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Dietary intake of polyphenols and risk of colorectal cancer and adenoma–A case-control study from Iran

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ABSTRACT

Objectives: The aim of this study is to examine the relationship between dietary polyphenols' classes and individual polyphenol subclasses and also the risk of Colorectal cancer (CRC) and colorectal adenomas (CRA).
Design: A hospital-based case-control study on the association between CRC and CRA and dietary polyphenols was conducted.
Setting: Overall, 129 colorectal cancers, 130 colorectal adenoma cases and 240 healthy controls were studied in three major general hospitals in Tehran province, Iran.
Results: In a multivariate-adjusted model for potential confounders, higher consumption of stilbenes (OR 0.49 for the highest vs. the lowest quartile; 95% CI = 0.24 − 0.99; p for trend = 0.013) was associated with the decreased risk of CRA. Moreover, an inverse association between the risk of CRC and the intake of total polyphenols (OR 0.05 for the highest vs. the lowest quartile; 95% CI = 0.01 − 0.19; p for trend = < 0.001), total flavonoids (OR 0.36 for the highest vs. the lowest quartile; 95% CI = 0.16 − 0.79; p for trend = 0.005), total phenolic acids (OR 0.24 for the highest vs. the lowest quartile; 95% CI = 0.10 − 0.56; p for trend = 0.002), anthocyanin (OR 0.21 for the highest vs. the lowest quartile; 95% CI = 0.08 − 0.55; p for trend = 0.001) and flavanols (OR 0.38 for the highest vs. the lowest quartile; 95% CI = 0.17 − 0.85; p for trend = 0.001) was observed.
Conclusion: The present study showed that a higher intake of total polyphenols, total flavonoids, total phenolic acids anthocyanin and flavanols was related to the decreased risk of CRC. The higher consumption of stilbenes was also inversely associated with the risk of CRA.

1. Introduction

Colorectal cancer (CRC) is the fourth leading cause of cancer mortality in both men and women.[1] In Iran, CRC is the fourth and third most commonly diagnosed malignancy in men and women, respectively.[2] Due to the increase in screening programs, allowing the detection and elimination of colorectal adenomas (CRA), the incidence and mortality of CRC have declined over the past two decades.[3]

Results from previous studies suggested that the environmental factors including life style (physical inactivity, obesity, alcohol consumption, and tobacco use) and various aspects of diet play a crucial role in CRC risk.[4,5] Epidemiological studies reported that the high intake of red/processed meat and low intake of vegetables and fruits were positively related to the risk of CRC. [6–8] Polyphenols are bioactive and antioxidant compounds existing in plant-based food such as fruits, vegetables, whole grains and beverages such as tea and coffee.[9] Based on their chemical structure, dietary polyphenols can be categorized into four major classes, namely, flavonoids, stilbenes, phenolic acids, and lignans.[9] In recent decades, experimental studies have provided potential anti-carcinogenic action of polyphenols including anti-proliferative, inhibition of angiogenesis and stimulation of apoptosis against CRC.[10,11] On the other hand, some studies have shown that polyphenol-rich foods may have a protective role against CRC.[12,13] Nevertheless, results from previous studies are rather inconsistent and controversial. In addition, the majority of studies have investigated the association between some polyphenols such as flavonoids and lignans,

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and the risk of CRC.[9,14]To our knowledge, there have been reported only two studies which have examined the relationship between other polyphenol classes and the risk of CRC,[15,16]However, none of them examined the relationship between polyphenol classes CRA as the main precursor of CRC.[17]

This study examines the relationship between dietary polyphenols' classes and individual polyphenol subclasses and also the risk of CRC and CRA in Tehran, Iran.

2. Method and materials

2.1. Study population

We conducted a hospital-based case-control study among Iranian adults who were admitted to the referral hospitals (Taleghani, Imam Hussein, Shohadaye Tajrish) in Tehran city (capital of Iran). CRC and CRA cases were newly diagnosed (< 3 months) patients with histopathological confirmation and colonoscopy findings, aged 30–79 and had no history of cancers of other sites and previous diagnosis of adenomatous polyp. The control subjects were patients admitted in other sections (due to traumas and orthopedic disorders, disk disorders, acute surgical conditions, eye, nose, ear, or skin problems) of same hospitals at the same time and same setting and only those with non-neoplastic conditions and not afflicted with diet related chronic diseases. Cases and controls were frequency-matched by sex and age (± 10 years). 536 people participated in our study (268 control, 134 CRC, 134 CRA), 28 controls, 5 CRC and 4 CRA based on inclusion and exclusion criteria, patients with incomplete food frequency questionnaire and total energy intakes outside the range of ± 3 standard deviation from the mean, were excluded. Finally, data from 129 CRC, and 130 CRA cases and 240 healthy controls were analyzed.

