

Is the nuclear factor kappa-b (NF-κB) pathway and inflammatory status associated with colorectal cancer?

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Abstract

Background: Although genetic predisposition has a role in the etiology of colorectal cancer, there are many other factors that affect its development. In this study, it was aimed to evaluate the NF-κB pathway, inflammatory status and dietary antioxidant capacity in individuals with colorectal cancer.

Methods: The study was carried out with 40 male subjects diagnosed with colorectal cancer aged between 39-65, years and a control group of the same number of healthy men. Subjects in the case and control groups were subdivided according to body mass index (BMI), as normal (BMI 20-24.9 kg/m²) or overweight/obese (BMI ≥25 kg/m²).

Results: At the end of the study, NF-κB and interleukin-22 levels were higher in the case group, but no significant difference was found between the groups. Interleukin-23 and 8-Hydroxy-2-deoxyguanosine levels in the case group classified as overweight/obese according to BMI were significantly higher than in the control group ($P = 0.001$ and $P < 0.001$, respectively). Considering diet antioxidant capacity, it was higher in individuals in the control group than in the case group. However, there was no significant difference between the groups.

Conclusion: Inflammatory status and reduced dietary antioxidant capacity are risk factors in the development of colorectal cancer.

Keywords: Colorectal cancer, dietary antioxidant capacity, NF-κB pathway, systemic inflammatory response, transcription factors.

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INTRODUCTION


Colorectal cancer begins as a tumor or tissue growth in the inner wall of the colon or rectum, and develops slowly over a period of 10-20 years.^[1] Especially the high turnover rate of intestinal epithelium makes this tissue the focal point for malignant transformations.^[2] Colorectal cancer is a multistage process involving inactivation of several genes

that suppress the tumor and DNA repair, and activation of some oncogenes. In addition to genomic instability, epigenetic changes caused by abnormal methylation and histone modifications may play a role in the development of colorectal cancer.^[3] Although basic molecular pathways that are important in the development of colorectal cancer have been identified,^[4] unspecified molecular mechanisms may

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also be responsible for colorectal carcinogenesis. One of the main pathways thought to play a role in the development of colorectal cancer is the nuclear factor (NF- κ B) pathway and the inflammatory state.^[5]

The hypothesis about the causal relationship between inflammation and cancer is that malignant neoplasm occurs at the site of chronic inflammation. When the relevant data are examined, it is seen that more than 15% of all malignancies start with a chronic inflammatory disease.^[6] Although the mechanism of inflammation that induces malignancy is not fully understood, one of the factors involved in this process is NF- κ B. NF- κ B is a transcription factor that plays an important role in cell differentiation and proliferation. Besides, as it is one of the main factors involved in the regulation of inflammation, it becomes an important molecule in maintaining activities of immune system.^[5] Tumor necrosis factor (TNF) and interleukin (IL)-6, which are responsible for the development of the inflammatory condition, are the basic cytokines that are thought to play a role in the development of colorectal cancer.^[7]

However, recently, IL-11, IL-17, IL-21, IL-22 and IL-23, with similar biochemical functions, are thought to affect colorectal cancer development.^[8,9] These cytokines produced by inflammatory cells in the presence of chronic inflammation contribute to the activation of the NF- κ B pathway. Activation of this pathway means survival for many cancer cells.^[6]

In this study, the effect of NF- κ B pathway and inflammatory status on colorectal cancer formation are examined. Also, the relationship between dietary antioxidant capacity and inflammatory status is discussed.

PATIENTS AND METHODS

Participants

This analytical, case-control type study was conducted with individuals diagnosed with colorectal cancer, who applied to the Medical Oncology Polyclinic of Ankara Numune Training and Research Hospital, and healthy individuals. Four different working groups were formed for the research. The first study group included 20 male patients with a body mass index (BMI) of 20-24.9 kg/m², who were recently diagnosed with colorectal cancer, or who had relapsed, and did not receive active radiotherapy or chemotherapy, and had no history of metastasis.

