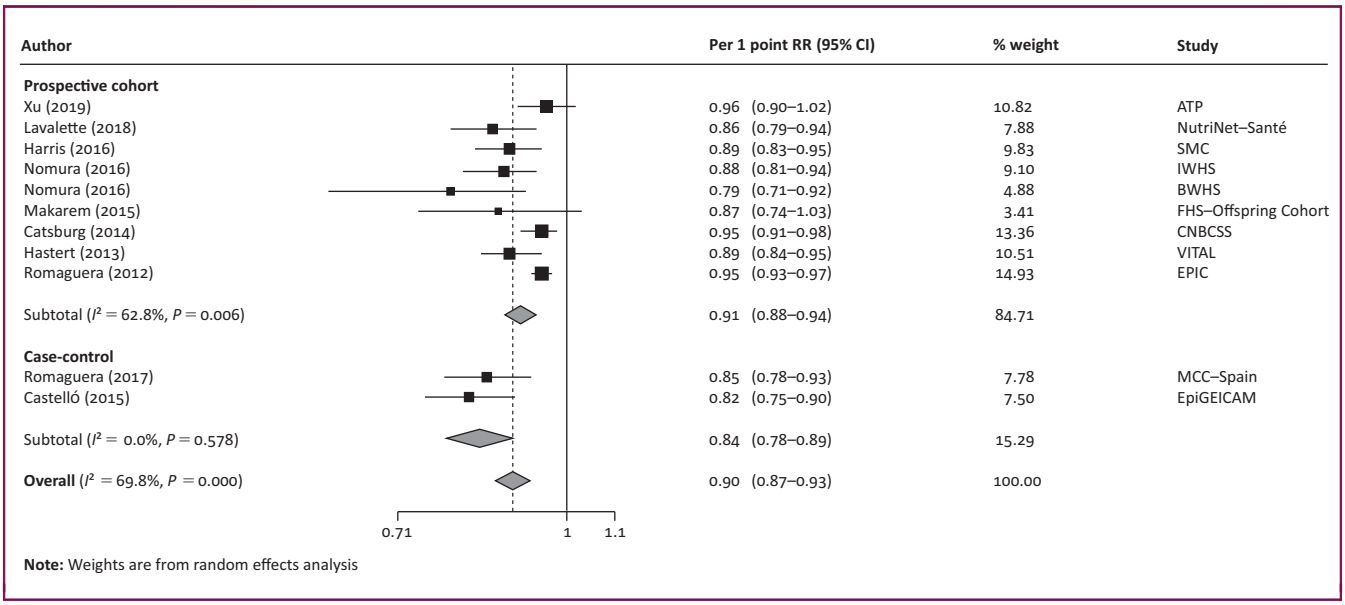

Figure 1. Dose-response meta-analysis of studies examining the association between adherence to the WCRF/AICR recommendations and breast cancer risk by study design.
The results from the study by Castelló et al.[50] were inverted and those from the study by Nomura et al.[44,45] were converted from 0.5- to 1-point increase. Dose-response estimates were calculated from the categorical data for the study by Xu et al.,[41] but not for the study by Fanidi et al.[49] (not included here), which did not provide enough data. The studies by Nomura et al.[44] (IWHS), Hastert et al.,[42] and Harris et al.[46] only included postmenopausal women.

Association with mortality

In the general population. Three cohort studies evaluated adherence to the 2007 WCRF/AICR recommendations and mortality in the general population[35–37] (Table 2, Figure 4A). Dose-response meta-analyses revealed inverse associations between adherence to the 2007 WCRF/AICR

Table 3. Subgroup meta-analyses of studies examining adherence to the WCRF/AICR score and breast and colorectal cancer risk

