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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Adherence to the WCRF/AICR Dietary Recommendations for Cancer Prevention and Risk of Cancer in Elderly from Europe and the United States: A Meta-Analysis within the CHANCES Project

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Abstract

Background: It is unknown whether dietary recommendations for cancer prevention are applicable to the elderly. We analyzed WCRF/AICR recommendations in cohorts of European and U.S. adults ages 60 years and above.

Methods: Individual participant data meta-analysis included 362,114 participants (43% women), from seven prospective cohort studies, free from cancer at enrollment. The WCRF/AICR diet score was based on: (i) energy-dense foods and sugary drinks, (ii) plant foods, (iii) red and processed meat, and (iv) alcoholic drinks. Cox proportional hazards regression was used to examine the association between the diet score and cancer risks. Adjusted, cohort-specific HRs were pooled using random-effects meta-analysis. Risk advancement periods (RAP) were calculated to quantify the time period by which the risk of cancer was postponed among those adhering to the recommendations.

Results: After a median follow-up of 11 to 15 years across cohorts, 70,877 cancer cases were identified. Each one-point increase in the WCRF/AICR diet score [range, 0 (no) to 4 (complete adherence)] was significantly associated with a lower risk of total cancer [HR, 0.94; 95% confidence interval (CI), 0.92–0.97], cancers of the colorectum (HR, 0.84; 95% CI, 0.80–0.89) and prostate (HR, 0.94; 95% CI, 0.92–0.97), but not breast or lung. Adherence to an additional component of the WCRF/AICR diet score significantly postponed the incidence of cancer at any site by 1.6 years (RAP, −1.6; 95% CI, −4.09 to −2.16).

Conclusions: Adherence to WCRF/AICR dietary recommendations is associated with lower risk of cancer among older adults.

Impact: Dietary recommendations for cancer prevention are applicable to the elderly. *Cancer Epidemiol Biomarkers Prev; 26(1); 136–44. ©2016 AACR.*

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Introduction

For someone aged 60 years and above, average life expectancy in the year 2012 in Europe and the United States was estimated to be another 22 years. Life expectancy is expected to increase even more in the future (1). One major problem of an aging population is the increase in the incidence of chronic diseases such as cancer (2), which results in decreasing quality of life and increasing care costs. It is of great importance to longer preserve health in old age, which may be influenced by changing behavioral risks such as diet (3). Results from epidemiological studies focusing on cancer in the elderly aged 60 years and above can provide evidence for public health interventions to postpone the diagnosis of cancer (4, 5).

In 2007, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) formulated recommendations for cancer prevention (3). The guidelines are based on quantitative meta-analyses of the most comprehensive collection of available published evidence on physical activity, weight management, and diet in association with cancer. A healthful diet is an important modifiable risk factor for decreasing cancer risk beyond not smoking, leading a physically active life and maintaining a healthy body weight. This has also been confirmed by Romaguera and colleagues who studied the WCRF/AICR recommendations in the EPIC study and found a significant inverse association between the 2007 WCRF/AICR dietary recommendations and cancer risk independent of physical activity and body mass index (BMI), in participants aged 25 to 70 years.

Whether the WCRF/AICR dietary recommendations support the prevention of cancer in an exclusively elderly population remains unknown. A matter of concern, in the elderly, is related to the critical window for cancer prevention, which might have passed after the age of 60 years (6). The aim of the current research was to confirm the associations between the 2007 WCRF/AICR dietary guidelines with total and site-specific cancer risks in elderly populations using harmonized data from 7 large cohort studies from Europe and the United States. In addition, this association was quantified as the time period by which the risk of cancer in elderly is postponed among those adhering to a healthy diet.

Materials and Methods

Study population

This individual participant-based meta-analysis was conducted using data from collaborating cohorts of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES; ref. 4). The aim of the CHANCES consortium was to combine and integrate prospective cohort studies to produce, improve, and clarify the evidence on the distribution and risk factors of chronic diseases in the elderly and their health, medical, and socioeconomic implications (www.chancesfp7.eu). Elderly were defined by the CHANCES consortium as being aged 60 years and above (4).

We included participants from the elderly segment of the European Prospective Investigation into Cancer and Nutrition (EPIC) study (7), known as EPIC-Elderly (8). The following 5 of 9 EPIC-Elderly cohorts shared data with the CHANCES consortium: Spain, the Netherlands, Greece, Sweden (Umea), and Denmark. Furthermore, we included participants of the NIH-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study in the United States (9) and the Rotterdam Study (10) from the Netherlands (NL). We excluded participants with incomplete follow-up information relevant for the analysis and participants with missing information on age, those with prevalent cancer at baseline and those who developed cancer during the first year of follow-up, as well as those with implausible values for BMI (>60 or <10 kg/m^2). NIH-AARP Diet and Health study also excluded participants whose total energy intake was more than two interquartile ranges above the 75th percentile or below the 25th percentile on the logarithmic scale (11). A total number of 361,616 participants (94% of the original source population) remained for further analysis.

Main characteristics of the cohorts have been described previously (7, 9, 10). The research procedures in all cohorts were in accordance with the ethical standards of the responsible institutional or regional committees. All participants gave written informed consent.

