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Adherence to nutrition-based cancer prevention guidelines and breast, prostate and colorectal cancer risk in the MCC-Spain case–control study

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Prostate, breast and colorectal cancer are the most common tumours in Spain. The aim of the present study was to evaluate the association between adherence to nutrition-based guidelines for cancer prevention and prostate, breast and colorectal cancer, in the MCC-Spain case–control study. A total of 1,718 colorectal, 1,343 breast and 864 prostate cancer cases and 3,431 population-based controls recruited between 2007 and 2012, were included in the present study. The World Cancer Research Fund/American Institute for Cancer Research (WCRC/AICR) score based on six recommendations for cancer prevention (on body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods and alcoholic drinks; score range 0–6) was constructed. We used unconditional logistic regression analysis adjusting for potential confounders. One-point increment in the WCRF/AICR score was associated with 25% (95% CI 19–30%) lower risk of colorectal, and 15% (95% CI 7–22%) lower risk of breast cancer; no association with prostate cancer was detected, except for cases with a Gleason score $\geq$7 (poorly differentiated/undifferentiated tumours) (OR 0.87, 95% CI 0.76–0.99). These results add to the wealth of evidence indicating that a great proportion of common cancer cases could be avoided by adopting healthy lifestyle habits.

What's new?
Prostate, breast and colon cancer share common environmental risk factors, but preventable causes remain largely unknown. Here the authors evaluated adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines on diet, physical activity and body fat for cancer prevention and risk of these cancers in Spain. They found an inverse association between adherence to the recommendations and colon cancer, postmenopausal breast cancer and poorly differentiated prostate cancer, underscoring the important role of preventable causes in the development of these cancers.

Substantial evidence indicates that extrinsic risk factors are major contributors to cancer development.[1] The World Cancer Research Fund estimates that about a quarter to a third of the commonest cancers are attributable to excess body weight, physical inactivity and poor diet, making these the most common causes of cancers after smoking.[2] This indicates that most cancer could be prevented by following a healthy lifestyle. In this sense, in 2007 the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) formulated a series of recommendations for cancer prevention based on diet, physical activity and body fatness, based on a comprehensive revision of the literature available at the time.[3] Adherence to these recommendations measured using an index score (WCRF/AICR score), has been associated to a lower risk of developing cancer, especially breast cancer, in a number of studies.[4–8] The association of the WCRF/AICR score with colorectal and prostate cancer has been less studied.[4,9,10]

Prostate (first among males), breast (first among females) and colorectal cancer (first considering both sexes together) are the most common tumours in Spain[11] and share common environmental risk factors, although preventable causes remain largely unknown. A population-based multicase–control study (MCC-Spain) was launched to evaluate the influence of environmental exposures and their interaction with genetic factors in risk of prostate, female breast and colorectal cancer, among others.[12] The aim of the present study was to evaluate the association between adherence to the WCRF/AICR recommendations for cancer prevention and prostate, breast and colorectal cancer risk, as well as tumour sub-types, in the MCC-Spain study.

Material and Methods

Study population

MCC-Spain is a multicentric case–control study with population controls and cases with common tumours in Spain (prostate, breast, colorectal, gastroesophageal and chronic lymphocytic leukaemia). Between September 2008 and December 2013, subjects aged 20 to 85 years and with a histologically-confirmed newly-diagnosed cancer of the prostate (International Classification of Diseases 10th Revision [ICD-10]: C61, D07.5), breast (C50, D05.1, D05.7), colon or rectum (C18, C19, C20, D01.0, D01.1, D01.2), were recruited in 23 Spanish hospitals from 12 Spanish provinces. Simultaneously, population-based controls frequency-matched to cases, by age, sex and region were randomly selected from primary care centres within hospitals' catchment areas. This ensured that, for each case, there was at least one control from the same region with the same sex and within the same 5-year age interval. After applying specific exclusion criteria

(excluding participants with no dietary data, implausible energy intake and anthropometric values, cases with no data on date of diagnosis, cases with more than 1 year between diagnosis and time of the interview, and breast cancer cases and controls with missing data on covariates for breast cancer risk models; see Flow Chart in Supporting Information for specific details) a total of 1,718 colorectal cancer cases, 1,343 breast cancer cases, 864 prostate cancer cases and 3,439 controls were included in these analyses. All participants signed an informed consent. Approval for the study was obtained from the ethical review boards of all recruiting centres. Additional information regarding the study design is provided elsewhere.[12]

Data collection

Purpose-trained interviewers administered a structured computerized epidemiological questionnaire in a face-to-face interview at enrolment. This questionnaire recorded sociodemographic and anthropometric data, family and personal background, gynaecological, obstetric, medical, residential and occupational history, smoking, and physical activity. The questionnaire in Spanish is available at www.mccspain.org.

Height and weight at different ages were self-reported and waist and hip circumference were measured with a tape. The body mass index (BMI, kg/m^2) was calculated from self-reported weight 1 year before the interview. Leisure time physical activity information (type of activity, frequency: days per week and hours per day, duration: age beginning and age ending) was available for all activities held over lifetime. The cumulative volume of physical activity (in MET $\times$ h/wk) was calculated for the last 10 years of life, excluding the last 2 years previous to the interview.

