Colorectal cancer and dysplasia risk of ulcerative colitis patients in a tertiary referral center in Turkey

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ABSTRACT

Background/Aims: *Patients with ulcerative colitis (UC) are at increased risk of colorectal cancer (CRC). High-grade dysplasia (HGD) and low-grade dysplasia (LGD) are premalignant conditions. The aim of this study is to evaluate the risk of CRC/dysplasia in patients with UC, and the related risk factors.*

Materials and Methods: *Medical records of 1659 patients dating between 1993 and 2016 were scanned from an inflammatory bowel disease database. A total of 801 patients with UC who underwent at least one colonoscopic procedure with at least 1-year follow-up period were included in the study. Clinical, endoscopic, and histopathological data were assessed.*

Results: *The mean disease duration was 6.7±6.6 years. The total disease duration was 5334 person-years duration (pyd), and 34% of patients had the disease for 8 years or longer. The prevalence of UC-associated CRC was 0.7%, and the prevalence of dysplasia was 0.85%. The overall incidence of CRC was determined to be 1.1/1000 pyd. The cumulative risk of CRC was 0.3% at 10 years, 1.3% at 20 years, and 5.9% at 30 years. The Cox regression analysis indicated that primary sclerosing cholangitis (HR:13.677, 95% CI:2.6-70.8, p = 0.012) was an independent risk factor for developing UC-associated CRC.*

Conclusion: *This study underlined the low risk of CRC and dysplasia in patients with UC in a tertiary referral center in the western part of Turkey. Primary sclerosing cholangitis was found to be the most important risk factor for the development of CRC in patients with UC. Identification of risk factors is important to categorize patients into subgroups to know which patients will require frequent surveillance.*

Keywords: *Ulcerative colitis, dysplasia, colorectal cancer*

INTRODUCTION

Ulcerative colitis (UC) is a putative risk factor for developing colorectal cancer (CRC); patients with UC are 2 to 5 times more likely to develop CRC than the general population, which is likely attributed to chronic inflammation, genetic factors, and acquired factors (1,2). UC-associated CRC constitutes approximately 1%-2% of all CRC cases, and it is the cause of death in 10%-15% of patients with inflammatory bowel disease (IBD) (3,4). The long-standing course of disease (5), extensive colitis with severe inflammation (1,6,7), young age at diagnosis (8), the concomitant diagnosis of primary sclerosing cholangitis (PSC) (9), positive family history of CRC (10), and the presence of pseudopolyps and pancolitis with backwash ileitis (11) are some of the reported risk factors for developing CRC in patients with UC.

The importance of dysplasia is to have a potential risk for developing CRC. Furthermore, if high-grade dysplasia (HGD) is diagnosed, there is a possibility to find CRC at the same time, or patients tend to have a risk of developing CRC in the near future. Therefore, colectomy is recommended for those with HGD (uni- or multifocal). However, the recommendation of colectomy is still being debated in low-grade dysplasia (LGD). Well known risk factors for dysplasia progression are the presence of concomitant PSC, disease duration, and a positive family history of CRC. Dysplasia can be flat, polypoid, localized, diffuse, or multifocal in UC. Surveillance colonoscopy with targeted and random biopsies at every 10 cm of the entire colon or each anatomic segment has been recommended to detect CRC in a curable stage and to reduce the UC-associated CRC mortality in patients (12-14).

In 2001, Eaden et al. (15) published a meta-analysis of 116 studies, which reported that the overall prevalence of CRC in any patient with UC was 3.7%. In the meta-analysis, the cumulative risks for each decade after diagnosis of UC was reported as 2.1% at 10 years, 8.5% at 20 years, and 17.8% at 30 years. Some recent studies showed an increased risk of CRC that was not as high as earlier (16), while some studies emphasized the decreased risk of CRC among patients with UC (16-18). The risk of CRC in UC is well known, but the risk estimates are still controversial and may vary among geographical regions.

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Although, not as clear as in sporadic CRC, genetic and epigenetic alterations can play a role in the carcinogenesis of UC-associated CRC (19). To determine the real risk of UC-associated CRC, long-term follow-up studies from different geographical regions of the world are needed.

