



## Healthy Eating Index (HEI-2020) score and colorectal cancer risk

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### ABSTRACT

**Purpose:** The aim of this study is to evaluate if the alignment with the 2020–2025 Dietary Guidelines for Americans (DGA), measured by the Healthy Eating Index 2020 (HEI-2020), is associated with colorectal cancer (CRC) risk in an Italian population.

**Methods:** A multicentric case-control study was carried out in Italy between 1992 and 1996. Cases were 1953 patients (males 58 %, median age = 62 years) admitted to major hospitals with incident, histologically confirmed CRC. Controls were 4154 patients (males 50 %, median age = 58 years) admitted to the same hospitals for acute non-neoplastic conditions. Participants' usual diet before study enrolment was collected using a validated food frequency questionnaire, and the alignment with DGA was assessed using the HEI-2020 score, ranging between 0 (no alignment) and 100 (complete alignment). Odds ratios (ORs) and the corresponding 95 % confidence intervals (CIs) were estimated using multiple logistic regression models including terms for selected socioeconomic, lifestyle factors, and potential confounders.

**Results:** The HEI-2020 score ranged from 29.4 and 97.0. Subjects in the highest tertile of scores had lower risk of CRC compared to those in the lowest tertile (OR: 0.69, 95 % CI = 0.60–0.80). Similar estimates were found for colon (OR: 0.70, 95 % CI = 0.59–0.83) and rectal cancer (OR: 0.69, 95 % CI = 0.56–0.85). The findings were also consistent across strata of different covariates.

**Conclusions:** Alignment with DGA was inversely associated with CRC risk in an Italian population.

### 1. Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide. In Europe, it is the second most frequent cancer and the second cause of cancer mortality for both sexes in 2020 [1]. It is influenced by a number of modifiable and non-modifiable risk factors [2]. Although genetics plays a role [3], lifestyle factors such as physical activity, alcohol drinking, tobacco smoking, and dietary habits can modify the risk of

CRC. Among dietary factors, consumption of fresh red and processed meat, and possibly a low consumption of fruits and vegetables, have been associated with increased risk, whereas high consumption of fiber-rich foods and dairy products, and possibly fish and vitamin C-rich foods, have been associated with decreased risk of CRC [2]. Moreover, healthy dietary patterns such as the Mediterranean diet or a diet with a favorable balance of pro- and anti-inflammatory factors, have been associated with a lower CRC risk [4], while Western diets increase the risk [5]. The overall diet quality, rather than the individual dietary

**Abbreviations:** BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; DGA, Dietary Guidelines for Americans; FFQ, food frequency questionnaire; HEI, healthy eating index; OR, odds ratio; UDSA, US Department of Agriculture; WCRF, World cancer Research Fund.

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components, could impact CRC risk.

The US Department of Agriculture (USDA) promotes a standardized tool, the Healthy Eating Index (HEI), for assessing overall diet quality, independent of quantity, by measuring the alignment with the Dietary Guidelines for Americans (DGAs), aiming at a general health promotion without targeting a specific disease. This tool allows the assessment of diet quality by analysing the consumption of different food groups on an energy-density basis, ensuring comparability between individuals with different calorie intakes. There are several releases of the HEI, following regular updates of the DGAs. The latest version, HEI-2020 [6], examines alignment with the 2020–2025 DGAs [7]. It considers the consumption of fruits, vegetables, beans, whole and refined grains, dairy, total and seafood/plant-based protein sources, fats, sodium, and sugar.

Higher HEI-scores (based on different DGAs releases) have been favorably related to various noncommunicable diseases including cardiovascular diseases, cancer mortality, type 2 diabetes, neurodegenerative diseases [8], as well as lung [9], digestive tract [10], head and neck [11, 12], breast [13] and pancreatic [14] cancers.

Regarding CRC, a web-based French cohort [15] found no association between various a priori healthy dietary patterns, including the Alternative-HEI 2010 score (based on recommendation for chronic diseases prevention) [16], and CRC risk. Cohort studies from North America, such as the Canadian Study of Diet, Lifestyle and Health and the Women's Health Initiative [17, 18], reported an inverse association between the most recent DGAs update and CRC risk, whereas no European studies examined the issue. Dietary factors included in the HEI-2020 score are recognized for their potential to influence CRC risk through various mechanisms, including modulating inflammation, immune regulation, DNA stability and CRC growth and progression [19–25].

The aim of this study is to investigate whether the alignment with the 2020–2025 DGAs may reduce the risk of CRC in an Italian population, using data from a large multicentric case-control study.