2.2. Data collection

For all participants, the necessary information includes socio-demographic characteristics, family history of cancer, family history of CRC, smoking habit and medical information (comorbidities, use of drugs and vitamin/mineral supplements). The weight of each individual with the least amount of clothing and a sensitivity of 100 g and height without shoes with a sensitivity of 0.1 cm were also measured. Physical activity was assessed by a validated questionnaire.[18]

2.3. Dietary assessment

Participants' dietary intake during 1 year before diagnosis for cases and 1 year before interview for controls were obtained by a valid and reliable semi-quantitative food frequency questionnaire (FFQ) consisting of 148 food items with standard serving size commonly consumed by Iranian people.[19] Participants were asked to specify their frequency of consumption for each food item on a daily, weekly, monthly or yearly basis. Dietary intakes were transformed into the average of daily intakes and the daily intake frequencies were converted to grams by using the household scales.[20]Daily energy, macronutrients and micronutrients consumption for participants were also computed by Nutritionist IV software. Since the Iranian food composition table (FCT) is not complete and comprehensive, the analysis of energy and nutrients were performed using the United States Department of Agriculture (USDA) food composition table.

2.4. Polyphenol assessment

To estimate the dietary intake of polyphenols, polyphenols from 80 food items were derived from an update version of phenol explorer database (www.phenol-explorer.eu) containing information on the effects of food processing on polyphenol content.[21] The intake of polyphenols was calculated via multiplying the polyphenol content by the daily consumption of each food.

2.5. Statistical analysis

Data analysis was performed by Statistical Package Software for Social Science, version 21 (SPSS Inc., Chicago, IL, USA). Normality of the data was checked using Kolmogorov-Smirnov's test. Baseline characteristics of participants were expressed as median (IQR) for quantitative variables, and frequency and percentages for qualitative variables. Comparison of baseline characteristics and dietary intakes between cases and controls were done using Chi Square test for categorical variables and Mann-Whitney test for continues variables, respectively. Logistic regression was used to determine the odds ratio (OR) with 95% confidence interval (CI) of CRC and CRA by quartile of polyphenols intake. In multivariable model, the potential confounding variables including comorbidity, cancer family history, colorectal cancer family history, physical activity, calcium supplement, and dietary intake of energy, vitamin C, and fiber. OR and 95% confidence interval (CI) were reported, and P-values < 0.05 were considered as statistically significant.

Table 1
General characteristics and dietary intake among study groups.

Variables	Controls(n = 240)	Cancers(n = 129)	Adenomas(n = 130)	P-value*	P-value†
Age(Mean ± SD)	55.08 ± 9.45	56.6 ± 11.5	56.46 ± 10.01	‡	‡
Gender (male) n(%)	133(55.4)	66(51.2)	59(45.4)	‡	‡
BMI(Mean ± SD)	26.93 ± 3.99	26.68 ± 5.49	26.72 ± 3.81	0.62	0.63
Smoking (yes) n(%)	42(17.5)	26(20.2)	27(20.8)	0.53	0.11
Comorbidity (yes) n(%)	41(17.1)	21(16.3)	40(30.8)	0.84	**0.002**
Family history of cancer in first degree (yes) n(%)	89(32.9)	66(51.2)	48(36.9)	**0.001**	0.43
Colorectal cancer family history in first degree (yes) n(%)	18(7.5)	10(7.8)	17(13.1)	0.15	0.08
Physical activity(Mean ± SD)(met/h/day)	40.06 ± 9.87	36.61 ± 15.11	38.54 ± 9.39	**0.008**	0.14
Vitamin D supplement (yes) n(%)	56(23.3)	28(21.7)	40(30.8)	0.72	0.11
Calcium supplement (yes) n(%)	35(14.6)	28(21.7)	32(24.6)	0.08	**0.01**
Dietary intake					
Energy intake(Mean ± SD)	2367.42 ± 673.1	2272.14 ± 574.02	2303.6 ± 669.9	0.17	0.38
Vitamin C (mg/1000 Kcal)	54.3 ± 23.7	36.9 ± 13.6	43.0 ± 16.8	< 0.001	< 0.001
Fiber (g/1000 Kcal)	15.0 ± 4.6	12.0 ± 3.8	12.8 ± 4.8	< 0.001	< 0.001

