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Colorectal Cancer Risk Associated with Reproductive Factors among Turkish Women

Gonca Karataş Baran[1], **Gül Pınar**[2*] **and Sevil Şahin**[2]

[1]*Department of Obstetrics and Women's Health, Institute of Health Sciences, Yıldırım Beyazıt University, Turkey*

[2]*Department of Nursing, Faculty of Health Sciences, Yıldırım Beyazıt University, Turkey*

[*]**Corresponding author:** Pinar G, Department of Nursing, Faculty of Health Sciences, Yıldırım Beyazıt University, Ankara, Turkey, **Tel:** +9(0)312-324155; **E-mail:** gpinar_1@hotmail.com.tr

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Abstract

Purpose: Our aim was to investigate the association between the female reproductive factors and colorectal cancer risk (CRC).

Methods: This descriptive and cross-sectional study was conducted with 196 women (50 years old and older) at Ankara Keçiören Training and Research Hospital (AKEAH), Maternity Polyclinic during June 16-July 30 2014 in Turkey. A Survey Form was used in data collection.

Results: Mean age of women who were included in the research scope was 57.2 ± 7.9. It was determined that 85.7% of women were not informed about CRC screening methods and 86.2% did not have CRC screening test. 83.6% of women were at low risk group for CRC, and approximately two out of five persons (16.4%) were in moderate risk group. We observed that presence of gynecological cancer; bowel disease, chronic disease and family history of bowel disease were associated with CRC risk ($p<0.05$). We observed no statistically significant associations between use of oral contraceptive and hormone therapy, menarche age, age at first birth, parity, menopausal age ($p>0.05$).

Conclusion: This study supports the assumption that there might be an association between reproductive factors and risk of CRC. Wider screening of risk factors should be explored in further.

Keywords: Colorectal cancer risk factors; Colorectal cancer screening; Reproductive characteristics; CRC risk group; Women aged 50 and over

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide, with 1.4 million new cases and approximately 694,000 deaths estimated each year [1]. In Turkey it is also a major health problem in women after breast and thyroid cancer. In our country, CRC incidence is approximately 7 per 100,000 with around 6,000 new cases are seen each year and 3,200 deaths annually. This is higher than that of previous reports in Turkey and the risk of CRC increases steadily with age, especially in females [2].

Many epidemiologic studies have been performed to investigate specific hypotheses about risk factors of CRC, including high meat and less fruit, vegetable, and fiber intake, sedentary lifestyle, diabetes mellitus, obesity, tobacco smoking, alcohol, non-steroidal anti-inflammatory drugs, polyps and high risk bowel syndromes such as inflammatory bowel diseases [3,4]. Besides, reproductive and hormonal factors, such as parity, age at birth of first child, age at menarche, and age at menopause, use of hormone therapy or oral contraceptive could be effective as well for lifetime exposure to endogenous estrogens [5-12]. CRC is one of the most treatable types of cancer when colorectal cancer is found at an early stage before it has spread. Familial history, especially first-degree relation may play an etiologic role in the development of CRC. Screening strategies, particularly for the diagnosis of precancerous polyps including fecal occult blood test (FOBT) annually, sigmoidoscopy every 5 years, barium enema every 5 years, or colonoscopy every 10 years, which may help the prevention of malignancy. Current regulations suggest that screening for CRC should be initiated in the general population for 50 years old and more, and for the high-risk group from a younger age [13].

CRC affects men and women almost equally but there are a limited number of studies with special focus on women for CRC risk. There is no such study in Turkey, particularly for reproductive factors so far. In this study, our purpose is to investigate the association between the reproductive factors and CRC risk in women who are 50 years old and over.

Materials and Methods

This descriptive and cross-sectional was conducted study at AKEAH Maternity Polyclinic in Turkey during June 16-July 30 2014. The sample size was estimated, as the margin of error is 0.07 confidence level is 95% by the sampling formula with no known population. On this basis, 196 women aged 50 years old and older were included. The women were randomly assigned to the study from patient list. The inclusion criteria of study were as follows: (1) being 50 years old and older, (2) not being a mental disability, (3) having open to

communication and collaboration and (4) being willing to participate in the study.