## 2. Materials and methods

We analyzed data from a case-control study conducted between 1992 and 1996 in six Italian areas: greater Milan area, urban areas of Genoa and Naples, and the provinces of Forlì, Latina and Pordenone-Gorizia [26]. Cases were 1953 patients with incident CRC histologically confirmed (1225 subjects had colon cancer and 728 subjects had cancer of the rectum or of the rectosigmoid junction) with no previous history of cancer, admitted to major general and teaching hospitals in the areas of recruitment. Median age was 62 years (range: 19–74 years). Controls were 4154 individuals (median age 58, range 20–74 years) with no previous history of cancer and admitted to the same hospitals for a wide spectrum of acute conditions: 23 % for traumas as sprains and fractures, 28 % for other orthopedic issues, 20 % for acute surgical conditions, 19 % for eye disorders, and 10 % for various other illness like dental, ear, nose and throat or skin conditions. Neoplastic conditions, as well as diseases related to long-term diet alterations or to known risk factors for CRC, were exclusion criteria for controls. Moreover, we excluded subjects whose cause of admission in hospital at the time of interview was diabetes, CVD, chronic liver diseases, chronic gastrointestinal diseases, chronic kidney diseases, obesity or weight loss of an unknown cause, even if they might have such conditions being treated. Overall, less than 5 % of the contacted individuals refused to participate in this study. The ethics committees of the participating hospitals approved the study protocols and participants gave written informed consent according to the regulations in force at the time of data collection. The study was conducted in accordance with the Declaration of Helsinki.

Data were collected by centrally trained interviewers with a structured questionnaire that included information on sociodemographic characteristics, anthropometric measures, lifestyle factors such as tobacco smoking, occupational physical activity, personal medical conditions, and family history of cancer. The usual dietary habits over the

past 2 years preceding cancer diagnosis (for cases) or hospital admission (for controls) were assessed by a food frequency questionnaire (FFQ), tested for validity [27] and reproducibility [28, 29]. The FFQ included questions about the average weekly consumption of 78 foods, food groups or recipes, and 5 alcoholic beverages. Open questions were also provided in the FFQ section to allow reporting regularly consumed foods that were not included in the questionnaire, and were considered in the analysis if consumed at least once a week. Specific questions about dietary fats were included in order to assess fats consumption in terms of quantities and quality. Food intakes greater or equal to once per month and lower than once per week were coded as 0.5 times per week. For each subject, the daily intake of macronutrients, micronutrients, dietary fiber, and total energy were estimated using an Italian food composition database [30], considering for every food item average portions or “natural” units (e.g., one egg).

### 2.1. HEI-2020

The HEI is a score assessing diet quality in terms of alignment with the DGAs. The HEI-2020 [6] is the latest version of the index, and refers to the 2020–2025 DGAs [7]. In this study, a HEI-2020 score was computed for every subject using the simple HEI scoring algorithm provided by the US National Cancer Institute [31]. The original HEI-2020 expressed food portions using US customary system units such as cups and ounces. This score is energy density-based, and it is a sum of 13 dietary components, including 9 adequacy components and 4 moderation components. Details on the HEI-2020 scoring system are provided in Table 1. In this study, total calories, including those from foods and alcoholic beverages, were used to compute the score. Since our FFQ was tailored for an Italian population, portions were originally described using the International System of Unit, based on grams; we therefore converted them in cups equivalents and ounces equivalents. Conversion criteria from grams to cups are listed in Supplementary Table 1 and thoroughly detailed in a previous publication [11], while we converted grams to ounces using the standard conversion factor of 28.4.

In our FFQ, only one item (whole grain bread) was considered for the whole grains adequacy component consumption. For the adequacy components, 10 points were given for a high and 0 points for a scarce consumption. Conversely, for the moderation components, 0 points were given for high and 10 points for limited consumption. Some sub-components pairs, like whole fruits and total fruits, had a maximum of 5 points each. Minimum and maximum reference standards for each score component as described in the USDA webpage [32] are summarized in Table 1 and in detail in a previous study [11].

Thus, summing up all the components, the score ranged in theory from 0 to 100, with higher HEI-2020 scores indicating a greater alignment with the 2020–2025 DGAs [7].