Cancer ascertainment

Cancer cases across cohorts were assessed by linkage to population cancer registries. Active follow-up was performed in EPIC-Elderly Greece including inquiries by email or telephone to participants, municipal registries, regional health departments, physicians, and hospitals. Start of follow-up was defined as the date of enrollment and end of follow-up was defined as the date of cancer diagnosis, death, or last completion of follow-up. Data on cancer incidence were coded according to the 10th (Rotterdam Study, EPIC-Elderly) and O-3 (NIH-AARP) revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) codes. The first primary carcinoma was considered for analysis because the focus of the analysis was on cancer incidence. In EPIC-Elderly and NIH-AARP, total cancer was defined as any incident cancer. For the Rotterdam Study, we used a total cancer variable which included incident cases of colorectal, lung, breast, and prostate cancers. These 4 cancers are most common among men and women in Europe and the United States (12).

Collection of covariates

Baseline data on age, sex, educational level, prevalence of chronic diseases, energy intake, physical activity, BMI, and smoking status were assessed by medical, dietary, and lifestyle questionnaires in all cohorts. Standardization of covariates was done according to common rules which were defined by the CHANCES partners that were responsible for data harmonization and coordination of statistical analyses. The result of the harmonization efforts can be found elsewhere (13). EPIC-Elderly and the Rotterdam Study provided data on measured height and weight. For the NIH-AARP Study, self-reported data on height and weight were used. In the Rotterdam Study, no baseline measurements of physical activity were available. Therefore, for all participants in the Rotterdam Study, physical activity assessed 6 years after baseline was used as a proxy measure for physical activity at baseline. For participants who developed cancer between baseline and 6 years of follow-up, information on physical activity was assumed to be missing. Information on physical activity in the Swedish and Danish cohorts of the EPIC-Elderly Study was not available at the time of data analysis. Potential confounding variables were selected on the basis of sound evidence regarding their associations with the WCRF/AICR diet score and cancer risk (14).

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Dietary assessment

All cohorts applied a validated Food Frequency Questionnaire (FFQ) for the assessment of dietary intake (7, 9, 10). EPIC-Elderly Spain assessed dietary intake with a validated diet history questionnaire (15). The total number of FFQ items, reference period, and mode of administration (interview or self-reported) differed across cohorts. Details regarding dietary assessment methods across cohorts were shown earlier (16). The translation of foods into nutrients was performed by using national food composition tables (NIH-AARP; ref. 17), Rotterdam Study (18), or the EPIC Nutrient Database (EPIC-Elderly; ref. 19). Within CHANCES all dietary variables were harmonized prior to analysis (13).

WCRF/AICR diet score

The WCRF/AICR issued 10 recommendations for the prevention of cancer. Five recommendations relate to dietary intake, of which we were able to include 4 in our data analysis: (i) limit the consumption of energy-dense foods and avoid sugary drinks; (ii) eat mostly foods of plant origin; (iii) limit the intake of red meat and avoid the consumption of processed meat; and (iv) limit alcoholic drinks. The fifth recommendation to limit the consumption of salt and to avoid moldy cereals (grains) or pulses (legumes) was not applied for the following analysis because of insufficient available data in the CHANCES cohorts. On the basis of concordance with the dietary recommendations of the WCRF/AICR, we created a 4-point WCRF/AICR diet score. Complete adherence to each of the recommendations contributed with one point to the total score. None adherence contributed with 0 points. The final score ranged from 0 to 4. A higher WCRF/AICR diet score represents greater adherence to the recommendations. Details on the score construction and cutoff values used are described in Table 1 and were elaborated earlier by Romaguera and colleagues (20). In brief, the components "limit intake of red and processed meat" (iii) and "limit alcoholic drinks" (iv) had no subcomponents, that is, participants received 1, 0.5, or 0 points depending on their individual level of adherence (recommendation was met, partially met, or not met, respectively). Participants were scored on the basis of recommendation-specific cutoffs (See Table 1). Recommendations included (i) energy-dense foods and avoiding sugary drinks and (ii) foods of plant origin had subcomponents that were scored first on the basis of either WCRF/AICR-specific cutoffs or cutoffs previously applied by Romaguera and colleagues (20). The component score for recommendations (i) and (ii) was calculated as the average of the subcomponents. The total WCRF/AICR diet score was calculated for each CHANCES participant by summing up the component scores.

In addition to the WCRF/AICR diet score, a WCRF/AICR diet plus score, including BMI and physical activity, was derived (range, 0–6 points). The following cutoff values, based on the operationalization by Romaguera and colleagues, were applied for BMI (in kg/m^2): <18.5 or ≥30 = 0 points, 25–29.9 = 0.5 points, 18.5–24.9 = 1 point. The scoring for physical activity was

Table 1. Operationalization of and adherence to the WCRF/AICR dietary recommendations for cancer prevention in the CHANCES consortium

