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The mediating effect of Mediterranean diet on the relation between smoking and colorectal cancer: a case–control study

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Background: The protective role of Mediterranean diet (MD) and the detrimental effect of smoking on colorectal cancer (CRC) have already been shown. The aim of this work was to evaluate the potential mediating effect of MD on the association between the aforementioned factor (smoking) and CRC. **Methods:** It is a case–control study. Two hundred fifty consecutive patients with CRC (63 ± 12 years, 59% males) and 250 age–sex group-matched controls, both from the area of Attica, were studied. Various socio-demographic, clinical, lifestyle (including detailed smoking habits) and dietary characteristics were measured. Adherence to the MD was evaluated using the MedDietScore (theoretical range 0–55). **Results:** Each unit increase in the MedDietScore was associated with 13% lower likelihood of CRC ($P < 0.001$). Smoking habits were associated with 2.9-fold the likelihood of CRC among participants who were away from the MD (i.e. MedDietScore < 29) and with 2.1-fold the likelihood of CRC among those who were close to the MD ($P < 0.05$). **Conclusions:** Adherence to the MD was associated with a less detrimental association of smoking habits with CRC, suggesting indirect benefits of adherence to this dietary pattern with regards to CRC morbidity and mortality.

Introduction

According to the International Agency for Research on Cancer (IARC) GLOBOCAN 2008 data, the colorectal cancer (CRC) incidence for both sexes was ranked at the third place worldwide, at the first place in Europe and at the third place in Greece (at the second place for women and at the fourth place for men), representing a major cause of cancer morbidity.[1] Among several factors, smoking seems to play an important role. A recent meta-analysis on smoking and CRC revealed that ever smokers had 18% higher risk as compared with never smokers, and this association was dose-dependent regarding pack-years.[2] Several mechanisms have

been proposed to explain the positive association between smoking and CRC, including the numerous genotoxic carcinogenic compounds produced, like polycyclic aromatic hydrocarbons, aromatic amines and heterocyclic amines, several of which can produce bulky DNA adducts.[3] In addition, polycyclic aromatic hydrocarbons and heterocyclic aromatic amines are also formed when meat is cooked on an open flame or at a high temperature for long time,[4] suggesting that smoking and dietary factors may share common pathways in CRC epidemiology. To our knowledge, only 11 case–control and 6 cohort studies examining the association between smoking and CRC incidence included dietary evaluation in their analyses.[2] The most frequently examined dietary components included were daily calorie intake,[5–8] fat,[5,6] vegetables,[7,9–12] fruits,[7,9,11] red meat,[5,9] fiber,[6,7] vitamin C,[6,7,10] vitamin E,[5,10] methionine,[5] calcium,[5] alcohol,[5,7–11] coffee[6,12,13] and tea intake[6,13] and number of meals.[12] However, taking into account that people consume meals and not single nutrients, the holistic approach of dietary evaluation predominated in the past 2 decades.[14] Moreover, epidemiological models have shown that lifestyle modification could have a comparable, or perhaps even greater, up till 50%, impact on CRC mortality rates compared with increased chemotherapy use during the next decades.[15] A healthy dietary pattern that has long been studied is the Mediterranean diet (MD), representing the dietary pattern usually followed among the populations bordering the Mediterranean Sea in the early 1960s, such as Crete, other parts of Greece, Spain and southern Italy, where olive trees grow. The traditional MD is characterized by a diet high in fruits, vegetables, cereals, potatoes, poultry, beans, nuts, lean fish and dairy products; small quantities of red meat; moderate alcohol consumption (1–2 glasses/day, usually with meals) and olive oil as an important daily fat source.[16,17] Unfortunately, over the past 40 years, food habits in the Mediterranean countries have changed enormously from the traditional pattern of the 1960s and have tended to move towards the food pattern typical of northern countries. One of the most significant changes is the fall in the availability of the carbohydrates and the increase in the availability of fats, especially those of animal origin.[18]

Beyond the direct cardioprotective effects of MD, as well as its protective relationships with some types of cancer,[18,19] several indirect mechanisms have also been proposed that, at the end, may promote human health. One of these effects is the protective association of the MD against the detrimental effects of smoking. The proposed protective mechanisms include antioxidant activity, inflammation inhibition, anti-mutagenic and anti-proliferative properties and involvement in cell signaling, cell cycle regulation and angiogenesis.[19] For example, anthocyanins have shown anti-carcinogenic activity[20]; resveratrol has a protective effect against cancer in all stages of carcinogenesis, inhibiting the transcriptional activation of the carcinogen-activating enzyme CYP1A1[21] or inhibiting the promotion of preneoplastic lesions by effects on multiple signaling systems, like the activation of the de novo ceramide synthesis pathway.[22]

However, the influence of overall dietary habits, like the MD, on the association between smoking habits and CRC risk has never been studied before. Thus, the aim of this work was to evaluate the effect of smoking habits on the likelihood of having CRC, as well as to evaluate the potential mediating effect of a healthy dietary pattern, that is, the MD, on the aforementioned relationship.