	Dose-response meta-analysis (1-unit increase)				Highest versus lowest meta-analysis			
	n	Summary RR (95% CI)	I^2 (%)	*Ph*	*n*	Summary RR (95% CI)	I^2 (%)	*Ph*
Breast cancer								
All studies[a,b]	11	0.90 (0.87–0.93)	69.8	<0.001	11	0.74 (0.65–0.83)	67.6	<0.001
Study design								
Prospective cohort	9	0.91 (0.88–0.94)	62.8	0.01	8	0.73 (0.64–0.83)	65.7	0.01
Case-control	2	0.84 (0.78–0.89)	0.0	0.58	3	0.74 (0.46–1.09)	80.8	0.01
Geographical location								
North America	6	0.91 (0.86–0.95)	61.4	0.02	5	0.76 (0.64–0.89)	53.4	0.07
Europe	5	0.88 (0.83–0.94)	80.0	<0.001	5	0.65 (0.52–0.82)	78.6	<0.001
South America					1	1.04 (0.77–1.40)	–	–
Menopausal status								
Premenopausal	4	0.89 (0.81–0.99)	38.6	0.18	4	0.80 (0.55–1.17)	61.5	0.05
Postmenopausal	7	0.86 (0.83–0.89)	12.3	0.35	7	0.66 (0.53–0.83)	71.5	<0.001
Hormone receptor								
HR positive	6	0.87 (0.83–0.91)	3.7	0.39	5	0.70 (0.47–1.04)	75.4	<0.001
HR negative	6	0.84 (0.77–0.91)	0.0	0.56	5	0.57 (0.40–0.80)	33.1	0.20
Colorectal cancer								
All studies[b]	10	0.86 (0.82–0.89)	53.2	0.02	9	0.62 (0.56–0.70)	49.7	0.04
Study design								
Prospective cohort	7	0.89 (0.86–0.91)	0.0	0.97	6	0.67 (0.57–0.78)	19.7	0.29
Case control	3	0.81 (0.76–0.88)	79.2	0.01	3	0.59 (0.53–0.66)	35.1	0.21
Geographical location								
Europe	5	0.84 (0.78–0.90)	75.8	<0.001	5	0.65 (0.56–0.75)	55.5	0.06
North America	4	0.89 (0.84–0.94)	0.0	0.87	3	0.55 (0.40–0.75)	22.5	0.28
North Africa	1	0.85 (0.82–0.89)	–	–	1	0.58 (0.51–0.66)	–	–
Site								
Colon	5	0.87 (0.80–0.94)	77.7	<0.001	5	0.60 (0.54–0.67)	1.6	0.40
Rectal	4	0.84 (0.78–0.91)	70.7	0.02	4	0.56 (0.49–0.64)	0.0	0.47

n denotes the number of risk estimates and *Ph* the *P* for heterogeneity.
[a] The cohort study by Makarem et al. 2015 was not included in the categorical meta-analysis of breast and colorectal cancers (it only provided dose-response estimates).
[b] The case-control study by Fanidi et al. 2015 could not be included in the dose-response meta-analysis of breast cancer (not enough information was provided to compute dose-response estimates).

