Dietary intake of branched-chain amino acids and colorectal cancer risk.

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ABSTACT

An adequate intake of branched-chain amino acids (BCAAs) is required for protein synthesis and metabolic functions, including insulin metabolism. Emerging studies found positive associations between BCAAs and the risk of various diseases sharing etiological aspects with colorectal cancer (CRC), including type 2 diabetes, obesity, and pancreatic cancer.

We investigated the relation between dietary BCAAs and CRC using data from a multicentric Italian case-control study, including 1953 cases of CRC (of these, 442 of sigmoid colon) and 4154 hospital controls with acute, non-neoplastic diseases. A validated food-frequency questionnaire was used to estimate the participants' usual diet and to assess dietary intakes of various nutrients, including energy, BCAAs and calcium. Odds ratio (ORs) and corresponding confidence intervals (CI) were computed by multiple logistic regression models adjusted for age, sex and other confounding factors, including total energy intake.

BCAA intake was inversely related to CRC risk (OR for the highest versus the lowest quintile, 0.73; 95% CI, 0.55-0.97), but the association was attenuated after adjustment for calcium intake (OR, 0.90; 95% CI, 0.65-1.25). A linear inverse association with sigmoid colon cancer risk remained also after adjustment for other dietary factors, including calcium intake (OR, 0.49; 95% CI, 0.27-0.87).

This study provides supporting evidence that higher levels of dietary BCAA intake are not associated with an increase of CRC risk, but confirms that they may be related to a reduced risk of sigmoid colon cancer.

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INTRODUCTION

Branched-chain amino acids (BCAAs) are essential amino acids (leucine, isoleucine and valine). Their main sources are meat, fish, legumes, dairy products and eggs. An adequate intake of BCAAs is required for protein synthesis and several metabolic and signalling functions, including insulin metabolism [1; 2].

Several studies suggested positive associations between dietary or plasma BCAAs and the risk of various diseases, including insulin resistance, type 2 diabetes, obesity, cardiovascular diseases and pancreatic cancer [1; 3; 4], which may share etiological aspects and mechanisms with CRC. There is evidence of an elevated risk of CRC with higher consumption of red meat [5], the most major source of BCAA. A study based on three US cohorts (The Nurses' Health Study, NHS, I and II, the Health Professionals Follow-up Study, HPFS) including a total of 3309 incident cases investigated the association between dietary BCAAs and colorectal cancer (CRC) risk, reporting no association with the intake of leucine, isoleucine and valine [6]. However, it found inverse association for distal colon in HPFS and rectum in NHS. A cross-sectional Japanese study on 629 cases of colorectal adenoma found that higher levels of plasma BCAAs were inversely associated with adenoma risk, a precursor lesion of CRC, in men but not in women [7].

To provide information on the issue, this article investigates the relation between dietary BCAAs and CRC with specific focus on distal subsites using data from a multicentric case-control study of CRC [8].

METHODS

A case-control study of CRC was conducted between January 1992 and June 1996 in six Italian areas [8]. Cases were subjects with incident, histologically confirmed CRC and no previous diagnoses of cancer. They included 1,953 subjects with cancer of the colon-rectum (1125 men and 828 women, median age 62, range 19–79, years) according to the International Classification of

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Diseases, 9th Edition (ICD-9). Of these, 185 were grouped into the right colon, including the caecum, ascending colon and hepatic flexure (ICD-9 153.0, 153.4, 153.5, 153.6), 188 into the transverse and descending colon (ICD-9 153.1, 153.2 and 153.7), 442 into the sigmoid colon (ICD-9 153.3), and 728 into the rectum, including the rectosigmoid junction (ICD-9 154.0–154.1). The remaining 410 cases belonged to other or unspecified anatomic subsites. One hundred forty-four cases (7.4%) had family history of CRC in first degree relatives; 26 (1.3%) received a previous diagnosis of intestinal adenomas.

Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment areas of cases for acute, non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases, or to long-term modifications of diet. They included 2,073 men and 2,081 women aged 19–74 years (median age 58) from the following diagnostic categories: orthopaedic traumas (27%) and other disorders (24%), acute surgical conditions (18%), eye diseases, and other miscellaneous diseases (31%). Seventy-six controls (1.8%) had family history of CRC in first degree relatives; 39 (0.9%) received a diagnosis of intestinal adenomas. There was no difference in terms of adenomas between cases and controls (p for χ^2 test, 1.63). On average, about 4% cases and controls, when invited, refused to participate in the study.