### 2.2. Statistical analysis

Differences in score distributions between cases and controls were evaluated with a Mann-Whitney *U* test. Unconditional logistic regression models were fitted to estimate the odds ratios (ORs) of CRC, and of colon and rectal cancers separately, and the corresponding 95 % confidence intervals (CIs) for the highest versus the lowest tertile of the HEI-2020 score (computed among controls). Models were adjusted for potential confounders, namely study centre, year of interview, sex, age (quinquennia), years of education (<7, 7–12, ≥12 years of schooling), body mass index (BMI <25, 25–29.9, ≥30 kg/m<sup>2</sup>), total energy intake (kcal, quintiles among controls), tobacco smoking (never, former, current smoker), alcohol intake (0, 0.5–1.5, 2–3.5, 4–7.5, ≥8 drinks per week), occupational physical activity (low, moderate, high/very high), and family history of CRC. Missing values for a few confounding variables were inputted in the most frequent categories, to avoid dropping the participant from the multivariate analyses. We further computed the test

**Table 1**

Healthy Eating Index-2020 (HEI-2020) scoring system, and median (minimum-maximum) daily intakes for each component of the score among 1953 colorectal cancer cases and 4154 controls, Italy, 1992-1996.

HEI-2020 components	Maximum score	Standard for maximum score	Standard for minimum score of zero	Daily intake, median (min-max)					
				Cases			Controls		
<b>Adequacy components</b>									
Total fruits	5	≥ 0.8c eq per 1000 kcal	No fruits	1.12*	(0.05–4.73)	c eq per 1000 kcal	1.26*	(0.00–5.91)	c eq per 1000 kcal
Whole fruits	5	≥ 0.4c eq per 1000 kcal	No whole fruits	0.44*	(0.00–2.57)	c eq per 1000 kcal	0.49*	(0.00–3.09)	c eq per 1000 kcal
Total vegetables	5	≥ 1.1c eq per 1000 kcal	No vegetables	1.80*	(0.00–7.25)	c eq per 1000 kcal	1.87*	(0.00–13.97)	c eq per 1000 kcal
Greens and beans	5	≥ 0.2c eq per 1000 kcal	No dark green vegetables or legumes	1.72*	(0.00–7.25)	c eq per 1000 kcal	1.79*	(0.00–13.66)	c eq per 1000 kcal
Whole grains	10	≥ 1.5 oz eq per 1000 kcal	No whole grains	0	(0.00–6.03)	oz eq per 1000 kcal	0	(0.00–5.90)	oz eq per 1000 kcal
Dairy	10	≥ 1.3c eq per 1000 kcal	No dairy	0.54*	(0.00–3.07)	c eq per 1000 kcal	0.56*	(0.00–3.62)	c eq per 1000 kcal
Total protein foods	5	≥ 2.5 oz eq per 1000 kcal	No protein foods	4.02*	(0.54–14.70)	oz eq per 1000 kcal	4.19*	(0.99–22.34)	oz eq per 1000 kcal
Seafood and plant proteins	5	≥ 0.8 oz eq per 1000 kcal	No seafood or plant proteins	0.99*	(0.00–5.03)	oz eq per 1000 kcal	1.08*	(0.00–8.38)	oz eq per 1000 kcal
Fatty acids	10	(PUFAs + MUFAs)/SFAs ≥ 2.5	(PUFAs + MUFAs)/SFAs ≤ 1.2	1.90	(0.86–4.16)		1.91	(0.72–4.36)	
<b>Moderation components</b>									
Refined grains	10	≤ 1.8 oz eq per 1000 kcal	≥ 4.3 oz eq per 1000 kcal	0.99*	(0.14–2.52)	oz eq per 1000 kcal	0.98*	(0.35–2.74)	oz eq per 1000 kcal
Sodium	10	≤ 1.1 g per 1000 kcal	≥ 2.0 g per 1000 kcal	4.31*	(0.21–11.45)	g per 1000 kcal	4.08*	(0.00–15.20)	g per 1000 kcal
Added sugar	10	≤ 6.5 % of energy	≥ 26 % of energy	1.47	(0.00–11.25)	% of energy	1.44	(0.00–10.63)	% of energy
Saturated fats	10	≤ 8 % of energy	≥ 16 % of energy	10.28*	(2.82–22.72)	% of energy	10.62*	(2.99–22.91)	% of energy
<b>Total HEI–2020</b>				<b>66.80*</b>	<b>(39.71–95.68)</b>		<b>67.54*</b>	<b>(29.38–97.01)</b>	

c eq: cups equivalents; MUFA: monounsaturated fatty acids; oz eq: ounces equivalents; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids  
\*p < 0.05 with Mann-Whitney test

for trend across tertiles. ORs were also estimated in strata of sex, age, years of education, BMI, tobacco smoking status, and alcohol drinking. Heterogeneity among strata was assessed with the likelihood ratio test. In addition, as a sensitivity analysis, we estimated the ORs of CRC removing in turn each score component from the score calculation in order to verify the potential influence of each component in driving the association. Since CRC is a rare disease and we involved incident cases, the OR is an approximation of relative risk of CRC.