The study was conducted in compliance with principles of Helsinki Declaration. Approval was obtained from the Ethical Board of the Ankara Keçiören Training and Research Hospital in order to conduct the study. Women were informed about the study by the researchers prior to study and the ones who agreed to participate were enrolled in the study. The data were collected by face-to-face interviews by using the data collection form that was prepared by the researchers by scanning the literature [2,6-15] as third parts.

1) Socio-demographic characteristics. This section consists of questions on age, marital status, education, employment, health security, income level perception, and the place of living.

2) Medical and reproductive characteristics. This section consists of questions about menarche age, first marriage age, parent kinship, first pregnancy age, number of pregnancy, number of births, number of miscarriage, history of oral contraceptive (OCC) use, menopause age, and history of hormone replacement treatment (HRT), history of diabetes, cancers, bowel disease, gynecologic operation.

Participants were asked whether they had ever used OCC (no, yes) and the total number of years of use (categorized as months). We defined parity as the total number of pregnancies lasting 6 months or longer. Age at first pregnancy was assessed as age at the first pregnancy lasting 6 months or longer (not applicable or as years). Number of miscarriages/abortions (spontaneous or induced) was recorded as the number of pregnancies lasting less than 6 months. Age at menarche, and the reason for menopause (natural or surgical) age at menopause were recorded in years.

3) CRC risk groups were evaluated by dividing them to four groups (average, low, moderate, high):

Very low (average) risk group: Individuals who were over 50 years of age, not having a previous adenomatous polyp, inflammatory bowel illness and family history were included in this group.

Low risk group: Individuals who were over 50 years of age, asymptomatic, not having a previous adenomatous polyp and inflammatory bowel illness, and who had a parent or sibling with colon polyp or cancer history at the age over 60 were included in this group.

Moderate level of risk group: Individuals who had previous adenomatous polyp or CRC history, having adenomatous or CRC history in one of the first degree kin before 60 years of age, having adenomatous polyp or CRC history in one or more individuals in the family, and having previous breast, endometrium or ovary cancer history were included in this group.

High-risk group: Individuals who had hereditary non-polyposis colorectal cancer history, and long term inflammatory bowel illness history were included in this group.

The data collected in the study were analyzed by SPSS 20 package program. Descriptive statistics of the socio-demographic, reproductive and medical characteristics of women are presented as numbers, percentages, mean, and standard deviation. Ki-square test was used to assess associations between variables (socio-demographic characteristics and CRC risk).

Mann-Whitney U test was used in the comparisons with two groups as a result of the normality tests of the data, and Kruskall-Wallis test was used in the comparison of 3 and above groups. The significance level was $p<0.05$.

Results

The mean age of the women was 57.2 ± 7.9 (min=50, max=86) (Table 1). The majority of the women (84.7) were married, 53.1% were elementary school graduates, 93.4% were unemployed, 56.1% had moderate income, and 83.7% lived at the city center.

Findings determined that 99.0% of the women were married at least once, 95.9% had at least one pregnancy, 68.6% gave 3 and over births, 77.0% did not use OCC before and 81.6% did not have parent's kinship. 83.6% of the women were in "low" risk group in terms of CRC and 16.4% were in "moderate" risk group. There were no women determined in the high-risk group.

