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Trends in colorectal cancer by subsite, age, and gender over a 15-year period in Adana, Turkey: 1993-2008

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Background/aims: *Analyzing temporal trends in cancer incidence rates can generate new insights for the significance of geographical and epidemiological variations of the disease. This study evaluated the time trends over a 15-year period in the frequencies of colon and rectum cancers at various subsites by gender and age.* ***Materials and Methods:*** *Data were obtained from a population-based cancer registry in Adana (a Mediterranean city of Turkey). Among the 47.783 microscopically-confirmed cancer cases during the 15-year period (1993 to 2008), 2.749 (5.8%) colorectal cancer cases were analyzed in three separate 5-year time periods.* ***Results:*** *The incidence of right-sided colon cancer was found to be increasing compared to the left-sided colon cancer (p=0.048) over time in total (19.8% in 1993-1997, 24.4% in 1999-2003, and 25.6% in 2004-2008). This proximal shift of cancers demonstrated a significant increase for females (p=0.041), but not for males. The incidence of right-sided colon cancer was found to increase in advanced age groups (over 70) of males and increase in younger age groups (over 50) of females. There was a corresponding continuous decline in the percentage of rectal cancer (not in distal cancers) in both genders.* ***Conclusions:*** *Although the frequency of colorectal cancer cases was found to be lower in our country when compared to Western countries, a similar right-sided colon cancer shift was observed. The apparent shift of colorectal cancer in young female patients may be related to the advances in diagnostic techniques and may indicate possible diagnostic bias for the female gender. These results also emphasize the importance of collecting regular cancer statistics and of closer follow-up to generate basic epidemiological data and to draw attention to this issue in further detailed analytical research studies.*

Key words: Colorectal cancer, subsite, age, gender, trends

Adana'da (Türkiye) kolorektal kanser sıklığının anatomik lokalizasyon, yaş ve cinsiyete göre 15 yıllık zamansal değişimi: 1993-2008

Giriş ve Amaç: *Kanser insidans hızlarının zamansal eğilimlerin analizi, önemli coğrafi farklılıkların yorumlanmasına yeni bakış açıları geliştirilmesini sağlayabilir. Bu çalışmada, Türkiye'nin Akdeniz Bölgesi'nde yer alan Adana'da kolon ve rektum kanser sıklığının anatomik lokalizasyon, cinsiyet ve yaş gruplarına göre 15 yıllık zamansal değişimi değerlendirilmiştir.* ***Yöntem:*** *Onbeş yıl (1993-2008) süresince topluma dayalı yerel kanser kayıt merkezinde histopatolojik tanı ile kaydedilen 47.783 kanser olgusu incelenmiş ve kolorektal kanser tanısı almış 2.749 (%5,8) vakada anatomik yerleşim ile cinsiyet ve yaş grubu arasındaki ilişki 5'er yıllık zaman dilimlerine göre analiz edilmiştir.* ***Bulgular:*** *Onbeş yıllık dönemde sağ kolon kanserlerinde anlamlı artış olduğu gözlenmektedir; (1993-1997 dönemi için %19.8, 1999-2003 için %24.4 ve 2004-2008 için %25.6) (p=0.048). Bu artış kadınlarda istatistiksel olarak anlamlı iken (p=0.041) erkeklerde anlamsızdır. Sağ kolon kanserleri, kadınlarda 50 yaş üzerinde artış gösterirken erkeklerde sadece 70 yaş üzeri grupta artış göstermektedir. Sağ kanserlerdeki artışa karşılık distal kanserlerde azalma görülmez iken her iki cinste de rektum kanserlerinde sürekli bir azalma olduğu görülmektedir.* ***Sonuç:*** *Çalışmada kolon kanserlerinin görülme sıklığının, batı toplumlarına göre daha düşük bulunmasına rağmen yıllar içinde sağ kolonda gözlenen artışın bu ülkelerdeki artışa benzer olduğu saptanmıştır. Sağ kolon kanserlerindeki artışının genç kadınlarda daha fazla olması, son on yılda kullanılan tanı yöntemlerinin farklılığına ve tanıda cinsiyet yanlılığına işaret ediyor olabilir. Subsegmental kolorektal kanserlerin zamansal değişimi, farklı etiyolojik, demografik ve coğrafik faktörler ve tanı yöntemlerindeki gelişmeler ile ilişkili olabileceğini düşündürmektedir. Elde edilen bulgular, ayrıntılı analitik çalışmalara temel oluşturması ve konuya dikkat çekmesi için kanser hızlarındaki değişimlerin düzenli toplanan kanser istatistikleri ile yakından izlenmesinin önemine işaret etmektedir.*

Anahtar kelimeler: Kolorektal kanser, anatomik lokalizasyon, yaş, cinsiyet, eğilim

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer type in males and the second in females worldwide, and the majority of the cases (almost 60%) are diagnosed in the developed regions (1-4). The incidence of the disease changes over time and varies regionally. There are three tendencies: 1- increasing (UK), 2- stable (New Zealand), and 3- decreasing (US and Western Europe). In the United States, CRC incidence rates have declined approximately 2-3 percent per year for the last 15 years (5). Incidence rates in most other Western countries have either been stable or slightly increased during the same period. In contrast, CRC incidence rates have rapidly increased in several areas, while low risk was determined in the Mediterranean region (including Israel, Spain), in a number of other countries within Eastern Asia (Hong Kong, Singapore), and in Eastern Europe (Hungary, Poland, Greece, Croatia) (1,3,4,6,7).