			EPIC-Elderly					
Operationalization of WCRF dietary recommendations	**Scoring**	**Rotterdam study *n* (%)**	**Spain *n* (%)**	**Sweden *n* (%)**	**Netherlands *n* (%)**	**Denmark *n* (%)**	**Greece *n* (%)**	**NIH-AARP study *n* (%)**
Total WCRF/AICR diet score								
	0–4	2.3 (0.6)	2.5 (0.7)	2.3 (0.5)	2.2 (0.6)	1.8 (0.7)	3.0 (0.5)	2.2 (0.6)
Limit the consumption of energy dense foods and avoid sugary drinks								
Energy density								
≤125 kcal/100 g/d	1.0	2,019 (52)	1,689 (34)	639 (21)	969 (16)	963 (6)	2,790 (31)	94,689 (30)
>125 to ≤175 kcal/100 g/d	0.5	1,572 (41)	2,616 (53)	1,769 (57)	3,952 (64)	7,927 (54)	6,019 (67)	171,733 (54)
>175 kcal/100 g/d	0	283 (7)	651 (13)	706 (23)	1,229 (20)	5,875 (40)	232 (3)	53,294 (17)
Sugary drink intake								
0 g/d	1.0	2,068 (53)	1,839 (37)	54 (2)	590 (10)	384 (3)	none	2,971 (1)
≤250 g/d	0.5	1,712 (44)	2,884 (58)	2,698 (87)	4,361 (71)	11,941 (81)	8,435 (93)	107,467 (34)
>250 g/d	0	94 (2)	233 (5)	362 (12)	1,199 (20)	2,440 (17)	606 (7)	209,278 (65)
Eat mostly foods of plant origin								
Fruit and vegetable intake								
≥400 g/d	1.0	2,188 (56)	3,519 (71)	493 (16)	2,355 (38)	4,952 (34)	8,266 (91)	236,467 (74)
200–400 g/d	0.5	1,491 (38)	1,109 (22)	1,210 (39)	3,118 (51)	6,334 (43)	706 (8)	66,817 (21)
<200 g/d	0.0	195 (5)	328 (7)	1,411 (45)	677 (11)	3,479 (24)	69 (1)	16,432 (5)
Dietary fiber intake								
≥25 g/d	1.0	175 (5)	2,011 (41)	571 (18)	1,761 (29)	6,817 (46)	1,604 (18)	68,055 (21)
≥12.5–<25 g/d	0.5	2,988 (77)	2,693 (54)	2,028 (65)	4,174 (68)	7,361 (50)	6,641 (73)	175,280 (55)
<12.5 g/d	0.0	711 (18)	252 (5)	515 (17)	215 (4)	587 (4)	796 (9)	76,381 (24)
Limit the intake of red meat and avoid processed meat								
Red and processed meat intake:								
Red meat < 500 g/wk and processed meat < 3 g/d	1.0	408 (11)	599 (12)	49 (2)	671 (11)	372 (3)	6,882 (76)	30,264 (9)
Red meat < 500 g/wk and processed meat 3 to <50 g/d	0.5	682 (18)	2,405 (49)	2,511 (81)	2,445 (40)	3,788 (26)	935 (10)	175,467 (55)
Red meat ≥ 500 g/wk or processed meat ≥ 50 g/d	0.0	2,784 (72)	1,952 (39)	554 (18)	3,031 (49)	10,605 (72)	1,224 (14)	113,985 (36)
Limit alcoholic drinks								
Ethanol intake: ≤20 g/d (men)	1.0	2,864 (74)	3,563 (72)	3,063 (98)	4,560 (74)	8,097 (55)	7,884 (87)	256,907 (80)
Ethanol intake: ≤10 g/d (women)								
Ethanol intake: 20 to ≤30 g/d (men)	0.5	513 (13)	491 (10)	45 (1)	744 (12)	2,701 (18)	519 (6)	25,866 (8)
Ethanol intake: 10 to ≤20 g/d (women)								
Ethanol intake: >30 g/d (men)	0.0	497 (13)	902 (18)	6 (0.2)	846 (14)	3,967 (27)	638 (7)	36,943 (12)
Ethanol intake: >20 g/d (women)								

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on the basis of the harmonized CHANCES variable "vigorous physically active" no (=0 points) or yes (=1 point) which was different from the scoring standards applied earlier (20).

Statistical analysis

Each of the 7 cohorts (Rotterdam Study, EPIC-Elderly Spain, EPIC-Elderly Sweden, EPIC-Elderly Greece, EPIC-Elderly Netherlands, EPIC-Elderly Denmark, and NIH-AARP) was analyzed separately using the same *a priori* defined analysis strategy. We applied Cox proportional hazard models to examine the associations between a one-point increase in WCRF/AICR diet score and total and site-specific cancer risks. The final HR and 95% confidence intervals (CI) for the association between the WCRF/AICR diet score and cancer risk was adjusted for age, sex, educational level [primary or less (low), more than primary but less than college or university (medium), and college or university (high)], which was used as a proxy measure for socioeconomic status across all cohorts; chronic diseases at baseline, including type 2 diabetes and cardiovascular disease (CVD); energy intake in kcal/d (continuous); vigorous physical activity (yes, no); BMI (continuous); smoking status (never, former, current), and intensity of smoking (former: 1–15 years; 16–30 years; >30 years of smoking and current: ≤15 cigarettes/d; >15–25 cigarettes/d; >25 cigarettes/d). The variable duration of smoking was not assessed in the NIH-AARP Study and was substituted by the number of years since quitting smoking (≥10 years; <10 years). Participants with missing data for the confounding variables were assigned to a separate category for each of these variables. EPIC-Elderly Spain and Netherlands consisted of more than one center. Analyses in these 2 cohorts were adjusted for center to correct for potential differences in baseline hazards within the cohorts.

In a sensitivity analysis, HR models for breast cancer in the NIH-AARP Study were additionally adjusted for covariables specific for women: menopausal status, use of contraceptives, parity, and hormone replacement therapy. The analysis was only performed in NIH-AARP, as the EPIC-Elderly Study and the Rotterdam Study provided insufficient data regarding these covariates specific for women.