The second study group, similarly to the first group, included 20 male patients who were recently diagnosed

with colorectal cancer or who had relapsed, did not receive active radiotherapy or chemotherapy, and had no history of metastasis, but with a BMI \geq 25 kg/m². The aim of forming different study groups according to BMI is to limit the effect of BMI on the biochemical parameters. In addition, patients who received active radiotherapy or chemotherapy, had a history of metastasis, or had a malignant disease other than a diagnosis of colorectal cancer, history of metabolic syndrome, cardiovascular, hepatic, chronic kidney, major hormonal or hematological, pulmonary, autoimmune, inflammatory disease (pancreatitis, Crohn's, ulcerative colitis, etc.), existing infectious disease, use lipid-lowering, anti-inflammatory, antithrombotic drugs, and food supplement users, were not included in either study group. The third and fourth study groups were planned as the control group. Therefore, a total of 20 healthy male subjects whose BMI ranged between 20-24.9 kg/m² were included in the third study group, and 20 male subjects with BMI \geq 25 kg/m² were included in the fourth study group. The study was completed with a total of 80 individuals. The study groups were matched according to age, smoking and alcohol use, to avoid significant differences in the biomarkers planned for the study. Besides, only male subjects were included in the study because the risk of developing colorectal cancer was higher in males than in women.^[10] A written consent form was signed for the individuals who participated in the study. Ethics committee approval of the study was obtained from Zekai Tahir Burak Women's Health Training and Research Hospital Clinical Research Ethics Committee, with the decision number 134/2017 dated 21.11.2017.

Data collection

The data required for the study were collected by a questionnaire form prepared by the researcher and applied to the patients with colorectal cancer and healthy control groups, by face-to-face interview technique. One tube venous blood sample was taken from the participants during the interview.

Antioxidant capacity of the diet was evaluated with a "3-day food consumption record" and "antioxidant food consumption frequency form". Antioxidant food consumption frequency form was developed from the questionnaire developed in 2009 by Satia *et al.*,^[11] With this form, the frequency and amount of consumption of fruits, vegetables, cereals, legumes, oilseeds, meat, eggs and dairy products, mixed meals, chocolate, sauces, oils and beverages in the last 1 month, were recorded. Antioxidant contents of foods were taken from a study which analyzed the antioxidant content of 3100 foods, by Carlsen *et al.*^[12] Dietary total antioxidant capacity obtained from a result

of analysis and calculations was recorded as “dietary total antioxidant capacity obtained from the antioxidant food consumption frequency form”. Antioxidant capacity of the diet from the three-day food consumption record was also analyzed by using the Nutrition Information Systems Package Program (BEBIS). However, since there is no database related to total antioxidant contents of foods in the BEBIS program, a database of antioxidant contents of foods was created by using the study results obtained from Carlsen *et al.*,^[12] and then the total antioxidant capacity of the diet was calculated. The total antioxidant capacity of the diet obtained from food consumption record was recorded as the “dietary total antioxidant capacity obtained from the food consumption record”.

Biochemical analysis

On the same day, 1 tube (10 mL) venous blood sample was taken from the participants by the unit nurse, for the evaluation of biomarkers. The samples were centrifuged and stored at -80°C until the day of analyses. Samples were studied by Enzyme-Linked Immunosorbent Assay (ELISA) method, as per the manufacturer's

instructions (Rel Assay ® Diagnostics kits, Mega Tıp, Gaziantep, Turkey).

In this method, the serum sample was first pipetted into the measuring tube coated with antibodies, then biotinylated antigen was added and the measuring tube was incubated at 37°C for 1 hour. At the end of the incubation period, washing with phosphate-buffered saline was performed to remove biotinylated antigen, not yet complexed with the antibody. Avidin peroxidase (avidin-HRP) was then added and incubated for 1 hour at 37°C to conjugate with the biotinylated antibody. After further washing, the color was transformed with tetramethylbenzidine (TMB), and sulfuric acid terminated the enzyme-substrate reactions. Color changes were measured by a spectrophotometer at 450 nm wavelength and the concentration of the studied parameters in the samples were calculated using the standard curve created by optical densities of the standards.

Statistical analysis

Data obtained from the volunteers were analyzed by using SPSS 22.0 program with appropriate statistical

Table 1: Demographic characteristics and anthropometric measurements of individuals in the case and control groups

Demographic Characteristics and Anthropometric Measurements	Case Group (n: 40)		Control Group (n: 40)		P
	n	%	n	%	
Age (year)					
X±SS (min-max)	55.8±7.48 (39-65)		53.7±6.28 (43-65)		P* = 0.112
Educational status					
Illiterate	3	7.5	-	-	P [†] = 0.178
Literate	2	5	1	2.5	
Primary school	18	45	19	47.5	
Secondary school	7	17.5	5	12.5	
High school	7	17.5	9	22.5	
University	2	5	6	15	
Postgraduate	1	2.5	-	-	
Working status					
Working	14	35	30	75	P [†] < 0.001
Not working	26	65	10	25	
Marital status					
Married	34	85	40	100	P [†] = 0.011
Single	6	15	-	-	
Smoking					
Yes	14	35	21	52.5	P [‡] = 0.064
No	7	17.5	10	25	
Quit smoking	19	47.5	9	22.5	
Alcohol use					
Yes	1	2.5	2	5	P [‡] = 1.000
No	39	97.5	38	95	
Family history of cancer					
Yes	16	40	13	32.5	P [‡] = 0.485
No	24	60	27	67.5	
Anthropometric measurements					
Height (cm) X±SS	167.9±6.87		174.7±7.21		P* < 0.001
Body weight (kg) X±SS	70.8±11.97		80.5±12.3		P* = 0.001
BMI (kg/m ²) X±SS	25.1±3.62		26.4±3.57		P* = 0.090
Body fat percentage (%) X±SS	21.4±6.55		21.9±4.77		P* = 0.648
Waist circumference (cm) X±SS	90.5±10.43		93.3±10.19		P* = 0.328