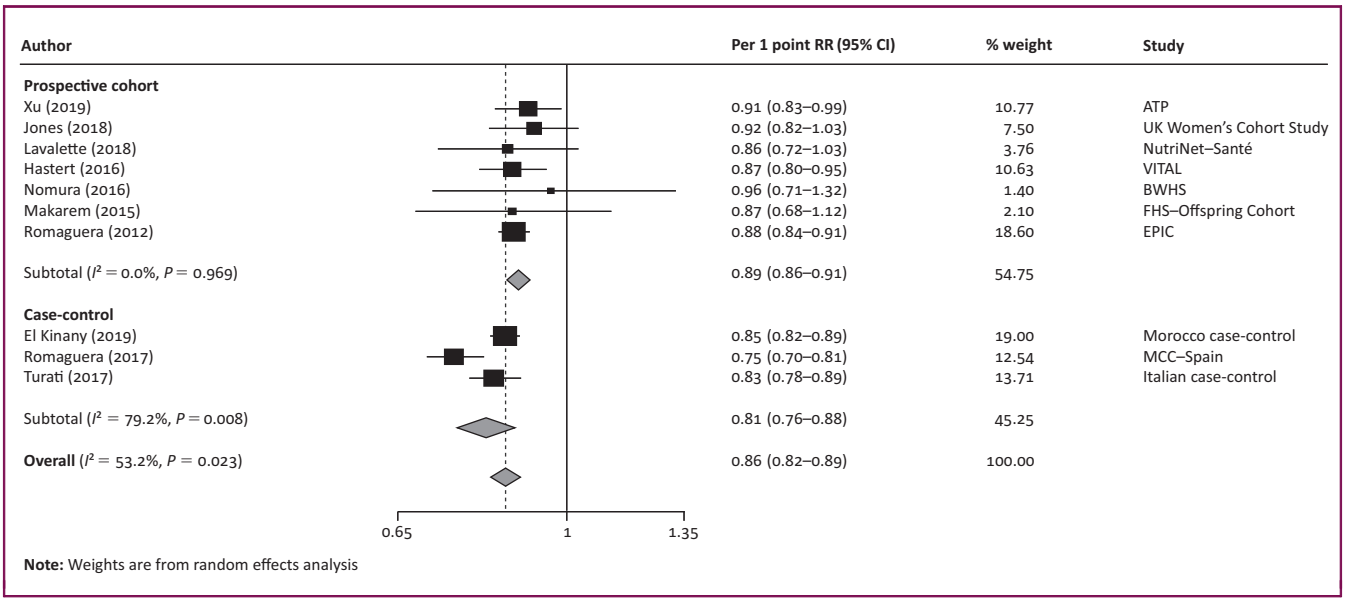

Figure 2. Dose-response meta-analysis of studies examining the association between adherence to the WCRF/AICR recommendations and colorectal cancer risk by study design.
Dose-response estimates were calculated from the categorical data for the study by El Kinany et al.[16] The results from Nomura et al.[47] were converted from 0.5- to 1-point increase.

score and overall mortality (RR 0.90, 95% CI 0.84—0.96) with a high heterogeneity between the two studies (I^2 94.9%, P for heterogeneity <0.001, n = 2) (data not shown). Greater adherence to the score was also associated with lower cancer-specific mortality (RR 0.91, 95% CI 0.89—0.92, I^2 0.0%, P for heterogeneity 0.86, n = 3) while null associations were reported for cardiovascular disease mortality (RR 0.90, 95% CI 0.77—1.04, I^2 96.2%, P for heterogeneity <0.001, n = 2).

In cancer survivors. Two cohort studies assessed the impact of following the 2007 WCRF/AICR recommendations (prediagnostic concordance) on survival in cancer patients (Table 2, Figure 4B). Inoue-Choi et al. found a lower all-cause mortality among older female cancer survivors with greater adherence to such recommendations ($HR_{highvslow}$ 0.67, 95% CI 0.49—0.90) yet null results were reported for cancer and cardiovascular specific mortality.[38] Similarly, Romaguera et al. reported a lower overall mortality ($HR_{highvslow}$ 0.79, 95% CI 0.65—0.98) and colorectal cancer mortality ($HR_{highvslow}$ 0.70, 95% CI 0.56—0.89) among colorectal cancer survivors showing higher adherence to the WCRF/AICR recommendations.[39]

Associations with other health outcomes and risk factors

A total of 13 cross-sectional studies evaluated the association between adherence to the 2007 WCRF/AICR score and other health outcomes both in cancer patients/survivors and in the general population.

In the general population. Three studies analyzed the association between adherence to the 2007 WCRF/AICR recommendations and markers of cancer risk. In a study of 107 patients undergoing upper gastrointestinal endoscopy for gastroesophageal reflux (high-risk population), higher adherence to the recommendations was inversely associated with Barrett's esophagus onset (one of the main risk factors of esophageal adenocarcinoma) and its evolution to early esophageal adenocarcinoma.[28] In another study of 3584 women attending breast cancer screening, higher adherence to the recommendations was associated with lower mammographic density, a predictor of breast cancer, mostly in postmenopausal women and non-smokers.[26] A small study including 75 healthy participants showed that higher adherence to the recommendations (plus a recommendation regarding smoking status) was associated with reduced expression of WNT-pathway-related markers of bowel cancer risk.[22] In addition, two studies on healthy populations explored the molecular mechanisms underlying the associations found. The largest study, involving 19 478 individuals, found that greater adherence to the 2007 WCRF/AICR recommendations was associated with healthier profile of plasma markers of inflammation (CRP, IL6, TNFαR2, and adiponectin), hormonal response (estrone and estradiol), and insulin response (C-peptide and TG/HDL), which was mainly driven by energy balance recommendations.[30] Another study in 275 premenopausal women found that women with a higher adherence score show lower levels of CRP and alpha-tocopherol but not F2-isoprostane.[25]