A structured questionnaire was used to collect data on socio-demographic characteristics, such as education and occupation, lifetime smoking and alcohol-drinking habits, physical activity, anthropometric measures, personal medical history, and cancer family history.

A reproducible [9] and validated [10] food frequency questionnaire (FFQ) was used to assess usual diet, including questions on the average weekly consumption of 78 foods, food groups or recipes, and of 5 alcoholic beverages. From these data, we obtained the intakes of energy and selected nutrients, including leucine, isoluecine, valine and calcium, using an Italian food-composition database, appropriately integrated with other data when needed [8; 11].

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Given the high collinearity between the intakes of leucine, isoluecine and valine (r ~ 1.00), we focused on the analyses of total BCAA intake instead of single BCAA intakes. We categorized BCAA intakes into quintiles (based on the distribution of controls) and estimated the odds ratios (ORs) and the 95% corresponding confidence intervals (CI) through multiple logistic regression models. The core model included terms for sex, age (quinquennia; categorically), study center (categorically), education (<7, 7-11, ≥12 years; categorically), occupational physical activity (low, medium, high; categorically), body mass index (BMI) (quintiles, categorically), alcohol consumption (quartiles; categorically), tobacco smoking (never, former, <15 and ≥15 cigarettes/day current smokers; categorically), family history of CRC (yes/no), aspirin use (yes/no), menopausal status and postmenopausal hormone use (premenopause, never and ever users in postmenopause; in women only, categorically) and total energy intake (quintiles; categorically).

BCAA intake was also entered as continuous variables for an increment of the difference between the 4^{th} and 1^{st} quintile upper cutpoints as a measure of variability in the data. Further models also included one term for the intake of protein, fiber, folate, vitamin D, calcium and various BCAA sources (read meat, chicken and poultry, fish and dairy products) at a time (quintiles; categorically).

RESULTS

Table 1 gives the mean (and standard deviation) of BCAA intake, age, BMI, and selected nutrient intakes and food consumptions according to the BCAA quintiles among controls. The distribution of potential confounders was reported across BCAA quintiles. Participants with higher BCAA intake were younger and more frequently women. They were more frequently alcohol drinkers and current smokers. Women with higher BCAA intake were more likely to be in postmenopause. Participants with higher BCAA intake reported a higher intakes of energy, proteins, fiber, folate, vitamin D, and calcium.

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Table 2 shows the mean intake of total BCAAs (16.1 g/day) and their quintile upper cutpoints (12.1, 14.5, 16.7, 19.8 g/day) among controls. Multiple logistic regression ORs of BCAA intake and their corresponding 95% CIs were given according to quintile (with the first quintile as reference category) as well as continuous increment of intake, for all CRC and by anatomic subsites, from two major confounder adjusted models which differ by the addition of calcium intake.

We observed a significantly inverse association between BCAA intake and CRC risk (OR for the highest versus the lowest quintile, 0.73; 95% CI, 0.55-0.97; p for trend, 0.023) that however disappeared after adjustment of calcium intake (OR, 0.90; 95% CI, 0.65-1.25; p for trend, 0.49). The continuous OR was 0.82 (95% CI, 0.69-0.98) in the first and 0.94 (95% CI, 0.77-1.14) in the second model. Analysing separately anatomic subsites, we observed a linear inverse association for sigmoid colon (OR for the highest versus the lowest quintile, 0.42; 95% CI, 0.25-0.72; p for trend, 0.001) which remained after the adjustment for calcium (OR, 0.49; 95% CI, 0.27-0.87; p for trend, 0.013), with continuous ORs about 0.60 in both models. No association was found for other subsites.

Table 3 gives the mean intake of leucine (7.3 g/day), isoleucine (4.1 g/day) and valine (4.7 g/day), as well as the logistic regression ORs of their quintile and continuous increment of intake overall according to the two adjusted models. The ORs for the three single BCAA intakes were almost identical to the ORs for total BCAAs.

The estimates did not appreciably differ when considering further adjustment for selected measures of dietary quality and BCAA sources (Table 4).

DISCUSSION

In this large case-control study, we found an inverse association between dietary BCAAs (leucine, isoleucine and valine) and CRC risk in multivariable models, which, however, was not confirmed

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after adjustment for calcium intake. When separately analyzing CRC sites, we observed that BCAA intake was inversely associated with sigmoid colon cancer risk also after adjustment for other dietary factors, including calcium intake.