*Mann Whitney U test. [†]Kruskal Wallis test. [‡]Pearson Chi square test

Table 2: Biochemical parameters and dietary antioxidant capacity of the subjects in the case and control groups

Variables	Case Group (n: 40)		Control Group (n: 40)		P	Difference Between Groups
	BMI 20-24.9 kg/m ² (G1) (n: 20) X ± SS (min-max)	BMI ≥25 kg/m ² (G2) (n: 20) X ± SS (min-max)	BMI 20-24.9 kg/m ² (G3) (n: 20) X ± SS (min-max)	BMI ≥25 kg/m ² (G4) (n: 20) X ± SS (min-max)		
Biochemical Parameters						
Nuclear factor kappa-B	11.9±14.80 (1.6-42.0)	16.7±16.87 (0.7-43.2)	9.4±4.97 (1.1-18.0)	7.4±6.93 (0.03-26.8)	0.980	G1-G3
Interleukin-17	603.9±249.54 (43.5-893)	671.0±173.02 (50.6-937.5)	301±194.88 (41.1-680)	1720.3±6175.28 (0.1-27210.8)	0.001	G1-G3
Interleukin-22	41767.9±21597.26 (1888-84751.5)	40778.6±26732.67 (640.2-78117.3)	31720.8±20518.43 (34.4-71459.8)	38939.3±26261.83 (468.7-95533)	0.549	G1-G3
Interleukin-23	15.3±1.39 (13.2-18.2)	113.5±60.75 (25.6-209.8)	14.3±1.19 (13.3-18.1)	17.7±9.90 (13.3-57.5)	0.995	G2-G4
8-Hydroxy-2'-deoxyguanosine (8-OHdG)	355.7±244.64 (42.8-722.7)	507.1±230.04 (144.9-757.9)	187.6±113.40 (19.2-397.5)	156.1±117.8 (0-393.2)	0.149	G1-G3
Dietary Antioxidant Capacity						
Dietary total antioxidant capacity*	1.93±1.02 (1-4.9)	2.40±1.09 (0.9-4.3)	2.21±0.75 (0.9-3.8)	2.52±1.48 (1.1-6)	0.057	G1-G3
Dietary total antioxidant capacity [†]	2.18±0.51 (1.2-3.1)	3.02±1.13 (1.5-5.4)	2.66±0.93 (1.4-5.3)	3.14±0.81 (1.6-4.8)	<0.001	G2-G4

Mann Whitney U test and Tamhane test. Statistically significant P values ($P < 0.05$) are written in bold. *Dietary total antioxidant capacity obtained from the antioxidant food consumption frequency form. [†]Dietary total antioxidant capacity obtained from food consumption record

methods. Descriptive values are expressed as number (n), percentage (%), arithmetic mean (\bar{x}) and standard deviation (SS). Pearson Chi-square test was used to compare categorical variables. The suitability of the variables to normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mann-Whitney U and Kruskal-Wallis tests were used since the data were not normally distributed. When more than two variables were compared, Tamhane test was used to determine which variables were significant. The relationship between the variables was examined by Spearman correlation analysis if the data were not normally distributed. The level of statistical significance was determined as $P < 0.05$.

RESULTS

In the demographic characteristics part, factors such as age, genetics, education, smoking, and alcohol, that are effective in colorectal cancer pathogenesis are discussed. In this study, no significant difference was found between the groups in terms of demographic characteristics and anthropometric measurements [Table 1].

Mean and standard deviation values of biochemical parameters, and dietary total antioxidant capacity of case and control subgroups are given in Table 2. According to the results of the study, NF- κ B and IL-22 values were higher in the case subgroups, but there was no significant difference between the groups ($P > 0.05$). Compared to the control group, IL-17 was found to be significantly higher in the case group classified as normal according to BMI (301.0 ± 194.88 and 603.9 ± 249.54 respectively;

$P = 0.001$). For IL-23 (113.5 ± 60.75 and 17.7 ± 9.90 respectively; $P = 0.001$) and 8-OH-dG (507.1 ± 230.04 and 156.1 ± 117.80 respectively; $P < 0.001$), the values in the case group classified as overweight/obese were significantly higher than in the control group. When dietary antioxidant capacity was examined, no significant difference was found between the case and control groups ($P > 0.05$). However, compared to the case group, dietary antioxidant capacity was higher in the control group.