In cancer patients or survivors. Only one study assessed the relationship between adherence to the recommendations and cancer aggressiveness. In 2212 newly diagnosed cases of prostate cancer, higher 2007 WCRF/AICR scores were associated with lower odds of highly aggressive prostate cancer [based on Gleason scores, serum prostate-specific antigen (PSA) and TNM classification stage of malignant tumors].[20] The rest of the studies addressed health status and quality of life. Two of them, one in adult survivors of childhood cancer[24] and one in patients with breast cancer

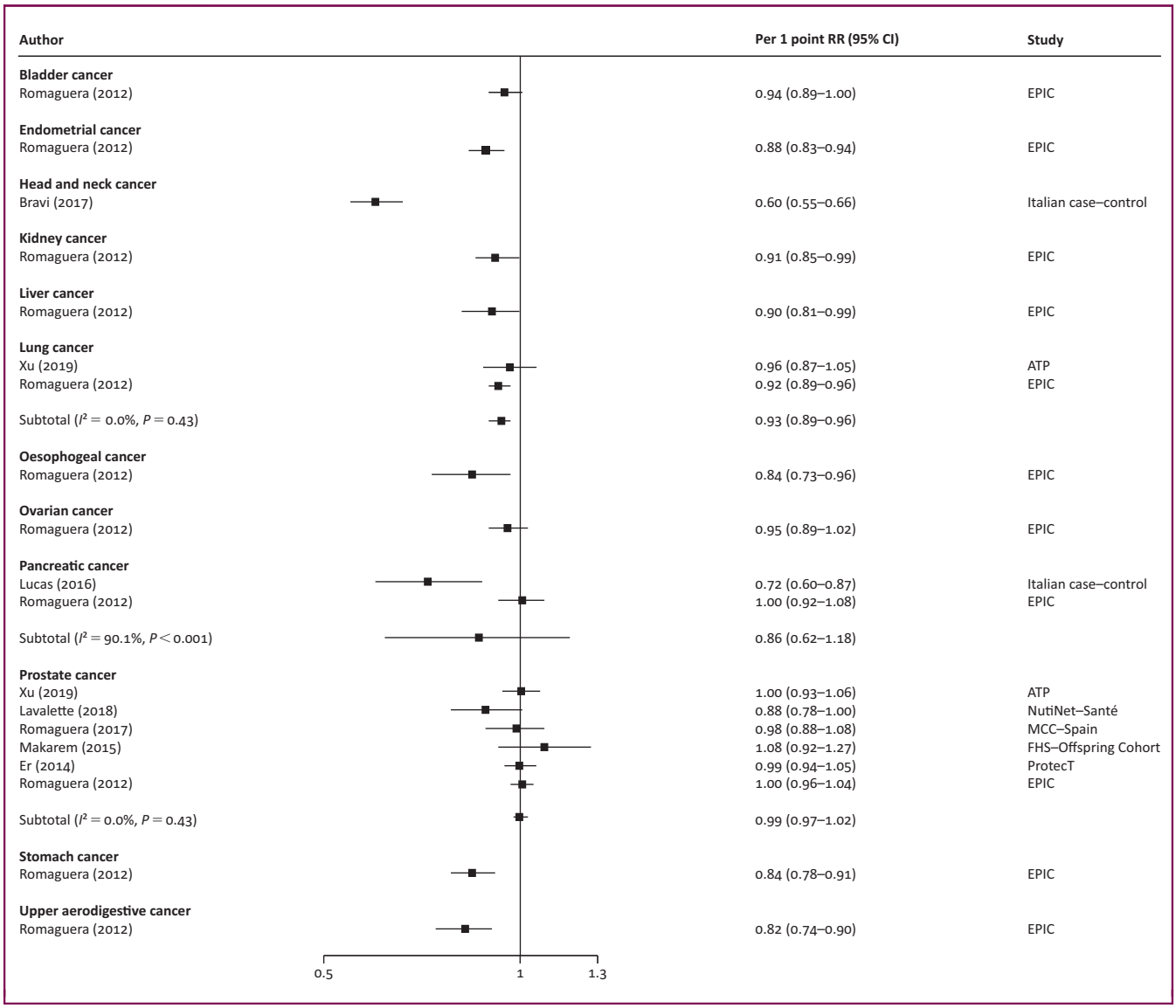

Figure 3. Dose-response cancer incidence umbrella review of cancers other than breast and colorectal cancer, summarized in Figures 1 and 2.
Dose-response estimates were calculated from the categorical data for the study by Xu et al.[41]

5 years after a cancer diagnosis,[29] reported an association between lower 2007 WCRF/AICR scores and metabolic equivalent of task (MetS) exercise capacity risk or prevalence, respectively. Regarding findings on health-related quality of life, the largest study, conducted on 2193 elderly female cancer survivors (average survival of 8.9 years), found that those who met a greater number of recommendations had better health-related quality of life, scoring higher in both the mental and physical components of the SF-36.[19] Two Dutch studies assessed quality of life in colorectal cancer survivors. The largest study,[23] including 1096 individuals (mean time since diagnosis 8.1 years), found better global health status, better physical, role, and social functional scales, and reduced fatigue in individuals with higher scores. In the other study[21] including 145 individuals (mean survival from diagnosis 5.7 years), greater adherence to the recommendations was not associated with an overall score of quality of life but with a better physical function and reduced fatigue. Finally, there were two studies on patients recently diagnosed with breast cancer, which resulted in discordant results. In one study of 1462 women diagnosed with early-stage breast cancer, adherence to the recommendations was associated with better global health status, physical and role functioning, and lower levels of fatigue, nausea/vomiting, dyspnea, loss of appetite, and diarrhea.[31] By contrast, a small study of 160 Korean women not only found no associations with a better global health-related quality of life but also reported more serious arm symptoms in those patients with higher 2007 WCRF/AICR scores.[27]

Study quality

In most studies, dietary and physical activity were typically collected using self-reported data, which can lead to exposure measurement error. Except for a few