Our data reinforce previous results from three large USA cohorts (the NHS I and II, and the HPFS) that did not support the hypothesis of a positive association between dietary BCAA and CRC risk [6], but suggested an inverse association for distal colon cancer, also after adjustment of calcium intake, as well as for rectal cancer [6]. In the NHS and HPFS cohorts, similar differential associations for distal cancer as compared to other colorectal subsites were observed for processed and unprocessed meat intake, too [12]. The absence of a clear mechanistic or biological explanation for different effects of BCAAs on CRC risk by location leaves however the interpretation open to further investigations and discussion. The BCAA metabolism and BCAT1 activity (enzyme involved in the first step of BCAA catabolism) could play functional roles in the progression of tumors [4]. Increased levels of plasma BCAAs were associated with an increased risk of pancreatic cancer in a nested case-control study of a Japan cohort [3]. They were also positively related to obesity, diabetes and insulin resistance [13; 14; 15], which are known risk factor for CRC [16; 17]. BCAAs upregulate glucose transporters and activate insulin secretion [2]. High BCAA levels activate the mammalian target of rapamycin complex one (mTORC1) that could be linked to the insulin resistance [1]. Elevated levels of blood insulin could cause alteration in the insulin-like growth factor (IGF), which is involved in the development of CRC [18].

BCAA supplementation in mice with obesity and hyperinsulinemia was found to improve insulin resistance and to inhibit the activation of the IGF/IGF-I receptor axis, thereby preventing the development of colonic premalignancies in an obesity-related colon cancer model [19]. However, only a few studies, on circulating BCAA levels tended to support the hypothesis of an inverse association between BCAAs and CRC risk, with unconvincing results. In particular, a metabolomics study found a significant reduction in terms of leucine and valine serum

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concentrations intake in 64 CRC cases as compared to 65 controls. This difference, however, was not confirmed when another mass spectrometry instrument was used [20]. Moreover, a cross-sectional study from Japan reported that plasma BCAA concentration was inversely associated with the risk of colorectal adenoma in 629 cases and 584 controls. However, besides the difference in the outcome and the limitations due to a cross-sectional design, there is low agreement between dietary and plasma BCAA levels [21] which may explain the difference with null results, observed in our and previous findings on dietary BCAAs. Plasma BCAAs can be interpreted as a marker of a metabolism alteration of BCAA levels related to insulin resistance [22].

Major sources of BCAA intake were red meat (26%), dairy products (13%), poultry (12%) and fish (7%) in our data. Most models further adjusted for these food groups, which are clearly overadjusted, did not alter the results, as did the inclusion of other nutrients in the models. In particular, no appreciable effect modification was observed in the model including dairy products, whose consumption is partially correlated with calcium intake. Only the adjustment for fish consumption and vitamin D slightly increased the OR estimates (0.82 and 0.87 for the highest versus the lowest quintile of BCAA intake, respectively), suggesting a possible role of vitamin D, in addition to calcium intake, in explaining the observed associations with colorectal cancer, in line with the literature [23; 24; 25; 26]. In an additional model, including both dietary calcium and vitamin D, no association with BCAAs was evident.

This study was sufficiently large to obtain precise risk estimates for BCAA intake. Cases and controls came from comparable catchment areas, participation was virtually complete reducing potential selection bias. Moreover, the hospital setting is unlikely to have reduced the comparability of diet recall by cases and controls [27], and the estimate of BCAA intake derives from a satisfactorily reproducible and valid FFQ [9; 10]. A limitation of this study is the lack of plasma samples to assess the circulating BCAA levels and to compare variability and risk estimates with results from dietary BCAAs. With reference to confounding, all ORs were adjusted for age and other major confounding factors, including education, physical activity and total energy.

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In conclusion, this study provides supporting evidence that higher levels of dietary BCAA intake are not associated with an increase of CRC risk, but may be related to a reduced risk of sigmoid colon cancer.

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Conflicts of interest: None**.**

Authorship:

MR and CLV designed the research; MR, FM and CLV drafted the manuscript; MR and FM conducted the analysis; MP contributed to the design of the analysis and interpretation of results. DS, AG and CLV designed and carried out the initial study; DS, AC, EC, AG and CLV were involved in the collection of the data. All authors contributed to the critical revision and approval of the manuscript.

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Table 1. Distribution of potential confounders by quintiles of branched-chain amino acid (BCAA) intake among 4154 controls. Italy, 1992-1996.