To date, there have been few studies addressing the clinical characteristics of patients with UC in Turkey (20-23). Indeed, only one study investigated the incidence of CRC and dysplasia and the related risk factors in Turkish patients with UC (24). In the aforementioned study, the enrolled patients with a disease duration longer than 10 years, which was composed of the patients in the surveillance group, were evaluated. There is still a lack of evidence to assess the magnitude of CRC risk and dysplasia in patients with UC in Turkey. This study aimed to assess the prevalence and incidence of CRC and dysplasia in patients with UC and to determine the related risk factors with long-term follow-up in a single tertiary referral center in Turkey.

MATERIALS AND METHODS

This study is a retrospective cohort study. Overall, a total of 1659 patient records were scanned in an IBD outpatient electronic database between 1993 and 2016. Clinical, endoscopic, and histopathological data of patients with UC were retrieved through an electronic chart system. The patients with Crohn's disease (n=522), indeterminate colitis, and microscopic colitis (collagenous or lymphocytic) (n=94), or other causes of colitis (infectious, nonspecific, drug, or radiation induced, etc.) (n=45) were excluded. Patients with UC who had a disease duration shorter than a year and/or insufficient data were also excluded (n=197). Accordingly, a total of 858 patients were excluded, and 801 patients were included in the study (Figure 1). The diagnosis of UC was confirmed regarding clinical (with the medical history and symptoms), laboratory, radiological, and endoscopical medical records, including histopathological examination. It was checked whether other forms of colitis were excluded.

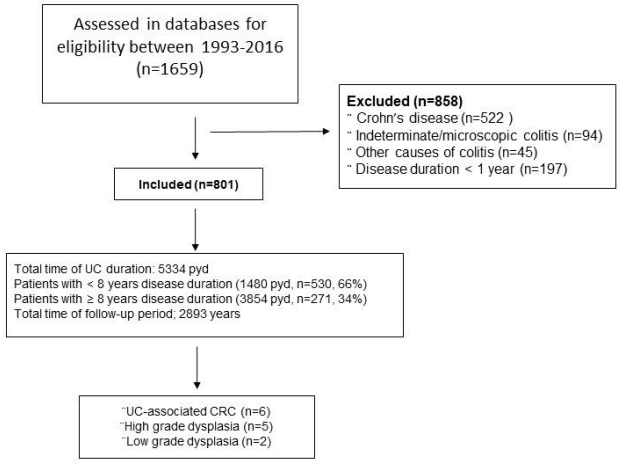

Figure 1. A flow diagram of the study
(Pyd: person-years duration, UC: ulcerative colitis, CRC: colorectal cancer)

Patient variables such as age, gender, smoking status, age at the UC onset, disease duration at the last visit and at the time of lesions diagnosis, and the family history of CRC and IBD were noted. Disease characteristics of the patients such as colonic extension; drugs for maintenance treatment; concomitant diagnosis of PSC; the presence of pseudopolyps in the colon; diagnosis of LGD, HGD, and UC-associated CRC; and survival status were recorded from the database. The extent of disease from colonoscopic appearance was classified according to the Montreal classification (14,25): E1 refers to proctitis (involvement limited to the rectum), E2 refers to left-sided colitis (involvement limited to the proportion of the colon distal to the splenic flexure), and E3 refers to extensive colitis (involvement extends proximal to the splenic flexure, including pancolitis).

The patients were divided into two groups according to the maintenance treatment. The patients in the first group were treated with oral and/or topical 5-aminosalicylic acid (5-ASA) or sulfasalazine (SSZ) treatment alone. The patients in the second group were treated with ongoing or experienced immunomodulator (IM) drugs (azathioprine, 6-mercaptopurine, etc.) in addition to 5-ASA with or without the anti-tumor necrosis factor α (anti-TNFα). Diagnosis of PSC was confirmed by records of impaired liver function tests, a positive antineutrophil cytoplasmic antibody test, and with magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiography.