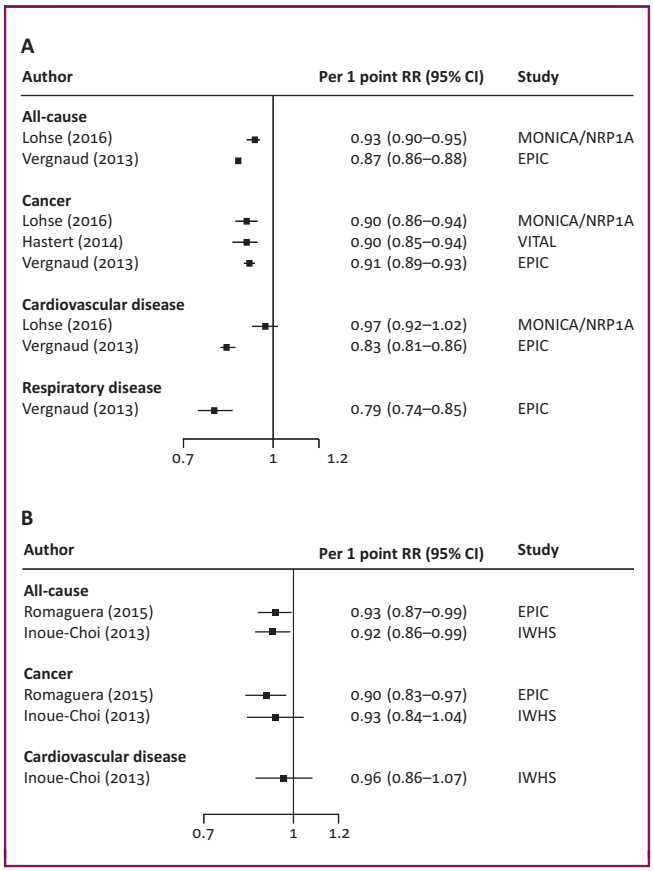

Figure 4. Dose-response mortality umbrella review of studies A) in the general population, and B) in cancer survivors.
Dose-response results for the study by Inoue-Choi et al.[38] were calculated from categorical results. Note that the study population in the article by Romaguera et al.[39] were only colorectal cancer cases (and cancer-specific results only refer to deaths due to colorectal cancer). The population identified by Inoue-Choi et al.[38] were women survivors of different types of cancer (the original article also provides estimates according to the primary cancer site, not included here).

studies,[21,23,27–29,37] dietary data was recorded mainly through a validated food frequency questionnaire (FFQ). FFQ validation methods generally relied on self-reported measures (i.e. 24-h recall or dietary records) rather than objective measures (i.e. nutrient biomarkers) and correlations were examined for dietary factors that were not always components of the 2007 WCRF/AICR score. Fewer studies reported the use of validated tools to assess physical activity[4,19,21,23,24,30,31,33,35,36,38–42,44–49] and again, were not always based on objective methods, such as accelerometers. Regarding limitations of study design, case-control studies reported stronger associations but significant associations were also observed in cohort studies, which are less prone to recall and selection bias. In addition, larger studies tended to report associations that were not confirmed in some small studies. Moreover, there were three hospital-based case-control studies[51,52,54] that were particularly prone to selection bias. All the cohort studies but one relied on a singular measure of exposure at baseline to construct their scores and thus could not account for any possible changes in dietary and lifestyle habits over time; the exception was the study by Nomura et al.[45,47] that analyzed a time-varying score using the Andersen-Gill model. Finally, all of the studies adjusted for several confounding factors, although there were great differences in the level of adjustment across studies (Table 2). Most of them, however, adjusted at least for age, sex (when applicable), education/socioeconomic status, and smoking.

DISCUSSION

This study provides the most comprehensive and up-to-date summary of evidence of the association between the 2007 WCRF/AICR recommendations and health outcomes. We reported, per each point increment in the score, a 10% and 14% reduction of breast and colorectal risk estimates, respectively, and, although based on fewer studies, a lower overall (−10%) and cancer-specific mortality (−9%) in the general population and better cancer survival. Several cross-sectional studies have also reported a healthier plasma marker profile and lower cancer risk factors in the general population and better health status and quality of life in cancer patients/survivors.

Our results are in line with a previous systematic review of cohort studies[55] that examined the associations between adherence to the 2007 WCRF/AICR and American Cancer Society cancer prevention guidelines and cancer risk and mortality. In our study, we further expanded the analysis to include case-control and cross-sectional studies and added newly published data, which allowed us to carry out site-specific meta-analyses. In the meta-analyses of breast and colorectal cancer, studies consistently observed inverse associations for both cancer types and although there was evidence of heterogeneity of study results, this was due to the difference in magnitude instead of the direction of the association. Fewer studies evaluated such associations with other cancer types. No associations were reported for prostate and pancreatic cancers, while results from two studies suggest an inverse link for lung cancer. Regarding lung cancer results, smoking was included as an adjusting covariate in both studies, but with different levels of specificity. Xu et al.[41] only considered tobacco exposure while Romaguera et al.[4] used a far more complete variable detailing both smoking status and intensity. The association with other cancer sites (e.g. endometrial, head and neck, liver, kidney, esophageal, ovarian, or stomach) has been investigated only in the EPIC study and thus merits further research. Mortality data is scarcer and mainly arises from the EPIC study, but results also point to an inverse association between adherence to the 2007 WCRF/AICR recommendations and overall mortality and cancer-specific mortality in healthy populations as well as a higher survival in those cancer patients following such recommendations. Moreover, several cross-sectional studies reported associations between higher adherence to the 2007 WCRF/AICR score and healthier plasma marker profile and lower cancer risk factors as well as reduced cancer aggression and better health status and quality of life in cancer patients/survivors.