Subjects were provided a semiquantitative Food Frequency Questionnaire (FFQ), which was a modified version from a previously validated instrument in Spain[13] to include regional products. The FFQ was self-administered and returned by mail or filled out face to face (overall response rate 88%). It included 140 food items with portion sizes specified for each item, and assessed usual dietary intake during the previous year. Cross-check questions on aggregated food group consumption were used to adjust the frequency of food consumption and reduce misreporting of food groups with large numbers of items.[14,15] Nutrient intakes were estimated using food composition tables published for Spain, and other sources.[16]

WCRF/AICR score construction

The WCRF/AICR score, incorporating six of the WCRF/AICR recommendations (regarding body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, and alcoholic drinks) was constructed. Detailed information on the operationalization of the score can be found in Table 1. Briefly, we assigned for each component, 1 point when the recommendation was met, 0.5 point when it was partially met and 0 point otherwise. When available, the quantitative criteria provided in the recommendations were used as cut-off points and intermediate cut-off points used in the literature or defined by the authors were used otherwise. For the recommendations including several sub-recommendations (foods and drinks that promote weight gain or plant foods), the final score was the average of each sub-recommendation score. Two recommendations (regarding the preservation, processing and preparation of foods and the recommendation on dietary supplements) and the two special recommendations (for cancer survivors and for mothers to breastfeed) were not included in the score. As the WCRF/AICR recommendations were not ranked according to priority, all major recommendations were summed to contribute equally to the total WCRF/AICR score. Therefore, the total WCRF/AICR score ranged from 0 to 6, with higher scores indicating greater concordance with the WCRF/AICR recommendations. The score was further categorized into sex-specific tertiles according to the distribution of the score in controls (see Table 2 for information on cut-off points).

Tumour sub-types

For most cancer cases, tumour subtype could be determined from pathology records. Colorectal cancer cases were divided into colon cancer and rectal cancer according to the tumour location. Breast cancer cases were sub-classified according to the estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor (HER2), in the following sub-types: hormone receptor positive tumours (HR+: ER+ or PR+ with HER2–); human epidermal growth factor receptor positive tumours (HER2+: independent of ER or PR), and triple negative tumours (TN: ER–, PR– and HER2–).[17] Prostate tumour aggressiveness was determined according to the Gleason score as moderately/well differentiated (Gleason score <7) and poorly differentiated/undifferentiated (Gleason score ≥ 7).[18]

Covariates

Several variables were considered in this study as potential confounders or effect modifiers of the studied associations. These were: age at the time of the interview; sex; educational level (in four categories: less than primary education, primary education, secondary education, university studies); area (in twelve regions); family history of any cancer as well as colorectal, breast, and prostate cancer in first degree relatives (yes, no and missing); smoking status (classified as never smokers, former smokers that quitted >10 years before the interview, former smokers that quitted 5 to 10 years before the interview, former smokers for <5 years combined with current smokers, and missing); and total energy intake (in kcal). For breast cancer cases and controls the following variables were also taken into account: menopausal status (premenopausal, postmenopausal); oral contraceptive use (never, ever); hormone replacement therapy use (never, ever, not known); age at menarche (<13 years old, ≥ 13 years old, missing); age at first pregnancy (no children, <26 years old,

Table 1. WCRF/AICR score construction

	Personal recommendations	Operationalisation	Scoring
Body fatness: Be as lean as possible without becoming underweight		BMI[1] $<$ 24.9 kg/m^2	**1**
	Maintain body weight within the normal range from age 21	BMI[1] 25–29.9 kg/m^2	**0.5**
		BMI[1] $>$30 kg/m^2	**0**
Physical activity: Be physically active as part of your everyday life	Be moderately physically active, equivalent to brisk walking, for at least 30 min every day	METS[2] $\geq$150 h/wk	**1**
		METS[2] $\geq$75–$<$150 h/wk	**0.5**
		METS[2] $<$75 h/wk	**0**
Foods and drinks that promote weight gain[3,4]: Limit consumption of energy-dense foods; avoid sugary drinks	Consume energy-dense foods sparingly	**ED**[5] $\leq$125 kcal/100 g/d	**1**
		ED[5] $>$125–$<$175 kcal/100 g/d	**0.5**
		ED[5] $>$175 kcal/100 g/d	**0**
	Avoid sugary drinks	Sugary drinks intake[6] = 0 g/d	**1**
		Sugary drinks intake[6] $\leq$250 g/d	**0.5**
		Sugary drinks intake[6] $>$250 g/d	**0**
Plant foods[3,4]: Eat mostly foods of plant origin	Eat at least five portions/servings (at least 400 g) of a variety of non-starchy vegetables and of fruits every day	F&V[7] intake $\geq$400 g/d	**1**
		F&V[7] intake 200–$<$400 g/d	**0.5**
		F&V[7] intake $<$200 g/d	**0**
	Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal	Dietary fibre intake $\geq$25 g/d	**1**
		Dietary fibre intake 12.5–$<$25 g/d	**0.5**
		Dietary fibre intake $<$12.5 g/d	**0**
Animal foods[3]: Limit intake of red meat and avoid processed meat	People who eat red meat to consume less than 500 g a week, very little if any to be processed	Red and processed meat $<$500 g/w and processed meat intake $<$3 g/d	**1**
		Red and processed meat $<$500 g/w and processed meat intake 3–$<$50 g/d	**0.5**
		Red and processed meat $\geq$500 g/w or processed meat intake $\geq$50 g/d	**0**
Alcoholic drinks[3]: Limit alcoholic drinks	If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women	Ethanol intake $\leq$20 g/d (♂) or $\leq$10 g/d (♀)	**1**
		Ethanol intake $>$20–30 g/d (♂) or $>$10–20 g/d (♀)	**0.5**
		Ethanol intake $>$30 g/d (♂) or $>$20 g/d (♀)	**0**