The subsite distribution of CRC also differs and, over the last 25 years, the incidence of adenocarcinomas located in the proximal colon has been found to slightly increase relative to the incidence rates in the distal colon and rectum (7-11). Several studies, however, showed a tendency for a proximal shift of cancer distribution, with right-sided lesions becoming more and left-sided lesions being less prevalent (8-14), but not without controversies (15-18). Currently, there is no plausible explanation for this distributional shift. Studies also suggest that the rates of occurrence of colorectal adenocarcinomas at particular anatomic subsites may be associated with distinctive geographic, demographic, and risk factor profiles (8-14). These geographic differences appear to be attributable to differences in the nutritional and environmental exposures that are considered to create a background of genetically determined susceptibility. Although Turkey seems to be at low risk for CRC as a Mediterranean country, rapid lifestyle changes occurred in the country as a result of globalization especially during the last two decades. There are very limited epidemiological population-based studies about the cancer incidences in the Turkish population, which has started to become an industrial society in recent years. Therefore, it is of importance to analyze the temporal trends in cancer incidence rates in relation to geographical variations, which may subsequently generate potentially new insights about the impact of various interventions. The aim of this study was to evaluate the time trends of the frequencies of colon and rectum cancers at various subsites among patients with different genders and age over a 15-year period in Adana, which is in the Mediterranean coast of Turkey.

MATERIALS and METHODS

The data between 1993 and 2006 were obtained from the population-based registry (performed by a mutual protocol between Cukurova University and the local health authority of the Turkish Ministry of Heath). The information about the cancer cases was routinely collected from the university, state and local private hospitals, and pathology laboratories by active registration method. After 2006, the registry was done in different organizations such as cancer surveys. Hence, the data for 2007-2008 were obtained from the Çukurova University Cancer Registry Center, which records the cases diagnosed only in the university departments. All CRC records checked for missing information such as unknown anatomical location, gender and age. The data were completed by the pathology and surgery department's records of the Çukurova University Hospital, providing almost 80% of the cases.

A total of 47.783 cases were registered in these two centers over a 15-year period. Incidences were calculated for the entire 1993-2008 period and for three separate 5-year periods: 1993-1997, 1999-2003, and 2004-2008. Since the records of 1998 were incomplete, the data of this year were not included in the study to avoid possible bias. The patients were analyzed according to successive 5-year periods to evaluate any possible shift in the site of tumors over time and in relation to gender and age. Five age groups for each gender (<40 years, 40-49 years, 50-59 years, 60-69 years, and ≥70 years) were selected with consideration of recommendations that average-risk individuals should begin the CRC screening at the age of 50. To determine the ratio of subsites (right/left CRC), the incidence in the right colorectal was divided by the left colorectal incidence.

Our analyses were limited to the primary invasive CRCs, which were microscopically confirmed. The lymphomas were not included. CRCs were coded according to the ICD-O-3 topography (site) codes and grouped into four major categories: 1 - Right-proximal colon cancers (RCC) - includes cecum (C18.0), ascending colon (C18.2), hepatic flexure (C18.3), transverse colon (C18.4), and splenic fle-

xure (18.5); 2 - Distal colon cancers (DCC) - includes the descending colon (C18.6) and sigmoid colon (C18.7); 3 - Rectal cancers (RC) - includes the recto-sigmoid junction (C19.9) and rectum NOS (C20.9), and 4 - Unspecified sites - includes appendix (C18.1), overlapping lesion of the colon (C18.8), colon not otherwise specified-NOS (C18.9). The terms "right-sided" and "left-sided" were used as synonyms for "proximal" and "distal plus rectum" locations. The fourth group was included in the statistics for the total CRC, but they were not analyzed as a separate group for subsite evaluation as the tumor site was unspecified.

A logistic regression analysis was performed to determine the independent risk factors related with right-sided and left-sided colon cancers. Having right or left colon cancer was considered as a dependent variable. The regression model consisting of male gender, younger age at diagnosis (<49 years), and first period of registration (1993-1997) was taken as reference categories. In addition, the joinpoint regression model was used to characterize changes in cancer proportions over time. Trends over a given time intervals were summarized with the annual percent change (APC). The APC was obtained by fitting a regression line through the logarithms of the proportions for the given time period by using the Joinpoint Regression Program Version 3.3.1 (http://srab.cancer.gov/joinpoint; Silver Spring, MD). This analysis allows identifying points where a significant change in the linear slope of the trend occurred. In this analysis, the best fitting points (the "joinpoints") were chosen where the rate significantly changed. The analysis starts with the 0 joinpoints (which is a straight line), and tests whether one or more joinpoints (1 joinpoints tested in this study) are significant. The incidence in the right colorectal was divided by the total CRC incidence to determine the proportion of CRC (R/T). Due to incomplete address information of our patients, it was not possible to calculate the adjusted incidence rate-AIR. Hence, Poisson variance using crude rate was used for the joinpoint analysis. Gender differences were analyzed using tests of parallelism. The hypothesis of parallelism of models for male and females was rejected at α=0.05. Statistical significance was assessed using x^2 tests for categorical variables and using the student's *t*-test or one-way ANOVA for continuous variables.

RESULTS

Trends in CRC

In the analysis of 15-year period, among the 47.783 diagnosed and microscopically-confirmed cancer cases, 2.749 (5.8%) were CRC. In general, the incidence of CRCs tends to increase by time period; it was 4.8% at the first period, 6.1% at the second period, and 6.2% at third period (Table 1).