The publication of the WCRF/AICR Second Expert Report demonstrated the importance of a structured process of

collection and review of available data and set the benchmark for evidence-based guidance.[3] It also provided evidence for the importance of shifting toward a holistic approach in cancer prevention through a set of recommendations underpinning a comprehensive package of healthy lifestyle habits. Its operationalization into the 2007 WCRF/AICR score, however, entails several limitations. First, integrating several lifestyle factors into a single index reduces the level of variability across individuals although it captures a general pattern. Secondly, the score is not weighted, assuming that all components are equally and additively related to health. Nevertheless, some recommendations might be more relevant to a specific outcome, such as breastfeeding in breast cancer, meat intake in colorectal cancer, or body mass index in obesity-related cancers. Thirdly, some components are correlated (i.e. physical activity, body fatness, and foods that promote weight gain). Finally, the score does not address other major risk factors for cancer such as smoking or sun exposure. Similarly, other factors, such as abdominal adiposity measurements (instead of body weight), may be better predictors of some cancer types.[56,57]

In 2018, the recommendations were updated, based on a comprehensive literature review of the past 10 years.[5] While remaining somewhat consistent with the previous report, there was a significant shift in emphasis to an integrated pattern of behaviors relating to diet, body fatness, and physical activity. There were also some specific key changes: (i) high-calorie foods and sugar-sweetened drinks are now separated into two independent recommendations (limit fast foods and limit sugar-sweetened drinks), (ii) there is no longer a recommendation for salt, and (iii) there is no level of alcohol consumption below which there is no increase in the risk of at least some cancers. Bearing in mind the inherent limitations of comparing the previous scoring approaches when operationalizing the 2007 cancer prevention recommendations, an international collaboration involving the US National Cancer Institute, members of WCRF/AICR with advice from the CUP panel, and other international researchers, has recently developed a standard scoring system of the updated recommendations. Upcoming studies using this new scoring system will help to draw firmer conclusions regarding the associations found as well as grow evidence in less explored (e.g. lung cancer) or unexplored cancer sites (e.g. hematological malignancies) and other relevant health outcomes (e.g. mortality, cancer survival or risk of other non-communicable diseases).

The strengths of our study include the generally high quality of publications included, the large number of endpoints examined, and the robustness of results from numerous subgroups and sensitivity analyses. Nevertheless, our results have some limitations. First, there is high heterogeneity in the score's operationalization across different studies, which hampers the direct comparability of the findings. Although we took into account the different ranges of the 2007 WCRF/AICR scores in the dose-response analysis, studies would have also differed by how accurately they measured anthropometric measures, dietary intake, and physical activity. While some degree of measurement error is inevitable, efforts should be made to feasibly address such limitations in upcoming observational studies, as recently recommended.[58] We excluded studies focusing only on dietary components as we were interested in studies with scores reflecting an overall lifestyle pattern. For some outcomes, the number of studies was too small to allow full exploration of heterogeneity or even perform meta-analyses. We included case-control studies, which might have been affected by recall bias (indeed, they tended to observe stronger associations), and potential selection bias. Regarding cohort studies, they may be affected by the healthy cohort effect; therefore, the preventable fraction in the general population is likely to be higher than the one reported here. Although we summarized the results of models with the highest level of adjustment, residual confounding cannot be ruled out. Finally, evidence of small-study bias or publication bias in some of the analyses suggests that the strength of the associations may have been slightly overestimated in a few cases but this is unlikely to substantially alter the overall findings of the study.

In conclusion, this systematic review and meta-analysis provide evidence that adhering to the 2007 WCRF/AICR cancer prevention recommendations is associated with a lower risk of breast and colorectal cancer incidence and mortality. Overall, primary prevention of cancer should emphasize the modification of multiple diet and lifestyle factors. Upcoming studies examining the recently updated WCRF/AICR cancer prevention recommendations will further clarify these associations.

FUNDING

This work was supported by the Biomedical Research Center Network of Epidemiology and Public Health [MS, no grant number] and the World Cancer Research Fund International [grant number 2007/SP01].

DISCLOSURE

The authors have declared no conflicts of interest.

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