The analyses were performed with SAS software version 9.4 [33].

**3. Results**

Supplementary Table 2 shows the distribution of the main characteristics of CRC cases and controls. Cases tended to be more educated, had a lower occupational physical activity, were more frequently former smokers and had more frequently a family history of CRC compared to controls. Table 1 shows reference values for all the dietary components of the HEI-2020 score, and their distribution among cases and controls. For whole grains, fatty acids and added sugar, no significant differences were found between cases and controls. The median of whole grains consumption was 0.0 since 87.5 % of cases and 86.1 % of controls did not consume any whole grain bread (data not shown). Median intakes (per 1000 kcal) were significantly different between cases and controls for most of the components of HEI score: total fruits, whole fruits, total vegetables, greens and beans, dairy, total protein foods, seafood and plant proteins, refined grains, sodium, saturated fats.

The total HEI-2020 score ranged between 29.38 and 97.01, and differed significantly between cases and controls (median among cases: 66.80, median among controls: 67.54).

Table 2 provides the ORs of CRC according to HEI-2020 score tertiles, adjusted for major confounders, and the upper cut-offs of tertiles (computed among controls). The OR was 0.90 (95 % CI = 0.79 – 1.03)

**Table 2**

ORs<sup>a</sup> and corresponding 95 % CIs for CRC, and of colon and rectal cancer separately, according to the Healthy Eating Index 2020 (HEI-2020) score, Italy, 1992-1996.

Category range <sup>b</sup>	Tertiles of HEI-2020 score			p for trend
	T1	T2	T3	
<b>Colorectal cancer</b>				
Cases:	740: 1385	678: 1381	535: 1388	
controls				
OR (95 % CI)	1 (ref)	0.90 (0.79–1.03)	0.69 (0.60–0.80)	< .0001
<b>Colon cancer</b>				
Cases:	448: 1358	434: 1381	343: 1388	
controls				
OR (95 % CI)	1 (ref)	0.93 (0.79–1.09)	0.70 (0.59–0.83)	< .0001
<b>Rectal cancer</b>				
Cases:	292: 1385	244: 1381	192: 1388	
controls				
OR (95 % CI)	1 (ref)	0.87 (0.72–1.06)	0.69 (0.56–0.85)	0.0006

BMI: body mass index; CI: confidence interval; CRC: colorectal cancer; OR: odds ratio; ref: reference category; T: tertile

<sup>a</sup> estimated by logistic regression adjusted for study centre, year of interview, sex, age, education, BMI, total energy intake, alcohol intake, occupational physical activity, tobacco smoking and family history of CRC

<sup>b</sup> computed among controls

for the second and 0.69 (95 % CI = 0.60 – 0.80) for the third tertile compared to the first. Corresponding estimates were 0.93 (95 % CI = 0.79 – 1.09) and 0.70 (95 % CI = 0.59 – 0.83) for colon, and 0.87 (95 % CI = 0.72 – 1.06) and 0.69 (95 % CI = 0.56–0.85) for rectal cancers. The tests for trend across tertiles were statistically significant.

Fig. 1 shows the ORs and corresponding 95 % CIs of CRC for the third versus the first HEI-2020 tertile in strata of selected covariates. The OR in males was 0.62 (95 % CI = 0.51 – 0.75) while in females it was 0.79 (95 % CI = 0.63 – 0.99) (p for heterogeneity = 0.017). The OR was 0.76 (95 % CI = 0.61 – 0.95) in subjects with BMI < 25 kg/m<sup>2</sup> and 0.65 (95 % CI = 0.53 – 0.79) in subjects with BMI ≥ 25 kg/m<sup>2</sup>, with no significant heterogeneity. In never smokers the OR was 0.78 (95 % CI = 0.63 – 0.96), 0.56 (95 % CI = 0.42 – 0.75) in former smokers, and 0.71 (95 % CI = 0.54 – 0.94) in current smokers, in the absence of significant heterogeneity. Considering alcohol intake, the OR was 0.72 (95 % CI = 0.53 – 0.97) in subjects drinking 0 - < 2 drinks/week, 0.49 (95 % CI = 0.27 – 0.87) for 2 to < 7 drinks/week, 0.70 (95 % CI = 0.59 – 0.83) for at least 7 drinks/week, with no significant heterogeneity. There was no material difference in strata of age.