Methods

Study design and sample

This is a case–control study. Between December 2009 and December 2010, 250 consecutive patients from the admission lists of Saint Savvas Cancer hospital ($n = 234$) and the Oncology Department of Alexandra General Hospital ($n = 16$) and with a first diagnosis of CRC (defined by biopsy or histology) were enrolled. The participation rate was 95%. For the same period, 250 subjects (controls) without any clinical symptoms, signs or suspicious of any type of cancer in their medical history were voluntarily selected from the general population (i.e. work or home places) on a feasibility basis. Controls were group matched to the patients by age (± 10 years), sex and socio-demographic characteristics (i.e. they were living in the same region). The participation rate was 80%. Saint Savvas Cancer Hospital is the major referral cancer hospital in Greece, receiving the majority of cancer patients of the country, whereas in Alexandra General Hospital, the Oncology Department of Athens University Medical School is located, also participating in the Hellenic Cooperative Oncology Group studies. Thus, cases are representative of all CRC cases from that general population where controls have also been selected. Both patients and controls were approached during their hospital visit (for the patients) or from the community (for the controls), for example, workplaces, home places, etc, by the study's investigators who were trained personnel. The investigators of the study performed the face-to-face interviews, as well as the evaluation of clinical symptoms and signs in the series of cases and controls.

The number of enrolled subjects ($n = 500$) was *a priori* decided through power analysis, to evaluate (two-sided) odds ratio equal to 0.75 for protective (or 1.33 for aggravating) factors, with statistical power of >77% at a significance level of <5%.

Bioethics

Before the face-to-face interview, all participants were informed about the aims of the study, agreed to give the requested information and signed an informed consent. The study's protocol has been approved by the hospitals' ethics committees (No. 15 299/416/22-12-2009).

Dietary assessment

A validated semi-quantitative food frequency questionnaire including 69 questions was used to collect dietary information from the participants.[23] Moreover, to assess overall dietary habits, the MedDietScore was calculated; this nutrition assessment tool is a relatively large-scale diet score (theoretical range 0–55) that evaluates the level of adherence to the MD and has already been found to be accurate and valid,[24] having a good discriminating ability for gastrointestinal cancers.[25]

Smoking habits

The evaluation of smoking habits included questions on smoking status (never; current, i.e. smoking at the time of interview or stopped within the past 3 months; former, i.e. stopped smoking >3 months), as well as on type and quantity of cigarettes or tobacco used, age of smoking initiation, duration of the habit, years since stopping and if participants have (or not) been passive smokers and for how long.

Other measurements

Age and sex of the participants were recorded. Weight and height were measured and body mass index (BMI) was calculated, and a cut-off point of 25 kg/m^2 was used in analyses. Abdominal fat was estimated with waist circumference measurement in centimetres.[26] Physical activity status was assessed for the past year before diagnosis as well as the preceding 5 years and classified as follows: sedentary (no exercise) or low active (<4 metabolic equivalent (MET)), moderately active (4–7 MET) and highly active (>7 MET), according to the activities reported. The latter two categories were combined and considered as physically active. Family history of CRC as well as colorectal adenomas occurrence was also recorded.

Statistical analysis

Continuous variables that were normally distributed are presented as mean ± SD, whereas categorical variables are presented as frequencies. Student *t*-test for independent samples was used to evaluate mean differences between normally distributed variables (i.e. BMI, waist circumference, MedDietScore), whereas the chi-squared test was used to test for dependency between categorical variables. Normality was evaluated using the P-P plots. Multiple logistic regression analysis was applied to evaluate the association of smoking habits and the likelihood of having CRC, after adjusting for potential confounding factors (i.e. age, sex, family history of CRC, physical activity, alcohol drinking, waist circumference as well as overall dietary habits through the MedDietScore). Moreover, the median cut-off of 29 for the MedDietScore (to define good adherence to the MD) was used in the stratified logistic regression analyses that were applied to evaluate the main research hypothesis, that is, the potential mediating effect of diet on the relationship between smoking and CRC. The results are presented as odds ratios and their corresponding 95% confidence intervals. All reported *P*-values were based on two-sided tests and compared with a significance level of 5%. Statistical calculations were performed with SPSS 18 software (SPSS Inc., Chicago, IL, USA).