Screening colonoscopies were started 8-10 years after the onset of UC symptoms, and surveillance colonoscopies were done according to the risk groups every 1-2 or 3-4 years as recommended in the guidelines (12-14). In the presence of PSC, colonoscopy was performed annually. Colonoscopy or rectosigmoidoscopy was performed at any time if the patient's symptoms were refractory. UC-associated CRC and dysplasia (HGD and LGD) were diagnosed histopathologically according to the Vienna classification (26) by an expert gastrointestinal (GI) pathologist and confirmed by another expert GI pathologist as well. All the patients diagnosed with CRC, LGD, or HGD in their colonic biopsy samples were reviewed and extracted from the pathology department database.

Table 1. The demographic data and disease characteristics of all UC patients

Demographic Data and Disease Characteristics (n=801)	Results
Mean age (years), Mean±SD (min-max)	46.7±15.2 (16-89)
Mean age at disease onset, Mean±SD (min-max)	40.5±15 (6-85)
Mean disease duration, Mean±SD (min-max)	6.7±6.6 (1-37)
Mean follow-up period, Mean±SD (min-max)	3.6±3.8 (1-21)
Disease durations in decades	
1-10 years	2343 pyd (n=625, 78%)
11-20 years	1990 pyd (n=137, 17%)
21-30 years	861 pyd (n=35, 4.5%)
>30 year	140 pyd (n=4, 0.5%)
Total	5334 pyd (n=801, 100%)
Gender	
Male, n (%)	475 (59.3)
Female, n (%)	326 (40.7)
Disease duration	
<8 years, n (%)	530 (66)
≥8 years, n (%)	271 (34)
Smoking status	
Currently smoker, n (%)	154 (19.2)
Former smoker, n (%)	128 (16)
Non-smoker, n (%)	519 (64.8)
IBD in family history, n (%)	62 (7.7)
CRC in family history, n (%)	16 (2)
Disease extent	
E1, n (%)	185 (23.1)
E2, n (%)	350 (43.7)
E3, n (%)	266 (33.2)
Treatment	
5-ASA* or SSZ alone, n (%)	699 (87.2)
5-ASA+IM**±anti-TNFα, n (%)	102 (12.8)
Concomitant PSC, n (%)	13 (1.6)
Pseudopolyps, n (%)	100 (12.5%)
UC-associated CRC, n (%)	6 (0.7)
Dysplasia	7 (0.85)
LGD, n (%)	2 (0.25)
HGD, n (%)	5 (0.6)
All-cause mortality, n (%)	53 (6.6)

* oral and/or topical treatment, ** ongoing or experienced IM treatment, pyd: person-years duration, UC: ulcerative colitis, CRC: colorectal cancer, IBD: inflammatory bowel disease, 5-ASA: 5-aminosalicylic acid, IM: immunomodulator, LGD: low-grade dysplasia, HGD: high-grade dysplasia, PSC: primary sclerosing cholangitis, SSZ: sulfasalazine.

Thereafter, patients were matched in the IBD database to avoid underestimating the diagnosis of the LGD, HGD, and CRC in the patients with UC. Polyps and/or cancer cases outside the diseased area were excluded from the study. Three lesion groups (CRC, HGD, and LGD) were combined and called a "lesion group" to avoid statistical errors due to the small number of groups. The remaining group of patients with UC without lesion(s) were called the "non-lesion group." Ethics committee approval was not received for this retrospective study. Informed consent was received from the patients and/or relatives.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Demographic and disease characteristics of patients were summarized by standard descriptive statistical methods. A chi-squared test was used for statistical comparison of the categorized variables, and the Mann-Whitney U and Kruskal-Wallis (Wilcoxon) rank-sum tests were used for comparison of the continuous variables between groups. A p-value of <0.05 was accepted as statistically significant with a 95% confidence interval. The Kaplan-Meier method was used to estimate the probabilities of the UC-associated CRC-free, dysplasia-free, and total lesion-free survival of the patients with UC (27). The Cox regression model was used to determine the related risk factors of UC-associated CRC and dysplasia (28).