Fig. 2 shows the ORs of CRC for the third vs the first tertile of the HEI-2020 score, after excluding in turn each score component from its calculation. The inverse association persisted after the exclusion of each component, with ORs ranging from 0.67 (95 % CI = 0.58–0.77), after the exclusion of fatty acids ratio, to 0.79 (95 % CI = 0.69–0.92), after the exclusion of refined grains.

#### 4. Discussion

Our findings, based on a large multicentric Italian study, support an inverse association between the HEI-2020 [6] – a score measuring the alignment with the 2020–2025 DGAs [7] – and CRC risk. After allowance for several potential confounders, including BMI, smoking,

drinking and physical activity, a 31 % reduction in the risk of CRC was estimated for subjects in the highest tertile of the HEI-2020 score, compared to those in the lowest tertile. The risk reduction tended to be consistent across strata of major covariates and cancer subsites, with no heterogeneity in strata of age, BMI, smoking status and alcohol intake. Our data highlight the importance of the overall diet in relation to CRC risk. While the median scores of cases and controls appear similar (although statistically different), removing each component of the HEI-2020 score from the analysis did not change the association, confirming the relevance of the whole dietary pattern over the specific role of single components on CRC risk reduction.

To our knowledge, this is the first European study evaluating the association between the HEI-2020 score and CRC risk. Currently, there are two North American cohort studies on HEI-2015 and CRC risk [17, 18], which estimated respectively a hazard ratio of CRC of 0.65 (95 % CI: 0.49–0.85) and of 0.93 (95 % CI: 0.89–0.98) for the highest versus the lowest HEI-2015 score quintile. Previously, HEI(1995), HEI-2005, HEI-2010 and Alternative HEI scores have been investigated in relation to CRC [4, 34–37], showing a generally consistent inverse association in both case-control and cohort studies. HEI-2015 and HEI-2020 scores refer to different release of the DGAs, but there is no material difference in their formulation [38], while all previous versions of HEI scores differ from each other.

All components of the HEI-2020 score might be involved in modulating CRC risk. Fruits, vegetables, legumes, and whole grains are valuable sources of dietary antioxidants and anti-inflammatory compounds, and act as chemopreventives in CRC [19]. Phenolic acids, polyphenols and flavonoids reduce inflammation by inhibiting tumor necrosis factor (TNF)–TNF receptor complexes and the expression of p65 and p50, decreasing TNF-α and interleukins (IL) like IL-6, IL-8, and IL-1β. They also stimulate MAPK phosphorylation, altering Bcl-2, Bcl-xl, and Bax expression, leading to cytochrome c release and promoting