[1]BMI, body mass index; constructed with data on reported body weight 1 year before the interview and self-reported height.
[2]METS, metabolic equivalents; constructed with data on reported level of physical activity during the last 10 years—excluding the 2 years before the interview.
[3]Food and nutrient data, including alcohol intake, was obtained from a validated FFQ administered at the moment of the interview that gathered information on dietary consumption during the previous year before the interview.
[4]For recommendations with two sub-recommendations, the final score for the recommendation was the average of the score obtained for each sub-recommendation.
[5]ED, energy density; ED was calculated as energy (kcal) from foods (solid foods and semi-solid or liquid foods such as soups) divided by the weights (g) of these foods. Drinks (including water, tea, coffee, juice, soft drinks, alcoholic drinks and milk) were not included in the calculation.
[6]Sugary drinks included both sugar-sweetened soft-drinks and commercial fruit & vegetable juices.
[7]F&V, fruits and vegetables, excluding starchy vegetables (sweet potatoes), canned fruit, dried fruit, and fruit juices.

Table 2. Characteristics of participants in the control group ($n = 3{,}439$) according to categories of the WCRF/AICR score (based on the tertile distribution in controls)

WCRF/AICR score range	Tertile 1 Men (0.25–3)/ women (0.5–3.5)	Tertile 2 Men (3.25–4)/ women (3.75–4.25)	Tertile 3 Men (4.25–6)/ women (4.5–6)	p^1
No. men (n = 1,757)/no. women (n = 1,682)	636/681	635/495	486/506	
Age, years (mean ± SD)	60.13 ± 12.15	63.67 ± 11.62	65.22 ± 11.67	*<0.001*
Educational level (%)				
Less than primary	16.78	17.52	18.25	*0.085*
Primary education	29.76	32.74	33.37	
Secondary education	32.73	27.88	27.32	
University	20.73	21.86	21.07	
Smoking status (%)				
Never smokers	39.10	42.74	53.73	*<0.001*
Former smokers (quitted ≥10 yr ago)	19.21	24.96	21.77	
Former smokers (quitted <10–5 yr ago)	7.44	8.14	5.65	
Former smokers (quitted <5 yr ago)/Smokers	33.94	23.81	18.35	
Missing	0.30	0.35	0.50	
Family history of cancer				*0.758*
Yes	20.73	20.27	21.47	
No	73.50	74.16	73.89	
Missing	5.77	5.58	4.64	
Total energy intake, kcal (mean ± SD)	1,956.7 ± 592.17	1,859.81 ± 545.83	1,819.96 ± 495.40	*<0.001*

[1] p value; obtained by one-way ANOVA for continuous variables or χ^2 test for categorical variables.

≥26 years old); number of children (continuous variable). As indicated, for some categorical variables there were individuals with missing data and these were coded as a separate category (for more information on number of missing, check Supporting Information Tables 1–3).

Statistical analyses

As descriptive analyses, we compared sociodemographic characteristics of controls across categories of the WCRF/AICR score. We also compared sociodemographic characteristics and potential risk factors for colorectal, breast and prostate cancer between cases and controls. χ^2 tests were used to evaluate the level of significance of the differences observed in categorical variables, and one-way ANOVA for continuous variables.

The association between adherence to the WCRF/AICR recommendations and colorectal, breast or prostate cancer risk was evaluated using unconditional logistic regression models. The exposure variable (WCRF/AICR score) was included in the model both as continuous variable (per 1-point increment) and as categorical variable (according to the tertile distribution in controls). The WCRF/AICR categorical variable was scored from 1 to 3, and trend tests were calculated on these scores. Two models with two levels of adjustments were used for each cancer. The minimally-adjusted model (Model 1) included as covariates: age, educational level, area and sex (for colorectal cancer models). The multiple adjusted model (Model 2) was further adjusted for family history of each cancer, smoking status and total energy intake. In analyses of breast cancer risk, Model 2 was also adjusted for menopausal status, oral contraceptive use, hormone replacement therapy use, age at menarche, age at first pregnancy, and number of children. Generalized additive models (GAM) were used to evaluate the exposure-response relationships on continuous variables, using a smoothed spline with 3 degrees of freedom. Visual inspection of the graphs revealed linear associations between the exposure and colon, breast and prostate cancer.