Trends in Subsite-Specific Rates by Time Period

After the exclusion of the noncarcinoma CRC (n=66) and the fourth group of ICD-O-3 subsite classification – site-unspecified cancers (n=492), RCC represented 23.8%, DCC represented 20.0%, and RC represented 56.2% of the total 2.191 site-specified cancers. The results indicated a shift toward the right colon over the 15-year period; the incidence of RCC was found to be significantly increasing (19.8% in 1993-1997, 24.4% in 1999-2003, and 25.6% in 2004-2008) compared to left-sided colon cancers (p=0.048) (Table 2).

Distribution of Cases by Subsites in Relation to Gender

Of the total 2.191 site-specified cancer cases, 1.216 (55.5%) were male and 975 (44.5%) were female. The proximal shift of cancers marked a significant increase for females (p=0.041), not for males (p=0.087). The percentage of right-sided colon cancer was stable during the 3 time periods in men (19.9%, 22.8%, and 22.3%, respectively), but increased in women (19.7%, 26.4%, and 29.8%, res-

Table 1. Distribution of colorectal cancers (CRC) by time intervals

	n (%)			
	First Interval (1993-1997)	**Second Interval (1999-2003)**	**Third Interval (2004-2008)**	**Total**
Total colorectal cancers	649 (4.8)	1.025 (6.1)	1.075 (6.2)	2.749 (5.8)
Non-adenocarcinoma	25 (3.9)	18 (1.8)	23 (2.1)	66 (2.4)
Adenocarcinoma	624 (4.6)	1.007 (6.0)	1.052 (6.1)	2.683 (5.6)
All other cancers	13.569	16.812	17.402	47.783

Table 2. Anatomic distribution of colorectal carcinoma cases by time periods

Site	Topography (ICD-O code)	1993-1997 n (%)	1999-2003 n (%)	2004-2008 n (%)	Total n (%)
Proximal (Right)	Cecum (18.0)	41 (6.6)	77 (7.6)	60 (5.7)	178 (6.6)
	Ascending (18.2)	34 (5.4)	68 (6.8)	104 (9.9)	206 (7.7)
	Hepatic flexure (18.3)	2 (0.3)	7 (0.7)	12 (1.1)	21 (0.8)
	Transverse (18.4)	14 (2.2)	31 (3.1)	37 (3.5)	82 (3.1)
	Splenic flexure (18.5)	10 (1.6)	13 (1.3)	12 (1.1)	35 (1.3)
Distal (Left)	Descending (18.6)	19 (3.0)	47 (4.7)	38 (3.6)	104 (3.9)
	Sigmoid (18.7)	67 (10.7)	114 (11.3)	154 (14.6)	335 (12.5)
Rectum (Left)	Recto-sigmoid junction (19.9)	43 (6.9)	77 (7.6)	53 (5.0)	173 (6.4)
	Rectum (20.9)	279 (44.7)	368 (36.5)	410 (39.0)	1057 (39.4)
Site unspecified	Appendix (18.1)	11 (1.8)	7 (0.7)	15 (1.4)	33 (1.2)
	Overlapping lesion (18.8)	10 (1.6)	16 (1.6)	12 (1.1)	38 (1.4)
	Unknown (18.9)	94 (14.9)	182 (18.1)	145 (13.8)	421 (15.7)
	Total	115	205	172	492
Total (Right)		101 (19.8)	196 (24.4)	225 (25.6)	522 (23.8)
Total (Left)		408 (80.2)	606 (75.6)	655 (74.4)	1669 (76.2)*
Total (Distal)		86 (16.9)	161 (20.1)	192 (21.8)	439 (20.0)
Total (Rectum)		322 (63.3)	445 (55.5)	463 (52.6)	1230 (56.2)**
Total		509	802	980	2191

*p=0.048 between right and left group. **p=0.004 between proximal, distal, and rectum group.

Table 3. Distribution of subsite colorectal cancers by time period related to gender

		Proximal n (%)	Distal n (%)	Rectum n (%)	p	Total n	Right/Left
1993-1997	Male	56 (19.9)	43 (15.3)	182 (64.8)		281	0.25
	Female	45 (19.7)	43 (18.9)	140 (61.4)	0.557	228	0.25
	Ratio M/F	1.2	1.0	1.3		1.2	
1999-2003	Male	100 (22.8)	89 (20.3)	249 (56.8)		438	0.30
	Female	96 (26.4)	72 (19.8)	196 (53.8)	0.503	364	0.36
	Ratio M/F	1.0	1.2	1.3		1.2	
2004-2008	Male	111 (22.3)	111 (22.3)	275 (55.3)		497	0.29
	Female	114 (29.8)	81 (21.1)	188 (49.1)	0.040	383	0.42
	Ratio M/F	0.9	1.4	1.5		1.3	
Total	Male	267 (22.0)	243 (20.0)	706 (58.0)		1216	0.28
	Female	255 (26.2)	196 (20.1)	524 (53.7)	0.055	975	0.35
	Ratio M/F	1.2	1.2	1.3		1.25	

p=0.087 for males and p=0.041 for females between 3 time points and subsites.

pectively). While the percentage of distal colon cancer was stable, there was a corresponding reduction in rectal cancers. The increase in the percentage of right-sided colon cancer in CRC cases was accompanied by a continuous decline in the percentage of rectal cancer in both genders. In all time intervals, the male-female ratio remained higher than 1 for all subsites except proximal site in 2004-2008 (M/F: 0.9). For proximal cancers, the male-female ratio tended to decrease in 15 years (M/F: 1.2 in 1993-1997, 1.0 in 1999-2003, and 0.9 in 2004-2008) (Table 3). The increase for proximal

colon cancer in the second and in the third 5-year period compared to the first period was greater in females (+6.7% for 1999-2003 and +10.1% for 2004-2008) than in males (+2.9% and +2.4%; respectively).