In Table 3, the relationship between biochemical parameters reflecting inflammatory status and various variables in the case group are examined. According to the results of the study, a significant positive correlation was found between IL-23 and 8-OHdG, which reflects DNA damage ($r = 0.349$ and $P = 0.027$), BMI ($r = 0.771$ and $P < 0.001$), body fat percentage ($r = 0.731$ and $P < 0.001$), waist circumference ($r = 0.574$ and $P < 0.001$) and dietary antioxidant capacity ($r = 0.393$ and $P = 0.012$), in the case group.

DISCUSSION

Colorectal cancer is the third most common cancer worldwide and fourth in terms of cancer-related mortality.^[13,14] Although genetic predisposition contributes to disease development, 90% of colorectal cancers occur sporadically.^[15] Therefore, it is important to examine the underlying causes of colorectal cancer. In this study, the effect of the NF- κ B pathway and inflammatory status on the pathogenesis of colorectal cancer is investigated. The relationship between dietary antioxidant capacity and inflammatory status was discussed.

Obesity is a known risk factor for many cancers.^[16] Studies examining the effect of body mass index on colorectal

Table 3: Correlation between parameters reflecting the inflammatory status and variables in the case group

Variables	Interleukin-17		Interleukin-22		Interleukin-23	
	r	P	r	P	r	P
Case Group (n=40)						
Nuclear factor kappa-B (NF-κB)	0.212	0.189	0.168	0.300	0.199	0.218
8-Hydroxy-2'-deoxyguanosine (8-OHdG)	0.181	0.264	0.181	0.264	0.349	0.027
Body Mass Index (BMI)	-0.079	0.626	-0.220	0.173	0.771	<0.001
Body fat percentage	-0.130	0.425	-0.112	0.492	0.731	<0.001
Waist circumference	-0.245	0.127	-0.204	0.207	0.574	<0.001
Dietary total antioxidant capacity*	-0.166	0.306	0.106	0.516	0.283	0.077
Dietary total antioxidant capacity†	-0.213	0.188	0.013	0.939	0.393	0.012

Spearman correlation analysis. Statistically significant P ($P < 0.05$) are written in bold. *Dietary total antioxidant capacity obtained from the antioxidant food consumption frequency form. †Dietary total antioxidant capacity obtained from food consumption records

cancer prognosis have reported an increased risk of mortality^[17,18] and recurrence of disease,^[17] compared with normal body weight, in overweight and obese subjects. The reasons obtained by the obesity factor to adversely affect the prognosis of the disease are, that the increase in body fat tissue may change the response to chemotherapy and radiotherapy,^[17] or that obesity may be responsible for biochemical changes such as increased insulin-like growth factor-1 (IGF-1) production and stimulated decreased immune function.^[17,19]

Similarly, a higher percentage of body fat or waist circumference is a risk factor for the development of colorectal cancer. Since adipose tissue is responsible for the unwanted metabolic risk profile such as hyperinsulinemia, systemic inflammation, low adiponectin, and high leptin level, all these may be the underlying potential mechanisms for colorectal cancer.^[20,21] However, in the present study, the difference between BMI, body fat percentage and waist circumference, were higher in the control group compared to the case group, although the difference was not significant. This may be due to body weight loss caused by illness in individuals in the case group. This is considered a possibility because body weight loss in the previous month was not been recorded.

The inflammatory state is characterized by the release of cytokines, growth factors, proteases, and reactive oxygen species (ROS), which are important in the promotion of leukocytes and in stimulating endothelial cells and fibroblasts. However, it has been reported that these components released during chronic inflammation may cause DNA damage or alter cell life cycle, and result in carcinogenesis. In particular, there is evidence that cytokines released during the inflammatory state may contribute to cancer development through NF-κB activation.^[6] In these studies, cancer tissue samples taken from patients with colorectal cancer, and normal tissue samples were examined, and it was found that NF-κB expression was increased in cancerous tissues.^[22-24] Cytokines produced by