	Quintiles of BCAAs					
	I	**II**	**III**	**IV**	**V**	p-value *
BCAA intake (g/day)						
Total BCAA	10.2 (1.6)	13.3 (0.7)	15.5 (0.6)	18.1 (0.9)	23.5 (4.1)	<0.001
Leucine (g/day)	4.6 (0.7)	6.1 (0.3)	7.1 (0.3)	8.2 (0.4)	10.7 (1.9)	<0.001
Isoleucine (g/day)	2.6 (0.4)	3.3 (0.2)	4.0 (0.2)	4.6 (0.2)	6.0 (1.0)	<0.001
Valine (g/day)	3.0 (0.5)	3.9 (0.2)	4.6 (0.2)	5.3 (0.3)	6.9 (1.2)	<0.001
Women (%)	67.4	52.4	53.4	43.2	34.1	<0.001
Age (years)	58.0 (11.0)	57.4 (10.5)	56.0 (11.2)	55.5 (11.4)	54.6 (11.7)	<0.001
Body mass index (kg/m^2)	25.7 (4.3)	25.7 (4.0)	26.0 (3.9)	25.8 (3.8)	26.0 (3.8)	0.53
Alcohol drinkers (%)	58.8	70.6	73.9	77.4	78.1	<0.001
Current smokers (%)	28.8	30.1	26.1	29.4	32.8	0.056
Family history of colorectal cancer (%)	1.4	2.5	1.7	1.2	2.3	0.21
Regular aspirin use	1.8	1.7	1.7	1.3	1.3	0.90
Medium/heavy occupational physical activity (%)	64.6	66.6	67.0	67.9	71.2	0.066
Postmenopausal among women (%)	73.8	68.7	66.0	64.4	69.6	0.022
Current hormone replacement therapy among postmenopausal women (%)	8.7	9.0	13.0	7.8	9.1	0.26
Total energy intake (kcal/day)	1575.7 (414.6)	2040.2 (417.1)	2340.2 (427.1)	2714.8 (480.7)	3464.9 (821.5)	<0.001
Total protein (g/day)	59.3 (9.0)	76.9 (4.4)	89.4 (4.2)	103.8 (5.7)	113.6 (23.2)	<0.001
Animal protein (g/day)	37.0 (7.9)	48.7 (5.8)	57.5 (6.3)	67.2 (7.0)	89.3 (18.9)	<0.001
Plant protein (g/day)	22.3 (6.8)	28.1 (6.6)	31.9 (7.1)	36.5 (8.2)	44.3 (11.6)	<0.001
Dietary fiber (g/day)	17.6 (6.2)	21.5 (6.1)	23.8 (6.2)	26.5 (6.5)	31.8 (8.6)	<0.001
Folate (µg/ day)	189.5 (54.9)	235.4 (54.7)	262.4 (57.3)	291.6 (56.5)	361.2 (83.9)	<0.001
Vitamin D (IU/ day)	2.1 (1.0)	2.7 (1.1)	3.2 (1.2)	3.6 (1.2)	4.5 (1.6)	<0.001
Calcium (mg/ day)	655.4 (221.5)	856.3 (231.7)	977.8 (255.2)	1147.5 (307.1)	1511.9 (569.1)	<0.001
Unprocessed red meat (svg/ day)	2.7 (1.6)	3.6 (1.7)	4.3 (1.8)	4.9 (2.0)	6.2 (2.6)	<0.001
Processed red meat (svg/ day)	2.1 (1.6)	2.4 (1.7)	2.8 (1.9)	3.1 (2.1)	3.8 (2.8)	<0.001
Chicken and poultry (svg/ day)	1.4 (1.1)	1.6 (1.2)	1.8 (1.2)	2.0 (1.2)	2.5 (1.6)	<0.001
Fish (svg/ day)	1.4 (1.0)	1.6 (1.2)	1.9 (1.2)	2.0 (1.1)	2.3 (1.4)	<0.001
Dairy products (svg/ day)	3.1 (1.8)	4.0 (2.0)	4.3 (2.0)	4.9 (2.3)	6.2 (4.1)	<0.001

Continuous variables show as mean (standard deviation) *For continuous variables: one-way ANOVA; for categorical variables: χ_1^2 test.

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Table 2 Multiple logistic regression-derived odds ratios (OR) and corresponding 95% confidence intervals (CI) according to quintile of branched-chain amino acid (BCAA) intake among 1953 cases with colorectal cancer and 4154 controls overall and by anatomic subsites. Italy. 1992-1996.