CRC Risk Groups							
Socio-demographic Characteristics	**Low**		**Moderate**		**Total**		**Analysis**
	n	**%**	**n**	**%**	**n**	**%**	
Age (ort:57.2, min:50, max:86)	164	83.7	32	16.3	169	100	z=-0.246* p=0.805
Marital status							
Married	137	82.5	29	17.5	166	100	Fisher's Exact **p=0.424
Single	27	90	3	10	30	100	
Educational status							
Illiterate	29	80.6	7	19.4	36	100	X^2= 3.15 **p=0.371
Literate	24	75	8	25	32	100	
Elementary school	91	87.5	13	12.5	104	100	
High school and above	20	83.3	4	16.7	24	100	
Employment status							
Employed	12	92.3	1	7.7	13	100	Fisher's Exact **p=.698
Unemployed	152	83.1	31	16.9	183	100	
Income level perception							
My income is less than my expenses	61	85.9	10	14.1	71	100	X^2= 1.94 **p=0.387
My income is equal to my expenses	89	80.9	21	19.1	110	100	
My income is more than my expenses	14	93.3	1	6.7	15	100	
* Mann-Whitney U test, **Ki-Square Analysis and Fisher's Exact Test were used ($p<0.05$).							

Table 1: Distribution of some socio-demographic characteristics of women according to colorectal cancer risk groups.

According to the analysis in Table 1, there was no statistically significance between CRC risk groups and age, marital status, educational status, employment status and income level ($p>0.05$).

Reproductive Characteristics	CRC Risk Groups	Mean	Min	Max	SS	Analysis*
Age at menarche	Low	13	10	16	1.1	z=-0.474
	Moderate	13.2	11	16	1.4	p=0.636
Age at first marriage	Low	18.4	12	40	4	z=-0.639
	Moderate	19.3	13	40	5.4	p=0.523
Age at first pregnancy	Low	20.9	13	45	4.7	z=-0.492
	Moderate	20.2	14	28	3.8	p=0.623
Number of parity	Low	3.5	1	5	0.4	z=-0.735
	Moderate	3.01	0	4	0.8	p=0.532
Number of miscarriages	Low	1	1	3	1.2	z=-0.542
	Moderate	1.1	0	4	1.1	p=0.617
Age at menopause	Low	47.2	32	61	4.9	z=-0.876
	Moderate	48.2	40	55	4.2	p=0.381
OCC use-combined (≥2 years)	Low	4.2	1	24	4.8	z=-0.543
	Moderate	3.7	1	10	2.9	p=0.587
HRT use (≥2 years)	Low	3.2	1	8	2.5	z=-0.494
	Moderate	3	3	3	1.2	p=0.621
*Mann-Whitney U test was used (p<0.05)						

Table 2: Distribution of obstetric and gynecological characteristics of women according to colorectal cancer risk groups.

There were no associations of reproductive factors, including age at menarche, age at menopause, age at first marriage or pregnancy, number of miscarriages and parity with CRC risk (p>0.05). Although it is not statistically significant, those who had early menarche, older first marriage age and maternal age, late menopause age, low parity, never use of OCC (2 or more years) and HRT use had higher CRC risk (Table 2).

CRC Risk Groups							
Medical Characteristics	**Low**		**Moderate**		**Total**		**Analysis***
	n	**%**	**n**	**%**	**n**	**%**	
Menopause status							
Yes	136	82.4	29	17.6	165	100	x^2=0.64 p =0.408
No	28	90.3	3	9.7	€ 31.00	100	
Type of menopause							
Natural	118	84.3	22	15.7	€ 140.00	100	Fisher's Exact p=0.156
Surgical	18	72	7	28	€ 25.00	100	
History of gynecologic operation							
Yes	20	74.1	7	25.9	27	100	Fisher's Exact p=0.163
No	144	85.2	25	14.8	169	100	
History of gynecological cancer							
Yes	0	0	11	100	11	100	Fisher's Exact p=0.001*
No	164	88.6	21	11.4	185	100	
History of bowel disease							
Yes	11	61.1	7	38.9	18	100	Fisher's Exact p=0.014*
No	153	86	25	14	178	100	
Family history of bowel disease							
Yes	0	0	17	100	17	100	Fisher's Exact p=0.0001*
No	164	91.6	15	8.4	179	100	
History of diabetes							
Yes	36	72	14	28	50	100	x^2=5.62 p=0.018*
No	128	87.7	18	12.3	146	100	
*Ki-Square Analysis and Fisher's Exact Test were used (p<0.05)							

Table 3: Distribution of medical characteristics of women according to colorectal cancer risk groups.