Models 1 and 2 were also run after stratification according to a series of key variables that might influence the association between the WCRF/AICR score and cancer, including tumour sub-type, smoking status (never smokers *vs.* former/current smokers), sex (for colorectal cancer), and menopausal status (for breast cancer). The p for interaction was calculated by modeling cross-product terms between the WCRF/AICR score (as continuous variables) and smoking status, sex (for colorectal cancer) and menopausal status (for breast cancer).

In order to evaluate the independent association of each score component on cancer risk, we run Model 2 including all the individual components simultaneously, plus covariates. We conducted these analyses for total colorectal, total breast and total prostate cancer as well as for tumour sub-types.

As sensitivity analyses, we repeated all analyses excluding cases (161 colorectal, [23]1 breast and 128 prostate) with >6 months between cancer diagnosis and the date of interview.

Table 3. Association between WCRF/AICR score and colorectal cancer in the MCC-Spain Study

			WCRF/AICR score categories				
	No. Ca/Co		Tertile 1 OR (95% CI)	Tertile 2 OR (95% CI)	Tertile 3 OR (95% CI)	*p* for trend	Per 1-point increment in the WCRF/AICR score OR (95% CI)
All	1,718/3,312	Model 1	1.00	0.87 (0.75–1.00)	0.53 (0.44–0.62)	<0.001	0.75 (0.70–0.80)
		Model 2	1.00	0.88 (0.76–1.02)	0.54 (0.45–0.63)	<0.001	0.75 (0.70–0.81)
Men	1,097/1,717	Model 1	1.00	0.88 (0.73–1.05)	0.51 (0.41–0.64)	<0.001	0.74 (0.69–0.83)
		Model 2	1.00	0.93 (0.77–1.12)	0.54 (0.43–0.68)	<0.001	0.76 (0.71–0.85)
Women	621/1,595	Model 1	1.00	0.91 (0.72–1.15)	0.60 (0.47–0.78)	<0.001	0.81 (0.72–0.91)
		Model 2	1.00	0.89 (0.70–1.13)	0.61 (0.47–0.79)	<0.001	0.81 (0.72–0.91)
Current/former smokers	1,000/1,837	Model 1	1.00	1.02 (0.84–1.25)	0.72 (0.57–0.90)	0.012	0.84 (0.77–0.93)
		Model 2	1.00	1.02 (0.85–1.23)	0.68 (0.54–0.86)	0.004	0.83 (0.76–0.91)
Never smokers	708/1,464	Model 1	1.00	0.69 (0.54–0.88)	0.42 (0.33–0.55)	<0.001	0.67 (0.59–0.75)
		Model 2	1.00	0.74 (0.58–0.93)	0.44 (0.34–0.56)	<0.001	0.68 (0.60–0.76)
Colon cancer[1]	1,169/3,312	Model 1	1.00	0.86 (0.73–1.01)	0.51 (0.42–0.61)	<0.001	0.74 (0.69–0.80)
		Model 2	1.00	0.87 (0.74–1.02)	0.52 (0.43–0.63)	<0.001	0.75 (0.69–0.81)
Rectal cancer[1]	533/3,312	Model 1	1.00	0.86 (0.69–1.07)	0.52 (0.40–0.68)	<0.001	0.74 (0.67–0.83)
		Model 2	1.00	0.90 (0.72–1.12)	0.54 (0.41–0.71)	<0.001	0.76 (0.68–0.84)

Model 1: Logistic regression analyses adjusted for sex (except in models stratified by gender), age, educational level, and area. Model 2: Logistic regression analyses adjusted for sex (except in models stratified by gender), age, educational level, area, family history of colorectal cancer cancer, smoking (except in models stratified by smoking status), and total energy intake.
[1]In 16 colorectal cancer cases, tumour subtype was not available, hence were excluded.

We also repeated all models after excluding participants with missing data on covariates. Results did not materially change therefore are not displayed.

Statistical analyses were conducted using STATA version 14 (StataCorp, College Station, TX).

Results

Information about the variables used and the scoring criteria selected to construct the score is shown in Table 1. Information about past habits (previous to cancer diagnosis for cases) was used to assess the diet, body weight status, and physical activity habits.

Table 2 shows the distribution of key characteristics of controls according to categories of the WCRF/AICR score. Control participants with greater concordance with the WCRF/AICR recommendations were older, never smokers, and showed lower energy intake. No significant differences across categories of the score were observed in the educational level of participants or their family history of cancer.

The comparison of characteristics and risk factors of cancer between controls and colorectal, breast and prostate cancer are shown in the Supplementary online material (in Tables (1–3), respectively). Colorectal cancer cases and breast cancer cases showed significantly lower average WCRF/AICR score compared to their respective controls, while no differences were observed between prostate cancer cases and controls.

The association between WCRF/AICR and colorectal cancer is shown in Table 3. In the multiple adjusted model, individuals in the highest category of the score had an OR for colorectal cancer of 0.54 (95% CI 0.45–0.63) compared to individuals with low adherence to the recommendations (p for trend <0.001). Each point increment in the WCRF/AICR score was associated to 25% lower odds of having colorectal cancer (95% CI 19–30%). The risk estimates were similar in men and women (p for interaction 0.07, not shown in tables) and for colon and rectal cancer. The inverse association between the WCRF/AICR recommendations and colorectal cancer was stronger among never smokers (OR per point increment 0.68, 95% CI 0.60–0.76) than among former/current smokers (OR per point increment 0.83, 95% CI 0.76–0.91) (p for interaction 0.02, not shown in tables); nevertheless, the association between the WCRF/AICR score and colorectal cancer risk was statistically significant across all strata analysed.