RESULTS

A total of 801 patients with UC were included and analyzed between the years 1993 and 2016. The flow diagram of the study is presented in Figure 1. The total disease duration for 801 patients was 5334 pyd. A total of 271 (34%) patients were in the routine surveillance program with a total disease duration of ≥8 years and 3854 pyd. A majority of the patients in this program (214/217, 98.6%) had 10 years or longer of total disease duration.

The mean age of patients with UC (n=801) was found to be 46.7±15.2 (16-89) years, and the mean age at onset of UC was 40.5±15 (6-85) years. The mean disease duration and the mean follow-up period were determined to be 6.7±6.6 (1-37) years and 3.6±3.8 (1-21) years, respectively. The number of male patients (n=475) was slightly higher than female patients (n=326). Half of the patients had a high school education level or higher level. Almost one-third of the patients had pancolitis. A small proportion of patients had CRC in their family history and concomitant diagnosis of PSC. Pseudopolyps were present in 12.5% of patients. Most patients were only on 5-ASA or SSZ treatment in remission. Demographic data and disease characteristics of all patients with UC were summarized in Table 1.

Table 2. Characteristics of the patients at the time of diagnosis with UC-associated CRC, HGD, and LGD

Lesion groups	Age at the UC onset (year)	Gender	Age at lesions diagnosis (year)	Disease duration at lesions diagnosis (year)	Disease extent	Localization of lesions (CRC, dysplasia)	CRC in family history	Concomitant PSC	Pseudopolyps	Organ metastases	Total colectomy	Survival
UC-associated CRC												
1	43	male	64	21	E3	sigmoid	no	no	no	yes	yes	ex, after 2 years
2	44	female	49	5	E2	sigmoid	no	yes	no	yes	yes	ex. after 1 year
3	57	male	65	8	E2	ascendant & sigmoid	no	no	no	yes	yes	ex, after 3 years
4	19	male	36	17	E3	ascendant	no	no	no	yes	yes	ex, after 2 years
5	34	male	63	29	E3	rectum	no	no	yes	no	yes	alive, after 6 years
6	72	male	84	12	E2	descendant	no	no	no	no	yes	ex, after 7 years
HGD												
1	41	female	46	5	E2	rectum	no	no	no	no	yes	alive, after 6 years
2	31	male	47	16	E3	sigmoid	no	no	no	no	yes	alive, after 14 years
3	53	male	76	23	E2	sigmoid	no	no	yes	no	no*	alive, after 2 years
4	40	male	46	6	E3	descendant	no	no	no	no	yes	alive, after 7 years
5	29	male	44	15	E3	sigmoid	no	yes	yes	no	no**	ex, after 1 year***
LGD												
1	51	female	54	3	E3	transvers & rectum	no	no	no	no	no	alive, after 7 years
2	41	female	43	2	E3	rectum	no	no	no	no	no	alive, after 8 years

*Patient preference, **not suitable for surgical procedure due to complications of PSC-related cirrhosis, ***exitus due to cirrhosis complications. PSC: primary sclerosing cholangitis, UC: ulcerative colitis, CRC: colorectal cancer, LGD: low-grade dysplasia, HGD: high-grade dysplasia

Six (0.7%) patients with CRC, 5 (0.6%) with HGD, and 2 with (0.25%) LGD were diagnosed. UC-associated CRC was detected in 2 patients (33%) prior to the colonoscopy surveillance time and in 4 (67%) patients were detected in the surveillance time. Four (80%) of the 5 HGD lesions were polypoid, and 1 (20%) had a flat colonoscopic appearance. All patients with HGD were diagnosed at targeted biopsies (visible lesion). In the LGD group, 1 (50%) lesion was polypoid (visible lesion), whereas 1 lesion (50%) was invisible and diagnosed in a random biopsy. All the patients were in remission at the time of CRC, HGD, and LGD diagnosis.