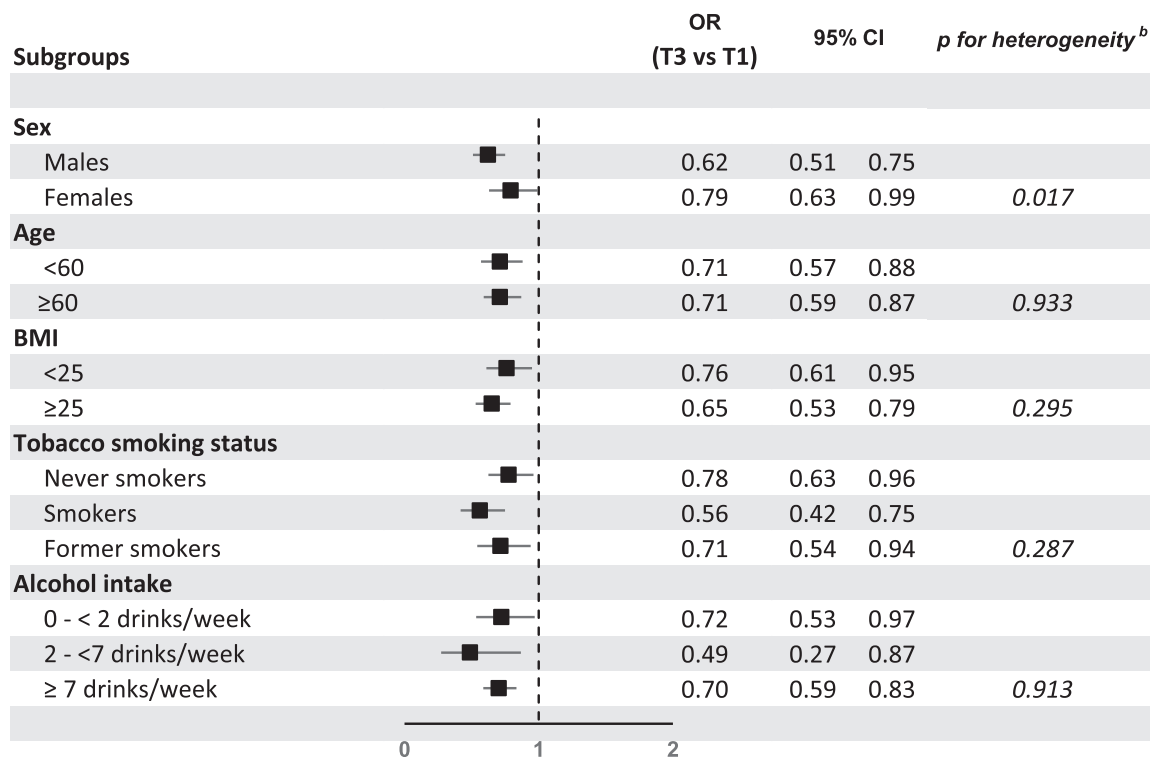


Fig. 1. ORs<sup>a</sup> and corresponding 95 % CIs for the highest (T3) versus the lowest (T1) tertile of HEI-2020 score in strata of selected factors. Italy, 1992–1996. <sup>a</sup> estimated by logistic regression adjusted for study centre, year of interview, sex, age, education, BMI, total energy intake, tobacco smoking, alcohol intake, occupational physical activity, and family history of CRC. <sup>b</sup> test for heterogeneity considered all three tertiles of the HEI-2020 score. BMI: body mass index; CI: confidence interval; CRC: colorectal cancer; OR: odds ratio; T: tertile.