Women in the highest category of the WCRF/AICR score showed an OR for breast cancer of 0.76 (95% CI 0.63–0.92) compared to women with lower scores (p for trend 0.007) (Table 4). The OR for breast cancer associated to 1 point increment in the score was 0.85 (95% CI 0.78–0.93). The association between the WCRF/AICR score and breast cancer risk was statistically significant for postmenopausal women (OR per point increment 0.78, 95% CI 0.70–0.87) while no effect was observed in pre-menopausal women (p for

Table 4. Association between WCRF/AICR score and breast cancer in the MCC-Spain Study

			WCRF/AICR score categories				
	No. Ca/Co		Tertile 1 OR (95% CI)	Tertile 2 OR (95% CI)	Tertile 3 OR (95% CI)	*p* for trend	Per 1-point increment in the WCRF/AICR score OR (95% CI)
All women	1343/1577	Model 1	1.00	0.95 (0.80–1.14)	0.80 (0.66–0.96)	0.022	0.88 (0.80–0.95)
		Model 2	1.00	0.94 (0.78–1.13)	0.76 (0.63–0.92)	0.007	0.85 (0.78–0.93)
Premenopausal	483/463	Model 1	1.00	1.34 (0.98–1.81)	1.01 (0.71–1.42)	0.634	1.00 (0.86–1.17)
		Model 2	1.00	1.28 (0.93–1.77)	0.97 (0.68–1.40)	0.822	0.99 (0.84–1.16)
Postmenopausal	860/1114	Model 1	1.00	0.78 (0.63–0.98)	0.69 (0.55–0.86)	0.001	0.82 (0.74–0.91)
		Model 2	1.00	0.76 (0.60–0.96)	0.64 (0.51–0.81)	<0.001	0.78 (0.70–0.87)
Current/former smokers	604/625	Model 1	1.00	0.86 (0.65–1.13)	0.74 (0.54–0.99)	0.041	0.81 (0.71–0.92)
		Model 2	1.00	0.84 (0.63–1.11)	0.70 (0.52–0.96)	0.024	0.80 (0.69–0.91)
Never smokers	736/950	Model 1	1.00	1.02 (0.80–1.32)	0.87 (0.65–1.07)	0.257	0.92 (0.81–1.03)
		Model 2	1.00	1.03 (0.80–1.29)	0.83 (0.66–1.08)	0.163	0.93 (0.82–1.04)
HR+[1]	902/1577	Model 1	1.00	0.97 (0.80–1.19)	0.84 (0.68–1.03)	0.105	0.89 (0.81–0.97)
		Model 2	1.00	0.98 (0.80–1.21)	0.81 (0.65–1.00)	0.061	0.87 (0.79–0.96)
HER2+[1]	231/1575	Model 1	1.00	0.89 (0.64–1.23)	0.57 (0.39–0.82)	0.005	0.82 (0.69–0.96)
		Model 2	1.00	0.84 (0.60–1.18)	0.53 (0.36–0.78)	0.002	0.79 (0.67–0.94)
TN[1]	94/1519	Model 1	1.00	0.94 (0.56–1.57)	0.93 (0.54–1.59)	0.792	0.88 (0.69–1.13)
		Model 2	1.00	0.99 (0.58–1.67)	0.89 (0.51–1.54)	0.690	0.87 (0.68–1.12)

Model 1: Logistic regression analyses adjusted for age, educational level, and area. Model 2: Logistic regression analyses adjusted for age, educational level, area, family history of breast cancer, smoking (except in models stratified by smoking status), total energy intake, hormone replacement therapy use, oral contraceptive use, age at menarche, age first pregnancy, number of children, menopausal status (except in models stratified by menopausal status).

[1]HR+, hormone receptor-positive tumours (ER+ or PR+ with HER2–); HER2+, human epidermal growth factor receptor positive tumours, independent of ER or PR; TN, triple negative tumours (ER–, PR– and HER2–). In 116 breast cancer cases, tumour subtype was not available, hence were excluded. In the analysis of HER2+ tumours, women with missing data on smoking status were excluded (two controls); in the analysis of TN tumours, women with missing data on smoking status and age at menarche were excluded (58 controls).

interaction 0.03, not shown in tables). The association between the WCRF/AICR score and breast cancer was significant for current/former smokers, but not significant in never smokers, although the *p* for interaction was not significant (*p* for interaction 0.09, not shown in tables). The association was significant for HER2+ tumours and HR+ tumours, and not significant for TN tumours.

No association was detected between adherence to the WCRF/AICR recommendations and prostate cancer risk (Table 5); however, when analyses were stratified according to tumour subtype, a borderline significant association was observed between the WCRF/AICR score and poorly differentiated/undifferentiated prostate cancer tumours: those in the highest category of the score had an OR of 0.73 (95% CI 0.52–1.01), compared to the lowest category (*p* for trend 0.094.). Each point increment in the score reduced poorly differentiated/undifferentiated prostate cancer risk by 13% (95% CI 1–24%). No effect modification by smoking status was detected (*p* for interaction 0.84, not shown in tables).