Characteristics of the lesion group (n=13) were as follows. The mean age at disease onset was 42.6±13.6 years, the mean age at diagnosis of the lesions was 55±14 years, and the median disease duration at the time of lesion diagnosis was 12 years (2-29). Nine (69%) patients were male, 2 (15.2%) had concomitant PSC, 6 (46.2%) had pseudopolyps, and all patients had an E2 and E3 disease extent. No patient had a family history of CRC in the lesion group. Three out of 5 HGD patients underwent total colectomy as recommended in the guidelines. One of the patients did not accept the operation, and 1 could not be operated due to complications as a result of PSC-related cirrhosis. The detailed characteristics of patients with UC-associated CRC, HGD, and LGD are shown in Table 2.

Statistically significant differences were found between the two groups (non-lesion and lesion) with respect to the total disease duration, presence of

Table 3a. The comparison of continuous variables among three groups (non-lesion, CRC, and dysplasia)

Patients Variables	Non-lesion Group (n=788)	Lesion Group (n=13)		p
		CRC (n=6) mean±SD (min-max), (median)	Dysplasia (n=7)	
Age at the UC onset (years)	40.5±15 (6-85), (39)	44.8±18 (19-72), (43.5)	40.9±9 (29-53), (41)	ns
Disease duration (years)	6.5±6.4 (1-37), (4)	17.2±10.5 (5-35), (15.5)	14.7±9 (7-29), (10)	<0.001*#
Age at lesion diagnosis (years)	no lesion	60.2±16.2 (36-84), (63.5)	50.9±12 (43-76), (46)	ns

*Comparison of mean disease duration (years) among three groups (non-lesion, CRC, dysplasia) was significant (Kruskal-Wallis test, Kruskal-Wallis test value=16.726, p<0.001 with CI of 95%).

#in binary comparison of the mean disease duration between the non-lesion and CRC groups and between the non-lesion and dysplasia groups, which demonstrated a significant difference (Mann-Whitney U test, Mann-Whitney U test value=739,500, p<0.003 with CI of 95%), SD: standard deviation, ns: not significant, CRC: colorectal cancer.

Table 3b. The comparison of the categorical variables among three groups (non-lesion, colorectal cancer, and dysplasia)

Patients Variables	Non-lesion Group (n=788) (n, %)	Lesion Group (n=13)		p
		CRC (n=6) (n, %)	Dysplasia (n=7) (n, %)	
Gender (male)	466 (59.1)	5 (83.3)	4 (57.1)	0.482
Smoking status				
Currently smoker	126 (16)	1 (16.7)	1 (14.3)	
Former smoker	152 (19.3)	1 (16.7)	1 (14.3)	
Non-smoker	510 (64.7)	4 (66.7)	5 (71.4)	0.996
IBD in family history	60 (7.6)	2 (33.3)	0 (0)	0.047*
CRC in family history	16 (2)	0 (0)	0 (0)	0.872
Disease extent				
E1	185 (23.5)	0 (0)	0 (0)	
E2	345 (43.8)	3 (50)	2 (28.6)	
E3	258 (32.7)	3 (50)	5 (71.4)	0.042**
Treatment				
5 ASA alone	688 (87.3)	5 (83.3)	6 (85.7)	
5 ASA+IM±anti TNFα	100 (12.7)	1 (16.7)	1 (14.3)	0.956
Pseudopolyps	97 (12.3)	1 (16.7)	2 (28.6)	0.411
Concomitant PSC	11 (1.4)	1 (16.7)	1 (14.3)	0.000***

*The difference was significant among the non-lesion, CRC, and dysplasia groups. In the binary comparisons, the significance was based on the differences between the non-lesion and CRC groups and between the CRC and dysplasia groups (chi-squared test value=6.108, p=0.047 with CI of 95%). **There were no significant differences among the three groups, but the difference was significant in the binary comparison of the lesion and non-lesion groups (chi-squared test value=6.329, p=0.042 with CI of 95%). ***There was significant difference among the non-lesion, CRC, and dysplasia groups (chi-squared test value15.789, p=0.000 with CI of 95%), 5-ASA: 5-aminosalicylic acid, IM: immunomodulator, PSC: primary sclerosing cholangitis, anti-TNF: anti-tumor necrosis factor

IBD in the family history, disease extension, and concomitant PSC (p<0.05 with CI of 95%). There was no significant difference between the two groups with respect to all the other continuous and categorical variables (p>0.05 with CI of 95%). In a subgroup analysis, significant differences were found between the three groups (non-lesion, CRC, and dysplasia) with respect to the total disease duration, presence of IBD in family history, disease extension, and concomitant PSC (p<0.05 with CI of 95%). However, no significant difference was found between three groups with respect to all other continuous and categorical remaining variables (p>0.05 with CI of 95%). Data are shown in Tables 3a and 3b.