‡ Matched variables of the study.
* p-value between cancers and controls.
† p-value between adenomas and controls independent sample *t*-test was used for continuous variables and Chi-square was used for categorical variables. MET: Metabolic equivalent.

Table 2
Intake of polyphenols between groups.

Polyphenols	Controls(n = 240)	Cancers(n = 129)	Adenomas(n = 130)
Total polyphenols (mg/d)	1853 (1597-2325)	1496 (1248-1785)[a]	1696 (1297-2159)[a]
Lignans (mg/d)	6.02 (4.2-8.3)	4.6 (3.3-5.8)[a]	5.2 (3.0-7.5)[a]
Stilbenes (mg/d)	0.08 (0.05-0.13)	0.06 (0.03-0.09)[a]	0.06 (0.03-0.13)[a]
Total flavonoids (mg/d)	741 (561 – 949)	617 (454-838)[a]	691 (520-899)
Flavonoids subclasses			
Flavonols (mg/d)	505 (340-664)	385 (304-622)[a]	428 (326-614)
Flavanols (mg/d)	86.0 (60.8-120.4)	70.3 (51.3-104.1)[a]	76.1 (57.4-105.9)
Flavanones (mg/d)	104.7 (79.4-142.2)	86.5 (63.1-108.4)[c]	129.9 (90.8-171.3)
Flavones (mg/d)	16.8 (13.3-22.7)	13.3 (8.8-17.1)[c]	20.3 (13.2-27.3)
Anthocyanins (mg/d)	23.7 (16.2-34.4)	15.7 (8.7-25.8)[a]	18.8 (10.3-34.0)[a]
Total phenolic acids (mg/d)	216 (174-306)	175 (137-235)[a]	208 (148-275)[a]
Phenolic acids subclasses			
Hydroxibenzoic acids (mg/d)	132 (104-177)	116.5 (84.8-160.5)[a]	124.5 (89.6-162.3)
Hydroxicinamic acids (mg/d)	76.3 (54.4-76.3)	58.5 (44.0-77.2) [a]	65.8 (46.8-103.1)[a]

a,b,c superscript letters show significant difference between controls and cancers group or controls and adenoma groups (Mann − whitney test): [a] value significantly different from control group, [b] value significantly different from cancer group, [c] value significantly different from adenoma group.

3. Result

The distribution of sociodemographic, anthropometric, lifestyle-related characteristics and dietary intake of the participants are shown in Table 1. By frequency matched design, age and gender were similar between the groups. Cancer cases were more likely to have family history of cancer in first degree. However, the adenoma cases were more likely to have at least one comorbidity and higher intake of calcium supplement. Controls have significantly higher intake of fruits, vegetables, vitamin C and fiber as compared to CRC and CRA cases. Moreover, controls have significantly higher physical activity only rather than the CRC cases. Table 2 shows the distribution of dietary polyphenols' intake across the cancers, adenomas and controls group. According to this table, controls have higher intake of total polyphenols, lignans, stilbenes, Anthocyanin, total phenolic acids andhydroxicinamic acid as compared to CRC and CRA cases. While Consumption of total flavonoids, flavonol, flavanol and hydroxibenzoic acid in controls was higher only rather than the CRC cases. Likewise, intake of flavanone and flavone was higher in CRA cases as compared to the CRC cases. The ORs and 95% CIs for CRA risk and intakes of polyphenols are presented in Table 3. In a multivariate-adjusted model for potential confounders, only high consumption of stilbenes (OR 0.49 for the highest vs. the lowest quartile; 95% CI = 0.24 − 0.99; p for trend = 0.013) was associated with the decreased risk of CRA. Table 4 presents the ORs and 95% CIs between the intakes of polyphenols and the risk of CRC. After adjusting for several confounding factors, an inverse association between the risk of CRC and the intakes of total polyphenols (OR 0.05 for the highest vs. the lowest quartile; 95% CI = 0.01 − 0.19; p for trend = < 0.001), total flavonoids (OR 0.36 for the highest vs. the lowest quartile; 95% CI = 0.16 − 0.79; p for trend = 0.005) and total phenolic acids (OR 0.24 for the highest vs. the lowest quartile; 95% CI = 0.10 − 0.56; p for trend = 0.002) was observed. The ORs and 95% CIs between subgroups of Flavonoids and Phenolic Acids and the risk of CRA are presented in Fig. 1. No significant association was observed between subgroups of flavonoids and phenolic acids and the risk of CRA. Fig. 2 shows the ORs and 95% CIs between subgroups of flavonoids and phenolic acids and the risk of CRC. After adjusting for confounders, the intake of anthocyanin (OR 0.21 for the highest vs. the lowest quartile; 95% CI = 0.08 − 0.55; p for trend = 0.001) and flavanols (OR 0.38 for the highest vs. the lowest quartile; 95% CI = 0.17 − 0.85; p for trend = 0.001) was inversely associated with the risk of CRC.