Results

In table 1, the basic characteristics of patients and controls are presented. MedDietScore was higher in controls as compared with the patients. There was a strong association between smoking habits, especially former, and presence of CRC ($P < 0.001$). As far as it concerns the type of cigarettes usually smoked, patients preferred heavy cigarettes, whereas controls preferred lights ($P < 0.001$). Heavy alcohol drinking was also associated with presence of CRC ($P < 0.001$). BMI was higher in controls as compared with patients ($P < 0.05$), but CRC patients tended to have increased waist circumference as compared with controls ($P < 0.10$). Moreover, family history of CRC prevailed more frequently in patients than in controls (table 1).

Table 1 Smoking and dietary habits in a sample of 250 CRC cases and 250 age–sex group-matched controls

	CRC patients *n* = 250	Controls *n* = 250	*P*
Age (years)	63 ± 12	55 ± 13	<0.001
Male sex, *n* (%)	147 (59%)	112 (44.8%)	<0.001
MedDietScore (0–55)	29.4 ± 4	31.1 ± 4	<0.001
Smoking habits			<0.001
Never, *n* (%)	87 (34.8%)	129 (51.6%)	
Current, *n* (%)	66 (26.4%)	73 (29.2%)	
Former, *n* (%)	97 (38.8%)	48 (19.2%)	
Years of smoking habit	20.2 ± 19	11.2 ± 13	<0.001
Years since stopping smoking	4.6 ± 9	3.3 ± 7	0.10
Years being passive smoker	22.4 ± 19	13.8 ± 16	<0.001
Type of cigarette or tobacco			<0.001
Light cigarettes, *n* (%)	63 (25.4%)	74 (30%)	
Heavy cigarettes, *n* (%)	90 (36.3%)	35 (14.2%)	
Tobacco or pipe, *n* (%)	2 (0.8%)	8 (3.2%)	
Physical activity (yes), *n* (%)	130 (52%)	147 (58.8%)	0.12
BMI (kg/m^2)	26.5 ± 4.3	27.3 ± 5.2	0.04
Waist circumference (cm)	98.3 ± 13.8	94.8 ± 15.5	0.09
Alcohol intake, *n* (%)			<0.001
Never/rare, <12 g/day	125 (50.4%)	122 (49.0%)	
12–35 g ethanol/day	38 (15.3%)	88 (35.3%)	
26–48 g ethanol/day	36 (14.5%)	29 (11.6%)	
48+ g ethanol/day	49 (19.8%)	10 (4.0%)	
Family history of CRC, *n* (%)	39 (15.9%)	17 (6.9%)	0.001

Data are presented as mean ± standard deviation for normally distributed continuous variables and as percentages for categorical variables. *P*-values derived using the *t*-test or the chi-squared test.

Smoking, BMI, waist circumference, physical activity, overall dietary habits and likelihood of CRC

Smoking (former) was strongly associated with CRC (model 1, table 2), after adjusting for age, sex, family history of CRC, physical activity, alcohol drinking and waist circumference, but without adjusting for the level of adherence to the MD; however, the effect size of the relationship between former smoking and CRC was reduced by 36% when dietary habits, through the assessment of the level of adherence to the MD using the MedDietScore as potential confounder (i.e. odds ratios 2.29 and 1.95 before and after adjustment, respectively), were taken into account (model 2, table 2). Moreover, participants reported ever smokers (current or in the past) had 2.03 times higher odds of having CRC (95% CI 1.33–3.08), after adjusting for age, sex, family history of CRC and BMI. Neither BMI ($P = 0.06$) nor waist circumference ($P = 0.20$) was associated with CRC (model 2, table 2), after adjusting for age, sex, family history of CRC, smoking habits, physical activity status and MedDietScore. Physical activity was also not associated with CRC, whereas only including alcohol drinking significantly increased the odds of CRC (table 2). MedDietScore was inversely associated with the likelihood of CRC, after adjusting for all the aforementioned variables. When years of smoking were taken into account in models 1 and 2, a positive association was also revealed with regards to the likelihood of having CRC (OR per 1 year = 1.05, 95% CI 1.02–1.07 and OR = 1.04, 95% CI 1.01–1.07, respectively). As far as it concerned the type of cigars and CRC, no association was found ($P = 0.19$ and $P = 0.37$ for models 1 and 2, respectively) (data not shown here).