Bowel and CRC screening characteristics	Bowel disease history*						
	Yes		No		Total		Analysis
	n	%	n	%	n	%	
Bowel habits*							
At least once a day	9	50	137	77	146	74.5	Fisher's Exact p=0.021***
Once every two days or longer	9	50	41	23	50	25.5	
Symptoms on bowel disease during the past 6 months**							
There is no symptom/finding	4	22.2	125	70.2	129	65.8	X^2= 14.68 p=0.000***
There is at least one symptom/finding	14	77.8	53	29.8	67	34.2	
CRC screening							
I had at least one of them.	12	44.4	15	55.6	27	100	Fisher's Exact p=0.0001***
I didn't have any of them made.	6	3.6	163	96.4	169	100	

* Bowel disease; polyp-adenoma, spastic colon, hemorrhoid, Crohn's disease, ulcerative colitis

**Bowel disease symptoms; bloody stool, constipation, feeling of rectal mass/bulge, mucus in stool, foul smelling stool, bloating-gas, stomach upset, loss of appetite, nausea-vomiting, fatigue.

*** Ki-Square Analysis and Fisher's Exact Test were used (p<0.05).

Table 4: Distribution of characteristics related to bowel and crc screening of women according to bowel disease history.

In Table 3, women who had diabetes history, had bowel disease, bowel disease history in family, diagnosed with gynecological cancer

(endometrium, cervix, ovary) and had gynecologic operation (oophorectomy, hysterectomy) were in more risk for CRC ($p<0.05$).

As it is seen in Table 4, it was determined that women who didn't have a bowel disease had defecation more regularly (77.0%). It was observed that women who had a bowel disease experienced more symptoms/finding during the past 6 months (77.8%) ($p<0.05$). Majority of women did not have CRC screening previously (96.4%) ($p<0.05$).

Discussion

Adenomatous polyposis is primary precursor lesion of CRC. In addition, presence of bowel disease history is a significant finding for CRC risk such as chronic ulcerative colitis, inflammatory colon disease and Crohn's illness [14,15]. There was bowel disease history in 18.9% of women in our study (22.2% polyp-adenoma, 16.7% spastic colon, 38.9% hemorrhoid, 11.6% ulcerative colitis, 10.8% Crohn's illness). Moreover, women experience indicators during the last six months such as "bloody stool, irregular defecation, feeling mass/bulge by hand, and mucus in stool, foul smelling stool, gas-bloating, stomach upset, loss of appetite, nausea-vomiting, and fatigue". The conducted analyses similarly to other studies show that persons who have bowel disease are in higher risk for CRC ($p<0.05$).

Estrogen receptor is present in human colonic epithelium. Greater endogenous estrogen (estradiol) exposure may stimulate mutagenic events and proliferation of carcinoma cells. Exogenous estrogens prevent the development of CRC. The recent Women's Health Initiative (WHI) estrogen-plus-progestin trial reported a 37 percent lower risk of CRC [16]. In the present study, the present finding of a trend of decreasing risk with increasing age at menarche for CRC. Indeed, there is no convincing data relating age at menarche to risk of CRC ($p>0.05$). Similarly in a different study, age at menarche did not seem related to CRC risk [17].

In a study, it was indicated that in persons who had early menarche CRC risk was higher [18]. Estrogen production before puberty could increase CRC cell numbers and cause DNA mutation therefore it is considered to be a risk factor for CRC [7,10]. We did not find statistically significant associations between parity and the risk of CRC, but it was determined in our study that CRC risk decreased in women who had menarche at a later age ($p>0.05$). A similar decreasing trend was observed in previous studies [5,7,10,19].