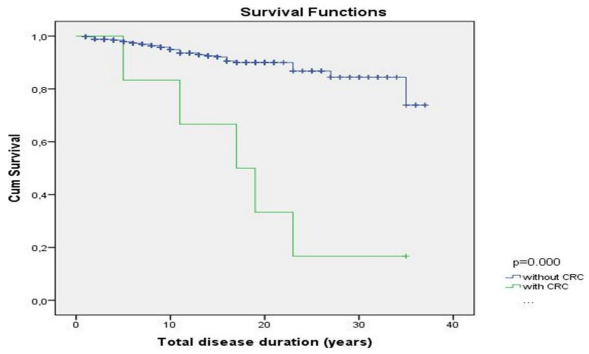

Figure 2. Survival analysis of ulcerative colitis (UC)-associated colorectal cancer (CRC). Kaplan-Meier curves show the cumulative survival analysis with and without CRC in patients with UC. Patients with UC-associated CRC had reduced survival compared to patients without UC-associated CRC (p=0.000)

Table 4. Incidence and prevalence of the UC-associated CRC and dysplasia in the patients with UC

	CRC	Dysplasia
Overall prevalence	0.75%	0.87%
Overall incidence (in 1000 pyd)	1.1	1.3
Incidence in decades (in 1000 pyd)		
1-10 years	0.24	1
11-20 years	1	0.36
21-30 years	2	1
Cumulative incidence		
at 10 years	0.3%	0.5%
at 20 years	1.3%	3.4%
at 30 years	5.9%	17.9%

CRC: colorectal cancer, UC: ulcerative colitis

The overall survival and CRC-free survival through a maximum of 21-year follow-up are shown in the Kaplan-Meier curves displayed in Figure 2. A Cox regression analysis indicated that only the presence of concomitant PSC (HR: 13.677 95% 2.6-70.8, p=0.012) was an independent risk factor for developing CRC in patients with UC. The overall prevalence of UC-associated CRC was 0.75%. The overall risk of CRC was 1.1/1000 pyd. The overall risk of dysplasia was 1.3/1000 pyd. Cumulative risks of CRC were 0.3% at 10 years, 1.3% at 20 years, and 5.9% at 30 years (Table 4).

DISCUSSION

In this study, we reported low incidence rates of CRC, HGD, and LGD in patients with UC and a long-term follow-up in a tertiary referral center in the western part of Turkey. The overall incidence of UC-associated CRC was found to be 1.1/1000 pyd (0.1% annually), and the overall incidence of dysplasia was found to be 1.3/1000 pyd with up to 37 years of disease duration and up to 21 years of the follow-up period. These incidences of UC-associated CRC were lower than those previously reported in the literature (15).

It is well known that patients with UC are at higher risk of developing CRC than the general population (29). This risk was found to be high in a meta-analysis published by Eaden et al. (15). However, in a recent meta-analysis of 58 articles from referral centers and population-based cohorts, the risk of CRC in patients with UC decreased dramatically over the past decades (16). A recent population-based study of 47.374 Danish patients with IBD reported that there was no increased risk over the past 30 years, except for special subgroups with UC (5). Similar to recent studies, our results supported the presence of a low risk of CRC in patients with UC. The estimated risk of UC-associated CRC may vary by geographical region and study design. As expected, the risk of UC-associated CRC may be higher in referral center studies when compared with population-based studies because of the inclusion of more severe and complicated patients in the referral centers. Furthermore, the meta-analysis of Eaden et al. (15) was criticized because of the selective collection of severe patients from tertiary referral centers that may result in the overestimation of the CRC risk (4). Interestingly, we found that the overall risk of CRC was low. This finding suggested that such an increased risk is not as high as previously reported. Possible mechanisms for this reduced risk of CRC in patients with UC over the past decades may be the better control of inflammation. Increasing use of 5-ASA, which also have anti-cancer effects, seems to reduce the CRC incidence (30). Furthermore, a better adherence to screening and surveillance programs, as well as the proper use of colectomy and regular follow-up, may play important roles in risk reduction (4).