Table 3
Odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal adenoma according to quartile of each class of dietary polyphenols among controls.

	Quartiles of dietary intake				
Polyphenols classes	Q1	Q2	Q3	Q4	P for trend
Total polyphenols					
Age adjusted model	1.00 (ref)	0.49 (0.27-0.89)	0.47 (0.26-0.87)	0.49 (0.27-0.89)	0.034
Multivariable adjusted model*	1.00 (ref)	0.63 (0.33-1.23)	0.53 (0.25-1.09)	0.65 (0.28-1.47)	0.417
Total flavonoids					
Age adjusted model	1.00 (ref)	0.84 (0.46-1.52)	0.81 (0.44-1.47)	0.73 (0.39-1.33)	0.317
Multivariable adjusted model*	1.00 (ref)	0.84 (0.44-1.59)	0.68 (0.35-1.32)	0.78 (0.39-1.58)	0.444
Total phenolic acids					
Age adjusted model	1.00 (ref)	0.50 (0.27-0.93)	0.81 (0.46-1.44)	0.55 (0.30-1.02)	0.171
Multivariable adjusted model*	1.00 (ref)	0.50 (0.26-0.98)	0.78 (0.41-1.47)	0.47 (0.22-0.98)	0.108
Lignans					
Age adjusted model	1.00 (ref)	0.53 (0.29-0.97)	0.62 (0.34-1.10)	0.46 (0.25-0.84)	0.019
Multivariable adjusted model*	1.00 (ref)	0.76 (0.39-1.47)	1.19 (0.60-2.37)	1.04 (0.47-2.27)	0.762
Stilbenes					
Age adjusted model	1.00 (ref)	0.54 (0.30-0.95)	0.35 (0.18-0.66)	0.39 (0.21-0.73)	< 0.001
Multivariable adjusted model*	1.00 (ref)	0.52 (0.28-0.97)	0.40 (0.20-0.80)	0.49 (0.24-0.99)	0.013

* Model 1: Additionally adjusted for comorbidity, cancer family history, CRC family history, physical activity, calcium supplement, dietary intake of energy, vitamin C, and fiber.

Table 4
Odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal cancer according to quartile of polyphenols intake.