The adjusted individual HR estimates for each cohort were summarized by random-effects meta-analysis. Between-study heterogeneity was determined by the I^2 statistic (21). In a sensitivity analysis, the NIH-AARP Study was excluded from the random effects meta-analysis to determine whether this cohort was driving the results, given its larger sample size. Risk advancement periods (RAP; ref. 22) and 95% CIs were calculated from the results of multivariable regression models. In short, RAPs are calculated by dividing the regression coefficient of the association between the WCRF/AICR diet score and cancer risk by the regression coefficient of the association between age in years and cancer risk. This measure can be understood as the time period by which the risk of cancer could be postponed through the adherence to an additional WCRF/AICR recommendation.

Potential effect modification was tested in each cohort separately by the inclusion of an interaction term between the WCRF/AICR diet score (continuous) and baseline age (60–65 and >65 years), sex, smoking (never, former, current smoker), and prevalent chronic diseases (CVD, diabetes type 2). To examine the relative importance of the single WCRF/AICR diet components, we excluded one WCRF/AICR diet component at a time from the WCRF/AICR diet score, while including this component as a covariate in the model. Furthermore, the WCRF/AICR recommendations on BMI and physical activity were removed from the HR model and included in the score (WCRF/AICR diet plus score) to assess the additional impact of BMI and physical activity on cancer risk. The WCRF/AICR diet plus score was applied in all CHANCES cohorts except for EPIC-Elderly Denmark and Sweden because at the time of data analysis, the physical activity variable was not available. Comparisons between pooled HR estimates derived from the WCRF/AICR diet score and diet plus score were made using the same set of cohorts. For random-effects meta-analysis, we used the Metafor package in R (version 2.15.0). All other analyses were performed using SAS version 9.2. $P < 0.05$ was considered statistically significant.

Results

Median length of follow-up ranged between 11 and 15 years. During that time, 70,877 total, 6,931 breast, 8,193 lung, 4,975 prostate, and 6,507 colorectal cancer cases were identified (Table 2). Mean age at baseline ranged from 60 years in EPIC-Elderly Sweden to 70 years in the Rotterdam Study. Baseline characteristics for physical activity and education differed between cohorts. A large proportion of people with low physical activity levels and a low level of education were observed in EPIC-Elderly Spain and Greece.

Country-specific dietary characteristics can be found in Table 1. EPIC-Elderly Spain and Greece had the greatest dietary quality (highest WCRF/AICR score) in comparison to the other countries included. A large proportion in both cohorts adhered well to the recommendations "Eat mostly foods of plant origin" and "Limit the intake of red meat and avoid processed meat." EPIC-Elderly Denmark had the lowest WCRF/AICR score in comparison to the other cohorts, which was driven by a large proportion not adhering to the recommendation "Limit the consumption of energy dense foods and avoid sugary drinks" and "Limit the intake of red meat and avoid processed meat." The largest proportion of sugary drink consumers was observed in the United States cohort, the NIH-AARP Study. Figure 1A–E shows the forest plots for the associations between a one-point increase in WCRF/AICR diet score and total cancer and cancer-specific risk. No significant effect modification or marked levels of heterogeneity were observed for any cancer site. Therefore, no stratified HR estimates are presented.

Total cancer

A one-point increase in the WCRF/AICR diet score was statistically significantly inversely associated with total cancer (Fig. 1A) risk. Heterogeneity was low. After the exclusion of the NIH-AARP Study, HR estimates were slightly weaker (HR, 0.96; 95% CI, 0.93–1.00). The pooled RAP estimate for total cancer was −1.57 years (95% CI, −4.09–2.16). This result means that the risk of cancer could be postponed by about 1.6 years in elderly aged 60 years and above, for each additional WCRF/AICR recommendation followed. The exclusion of single WCRF/AICR dietary component slightly changed the HR estimate for total cancer risk (≤0.02 above or below the initial HR estimate). The comparison between the WCRF/AICR diet score and the diet plus score derived in the Rotterdam Study, EPIC-Elderly Spain, Greece, the Netherlands, and NIH-AARP revealed similar pooled HR estimates for the association with total cancer risk [HRs of 0.95 (0.91–1.00) and 0.98 (0.92–1.04), respectively].

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Table 2. Baseline characteristics, follow-up, and cancer incidence of participants in the 7 cohorts of the CHANCES consortium