The association between adherence to the individual WCRF/AICR recommendations and colorectal, postmenopausal breast, and poorly differentiated/undifferentiated prostate cancer risk, is shown in Table 6. We decided to show in this table these analyses for postmenopausal breast cancer and poorly differentiated/undifferentiated prostate cancer because these tumours were *a priori* associated with the WCRF/AICR score (results for total breast and total prostate cancer, as well as other subtypes of colorectal, breast and prostate cancer can be found in the Supporting Information Tables 4–7). Meeting the recommendations on body fatness, physical activity, consumption of foods/drinks that promote weight gain, consumption of plant foods and consumption of red/processed meat was associated to a significant lower risk of colorectal cancer, as well as colon cancer (for rectal cancer, all these recommendations but body fatness were also significantly associated with lower risk). Meeting the recommendation for body fatness and consumption of foods/drinks that promote weight gain was associated with lower risk of postmenopausal breast cancer as well as total breast cancer. In premenopausal women, meeting the recommendation on body fatness was associated with higher risk of breast cancer, whereas meeting the recommendation for consumption of foods/drinks that promote weight gain was associated with lower risk. Having a healthy body weight was associated with

Table 5. Association between WCRF/AICR score and prostate cancer in the MCC-Spain Study

			WCRF/AICR score categories				
	No. Ca/Co		Tertile 1 OR (95% CI)	Tertile 2 OR (95% CI)	Tertile 3 OR (95% CI)	*p* for trend	Per 1-point increment in the WCRF/AICR score OR (95% CI)
All men	864/1,236	Model 1	1.00	1.12 (0.91–1.38)	0.96 (0.75–1.38)	0.891	0.98 (0.89–1.08)
		Model 2	1.00	1.10 (0.89–1.36)	0.93 (0.72–1.20)	0.715	0.98 (0.88–1.08)
Current/former smokers	602/901	Model 1	1.00	1.22 (0.96–1.57)	0.89 (0.66–1.20)	0.707	0.95 (0.85–1.07)
		Model 2	1.00	1.23 (0.96–1.58)	0.99 (0.63–1.35)	0.726	0.99 (0.88–1.11)
Never smokers	260/333	Model 1	1.00	0.78 (0.51–1.20)	0.71 (0.45–1.13)	0.225	0.93 (0.76–1.12)
		Model 2	1.00	0.83 (0.53–1.28)	0.78 (0.49–1.25)	0.307	0.97 (0.80–1.18)
Undifferentiated[1]	445/1,234	Model 1	1.00	1.07 (0.83–1.39)	0.69 (0.50–0.94)	0.183	0.85 (0.76–0.96)
		Model 2	1.00	1.01 (0.78–1.34)	0.73 (0.52–1.01)	0.094	0.87 (0.76–0.99)
Moderately/well differentiated[1]	405/1,236	Model 1	1.00	1.19 (0.91–1.56)	1.24 (0.91–1.56)	0.145	1.11 (0.98–1.26)
		Model 2	1.00	1.20 (0.91–1.60)	1.27 (0.92–1.76)	0.130	1.13 (0.99–1.29)

Model 1: Logistic regression analyses adjusted for age, educational level, and area. Model 2: Logistic regression analyses adjusted for age, educational level, area, family history of prostate cancer, smoking (except in models stratified by smoking status) and total energy intake.
[1]Aggressivity of prostate cancer according to Gleason score: undifferentiated (Gleason score ≥ 7); moderately/well differentiated (Gleason score <7). In 14 prostate cancer cases, tumour subtype was not available, hence were excluded. In the analysis of undifferentiated tumours men with missing data on smoking status were excluded (two controls).

lower risk of HR+, HER+ and TN breast tumours; meeting the recommendation for consumption of foods/drinks that promote weight gain was associated with lower risk of HR+ and HER+ tumours; and meeting the physical activity recommendation with lower risk of HER+ tumours. Meeting the recommendation on plant foods and red/processed meat consumption was associated to a significant lower risk of poorly differentiated/undifferentiated prostate cancer. No single component was significantly associated with total prostate cancer and moderately/well differentiated prostate cancer.

Discussion

In this large, population-based study, we have found an association between greater adherence to the WCRF/AICR recommendations for cancer prevention and lower colorectal cancer and breast cancer risk (particularly in postmenopausal women). No association was observed with total prostate cancer but an inverse association was observed for poorly differentiated/undifferentiated prostate tumours.