During gestation, estrone is predominant estrogen in circulation. Whereas estradiol has been demonstrated to have proliferative features in colon cell, estrone has been shown to exert anti-proliferative effects in the colon cell and protective against CRC. Pregnancy is also leads to production of progesterone, which opposes the mutagenic changes of estrogen in reproductive tract and colon tissues [6]. According to the Nurses' Health Study, which reported a statistically significant association between older age at first pregnancy or parity and risk of CRC. Most of the studies observed that older age at first pregnancy and number of parity was associated with risk of CRC [6,7,9,20,21].

A cohort study demonstrated that compared with nulliparous women, women who had given birth to two or more children had a decreased risk of CRC [22]. CRC risk decreased 34% in women who had 5 and more births [6]. In contrast to their results, a different study fulfilled in the Europe, observed no association between parity and the risk of CRC [23]. In our study, miscarriages, parity and later age at birth of first child status were not associated with the risk of CRC ($p>0.05$). In a case-control study has shown an inverse association between number of parity and risk of CRC [18].

Later menopause is associated with the higher number of ovulatory cycles and increased estrogen exposure [24]. In our study, we did not observe any consistent pattern in the relationship between age at menopause and risk of CRC ($p>0.05$). In the study of Nichols et al. [6] CRC risk was found low in premenopausal women in comparison to postmenopausal women.

According to the WHI trial, where postmenopausal HRT use has been associated with a 40% reduction of CRC incidence [16]. In the other studies, use of HRT was not associated with decreases in CRC risk [17,25]. Although we also failed to find the relationship between age at menopause and CRC, there is a difference of late age at menopause with significantly elevated risk of CRC ($p>0.05$). Other studies support these results [6,26].

We observed a statistically significant increase in CRC risk associated with family history of bowel disease. In the study of Ouakrim et al. [27] it was determined that the screening in individuals having CRC in family history decreased CRC mortality significantly.

In meta-analysis of 24 studies, it was determined that CRC risk increased in individuals having first-degree kin with CRC [26]. In the present study similarly, CRC risk in persons who have first-degree kin with bowel disease increased significantly ($p<0.05$). It is crucial that family history is taken and screening is carried out in regular intervals for early intervention in persons who have CRC risk.

OCC may protect against CRC by reducing number of ovulation cycles and endogenous estrogen levels. OCC hormones may also suppress of insulin like growth factor I and synthesis or secretion of bile acids, which are inversely associated with the risk of CRC [28].

The associations between use of OCC and risk of CRC did not observe in our study ($p>0.05$). In the study of Lin et al. [29] it was determined that people who used OCC had lower risk of CRC in comparison to those who did not use it at all. In the WHI Clinical Trial, combined OCC was determined to protect against CRC, whereas estrogen alone had no effect [16].

In the present study, it is observed that persons who had cancer history (endometrium, ovary, cervix) were under more risk for CRC ($p<0.05$). Literature emphasizes that CRC risk increases in women who had breast, ovary and/or endometrium cancer [12,30]. In the light of all of these results, people with breast cancer and women's genital organ cancer should have periodical CRC screening. Hyperinsulinemia is a human CRC promoter. Diabetes mellitus has already considered as a risk factors of CRC [31]. In the study of Yuhara et al. [4] it was concluded that diabetes mellitus is related to CRC risk increase. Similar differences were also observed in our study ($p<0.05$).

Conclusion and Suggestions

This study confirms that, there is a modestly association between female some reproductive factors and the risk of CRC. Furthermore, it was observed that awareness of women about CRC screening programs was inadequate.

In this sense, by considering the health system and high treatment costs and prognosis, strategies must be developed to increase awareness of the general population about CRC screening tests. All of these findings should be pursued in further epidemiologic studies.

Limitations of the research

This study is limited with the women who applied to AKEAH Maternity Polyclinic and individual statements of these persons and with the indicated time interval.

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Conflicts of interest

There are no conflicts of interest.

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