		EPIC-Elderly					
Cohort	**Rotterdam study**	**Spain**	**Sweden**	**Greece**	**Netherlands**	**Denmark**	**NIH-AARP**
N	3,874	4,956	3,114	9,041	6,150	14,765	319,716
Median follow-up, y	15	13	13	10	12	11	11
Women[a]	2,327 (60)	2,813 (57)	1,604 (52)	5,433 (60)	5,855 (95)	7,872 (53)	128,259 (40)
Age, y[b]	70 ± 7	63 ± 2	60 ± 1	67 ± 5	64 ± 3	63 ± 2	66 ± 3
BMI[b]	27 ± 4	30 ± 4	26 ± 4	29 ± 5	26 ± 4	26 ± 4	27 ± 5
Cancer incidence[a]							
Total cancers	557 (14)	755 (15)	571 (18)	733 (8)	1,024 (17)	3,134 (21)	64,103 (20)
Breast	120 (3)	55 (1)	55 (2)	63 (1)	203 (3)	321 (2)	6,114 (2)
Lung	136 (4)	48 (1)	24 (1)	119 (1)	63 (1)	333 (2)	7,470 (2)
Prostate	134 (3)	123 (3)	132 (4)	58 (1)	16 (0.3)	314 (2)	4,198 (5)
Colorectal	171 (4)	81 (2)	61 (2)	85 (1)	136 (2)	300 (2)	5,673 (2)
Vigorous physical activity[a]							
No	408 (11)	4,666 (94)	n.a.	7,051 (78)	2,488 (40)	n.a.	163,006 (51)
Education[a]							
Low	1,428 (37)	4,240 (86)	1,707 (55)	8,238 (91)	2,054 (33)	6,064 (41)	2,549 (1)
High	284 (7)	310 (6)	361 (12)	275 (3)	665 (11)	2,308 (16)	222,546 (70)
Smoking[a]							
Never	1,352 (35)	3,319 (67)	1,861 (60)	6,119 (68)	2,932 (48)	4,547 (31)	110,304 (35)
Current	810 (21)	827 (17)	504 (17)	1,042 (12)	1,084 (18)	4,878 (33)	32,413 (10)
Duration of smoking[a,c]							
1–15 y	364 (9)	157 (3)	151 (5)	287 (3)	526 (9)	1,290 (9)	126,079 (40)
16–30 y	517 (13)	337 (7)	287 (9)	506 (6)	862 (14)	1,796 (12)	39,082 (12)
>30 y	810 (21)	1,115 (23)	628 (20)	1,831 (20)	1,682 (27)	6,614 (45)	n.a.
Number of cigarettes smoked per day[a]							
1–15	488 (13)	334 (7)	n.a	596 (39)	788 (13)	2,846 (19)	21,731 (7)
16–25	218 (6)	196 (4)		325 (25)	233 (4)	1,184 (8)	6,628 (2)
>25	29 (1)	53 (1)		217 (61)	23 (0.4)	194 (1)	4,054 (1)

[a]*N* (%), numbers do not add up to 100%. The category including missing values is not presented in the table.
[b]Mean and SD.
[c]Duration of smoking 1–15 years <10 years in NIH-AARP; 16–30 years = >10 years in NIH-AARP; >30 = not applicable to NIH-AARP.

Colorectal cancer

We found the strongest association between a-one point increase in the WCRF/AICR diet score and colorectal cancer (Fig. 1B) risk (HR, 0.84; 95 CI, 0.80–0.89). Heterogeneity was again low. The association for colorectal cancer remained similar after the exclusion of the NIH-AARP Study (HR, 0.83; 95% CI, 0.73–0.96). On the basis of the pooled RAP estimate, risk of colorectal cancer could be postponed by about 3.1 years, in elderly aged 60 years and above, for each additional WCRF/AICR recommendation followed (RAP, −3.13 years; 95% CI, −1.86 to −1.29). Similar to total cancer risk, HR estimates for colorectal cancer changed marginally after exclusion of single WCRF/AICR component. The associations between the WCRF/AICR diet score (HR, 0.84; 95% CI, 0.81–0.88) and diet plus score (HR, 0.85; 95% CI, 0.83–0.88) were not remarkably different.

Prostate cancer

A one-point increase in the WCRF/AICR diet score was statistically significantly inversely associated with prostate cancer (Fig. 1C) risk. The level of heterogeneity was 0%. HR estimates were slightly weaker after exclusion of NIH-AARP (HR, 0.95; 95% CI, 0.81–1.12). Exclusion of single WCRF/AICR component and inclusion of BMI and physical activity revealed robust results.

Breast cancer

The WCRF/AICR diet score was not statistically significantly associated with breast cancer (Fig. 1D) risk (HR, 0.93; 95 CI, 0.86–1.00; I^2 = 8%). The association weakened after the exclusion of the NIH-AARP study (HR, 0.99; 95 CI, 0.86–1.13; I^2 = 2%). HR estimates for breast cancer in the NIH-AARP study did not remarkably change after the inclusion of confounding variables specific for women or after exclusion of single WCRF/AICR diet component and inclusion of BMI and physical activity.

Lung cancer

The WCRF/AICR score diet score was not associated with lung cancer (Fig. 1E) risk (HR, 0.99; 95 CI, 0.84–1.17). Heterogeneity was high. After the exclusion of the NIH-AARP study, the HR estimate flipped and the level of heterogeneity became zero (HR, 1.10; 95% CI, 0.97–1.25; I^2 = 0%). Exclusion of single WCRF/AICR diet component and inclusion of BMI and physical activity changed the HR estimates slightly but the association did not reach statistical significance.

Discussion

In this meta-analysis of 7 prospective cohort studies from Europe and the United States, forming part of the CHANCES consortium, we found a 6% lower risk for development of cancer in elderly (≥60 years of age) for each one-point increase in adherence to the WCRF/AICR score. This score relates directly to dietary recommendations for cancer prevention issued by the WCRF/AICR in their 2007 report (3). The greatest risk reduction of 16% was observed for the association between the adherence to one additional WCRF/AICR dietary recommendation and colorectal cancer risk, with a corresponding RAP of 3.1-year delay in colorectal cancer development.