BCAAs	*Mean (SD)*[*]	**Quintile of BCAA intake[†]. OR (95% CI)**					**χ^2 trend (p-value)**	**Continuous OR[§]**
		1[‡]	**2**	**3**	**4**	**5**		
Lower/ upper cutpoints (g/day)	*16.13 (4.96)*	*3.91/12.10*	*12.10/14.48*	*14.48/16.70*	*16.71/19.82*	*19.83/60.45*		
Controls		*831*	*831*	*831*	*831*	*830*		
Colon-rectum								
Cases		*391*	*396*	*367*	*393*	*406*		
Model I[‖]		1	0.89 (0.73-1.09)	0.76 (0.61-0.96)	0.76 (0.59-0.98)	0.73 (0.55-0.97)	5.20 (0.023)	0.82 (0.69-0.98)
Model II[¶]		1	0.96 (0.78-1.18)	0.86 (0.67-1.10)	0.90 (0.68-1.19)	0.90 (0.65-1.25)	0.47 (0.49)	0.94 (0.77-1.14)
Right colon								
Cases		*33*	*34*	*36*	*49*	*33*		
Model I[‖]		1	0.75 (0.43-1.31)	0.71 (0.38-1.30)	0.86 (0.45-1.66)	0.52 (0.24-1.12)	1.43 (0.23)	0.63 (0.40-1.00)
Model II[¶]		1	0.82 (0.46-1.45)	0.83 (0.43-1.58)	1.13 (0.55-2.34)	0.76 (0.32-1.82)	0.01 (0.91)	0.75 (0.44-1.27)
Transverse and descending colon								
Cases		*31*	*38*	*35*	*49*	*35*		
Model I[‖]		1	1.07 (0.61-1.87)	0.93 (0.50-1.75)	1.10 (0.56-2.17)	0.80 (0.37-1.74)	0.23 (0.63)	0.92 (0.57-1.48)
Model II[¶]		1	1.32 (0.73-2.37)	1.24 (0.63-2.44)	1.61 (0.76-3.43)	1.22 (0.50-2.95)	0.25 (0.62)	1.07 (0.63-1.83)
Sigmoid colon								
Cases		*95*	*90*	*100*	*82*	*75*		
Model I[‖]		1	0.80 (0.56-1.13)	0.75 (0.51-1.12)	0.53 (0.34-0.84)	0.42 (0.25-0.71)	11.64 (0.001)	0.58 (0.41-0.80)
Model II[¶]		1	0.85 (0.59-1.23)	0.83 (0.54-1.27)	0.60 (0.36-0.99)	0.49 (0.27-0.87)	6.14 (0.013)	0.61 (0.42-0.89)
Rectum								
Cases		*33*	*27*	*30*	*37*	*32*		

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Model I[‖]	1	1.00 (0.75-1.33)	0.85 (0.61-1.18)	0.91 (0.63-1.32)	0.93 (0.61-1.40)	0.24 (0.62)	0.86 (0.66-1.10)
Model II[¶]	1	1.05 (0.78-1.42)	0.93 (0.65-1.33)	1.06 (0.71-1.59)	1.16 (0.72-1.85)	0.23 (0.63)	0.98 (0.74-1.31)

[*]Mean intake and standard deviation (SD) among controls;
[†]Control generated quintiles;
[‡]Reference category;
[§]Estimated for an increment of 4th menus 1st cutoff quintile;
[‖]Adjusted for sex, age, study center, education, occupational physical activity, body mass index, alcohol consumption, tobacco smoking, family history of colorectal cancer, aspirin use, menopausal status and postmenopausal hormone use, and total energy intake;
[¶]Further adjusted for calcium intake.

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Table 3 Multiple logistic regression-derived odds ratios (OR) and corresponding 95% confidence intervals (CI) according to quintile of leucine, isoleucine and valine intakes among 1953 cases with colorectal cancer and 4154. Italy. 1992-1996.