In recent years there has been an increased interest in the study of the WCRF/AICR score and cancer risk. The novelty of this score is that, as with the study of dietary patterns, it permits to evaluate diet as a whole, accounting for possible synergistic effects between nutrients on disease risk; also it is constructed based specifically on nutritional recommendations for cancer prevention; and it incorporates not only dietary factors, but also physical activity and body fatness, hence being an indicator of an overall healthy lifestyle. In fact, in this as well as other studies, the WCRF/AICR score tends to be higher among never smokers compared to former and current smokers.[4,9,19–21]

Our study shows a clear inverse association between greater adherence to the WCRF/AICR recommendations and both colon and rectal cancer risk. This association is expected given that several recommendations (i.e. body fatness, physical activity, fibre intake, consumption of red and processed meat, and alcohol consumption) are regarded as convincing risk factors for colorectal cancer[22]; nevertheless, only few studies had investigated this association. In the EPIC cohort, a point increment in the WCRF/AICR score was associated to a HR for colorectal cancer of 0.88 (95%CI 0.84–0.91).[4] A study based on the Framingham Offspring cohort found a HR for colorectal cancer of 0.87 (95% CI 0.68–1.12) associated with one-point increment in the score, although in this case the association was not statistically significant, probably due to the low number of cases ($n = 63$).[10] Another study conducted with EPIC participants that developed colorectal cancer, found that higher pre-diagnostic concordance with the WCRF/AICR recommendations, improved survival in these patients.[23] We found that never smokers showed a stronger inverse association between the score and colorectal cancer risk, than former and current smokers. Some studies evaluating the association between fruit and vegetable consumption and colorectal cancer risk also reported a similar effect modification by smoking status,[24] suggesting that tobacco may counteract the potential beneficial effect of these food items on cancer risk. When we analysed the individual association of each recommendation with colorectal cancer risk, we observed significant associations in the expected

Table 6. Mutually adjusted OR and 95% confidence intervals (95% CIs) for colorectal, postmenopausal breast and undifferentiated prostate cancer, associated with the components of the WCRF/AICR score

	Colorectal cancer			Postmenopausal breast cancer			Undifferentiated prostate cancer		
	No. Ca/Co	OR (95% CI)[1]	*p* for trend	No. Ca/Co	OR (95% CI)[2]	*p* for trend	No. Ca/Co	OR (95% CI)[3]	*p* for trend
Body fatness									
0	419/654	1.00		208/215	1.00		113/279	1.00	
0.5	790/1,388	0.94 (0.80–1.10)		325/382	0.84 (0.65–1.09)		231/647	0.87 (0.66–1.16)	
1	509/1,270	0.84 (0.71–1.00)	***0.047***	327/517	0.53 (0.41–0.69)	***<0.001***	101/308	0.82 (0.59–1.15)	*0.256*
Physical activity									
0	1,065/1,744	1.00		465/592	1.00		231/660	1.00	
0.5	128/357	0.63 (0.50– 0.79)		99/138	0.79 (0.59–1.07)		57/123	1.38 (0.95– 2.00)	
1	525/1,211	0.67 (0.58– 0.77)	***<0.001***	296/384	0.86 (0.70–1.06)	*0.131*	157/451	0.91 (0.70–1.17)	*0.541*
Foods that promote weight gain									
0–0.25	255/398	1.00		90/78	1.00		75/189	1.00	
0.5	612/1,127	0.77 (0.63–0.95)		273/312	0.69 (0.48–1.00)		166/484	0.88 (0.62–1.25)	
0.75	591/1,192	0.61 (0.50–0.76)		341/433	0.62 (0.42–0.89)		153/410	0.95 (0.66–1.39)	
1	260/595	0.53 (0.41–0.68)	***<0.001***	156/291	0.42 (0.28–0.64)	***<0.001***	51/151	0.81 (0.50–1.31)	*0.646*
Plant foods									
0–0.25	260/453	1.00		92/96	1.00		75/208	1.00	
0.5	396/778	0.73 (0.59–0.90)		184/232	0.72 (0.50–1.04)		136/323	1.14 (0.80–1.64)	
0.75	570/1,119	0.62 (0.50–0.76)		321/444	0.67 (0.47–0.94)		124/365	0.78 (0.54–1.14)	
1	492/962	0.48 (0.38–0.61)	***<0.001***	263/342	0.66 (0.45–0.96)	*0.064*	110/338	0.70 (0.46–1.07)	***0.015***
Red and processed meat									
0	371/527	1.00		70/106	1.00		110/268	1.00	
0.5	1,077/2,170	0.76 (0.64–0.90)		610/756	1.26 (0.89–1.78)		289/773	0.91 (0.68–1.21)	
1	270/615	0.63 (0.50–0.79)	***<0.001***	180/252	1.15 (0.77–1.71)	*0.848*	46/193	0.57 (0.37–0.89)	***0.023***
Alcohol intake									
0	255/393	1.00		59/62	1.00		86/238	1.00	
0.5	175/405	0.69 (0.54–0.89)		69/97	0.75 (0.46–1.23)		65/184	1.14 (0.76–1.71)	
1	1,288/2,514	0.92 (0.76–1.11)	*0.979*	732/955	0.81 (0.55–1.21)	*0.497*	294/812	1.05 (0.77–1.44)	*0.870*

[1]Logistic regression analyses adjusted for sex, age, educational level, area, family history of colorectal cancer, smoking, and total energy intake. All components were mutually adjusted for each other.
[2]Logistic regression analyses adjusted for age, educational level, area, family history of breast cancer, smoking, total energy intake, hormone replacement therapy use, oral contraceptive use, age at menarche, age first pregnancy, number of children. All components were mutually adjusted for each other.
[3]Logistic regression analyses adjusted for age, educational level, area, family history of prostate cancer, smoking, and total energy intake. All components were mutually adjusted for each other. In the analysis of undifferentiated tumors men with missing data on smoking status were excluded (two controls).

directions between all components of the score and colon and rectal cancer, except for body fatness that was associated with colon but not with rectal cancer, and alcohol intake that was not associated with neither colon nor rectal cancer.