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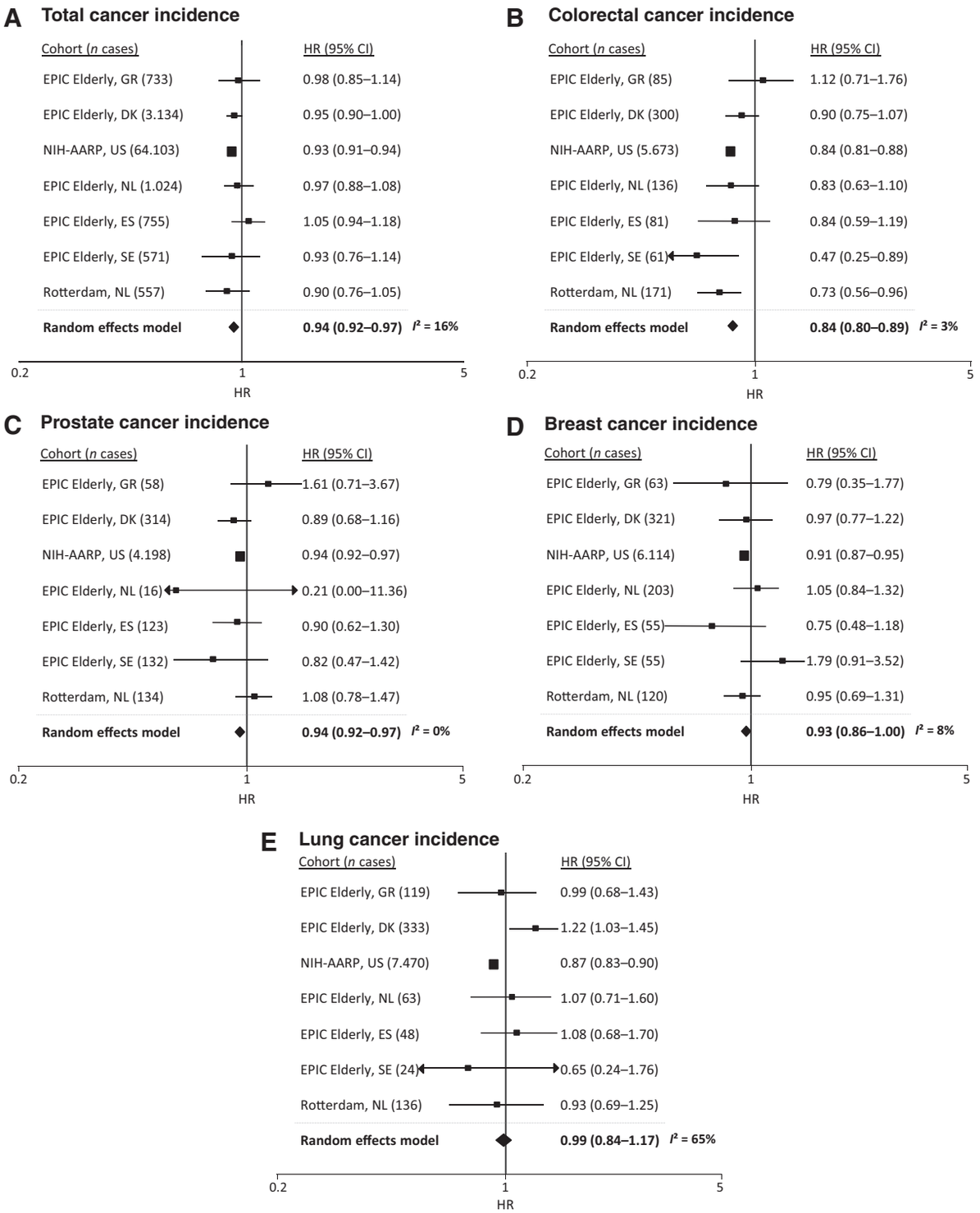

Figure 1.

A–E, Cohort-specific and pooled adjusted HRs of total and site-specific cancer risk in relation to a one-point increase in WCRF/AICR diet score, in the CHANCES, 1988–2011. The numbers of incident cases are indicated in brackets. Bars, 95% CIs. I^2 values are expressed as the percentage of total variability caused by heterogeneity. All data were obtained from CHANCES (www.chancesfp7.eu). DK, Denmark; ES, Spain; GR, Greece; NL, Netherlands; SE, Sweden; US, United States.

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The WCRF/AICR recommendations intend to prevent total cancer occurrence. Therefore, we decided to perform some additional analysis like the calculation of RAPs for this outcome and for colorectal cancer, as for this cancer, outcome associations were strongest. The calculation of RAPs is an important and novel contribution to the present findings. RAPs considerably enhance communication on the impact of adhering to a healthy diet according to WCRF/AICR recommendations on risks of cancer development in elderly populations. Our results showed that following a healthy diet at the age of 60 adds 1.6 additional years lived without cancer and 3.1 additional years without colorectal cancer. The postponed diagnosis of cancer, as shown in this article, reflects the importance to promote a healthy diet later in life. RAP estimates were also presented in an earlier EPIC study on the association between the WCRF/AICR score and all-cause mortality (23). Adherence to a healthy diet was shown to postpone premature death by 1.2 years. A weaker estimate for all-cause mortality in comparison to cancer risk would be expected, as all mortality outcomes are taken into consideration irrespective of their association with the recommendations.