There were few studies in the literature that investigated the risk of CRC and dysplasia in patients with UC in Turkey. Two different Turkish studies have taken part in the meta-analysis of Eaden et al. (15); one of them included 60 patients with UC, and no CRC was detected among the 25 patients who had been diagnosed for at least 2 years (20). The other study reviewed 204 patients with UC and 2 patients (1%) diagnosed with CRC (21). These two studies (20,21) reflected the data over the past 4 decades; interestingly, the risk of CRC in patients with UC in Turkey was also low in the 1970s. The limitations of these

two studies were that they had a very small proportion of patients with a long-standing disease course. One of the advantages of the present study is that one-third of the patients had over 8 years of disease duration and a long-term follow-up period. Therefore, cumulative risk appraisal can be made over the years. From 2004 to 2006, the Turkish Ministry of Health Cancer Statistics reported that the age-standardized incidence rate of CRC Turkey is 17 in men and 11.7 in women per 100.000 persons (31). The CRC risk still remains higher in patients with UC than the sporadic CRC risk in the general population in Turkey. The overall incidence of UC-associated CRC was found to be lower than those previously reported in the literature, but it was observed that this risk significantly increased: 1.3% at 20 years and 5.9% at 30 years during the long course of the disease.

Recently, Kekilli et al. (24) published a paper of a single tertiary referral center experience from Turkey to determine the incidences of dysplasia, adenomatous polyp, and CRC of patients with UC with a long-term follow-up between 1994 and 2008. UC-associated CRC was detected in 3 (1%) of the cases, and dysplasia was found in 11 (4%). A total of 275 patients that entered their surveillance program having disease for at least 10 years were evaluated and analyzed. Unlike this study, we included all the patients in the analysis of our study even if they had less than 10-year disease duration due to the detection of CRC in 2 individuals in the 3rd and 5th years of disease. On the one hand, this approach could influence the ratios, but on the other hand, it reflected the real-life experience. However, the low incidence of UC-associated CRC found in our present study supports the relevant results of the only previous study (24). Supporting our data, Lutgens et al. (16) found that 22%-28% of patients developed CRC prior to the colonoscopy surveillance time. In parallel with our results, a low CRC incidence rate (2/1000 pyd) was reported in Scandinavian countries, whereas higher incidence rates were reported from the United Kingdom and the United States (4/1000 pyd and 5/1000 pyd, respectively) (15). It is clear from that since the 1970s, the results of studies in published tertiary referral centers from Turkey have indicated low incidences of UC-associated CRC and dysplasia compared to other geographical locations throughout the world. Similarly, our study findings supported the presence of low risk. In the same manner, the CRC incidence rate of 1.45% in patients with UC was reported from Greece, which was very close to Turkey (32). The researchers concluded that the Mediterranean diet might be a factor for this low risk, whereas another study emphasized the apoptotic process and molecular-based ethnic differentiations for the low risk in Greek patients with IBD (32, 33). Considering the aforementioned statements, it is thought that hereditary and environmental factors play an important role in the development of CRC in UC.