	Quartiles of dietary intake				
Polyphenols classes	Q1	Q2	Q3	Q4	P for trend
Total polyphenols					
Age adjusted model	1.00 (ref)	0.34 (0.19-0.61)	0.29 (0.16-0.54)	0.07 (0.02-0.18)	< 0.001
Multivariable adjusted model*	1.00 (ref)	0.40 (0.20-0.81)	0.31 (0.14-0.67)	0.05 (0.01-0.19)	< 0.001
Total flavonoids					
Age adjusted model	1.00 (ref)	0.53 (0.30-0.95)	0.43 (0.23-0.79)	0.34 (0.18-1.03)	0.001
Multivariable adjusted model*	1.00 (ref)	0.57 (0.28-1.13)	0.38 (0.18-0.78)	0.36 (0.16-0.79)	0.005
Total phenolic acids					
Age adjusted model	1.00 (ref)	0.36 (0.20-0.67)	0.45 (0.25-0.81)	0.25 (0.13-0.50)	< 0.001
Multivariable adjusted model*	1.00 (ref)	0.34 (0.16-0.70)	0.44 (0.21-0.90)	0.24 (0.10-0.56)	0.002
Lignans					
Age adjusted model	1.00 (ref)	0.92 (0.53-1.59)	0.48 (0.26-0.88)	0.12 (0.04-0.30)	< 0.001
Multivariable adjusted model*	1.00 (ref)	1.55 (0.80-3.00)	1.40 (0.65-3.00)	0.33 (0.11-0.97)	0.109
Stilbenes					
Age adjusted model	1.00 (ref)	0.70 (0.40-1.22)	0.34 (0.18-0.66)	0.30 (0.16-0.59)	< 0.001
Multivariable adjusted model*	1.00 (ref)	0.80 (0.41-1.54)	0.45 (0.21-0.96)	0.64 (0.29-1.41)	0.062

* Model 1: Additionally, adjusted for comorbidity, cancer family history, CRC family history, physical activity, calcium supplement, dietary intake of energy, vitamin C, and fiber.

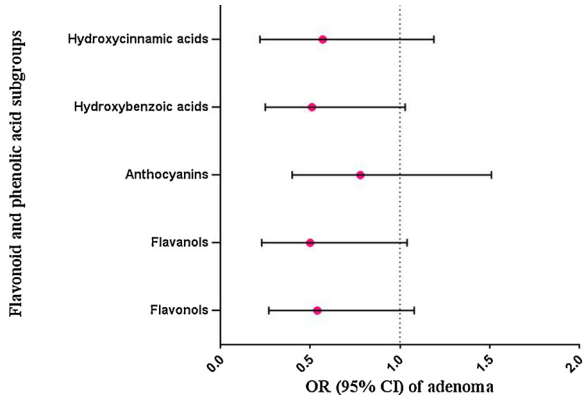

Fig. 1. The OR (95% CI) of adenoma in the highest compared to the lowest quartile of dietary flavonoid and phenolic acid subgroups in the final adjusted model.

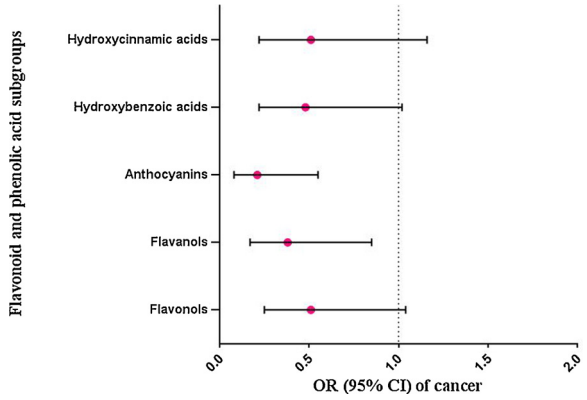

Fig. 2. The OR (95% CI) of cancer in the highest compared to the lowest quartile of dietary flavonoid and phenolic acid subgroups in the final adjusted model.

4. Discussion

In the present study, higher intake of total polyphenols, total flavonoids, total phenolic acids anthocyanin and flavanols was related to the decreased risk of CRC. Moreover, the higher consumption of stilbenes was inversely associated with the risk of CRA.

The majority of studies with regard to the polyphenol intake were focused on some particular classes of polyphenols and flavonoids whereas evaluating the intake of polyphenol subclasses has been less studied.[22–24]

Intake levels of different classes of polyphenols are varied among the previous studies.[25,26] The heterogeneity of individual food-composition and different dietary patterns in the populations makes the comparison of polyphenol intakes in different people rather difficult.[27]

Numerous studies have obtained an inverse relationship between the flavonoid intake and the CRC risk.[28,29]

The results found in our study are similar to those of Iowa Women's Health Study and also Netherlands Cohort Study.[30,31] Those studies found an inverse association between the flavanol intake and the rectal cancer risk. In the Polyp Prevention Trial, a negative relationship between the advanced recurrent of adenoma risk with flavonoid and flavonoid subclass intake has been found.[32] Several studies showed inverse associations with all flavonoid and subclasses.[33,34]