The ratio of right-sided and left-sided CRC was below 0.5 value for all years, but it was increasing during the 15-year period (Figure 1). The ratio of R/L was raised from 0.25 to 0.28 in males and raised from 0.25 to 0.42 in females from the first interval to the third one.

Joinpoint analysis was performed to identify the year that the increase in incidence began in the male and female patient population with cancer of the right side. Result of minimum (0) joinpoint analysis of right cancer is shown in Figure 2A. The slope of males was found to be statistically insignificant from 0, while the slope of females was found to be significant from 0. The segmented Poisson regression model, which included one joinpoint that corresponded to the years of statistically significant changes in proportion trend, is shown in Figure 2B. The joinpoints were found at 1996 for males and at 1997 for females. The adenomatous polyposis coli (APC) in segment 1 for 1993-1996 was found significant (16.4%) (95% CI:2.4 to 32.4), while the APC in segment 2 for 1996-2008 was insignificant (0.2%) (95% CI:-1.3 to 0.8), from 0 in males. In contrast, the APC was found to be significant from 0 in females for both in segment 1 and segment 2. The APC was 9.8% for 1993-1997 (95% CI:2.1 to 18.0) and 2.9% for 1997- 2008 (95% CI:1.8 to 4.2). Test for parallelism -used to compare whether the two regression functions are parallel - found to be significant (p=0.001) and showed that the gender sets of trend data were not parallel between male and female.

Distribution of Cases by Subsites Related to Gender and Age

The mean age of patients with right colon lesions (58.4 years) was higher than that of patients with left colon lesions (57.6 years) and rectal lesions (56.6 years) in males (p=0.183). The mean age of patients with right colon lesions (60.0 years) was significantly higher than that of patients with either left colon lesions (55.6 years) or rectal lesions (55.8 years) in females. The mean age of the patients was significantly increasing by the time period for proximal colon in females (55.8±13.2 in 1994-1998, 59.1±12.4 in 1999-2003, and 62.6±13.5 in 2004-2008, respectively) (p=0.0001), but it was not significantly different in males (55.6±12.2 in

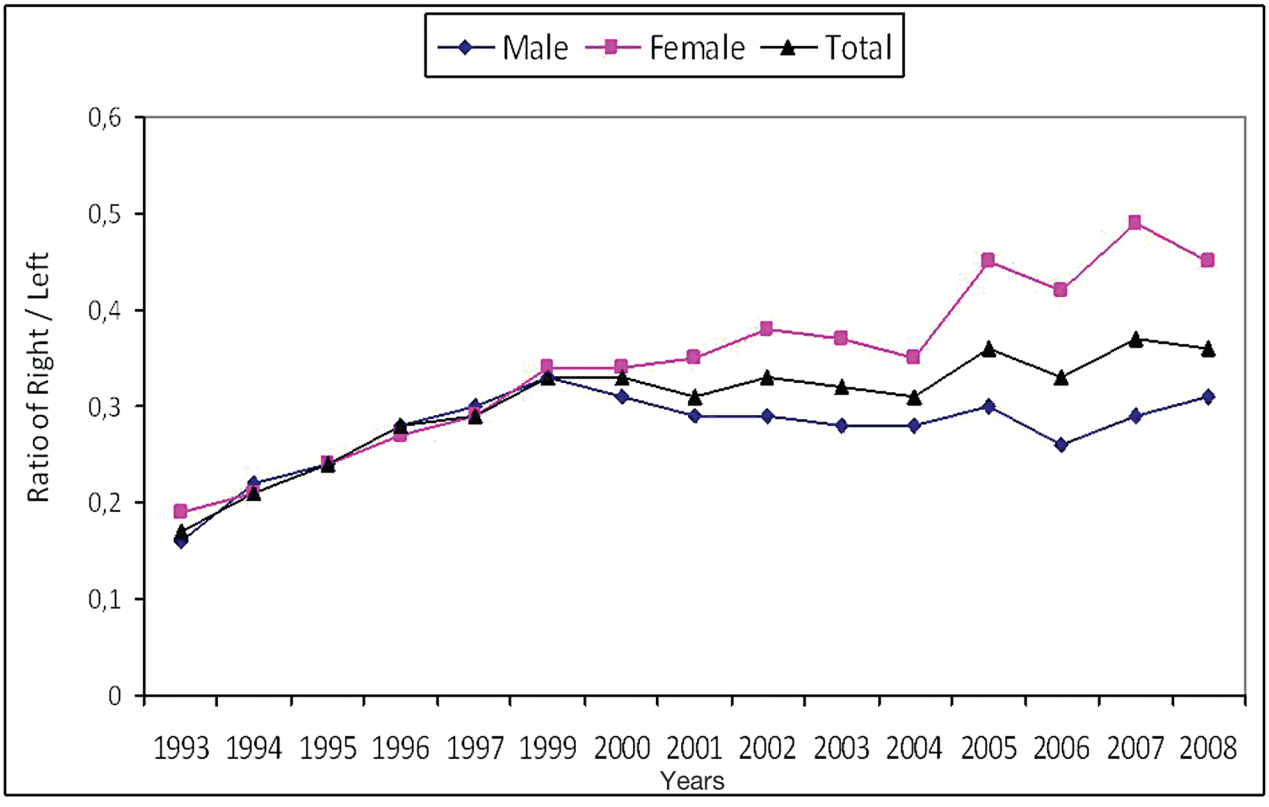

Figure 1. Ratio of right/left colorectal cancers for male, female, and total cases; from 1993 to 2008.