Little is known about the features of CRC in patients with UC. To date, the known risk factors for the development of CRC in patients with UC are the presence of extensive colitis, long duration of colitis, concurrent PSC, a family history of CRC, smoking, pseudopolyps, and persistent active inflammation (7,15,16,34,35). According to the literature, we determined statistically significant differences between the non-lesion and lesion groups compared to the disease duration, disease extension, presence of IBD in family history and concomitant PSC. Surprisingly, there was no significant difference between the lesion and non-lesion groups among the three groups when the other known risk factors were compared. This finding might be due to the small number of patients in the lesion groups, and thus, the results should be interpreted carefully. Actually, there were some important findings that should be noted in CRC and dysplasia groups. First, there was not any E_1 disease extension detected in the lesion group, and all the patients had E_2 or E_3 disease. It has been well documented in previous studies that extensive disease carries the highest risk, whereas distal colitis carries the lowest risk for developing UC-associated CRC (2,35), and our results are in line with this literature. Therefore, patients with extensive or left-sided colitis are more likely to develop CRC and should be followed strictly in surveillance programs as recommended in the guidelines. Second, over 80% of patients were male in the CRC group, which was slightly higher than the percentage in the non-lesion group (80% vs 59%). This result was similar to some population-based studies, in which slightly higher percentages of male patients were found in the CRC groups, but they did not reach statistical significance (5,36). In a recent multicenter epidemiologic study about CRC in Turkey, it was reported that 60% of patients were male in the sporadic CRC group (37). It appears that there is a slightly higher risk of UC-associated CRC in male patients. Third, concomitant PSC was present in 16.7% of the UC-associated CRC group, whereas it was present in 1.4% of the non-lesion group. Similarly, it was reported that concomitant PSC was present in 2%-5% of the patients with UC in the literature. Additionally, in the cox analysis, the presence of concomitant PSC was identified as an important risk factor for the CRC development in patients with UC, which was consistent with the literature. Therefore, patients with UC with concur-

rent PSC should be encouraged to adhere to the recommended surveillance and colonoscopy program for CRC and/or dysplasia detection in the early stage. In addition, we found statistically significant differences between the non-lesion and lesion groups in terms of a family history of IBD, although there is, as yet, no possible explanation of this observation. We believe that this finding must be interpreted carefully due to the small number of cases in the lesion group. The average ages of the UC onset were not different between the lesion and non-lesion groups in the analysis. The mean age of lesion diagnosis was detected at 60.2 years in the UC-associated CRC group. It was reported that the average age was 43.2 years in the meta-analysis by Eaden et al. (15) and 50.9 years in Eastern Europe, which was 10 to 15 years younger than the sporadic CRC (62.2 years) (34). Data of the multicenter study from Turkey showed that the mean age was 58.9 years in the non-IBD-CRC group (37). Indeed, these findings supported that the average age of UC-associated CRC diagnosis showed similarity to the average age of sporadic CRC in the Turkish population.

Unlike the literature, in our series, no patient had a family history of CRC in the lesion groups, and 2% of patients in the non-lesion group had a family history of CRC. The ratio of patients with a family history in the Turkish population was reported as 7.4% in sporadic colon cancer (37). These observational data indicate that underlying chronic inflammation may contribute to CRC in patients with UC. On the other hand, although no known certain genetic basis has been demonstrated to explain the development of CRC in the UC setting, a recently published meta-analysis showed that different genetic characteristics exist between IBD-associated CRC and sporadic CRC (38). The meta-analysis suggested that some mutations increased both the risks of IBD and IBD-associated CRC in patients, but not the risk of sporadic CRC. Furthermore, an association was present between single-nucleotide polymorphisms and IBD-associated CRC in patients with IBD in the same meta-analysis. In the future, further genetic studies may elucidate the ongoing discussion on the actual cancer risk and its geographical differences in patients with UC.

Finally, it is important to identify the true magnitude of risk of UC-associated CRC and to know what the significant risk factors are and how these risk factors contribute to the development of CRC in these patients. The main limitation of our study was that it was retrospective, and the strengths of the study were the presence of a high number of patients, long disease course, and long-term follow-up period. The present study represents the results of a single institution. Thus, further population-based studies are needed to confirm our study results.

In conclusion, this study from a tertiary referral center in Turkey revealed that there is a low risk of CRC and dysplasia in the patients with UC. These low ratios may be associated with genetic and environmental factors. Therefore, epidemiological studies are important to identify the risk factors of UC-associated CRC to categorize patients into subgroups who need frequent surveillance and to develop national surveillance strategy policies. Further population-based studies are needed to verify the low incidence and prevalence of UC-associated CRC and dysplasia in Turkey.

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Informed Consent: Written informed consent was obtained from patients and/or relatives who participated in this study.

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