In a clinical trial, intervention with a flavonoid mixture was presented to decrease the colon cancer recurrence risk in patients with resected colon cancer.[35] In contrast, no significant association was found between the flavonoid intake and the CRC recurrence in patients in an observational study.[14]

In a meta-analysis, a significant reduction in the incidence of colorectal adenoma recurrence by flavones and flavan-3-ols was found in several studies. However, no significant difference was found in the combined results of total flavonoids between the highest and the lowest flavonoid intake and the prevention of colorectal neoplasms in some studies.[36]

These information are further supported by some studies, which have concluded that many apoptotic markers are induced upon exposure of colon cancer cells to polyphenols.[37]This may be mediated by several mechanisms such as their potential to affect the inflammatory level found in cocoa polyphenols that have inhibited the inflammatory stimulated colon cancer in animal models.[38]The actions of polyphenols on the gut microbiota are rather specific.[39]The potential to modify the gut ecology and increase the beneficial bacteria species and butyrate-producing microbes could lead to a decrease in the colorectal cancer risk.[40]Moreover, flavonoids exert their anti-inflammatory activities through inhibiting cycloxygenase-2 (COX2) in colon cancer cells, which could be related to a decreased risk of colorectal cancer.[41]Plant flavonoids stimulate apoptosis and suppress the growth of colon cancer

cells.[42]

In another research, which evaluated the association between polyphenol classes and CRC risk, Zamora-Ros et al. used the data on intake of flavonoids in the EPIC cohort to study the associations between the flavonoid intake and the CRC risk.[43] They have stated no association between the intake of flavonoids and flavonoid subclass and the CRC risk. Accordingly, a recent study, based on two large US cohorts, the Health Professionals Follow-Up Study and the Nurses' Health Study, showed no associations between the intake of flavonoids and flavonoid subclasses and the risk of CRC.[44]

We showed in this study that a higher intake of anthocyanin was associated with the lower risk of CRC. Recent studies suggest that anthocyanins should exert incredible cytotoxic effects on malignant cells. These results showed that apoptosis could be activated by the caspases and their activation played main roles in apoptosis.[45,46]

Also, in our study, the higher consumption of stilbenes was inversely related to the risk of CRA. Studies have shown that stilbenes suppress the proliferation of a variety of cancer cells, including colon, breast, pancreas, melanoma, and others.[47,48]

Some mechanisms of action include the transcription factor NF-κB inhibition, regulation of cytochrome P450 enzymes, and inhibition of expression and activity of inflammation-related enzymes.[49,50]

Such controversies in the reported results may be explained by several reasons. One of the main reasons could be the differences in the methods for measuring polyphenols and probable problems in measurements.[9] For example, polyphenol content may be missing for foods, and polyphenol profiles are noticeably different between similar foods. The variations in polyphenol contents upon processing such as storing, cooking, freezing, and canning could be another reason.[51]On the other hand, the amount, the kind and the source might be different in various countries. The dietary intake could be higher in Asia and in countries that follow the Mediterranean diet.[52,53]The lower risk of cancers, particularly colon, prostate and breast cancers in Asians implies that flavonoid components possess protective effects of diets rich in vegetables and fruits.[53] Our study has several advantages. First, this research is one of the first ones in a Middle Eastern population to explore the relationship between dietary total polyphenol, polyphenol classes and subclasses and the risk of CRC and CRA. Second, using validated instruments and the ability to control for potential confounders. Third, use of new patient cases, using hospital controls and administering FFQs by trained interviewers.

In contrast, several limitations are also inherent in the present study. The variety of polyphenols composition is complex and use of FFQs may lead to measurement errors. In addition, the selection and recall bias are difficult to avoid; however, it was attempted to reduce these problems by using new patient cases via hospital controls and administering FFQs by trained interviewers in a hospital setting. Moreover, the current study is not able to investigate the long-term effects of risk factors on the incidence of CRC and CRA. A cohort or longitudinal study will be needed to assess the relationship between the risk factors such as diet and risk of chronic diseases.

In conclusion, the present study showed that the high intake of flavonols, total phenolic acids and hydroxicinamic acids were related to the decreased risk of CRC. Moreover, the higher consumption of stilbenes was inversely associated with the risk of CRA. To understand the interactions between diet and health, an evaluation of the diet with all its complexity of foods would be needed. This complexity explains the exposure to food bio-actives and impacts on human health.

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