	Mean (SD)[*]	**Quintile of BCAA intake[†]. OR (95% CI)**					**χ^2 trend (p-value)**	**Continuous OR[§]**
		1[‡]	**2**	**3**	**4**	**5**		
Leucine	*7.34 (1.45)*							
Model I[‖]		1	0.91 (0.75-1.11)	0.75 (0.60-0.94)	0.78 (0.60-1.00)	0.73 (0.55-0.97)	5.32 (0.021)	0.83 (0.70-0.98)
Model II[¶]		1	0.98 (0.80-1.21)	0.85 (0.66-1.08)	0.92 (0.70-1.22)	0.91 (0.65-1.22)	0.46 (0.50)	0.95 (0.78-1.15)
Isoleucine	*4.06 (1.25)*							
Model I[‖]		1	0.84 (0.69-1.03)	0.76 (0.61-0.96)	0.73 (0.57-0.94)	0.71 (0.53-0.94)	5.66 (0.017)	0.82 (0.69-0.98)
Model II[¶]		1	0.90 (0.73-1.10)	0.85 (0.67-1.08)	0.85 (0.64-1.12)	0.86 (0.63-1.18)	0.84 (0.36)	0.93 (0.77-1.12)
Valine	*4.73 (1.45)*							
Model I[‖]		1	0.86 (0.71-1.05)	0.73 (0.58-0.91)	0.75 (0.58-0.96)	0.71 (0.53-0.94)	5.65 (0.018)	0.82 (0.69-0.97)
Model II[¶]		1	0.92 (0.75-1.13)	0.82 (0.64-1.04)	0.88 (0.67-1.17)	0.88 (0.63-1.22)	0.59 (0.44)	0.93 (0.77-1.13)

[*]Mean intake and standard deviation (SD) among controls;
[†]Control generated quintiles;
[‡]Reference category;
[§]Estimated for an increment of 4th menus 1st cutoff quintile;
[‖]Adjusted for sex, age, study center, education, occupational physical activity, body mass index, alcohol consumption, tobacco smoking, family history of colorectal cancer, aspirin use, menopausal status and postmenopausal hormone use, and total energy intake;
[¶]Further adjusted for calcium intake.

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Table 4 Multiple logistic regression-derived odds ratios (OR) and corresponding 95% confidence intervals (CI) according to quintile of branched-chain amino acid (BCAA) intake among 1953 cases with colorectal cancer and 4154 controls after adjustment of dietary factors. Italy. 1992-1996.

	Quintile of BCAA intake*. OR (95% CI)					**χ^2 trend (p-value)**	**Continuous OR‡**
	1†	**2**	**3**	**4**	**5**		
Model I§ + protein	1	0.68 (0.46-1.01)	0.63 (0.37-1.07)	0.47 (0.25-0.90)	0.41 (0.20-0.87)	4.02 (0.045)	0.83 (0.65-1.05)
Model I§ + fiber	1	0.91 (0.75-1.10)	0.79 (0.63-0.99)	0.78 (0.61-1.01)	0.76 (0.57-1.01)	5.20 (0.023)	0.82 (0.69-0.98)
Model I§ + folate	1	0.91 (0.74-1.11)	0.80 (0.63-1.00)	0.81 (0.62-1.05)	0.73 (0.55-0.97)	2.73 (0.098)	0.86 (0.72-1.03)
Model I§ + vitamin D	1	0.93 (0.76-1.14)	0.83 (0.65-1.05)	0.85 (0.65-1.12)	0.87 (0.64-1.19)	0.85 (0.36)	0.93 (0.77-1.12)
Model I§ + red meat	1	0.87 (0.71-1.07)	0.74 (0.58-0.93)	0.72 (0.56-0.94)	0.69 (0.51-0.92)	6.63 (0.010)	0.79 (0.66-0.95)
Model I§ + fish	1	0.92 (0.75-1.12)	0.81 (0.64-1.01)	0.82 (0.63-1.06)	0.82 (0.13-1.09)	2.11 (0.15)	0.88 (0.74-1.05)
Model I§ + chicken and poultry	1	0.89 (0.73-1.08)	0.75 (0.60-0.95)	0.765 (0.58-0.97)	0.72 (0.54-0.97)	5.02 (0.025)	0.82 (0.68-0.98)
Model I§ + dairy products	1	0.89 (0.73-1.09)	0.77 (0.61-0.97)	0.77 (0.60-1.00)	0.75 (0.56-1.00)	4.08 (0.043)	0.84 (0.70-1.00)

*Control generated quintiles;
†Reference category;
‡Estimated for an increment of 4th menus 1st cutoff quintile;
§Adjusted for sex, age, study center, education, occupational physical activity, body mass index, alcohol consumption, tobacco smoking, family history of colorectal cancer, aspirin use, menopausal status and postmenopausal hormone use, and total energy intake.

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