Several studies had evaluated the association between the WCRF/AICR score and breast cancer risk and most,[4,5,20,21,25] but not all[6,8,10] of them have reported a statistically significant reduced breast cancer risk in women following the WCRF/AICR recommendations. When we stratified by menopausal status, we observed this association in postmenopausal women, but not in premenopausal women. After careful examination of the individual association of each recommendation with postmenopausal and premenopausal cancer risk, we could confirm that the recommendation on body fatness was driving these results: we observed that having a normal body mass index was associated with a lower risk postmenopausal breast cancer and a higher risk of premenopausal breast cancer. Greater body fatness is a convincing risk factor for postmenopausal breast cancer, but a probable protective factor against premenopausal breast cancer.[26] The inverse association between the WCRF/AICR score and breast cancer was stronger for HER2+ tumours, then for HR+ tumours and not significant for TN tumours. This is in agreement with previous studies looking at these associations,[7,21,27] and might be explained by the different number of individual components associated with the different tumour subtypes. We found that consumption of foods and drinks that promote weight gain was associated with breast cancer risk. This association had also been reported in previous studies[6,7]; however, it should be noted that results reported on the association between the individual WCRF/AICR recommendations and breast cancer risk are very inconsistent across studies.

The null association between adherence to the WCRF/AICR recommendations and overall prostate cancer risk is consistent with findings from the three previous studies published on the topic[4,9,10] and consistent with the lack of association of diet and prostate cancer. We observed a reduced risk of poorly differentiated/undifferentiated prostate tumours—those with a Gleason score $\geq$7, also defined as high-grade tumours—in men belonging to the highest tertile of the WCRF/AICR score compared to the lowest. A previous case–control study that evaluated prostate aggressiveness in relation to the WCRF/AICR score, found no association regardless of tumour stage or grade[9]; however, a cross-sectional analysis in newly diagnosed prostate cancer patients found that greater adherence to the recommendations was associated with lower risk of highly aggressive prostate cancer based on Gleason scores, serum PSA and TNM stage.[28] The literature also indicates that obesity is a risk factor for advanced prostate tumours only (no conclusions have been drawn regarding obesity and non-advanced or total prostate cancer).[29,30] These observations underscore the importance of evaluating prostate tumour sub-types in studies of lifestyle factors and prostate cancer risk: men with healthier behaviours may potentially participate more in prostate cancer screening and may be more likely to be diagnosed with forms of low-grade prostate cancer, hence obscuring any possible association. We did not find a significant association between body fatness and prostate cancer; our results indicate that meeting the specific recommendations on plant foods and animal foods was associated to lower risk of undifferentiated prostate cancer; however these observations are not supported by the current literature.[29,31–33]

As limitations of this study, we should mention the use of recent dietary data given the case–control design of the study (the FFQ collected information on consumption during the previous year). In order to partly account for possible changes in dietary habits after cancer diagnosis, we systematically excluded from the analysis participants that responded to the dietary questionnaire $\geq$1 year after cancer diagnosis, and as sensitivity analyses we excluded those with $\geq$6 months between diagnosis and interview, with no change in results. For other variables of interest (i.e. body mass index, physical activity or smoking status) we used information reported on past exposures (i.e. 1, 2 or 5 years before the interview, respectively). The use of self-reported data may lead to recall bias; however, if recall bias exists, it would probably be non-differential, thus implying an underestimation of the effects studied. Dietary data might be also subject to measurement error; nevertheless, we used a previously validated FFQ for Spanish populations, and aggregated food group data was corrected using cross-check questions. To avoid potential selection bias in cases, we intended to recruit all cases with a first diagnosis of cancer in the selected health areas, ensuring few incident cases were missed in the study. We may have been limited by the small sample size and lack of statistical power to detect significant associations when evaluating certain subgroups. Finally, although we adjusted for a range of potential confounders, residual confounding cannot be totally ruled out.

Advantages of the study include the substantial sample size of histologically-confirmed incident cancer cases, with specific information on tumour sub-type. This allowed us to carry out an exhaustive evaluation of the association between the WCRF/AICR score and certain tumour sub-types and detect associations that had not been reported in the past. We constructed the WCRF/AICR score using scoring criteria that had been widely applied across studies, hence allowing comparability of these results with those of previous studies. Finally, the multicentric nature of the study, with rural and urban areas included, allowed a wide geographic variability of dietary intake data.

In conclusion, in this Spanish population-based case–control study, greater adherence to the WCRF/AICR cancer prevention recommendations on diet, physical activity and body fatness was associated to lower colorectal cancer, breast cancer (in postmenopausal women) and poorly differentiated/undifferentiated prostate cancer. These results add to the wealth of evidence indicating that a great proportion of

common cancer cases could be avoided by adopting healthy lifestyle habits.

Ethical Standards

All participants signed an informed consent prior to their inclusion in the study. The study has been approved by the ethics committees of all participating centres and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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