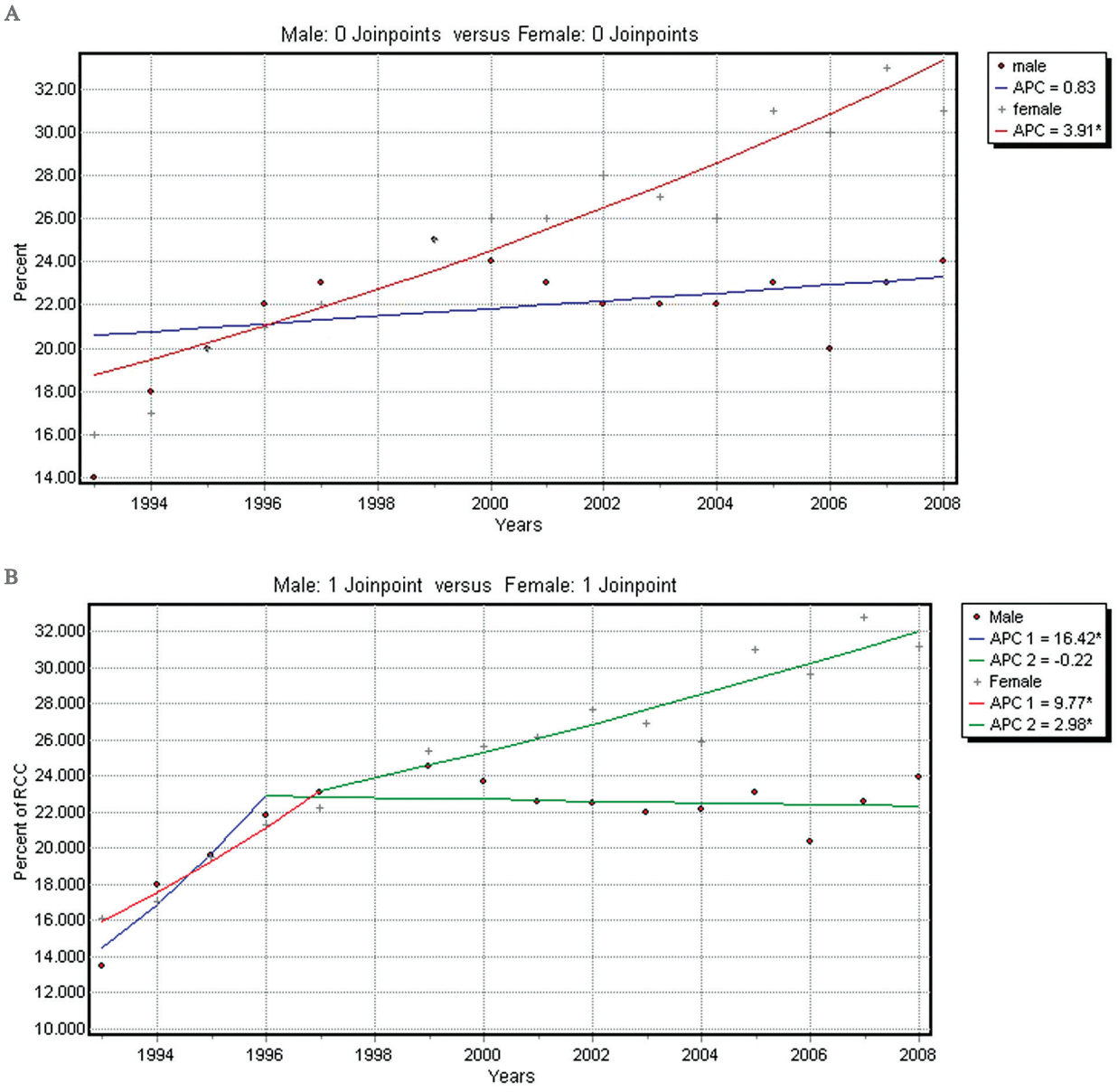

Figure 2. Joinpoint analysis of right-sided colon cancer among male and female patients. **A:** Regression model include 0 joinpoints, **B:** Segmented regression model include one joinpoints. APC: Annual Percent Change, *p<0.05.

1994-1998, 58.3±13.0 in 1999-2003, and 59.8±14.1 in 2004-2008, respectively) (p=0.186).

A total of 12.4 (n=332) percent of the patients were younger than 40 years of age, 17.0% (n=457) were in the 40-49 age group and 20.5% (n=549) were older than 70 years. The rectum involvement was high in the age group younger than 40 years, and a continuous decline in the percentage of rectal cancer was observed in both genders in all age groups (Figure 3A). Right colon cancers were found to be progressively increased in females over 50 year of age according to the time periods. The percentage of RCC was increased with advancing age (over 70) and gradually increased in the youngest age group (under 40) in males (Figure 3B).

The distributions of subsite CRCs related to age by gender and time period and the male/female ratio are shown in Table 4. While the proximal cancers were significantly increasing, the rectal cancers decreased by time period, in the age group of 60-69 years (p=0.021), and in the age group of older than 70 (p=0.046) in females. In males, this significant difference was found only in the age group of older than 70 (p=0.002). The gender ratio for rectal cancer was over 1 and did not change with advancing age and time period. The gender

ratio for RCC was close to 1 in first period and showed a female excess after the second period. For RCC, the female predominance was more marked and occurred earlier, after 50 years of age.