A significant interaction was observed between smoking and MedDietScore on CRC ($P < 0.001$), suggesting a potential mediating effect of MD on the relationship between smoking and CRC. To evaluate this, the median MedDietScore value of 29 was used as a cut-off to stratify the participants as those with good and those with bad adherence to the MD. The effect of former smoking on CRC was significant in both groups (i.e. good or bad adherence to the MD); however, the effect size of smoking on CRC was much higher among those away from the MD pattern as compared with those who were close to this traditional dietary pattern (model 1, table 3). No significant association was observed with waist circumference (or BMI) and CRC, whereas physical activity was inversely associated with the likelihood of having CRC only among those who

Table 2 Results from multiple logistic regression analyses that evaluated the association of smoking habits and adherence of MD in relation to CRC likelihood in a sample of 250 cases and 250 age–sex group-matched controls

	Model 1 Odds ratio (95% CI)	Model 2 Odds ratio (95% CI)
Smoking habits		
Never	1.00	1.00
Current	1.15 (0.68–1.94)	0.94 (0.54–1.64)
Former	2.29 (1.38–3.78)	1.95 (1.16–3.29)
Physical activity (yes vs. no)	0.69 (0.43–1.09)	0.76 (0.47–1.22)
Waist circumference (per 1 cm)	0.99 (0.98–1.01)	0.98 (0.97–1.00)
Alcohol intake		
Never/rare, <12 g/d	1	1
12–35 g ethanol/d	0.48 (0.27–0.85)	0.62 (0.34–1.13)
26–48 g ethanol/d	1.02 (0.51–2.08)	1.68 (0.79–3.58)
48+ g ethanol/d	3.92 (1.71–8.97)	4.19 (1.79–9.76)
MedDietScore(per 1/55 unit)	–	0.87 (0.82–0.92)

Both models were also adjusted for age, sex and family history of CRC.

Table 3 Results from multiple logistic regression analyses that evaluated the association of smoking habits and CRC, stratified by the mediator factor, i.e. the MedDietScore, in a sample of 250 cases and 250 age–sex group-matched controls

	Model 1	Model 2
Away from the MD (MedDietScore $\leq$ 29)		
Smoking habits		
Never	1.0	1.0
Current	1.54 (0.66–3.58)	1.23 (0.48–3.12)
Former	2.68 (1.10–6.54)	2.74 (1.05–7.11)
Waist circumference (per 1 cm)	1.02 (0.97–1.06)	1.02 (0.97–1.06)
Physical activity status (yes vs. no)	0.77 (0.38–1.56)	0.75 (0.56–1.59)
Alcohol intake		
Never/rare, <12 g/day	–	1.0
12–35 g ethanol/day	–	0.29 (0.10–0.82)
26–48 g ethanol/day	–	1.99 (0.36–11.08)
48+ g ethanol/day	–	4.74 (1.38–16.24)
Close to the MD (MedDietScore >29)	Model 1	Model 2
Smoking habits		
Never	1.0	1.0
Current	1.10 (0.53–2.28)	1.09 (0.51–2.31)
Former	2.32 (1.12–4.80)	2.17 (1.03–4.59)
Waist circumference (per 1 cm)	1.03 (0.99–1.07)	1.03 (0.99–1.06)
Physical activity status (yes vs. no)	0.44 (0.24–0.81)	0.44 (0.24–0.80)
Alcohol intake		
Never/rare, <12 g/day	–	1.0
12–35 g ethanol/day	–	0.84 (0.39–1.78)
26–48 g ethanol/day	–	1.41 (0.57–3.48)
48+ g ethanol/day	–	3.43 (1.04–11.32)

All models were also adjusted for age, sex, BMI and family history of CRC.

were close to the MD, but lost its significance when the analysis was focused on the participants who were away from the traditional dietary pattern.