inflammatory cells in the presence of chronic inflammation contribute to the activation of the IkappaB kinase (Ikk)/NF-κB pathway. Activation of this pathway means survival for many cancer cells.^[6] Because NF-κB can prevent apoptosis by increasing the accumulation of reactive oxygen species, it can stimulate the expression of cytokines and further contribute to inflammation-related tissue damage,^[6] and resistance to apoptosis.^[5] It can play a role in the regulation of genes that are important for the growth and proliferation of cells such as Cyclin D1 and cMyc.^[6] Also, the upregulation of factors involved in angiogenesis, such as vascular endothelial growth factor (VEGF), is regulated by the NF-κB pathway.^[25] Besides, another factor supporting angiogenesis, cyclooxygenase-2 (COX2) can be stimulated with NF-κB.^[6] In this study, although the difference was not significant, the NF-κB value was found to be higher in the case subgroups compared to the control subgroups. However, there was no significant relationship between the NF-κB pathway and inflammatory markers.

Tumor necrosis factor (TNF) and IL-6, which are responsible for the development of the inflammatory condition, are the basic cytokines that are thought to play a role in the development of colorectal cancer.^[7] Recently, however, IL-11, IL-17, IL-21, IL-22 and IL-23, that have similar biochemical functions, are also thought to affect the development of colorectal cancer.^[8,9] In particular, IL-17 is involved in the regulation of the NF-κB signaling pathway, chemokines, growth factors, and adhesion molecules.^[26] Therefore, IL-17 has an important effect on colorectal cancer development and prognosis. In studies related to this, it has been reported that IL-17 stimulates the NF-κB signaling pathway in individuals with colorectal cancer, and stimulation of this pathway promotes migration of colorectal cancer cells, and adversely affects the prognosis of the disease.^[27,28] Interleukine-23 is also involved in the regulation of the inflammatory state and thus in the formation of inflammation-related cancers.^[9] It is known that increased IL-23 and IL-23 receptors are associated with rapid metastatic disease prognosis in colorectal cancer.^[29]

In this study, IL-17 was found to be significantly higher in the case group classified as normal according to BMI compared to the control group ($P = 0.001$). In the case group with high BMI, IL-23 value was significantly higher than in the control group ($P = 0.001$). Especially in the case group, this is evidenced by the significant positive correlation between IL-23, BMI and body fat percentage, because the increase in the production of free radicals, decrease in antioxidant capacity, increased adipose tissue and cell damage due to increased oxygen use associated with obesity may trigger the inflammatory state.^[30]

In the study, the 8-OHdG value reflecting DNA damage was found to be significantly higher in the case subgroup with high BMI, compared to the control group ($P < 0.001$). The condition that causes oxidative damage is not only the overproduction of ROS but also failure in mechanisms associated with the antioxidant defense system, or DNA repair. Reactive oxygen species are also responsible for the stimulation of the NF- κ B signaling pathway, which may increase the expression of inflammatory cytokines.^[31] Therefore, an increase in oxidative stress may stimulate the inflammatory state and an increase in inflammation may be responsible for DNA damage. In this study, in accordance with the literature, there was a significant positive correlation between IL-23 levels and 8-OHdG, reflecting DNA damage ($P = 0.027$).

Antioxidant nutrients are involved in capturing free radicals and protecting cells against oxidative stress responsible for processes that initiate carcinogenesis, such as inflammation, cell proliferation, mutation in genes, and DNA damage.^[32] However, instead of evaluating the antioxidant nutrients alone, it is more important to collectively evaluate the antioxidants in the diet. Since antioxidants can act synergistically to play a protective role against carcinogenesis, by reducing oxidative stress.^[33] In this study, the total antioxidant capacity of the diet was calculated from the frequency of food consumption form and food consumption record. Dietary total antioxidant capacity obtained from food consumption frequency form and food consumption record was higher in the control group compared to the case group, but no significant difference was found between the groups ($P > 0.05$).

CONCLUSION

Despite this, the study has a few limitations. Seasonal differences due to long study data collection time may be an important factor affecting the results of dietary consumption frequency and dietary antioxidant capacity.

Further, it may be useful to strengthen the results of the study by reaching a larger number of samples in studies to be planned similar to this study.

In conclusion, colorectal cancer is an important health problem with a high prevalence rate. Therefore, the factors that play a role in the development of the disease or the underlying mechanisms should be well known, and appropriate recommendations should be made for risk factors that can be modified. Inflammation, increased oxidative stress and DNA damage are the factors that affect the development of the disease. Besides, the lack of an effective antioxidant defense system to neutralize the effect of these factors due to a decrease in antioxidant capacity may contribute to the deterioration of disease prognosis. For this reason, it is important to increase the intake of antioxidant nutrients with adequate and balanced nutrition to support the antioxidant defense system, and prevent the increase in oxidative stress.

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Conflicts of interest

There are no conflicts of interest.

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