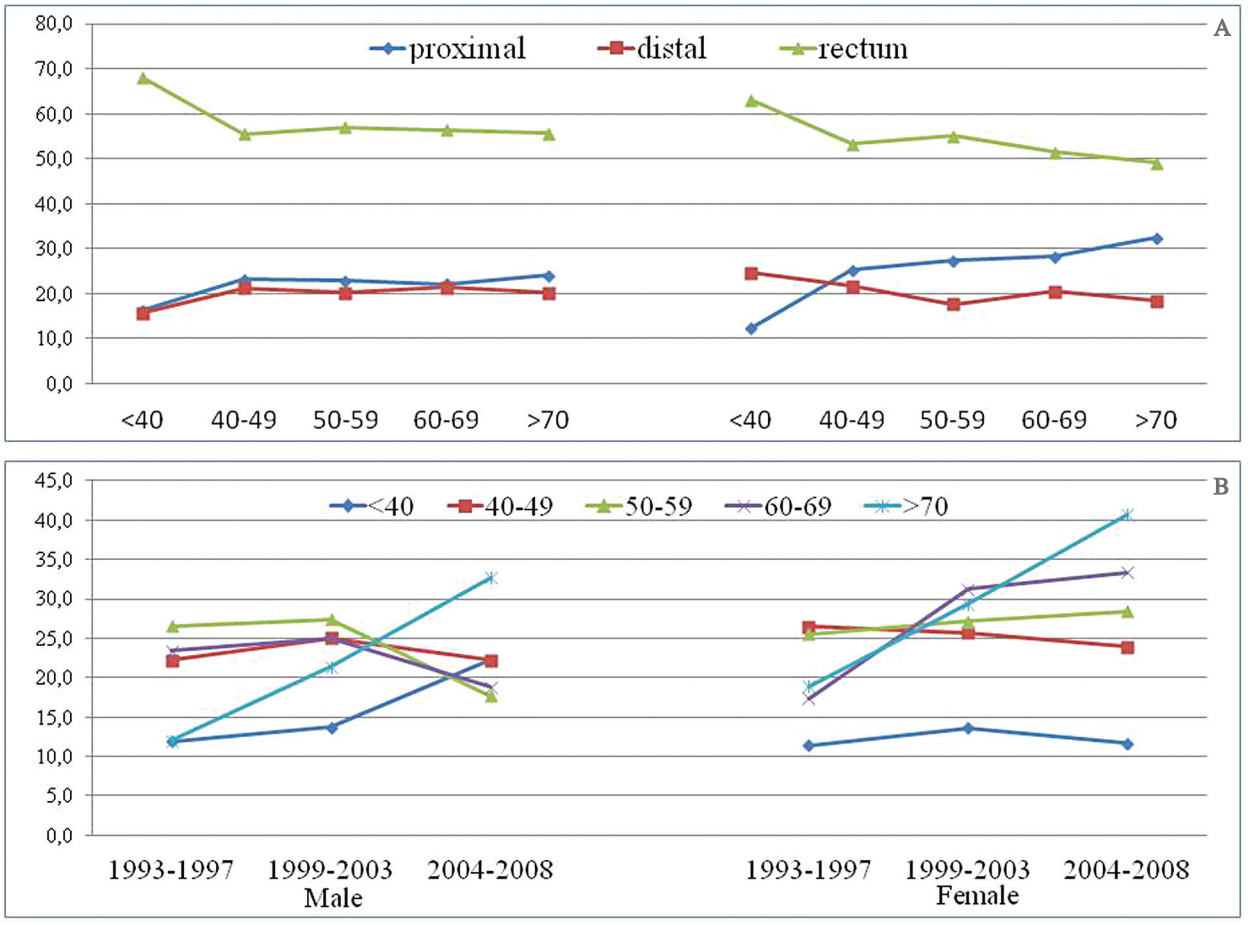

Figure 3. Age distributions of CRC related to gender. **A.** Distribution of proximal, distal, and rectum cancer cases related to age groups, **B.** Distribution of proximal cancer cases related to age groups by time period.

Table 4. The distribution of colorectal cancers in relation to subsite and age groups by gender and time periods

		Male %			Female %			Male/Female Ratio		
Age	Subsite	1993-1997	1999-2003	2004-2008	1993-1997	1999-2003	2004-2008	1993-1997	1999-2003	2004-2008
≤49	Proximal	17.2	20.3	22.2	18.8	21.1	19.1	0.9	1.0	1.2
	Distal	12.6	21.1	20.7	21.7	23.7	22.7	0.6	0.9	0.9
	Rectum	70.1	58.5	57.0	59.4	55.3	58.2	1.2	1.1	1.0
50-59	Proximal	26.6	27.5	17.7	25.5	27.2	28.4	1.0	1.0	0.6
	Distal	17.2	20.6	21.3	19.1	19.8	14.8	0.9	1.0	1.4
	Rectum	56.3	52.0	61.0	55.3	53.1	56.8	1.0	1.0	1.1
60-69	Proximal	23.4	25.0	18.8	17.3	31.3	33.3	1.4	0.8	0.6
	Distal	18.2	22.0	23.1	18.7	16.7	25.3	1.0	1.3	0.9
	Rectum	58.4	53.0	58.1	64.0	52.1	41.4*	0.9	1.0	1.4
≥70	Proximal	12.0	21.4	32.7	18.9	29.4	40.7	0.6	0.7	0.8
	Distal	12.0	19.4	25.0	13.5	17.6	20.9	0.9	1.1	1.2
	Rectum	76.0	59.2	42.3*	67.6	52.9	38.4*	1.1	1.1	1.1

*p<0.05 between time periods and subsite within age group.