Similar analyses to those reported in this article on the association between the WCRF/AICR diet recommendations and cancer risk were previously performed by Romaguera and colleagues (20) in the whole EPIC Study, including younger adults and a wider range of EPIC subcohorts. Their main analysis included the WCRF/AICR dietary recommendations, BMI, and physical activity and showed a significant inverse association between the WCRF/AICR score and cancer risk (HR, 0.92; 95% CI, 0.89–0.96). The sensitivity analysis based on the WCRF/AICR dietary recommendations and cancer risk revealed similar results to their main analysis. The strongest association that they observed was also for colorectal cancer. The other cancer-specific outcomes were comparable to the results reported in this article except for lung cancer. Romaguera and colleagues indicated a significant inverse association between the WCRF/AICR score and risk of lung cancer. In our study, we observed a null association for the overall pooled HR estimate of lung cancer. Considering the heterogeneity in smoking prevalence comparing the CHANCES cohorts with other cohorts, residual confounding by smoking may explain the differences in results.

The research group from the Framingham Offspring (24) cohort examined the association between the WCRF/AICR recommendations and cancer risk in an American population with a mean age of 66 years. They reported similar HRs to our estimates for the association between the WCRF score total cancer, colorectal cancer, and breast cancer risk. However, CIs were broader and did not reach statistical significance.

Our results which were based on 5 cohorts of the older EPIC subjects from the study of Romaguera and colleagues (20), but also included elderly subjects from the NIH-AARP Study and the Rotterdam study, fit with the evidence reported previously. Interestingly, earlier dietary recommendations of the WCRF/AICR released in 1997 were reported not to be associated with cancer risk in a population of older women aged between 55 and 69 years at baseline (HR, 0.93; 95% CI, 0.78–1.10; ref. 6). The difference in results may be related to a larger study size of the current study, offering greater power and more precision and/or an extended formulation of dietary guidelines in the 2007 WCRF/AICR recommendations release. The new developments regarding the recommendations led to the inclusion of dietary fiber instead of complex carbohydrates, more refined definitions of alcohol and red meat intake and consideration of energy density and sugary drinks in the 2007 WCRF/AICR score (6, 20).

The strength of the observed associations for diet and colorectal cancer in all of the presented cohorts is not entirely surprising, as this anatomical site showed convincing associations with diet in the 2007 WCRF/AICR report as well (3). Since that date, the WCRF Continued Update Project has further strengthened the evidence pertaining to dietary fiber, red and processed meat, and colorectal cancer risk (25, 26).

Results for breast cancer fit with the literature (27–30). Although, earlier studies reported strong inverse association with breast cancer risk. Estimates ranged from HR of 0.40 (95% CI, 0.25–0.65; ref. 27) to 0.76 (95% CI, 0.67–0.87; ref. 29) comparing the adherence with more than 5 and 6 recommendations versus 1 and 0, respectively. These discrepancies in results with previous studies may be explainable by different reference categories used. Specific studies regarding the association between the WCRF/AICR recommendations and prostate cancer are scarce so far. In general, associations between dietary factors and hormone-related cancer, that is, breast and prostate cancer, are weaker than those for colorectal cancer (3).

For the present study, the WCRF/AICR recommendation for sodium and moldy foods was not scored because of insufficient data in the CHANCES cohorts. Sodium would be most important regarding the prevention of stomach cancer, whereas moldy foods are important for liver cancer (3). None of these cancer outcomes were considered separately in the current analysis. Therefore, HR estimates are not expected to change substantially if these components would have been additionally included in the score.

Strength

This meta-analysis of individual participant data has several strengths. The broad range of prospective cohort studies represent a wide coverage of Western populations and led to HR estimates which are likely transferable to health conscious elderly subjects in Europe and the United States. Other advantages of the present study were the use of harmonized variables and the application of the same analysis script across cohorts.

Limitations

The assessment of diet and other lifestyle factors only once at baseline represents a limitation of this study and most cohort studies. Diet, lifestyle, and other risk factors for disease occurrence might change during follow-up and could bias the HR estimate in either direction (31). An earlier study in elderly reported relatively stable dietary patterns over a period of 5 years (32). However, a final conclusion on the strength of potential bias, caused by diet changes later in life, cannot be drawn (33, 34). Residual confounding by covariates specific for women was explored in the NIH-AARP study and appeared to be unlikely. However, residual confounding by unmeasured (such as information on cancer screening) or incomplete measured covariates (e.g., physical activity and smoking) remains possible. Finally, even the application of standardized dietary assessment methods can result in measurement error and misclassification may have weakened the observed associations.

In conclusion, eating according to the WCRF/AICR dietary guidelines is associated with a lower risk of developing diet related cancers in elderly from Europe and the United States. Adherence to an additional WCRF/AICR dietary guideline increases the