Researchers have previously shown a linear dose-dependent association between alcohol consumption and CRC,[27] whereas our recent work revealed a J-shape effect of alcohol intake on CRC.[28] In the present analysis, the J-shaped association was evident only among those who were away from the MD (model 2, table 3); specifically, moderate alcohol drinking (i.e. <25 g/day) was associated with lower likelihood of having CRC, whereas excess drinking (i.e. >48 g/day) was associated with increased likelihood of CRC. Among participants close to the MD, only heavy alcohol drinking (i.e. >48 g/day) was associated with higher likelihood of CRC.

Discussion

The findings of the present work are in line with those described in previous studies as far as it concerns the cumulative effect of smoking on CRC development. However, in this work, it was revealed that a healthy dietary pattern, like the MD, may mediate the adverse effects of smoking on CRC; moreover, greater adherence to the MD had a constant protective association with the likelihood for having CRC, independently of other risk factors. Additionally, close adherence to the MD enhanced the protective effect of physical activity on CRC, whereas the already-reported J-shaped association of alcohol drinking was evident only among those who were away from the MD. Despite the limitations of case–control studies, our innovation was that for the first time a study examining risk factors for CRC applied a holistic dietary approach, revealing the mediating effect of MD on a series of risk factors. Thus, public health policies towards CRC prevention could emphasize on the greater adherence of healthy dietary patterns as effective goals for fighting the disease.

Increased abdominal fat has been associated with several types of cancer, including CRC,[26,29–31] and has been characterized as a convincing risk factor for CRC in the Second Expert Report.[32] In the present work, neither waist circumference nor BMI was associated with the likelihood of having CRC, when various potential confounders were taken into account. Physical activity had a protective association, particularly among participants with good adherence to the MD. It could be suggested that physical activity acts only synergistically and not independently, assuming that without being in a context of a healthy dietary pattern, that is, in this case, the Mediterranean, is not able to express its protective association.

Finally, the current analyses support our previous findings,[28] suggesting that moderate alcohol intake (i.e. 12–35 g ethanol/day) has a protective association with CRC, but only in participants with low adherence to the MD, whereas high intake (>48 g of ethanol) had a detrimental effect irrespective of the level of adherence to the MD. Despite the potential limitations of this study, it could be speculated that moderate alcohol intake, that is, mostly red wine in our case, characterized by a high content of antioxidant compounds, had a protective association irrespective of low adherence to the MD, by increasing total antioxidant content of this diet. Perhaps, because good adherence to the MD is characterized as an already-very-rich-in-antioxidant-compounds diet, no such protective association of moderate alcohol intake was observed.

Limitations

The major limitation of this study could be the recall bias, as in all case–control studies. However, an effort was made to minimize this limitation by choosing newly diagnosed consecutive patients and collecting all necessary subjects in a short period. Moreover, people who collected the data were trained, limiting the bias between the investigators. Selection bias, especially for the controls, is also a potential limitation of the study; however, the enrolled controls are representative of the general population, especially for the main exposure variables. In particular, the smoking and alcohol drinking rates, as well as the MedDietScore values, observed in the control group were similar to those reported by another population-based, randomly selected, large-scale and well-established survey, the ATTICA study[33]; a fact that implies that controls may represent the general population, at least for the main exposure variables studied here. The effect size measures used in case–control studies (i.e. odds ratios) tend to overestimate the actual effect of the cause on effect usually observed in prospective studies. As in all case–control studies, the results are not presenting a causative association between the factors examined, but only suggestions needing further investigation with cohort studies. Another limitation is the potential misclassification, that is, controls may have some health-related problems that could lead to the development of CRC in the near future, and this may have altered their dietary or smoking habits. Based on the fact that controls were voluntarily and not randomly selected, selection bias should be taken under consideration.

Conclusions

The main conclusion of the present study is that it revealed a mediating effect of a holistic healthy dietary pattern, the MD, on the relationship between smoking habits and the likelihood of CRC, underlying not only the direct effects of diet on CRC but also its indirect pathways. The latter enforces the need for promotion of a healthy dietary pattern, like the Mediterranean, as it could be a promising and inexpensive way to prevent future CRC events.

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Conflicts of interest: None declared.

Key points

- Former smoking habit increased the likelihood of CRC, irrespective of lifestyle habits.
- Adherence to the MD seemed to play a mediating effect on the relationship between smoking habits and CRC, as smoking habits were associated with 2.9-fold the likelihood of CRC among participants who were away from the MD and with 2.1-fold the likelihood of CRC among those who were close to the MD.
- Physical activity had a protective effect on CRC, particularly among participants with good adherence to the MD.

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