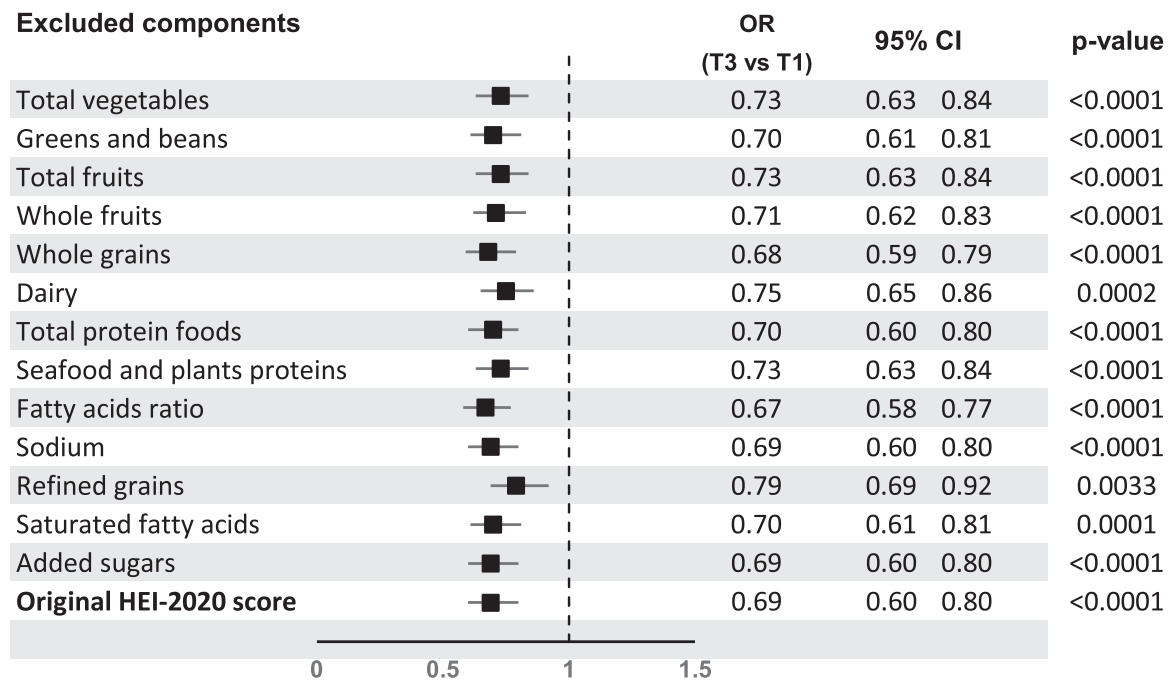


Fig. 2. ORs<sup>a</sup> and corresponding 95 % CIs for the highest (T3) versus the lowest (T1) tertile of HEI-2020 score after excluding each score component in turn. Italy, 1992–1996. <sup>a</sup> estimated by logistic regression adjusted for study centre, year of interview, sex, age, education, BMI, total energy intake, tobacco smoking, alcohol intake, occupational physical activity, and family history of CRC. BMI: body mass index; CI: confidence interval; CRC: colorectal cancer; OR: odds ratio; T: tertile.

apoptosis in CRC cells [19]. Other common compounds such as carotenoids, in addition to their antioxidant action, prevent the development of aberrant crypt foci and enhance gap junctional intercellular communication [20]. Glucosinolates, sulforaphanes, and isothiocyanates, mostly found in cruciferous and allium vegetables, arrest CRC cell cycles in the G1 or G2/M phases, limiting invasion and metastasis [19]. Plant-based foods are also rich in folate, which supports genomic stability through the synthesis of DNA precursors and methylation processes [21].

The protective effect of dietary fibers against CRC is primarily due to their fermentation by gut microbiota into short-chain fatty acids (SCFA). SCFA inhibit histone deacetylase (HDAC) inhibitors, which induces G1 cell cycle arrest, and activate GPCR, which promotes apoptosis by regulating Bcl-2, Bcl-xL, cyclin D1 and the death receptor pathway. They are also associated with miRNA regulation and with vascular endothelial growth factor and ERK2/MAPK signaling pathways inhibition [22].

Calcium sources such as dairy products exert a protective effect on CRC onset [2]. By binding to secondary bile acids, calcium decreases their concentration in the gut, preventing their stimulatory effect on the growth of mucosal cells, and promotes apoptosis in pre-cancerous cells [23]. In addition, lactic acid presented in fermented dairy products support gut epithelial repair and may inhibit the formation of aberrant crypt foci [23].

Dietary fats also have a role: while saturated fats in gut act as activators of TLR4, promoting chronic inflammation, omega-3 fats promote immune-regulatory phenotypes like M2 macrophage polarization, reducing intestinal inflammation [24]. A higher dietary glycemic index is associated with increased insulin levels and higher glycemia. This can lead to excessive production of IGF-1, which promotes CRC progression through several pathways, including inhibition of apoptosis and abnormal expression of oncogenes, such as MYC and KRAS and vascular endothelial growth factor in CRC cells [25]. The relationship between the dietary components included in the HEI-2020 score and CRC risk has been evaluated in several studies. Among adequacy components, some studies report a null or small association between the consumption of fruits and vegetables separately, while the combined consumption has

an inverse association with CRC risk [39, 40]. Regarding the greens and beans components, the evidence on legumes and CRC is currently sparse [40–42], while dark green vegetables, and particularly cruciferous vegetables, appear to be inversely associated with CRC risk [43–46]. The evidence on whole-grains [40, 47–49] is consistent, and shows a clear inverse association with CRC risk.

The World Cancer Research Fund (WCRF) [2] reports dairy to be protective, but there is conflicting evidence [50]. This may indicate that the variability of dairy products in terms of fats, salt, fermentation, and other factors, could play a role on the effect of dairy on CRC. The total protein foods component of HEI-2020 score includes the lean fraction of poultry, meat, seafood, offal, eggs, nuts, seeds, and legumes, excluding dairy or dairy alternatives. The seafood and plant proteins component includes only seafood, nuts, seeds, and legumes. A meta-analysis [51] on total dietary proteins and CRC risk reports no association. Fish [2,52], but not shellfish [53], has been inversely associated with CRC risk, and the consumption of shellfish has been proposed as a risk factor for CRC onset in Europe [54]. Substituting animal proteins with plant proteins may have a favorable effect on CRC, depending on the plant food sources [55, 56].

Regarding dietary fats, an inverse association between unsaturated fats and CRC risk has been suggested, but the evidence is inconsistent [57, 58]. Considering moderation components of the HEI-2020 score, refined grains were directly associated with colon cancer risk, while there was no association with CRC [40]. Limiting dietary salt intake was associated with a reduction of CRC risk [59]. Epidemiological evidence on the role of added sugar and saturated fats is conflicting [60, 61], possibly due to the variety of sources of sugar and fats and the effect of such nutrients on the overall diet. Anyway, the adherence to an overall dietary pattern rich in free sugars and saturated fats [2,62] is an established risk factor for CRC.