The mean changes (difference) of percentages between time periods compared to first period related to subsite of CRCs and age groups by gender are shown in Figure 4. Positive differences were found for right-side cancers in all age groups of females over 50 (+2% for 50-59, +12% for 60-69, and +15% for over 70 years), and only in the over 70 group in males (+14%). In parallel to this, the expected decrease with left site colon cancers occurs in rectum cancers subgroups but not in distal cancer subgroups.

The logistic regression analyses determined that female gender (OR:1.3, 95% CI:1.0-1.5, p=0.022), older age groups (OR:1.4, 95% CI:1.1-1.8, p=0.021 for group 60-69 and OR:1.5, 95% CI:1.2-2.1, p=0.003 for group >70), and latest time periods (OR:1.3, 95% CI:1.0-1.7, p=0.047 for the second time period and OR:1.4, 95% CI:1.1-1.8, p=0.022 for the third time period) are risk factors for right-sided cancers.

Of the total 2.683 cases, mucinous and signet ring carcinomas were found in 12.6% and 0.6% of cases, respectively. Mucinous carcinoma was more common on the right side. To have a preliminary idea about the stage of the cases, a data set was obtained from the pathology by request and from the result forms from operative records of the university pathology and general surgery department record system for the three different periods. The analysis of the stage of tumors was based on the tumor node metastasis (TNM) classification. The percentages of 305 colorectal cancers by stage at diagnosis were 3.0% in situ, 23.9% localized, 65.2% regional, and 7.9% distant stage. A slight variation in late-to-early stage incidence rates was observed by time period (18.1%, 25.0% and 26.4% for stage II; 14.5%, 17.1% and 18.7% for stage IIIB; 55.3%, 54.3% and 48.5% for stage IIIC; and 7.8%, 6.7% and 3.0% for stage IV, respectively) (data not shown).

DISCUSSION

Although colorectal malignancies rank fourth in overall frequency, it is the third most common site of new cases in men and second in women in the European Union-EU, where Age Standardized Incidence Rate-ASIR was found to be 39.9% in men and 25.2% in women in 2008 (range: 16.6-64.7) (3). According to the same source of data, the CRC incidence rate in Turkey was nearly less than one third of the rates of EU results; ASIR was 13.2% (the fifth most common cancer) in men and 9.1%

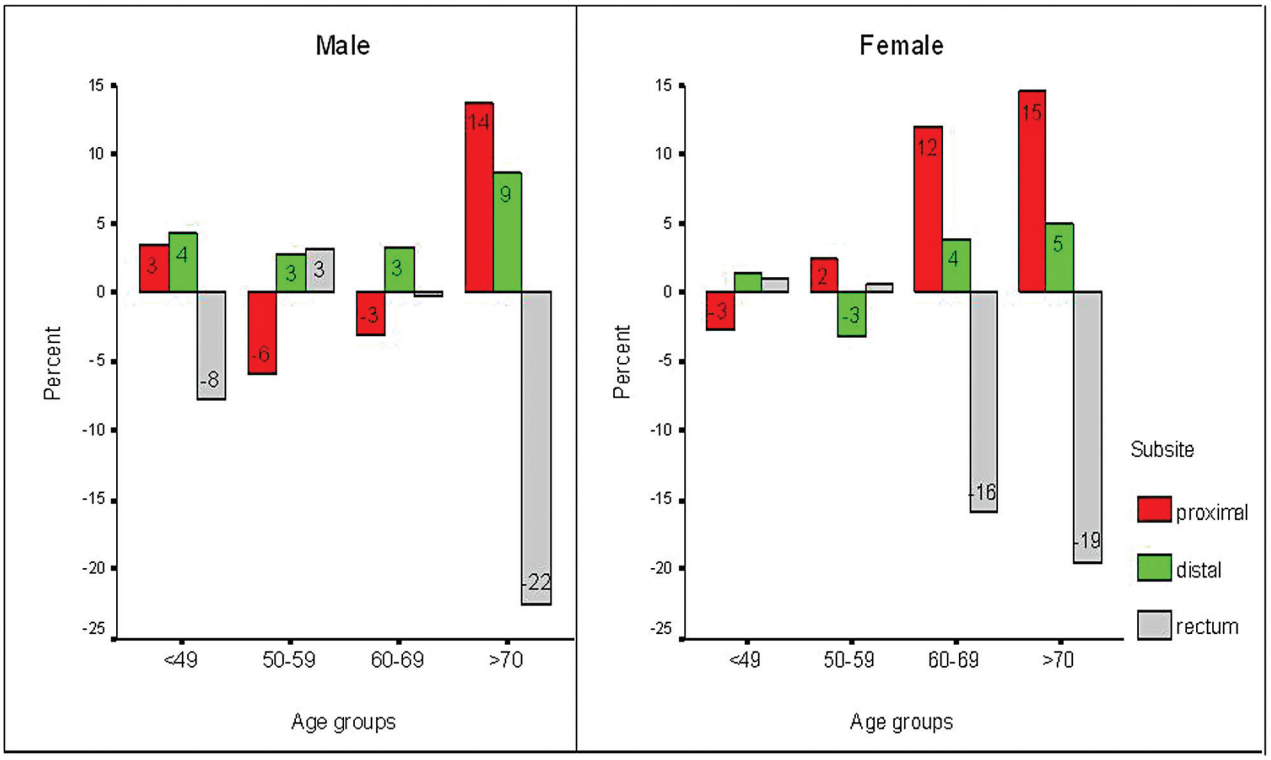

Figure 4. The mean percent difference between time periods compared to the first period according to subsite colorectal cancers by age groups in males and females.