number of years lived without any cancer by 1.6 and without colorectal cancer by 3.1 years. The WCRF/AICR dietary recommendations for cancer prevention require more promotion and implementation to reach the general public, decreasing the burden of cancer and improve quality of life of the elderly.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. WHO. Life expectancy: Life expectancy by WHO region 2013 [cited 2013 Jun 22]. Available from: http://apps.who.int/gho/data/view.main.690?lang=en.
2. IARC. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. Lyon, France: IARC; 2012[updated 2015; cited 2015 Nov 3]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
3. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: AICR; 2007.
4. Boffetta P, Bobak M, Borsch-Supan A, Brenner H, Eriksson S, Grodstein F, et al. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) project—design, population and data harmonization of a large-scale, international study. Eur J Epidemiol 2014;29:929–36.
5. Crimmins E. Trends in the health of the elderly. Annu Rev Public Health 2004;25:79–98.
6. Cerhan JR, Potter JD, Gilmore JME, Janney CA, Kushi LH, Lazovich D, et al. Adherence to the AICR cancer prevention recommendations and subsequent morbidity and mortality in the Iowa women's health study cohort. Cancer Epidemiol Biomarkers Prev 2004;13:1114–20.
7. Riboli E, Kaaks R. The EPIC Project: Rationale and study design. Int J Epidemiol 1997;26:S6–S14.
8. Trichopoulou A. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. Br Med J 2005;330:991–5.
9. Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: The National Institutes of Health-American Association of retired persons diet and health study. Am J Epidemiol 2001;154:1119–25.
10. Hofman A, Murad SD, Van Duijn CM, Franco OH, Goedegebure A, Arfan Ikram M, et al. The Rotterdam study: 2014 objectives and design update. Eur J Epidemiol 2013;28:889–926.
11. Wirfält E, Midthune D, Reedy J, Mitrou P, Flood A, Subar AF, et al. Associations between food patterns defined by cluster analysis and colorectal cancer incidence in the NIH-AARP diet and health study. Eur J Clin Nutr 2009;63:707–17.
12. WHO. Cancer fact sheet no. 2972013. [cited 2010 Dec 13]. Available from: http://www.who.int/mediacentre/factsheets/fs297/en/.
13. Kuulasmaa K, Palosaari T, editors. Contributors from Partners of the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES). CHANCES cohort descriptions, assessment of the availability and quality of data, and definitions of variables. MORGAM Project e-publications [Internet]. 2015; URN:NBN:fife201501151161. [cited 2015 Aug 4]. Available from: http://www.thl.fi/publications/morgam/chances_d9/index.html.
14. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
15. Relative validity and reproducibility of a diet history questionnaire in Spain. I. Foods. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition.1997;26:S91–9.
16. Jankovic N, Geelen A, Streppel MT, de Groot LCPGM, Orfanos P, van den Hooven EH, et al. Adherence to a healthy diet according to the World Health Organization guidelines and all-cause mortality in

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elderly adults from Europe and the United States. Am J Epidemiol 2014;180:978–88.
17. United States Department of Agriculture. Continuing survey of food intakes by individuals 1994–96, 1998 and diet and health knowledge survey 1994–96. Beltsville, MD: Beltsville Agricultural Research Service; 1998.
18. Dutch food composition table. The Hague, The Netherlands: Voorlichtingsbureau voor de Voeding; 1993.
19. Slimani N, Deharveng G, Unwin I, Southgate DAT, Vignat J, Skeie G, et al. The EPIC nutrient database project (ENDB): A first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. Eur J Clin Nutr 2007;61:1037–56.
20. Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96:150–63.
21. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60.
22. Brenner H, Gefeller O, Greenland S. Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases. Epidemiology 1993;4:229–36.
23. Vergnaud AC, Romaguera D, Peeters PH, Van Gils CH, Chan DSM, Romieu I, et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study. Am J Clin Nutr 2013;97:1107–20.
24. Makarem N, Lin Y, Bandera EV, Jacques PF, Parekh N. Concordance with World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) guidelines for cancer prevention and obesity-related cancer risk in the Framingham Offspring cohort (1991–2008). Cancer Causes Control 2015;26:277–86.
25. WCRF/AICR. Continuous Update Project (CUP) 2014 [cited 2015 Aug 4]. Available from: http://www.dietandcancerreport.org/cup/whats_new.php.
26. Norat T, Aune D, Chan D, Romaguera D. Fruits and vegetables: updating the epidemiologic evidence for the WCRF/AICR lifestyle recommendations for cancer prevention. Cancer Treat Res 2014;159:35–50.
27. Hastert TA, Beresford SAA, Patterson RE, Kristal AR, White E. Adherence to WCRF/AICR cancer prevention recommendations and risk of post-menopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2013;22:1498–508.
28. Harris HR, Bergkvist L, Wolk A. Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and breast cancer risk. Int J Cancer 2016;138:2657–64.
29. Nomura SJO, Inoue-Choi M, Lazovich D, Robien K. WCRF/AICR recommendation adherence and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors. Int J Cancer 2016;138:2602–15.
30. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. Int J Cancer 2014;135:2444–52.
31. Brenner H, Arndt V. Epidemiology in aging research. Exp Gerontol 2004;39:679–86.
32. Jankovic N, Steppel MT, Kampman E, de Groot LC, Boshuizen HC, Soedamah-Muthu SS. Stability of dietary patterns assessed with reduced rank regression; The Zutphen Elderly Study. Nutr J 2014;13:30.
33. Drewnowski A, Evans WJ. Nutrition, physical activity, and quality of life in older adults: summary. J Gerontol A Biol Sci Med Sci 2001;56:89–94.
34. Wakimoto P, Block G. Dietary intake, dietary patterns, and changes with age: an epidemiological perspective. J Gerontol A Biol Sci Med Sci 2001;56:65–80.

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Adherence to the WCRF/AICR Dietary Recommendations for Cancer Prevention and Risk of Cancer in Elderly from Europe and the United States: A Meta-Analysis within the CHANCES Project

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