HEI-2020 score does not take into account the consumption of red meat, overlooking a relevant dietary characteristic for the prevention of CRC and of other noncommunicable diseases [2]. In fact, it aims at promoting overall health diet as outlined by the DGAs, and therefore the total proteins component combines all animal proteins (except dairy)

and beans, in an effort to capture total protein intake. While beans consumption is evaluated together with other items (i.e. greens and beans and seafood and plant proteins), the score does not distinguish between red meat and poultry consumption, and therefore it does not highlight the lower CRC risk associated with low red meat consumption, in favor of poultry [63]. Conversely, the greens and beans component also includes consumption of dark green vegetables, other than of legumes, which are relevant sources of chemopreventive compounds as sulforaphanes and folate [19, 21, 64], with a favorable effect on CRC. However, evaluating individual dietary components separately does not shed light on the preventive potential of diet as a whole on CRC, and could conceal the effect of the overall diet quality. Many prudent dietary patterns have been associated with a reduction in CRC risk [4, 65–67], including adherence to the DGAs. Our Italian CRC case-control study showed a risk reduction of 33 % for a diet consistent with the recommendations of the World Cancer Research Fund [59], and a risk reduction of 48 % for the Mediterranean diet [68]. The lack specific items in the HEI-2020 score that consider important elements of the Southern European diet, such as olive oil and moderate alcohol consumption, may explain the weaker association with the HEI-2020 score. Additionally, the distinction between refined and whole-grains does not fully describe a common characteristic of the Italian diet: a staple food as pasta, always made from durum wheat, could be considered in between whole and refined in terms of fiber and micronutrients composition [30]. Nevertheless, the HEI-2020 enables a standardized assessment of critical dietary components, such as plant-based food, saturated fat, added sugar, and sodium — which are particularly relevant in assessing Western, including Italian [69], diet quality. Moreover, the absence of a comparable tool for evaluating adherence to Italian dietary guidelines makes the use of the HEI-2020 even more valuable.

In this study, selection bias has been limited by enrolling cases and controls in comparable catchment areas, and including controls that were admitted to hospital only for acute, non-neoplastic, non-diet related diseases. The almost complete participation rate is a major strength. Information bias was controlled by interviewing cases and controls in a similar setting, with a FFQ tested for the validity [27] and the reproducibility on food groups [28] and nutrients [29], although it may miss foods consumed that contribute to diet quality. Recall bias could be present, although it should not be differential between cases and controls, since awareness of the role of dietary habits in colorectal cancer etiology was unlikely in the Italian population at the time of data collection. Our dietary assessment did not include whole grain foods other than whole grain bread, reflecting the typical Italian diet in the period of the interviews. This may have limited the impact of the whole grains HEI-2020 item in the overall dietary assessment. Sample size was large, allowing us to detect significant risk estimates with high statistical power. We managed to control for several potential confounders, including BMI, tobacco smoking and alcohol drinking, although residual confounding could not be excluded.

## 5. Conclusion

In conclusion, alignment with the DGAs is inversely associated with CRC risk in an Italian population. While some dietary habits have evolved over the years, our results from a multicentric case-control study show that following the recommendations derived from the DGAs is beneficial. Although local dietary guidelines tend to show an even more favorable effect, the inverse association between HEI-2020 and CRC highlights the global relevance of this index. These findings may be considered in the formulation of nutritional recommendations for CRC prevention.

## CRedit authorship contribution statement

**Rossi Marta:** Writing – review & editing, Methodology. **La Vecchia Carlo:** Writing – review & editing, Investigation, Conceptualization.

**Bravi Francesca:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Augustin Livia:** Investigation. **Giacoia Attilio:** Investigation. **Toffolutti Federica:** Writing – review & editing. **Negri Eva:** Writing – review & editing, Investigation. **Polesel Jerry:** Writing – review & editing, Investigation. **Khaleghi Hashemian Dariush:** Writing – review & editing, Writing – original draft, Formal analysis. **Natale Arianna:** Writing – review & editing, Writing – original draft, Formal analysis.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Francesca Bravi reports financial support was provided by Italian Ministry of University and Research. Jerry Polesel reports financial support was provided by Italian Ministry of Health. Federica Toffolutti reports financial support was provided by Italian Ministry of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2025.102771.

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