(the second most common) in women for Turkey (3). Similar results were obtained in our study that CRC was the fourth most commonly diagnosed cancer in total, second in women and fifth in male in overall frequency. The CRC incidence in Turkey (as a Mediterranean country) seems to be lower compared to European countries, but it slowly increases in recent years. Although many studies emphasize the possible protective characteristics of the Mediterranean diet (19-21), a high increase in the incidence of colorectal carcinoma in recent years is reported in some Mediterranean (Split-Croatia, Greece) countries (7). The incidence increases were suggested to be the result of diet and lifestyle changes in these populations (6,7). It is known that the diet characteristics in the Mediterranean countries have extensively changed in recent years, with decreased intake of fruits and vegetables, and increased intake of refined grains, milk, sugar, meat, and animal protein (7, 21). Similarly, Turkey is becoming an industrial society as a country in transition, with some serious changes in the lifestyle and diet characteristics causing more Western style nutrition, which subsequently may increase the risk of CRC. Another explanation of the CRC increase in this study population can be the burden of refugees from the east of Turkey in the last 30 years. The immigrant citizens are usually from in the cities, in which the characteristic of diet is based on milk, meat, and animal protein, which are all proven to contribute to the increased risk of colon cancer.

Most of the previous studies analyzing the proportions of left-sided and right-sided colon cancer incidences over time have shown a rising proportion of right-sided colon tumors (8-14), while contrary reports also exist (15-18). In the present study, right-sided colon cancer rate was 23.8%, which is lower than that in the Western populations (35-45%).

Cancers arising in the proximal colon, distal colon, and rectum may have somewhat different disease etiologies. While some risk factors such as older age and male gender cannot be modified, changes in diet (e.g., increases in intake of vegetables and other sources of fibers and decreases in red meat intake and alcohol) and increase in physical activity, reduction of obesity, and quitting smoking may play a role in the recent decline of CRC incidence rates in Western countries (22-26). Results from prospective studies have suggested that the left-sided colon cancers have a stronger association with both alcohol consumption and dietary habits than the right-sited colon cancers (27-30). There is inconsistency in the reported association between physical activity and localization of the cancer, as some studies report stronger associations with left-sided colon cancers (27), while others, with right-sided. Factors that might be more linked to right-sided colon cancers include body mass index (BMI) (30) and smoking (31). Despite a notable lack of longitudinal data on lifestyle patterns in Turkey, the increasing prevalence of obesity and daily smoking especially in females (which is reported to be >56% of men and >30% of women particularly in the young population) might contribute to the trend of increase in the right-sided CRC compared to the left-sided ones.

In the Western world, the incidences of colon and rectum cancers increase at the ages between 50 and 80. In the present study, the mean age of all CRC cases was 56.9 showing that CRCs occur in earlier ages in this population compared to the Western populations. However, the mean survival age of this population is relatively low (70-75 years) and this may explain the decreased incidence of CRC in the elderly.

The findings of this study indicate that subsite-specific ratios of colorectal cancer may have gender- and age-related differences. Although CRC is often considered to be a disease of the elderly, recent studies have reported a significant rise in the incidence of CRC in younger populations (32-33). Certain risk factors including genetic predispositions and/or diet and lifestyle changes in the current era can lead to a rise in the incidence of cancers in younger patients. This finding can also be explained with increased availability of stool blood tests (e.g. fecal occult blood test) and structural screening tests (e.g. sigmoidoscopy and colonoscopy) for diagnostic procedures (32-33) resulting in the detection of previously undiagnosed cases and subsequently increasing CRC incidence rates.

The period-specific declines in rectal colon cancer can also be related to the effects of screening protocols. Although routine CRC screening programs has not been carried out for the general population in this region, the availability and access to colonoscopy and flexible sigmoidoscopy increased remarkably in health centers in the last decade in Turkey. The slight decrease in late vs. early stage incidence ratios by time period found in this study also support the value of screening. However, it should also be noted that the staging data of this

study included only a small proportion of the cases, as most of the late-stage and metastatic cancers were not operated or followed by general surgery and pathology department from which the study data was obtained. Therefore, our results are likely to be affected by the absence of these high-stage and distantly located cases leading to underestimation of these cancers.

The significant incidence rise of CRC especially in proximal locations in young female patients has important diagnostic implications requiring routine screening in females. Up to date, CRC is usually considered to be male-specific disease and women can, therefore, sometimes be overlooked for screening. Hence, the increasing right-sided prevalence of these lesions with age suggests that evaluation of the proximal bowel is particularly important in females.

The limitations of this study must be noted: the present data is based on histopathologic reports and forms collected by the local cancer registry. The data recorded in the pathology reports include age and gender but not the exact information of the region where patients live. Health institutions in Adana are referral centers for Mediterranean and east region of Turkey. Almost one-thirds of the patients come from neighborhood cities for diagnosis and treatment and the registry records used in this study include these patients also. We assume that nearly all newly diagnosed cases in the city were recorded, but due to the incomplete address information of the patients, it is not possible to calculate the exact adjusted incidence rate ratios (AIRR), which makes it hard to compare the data with other countries. However, since the main goal of this study was to determine the frequencies and trends of the anatomic location of the CRC cases rather than calculating the AIRR, all recorded cases were analyzed in the study.

The statistical analyses of the temporal trends in cancer incidence rates can result in significant variations which can potentially generate new insights about the impact of various interventions. The outcomes of the study emphasize, once more, the importance of cancer statistics as a source to evaluate the effects of preventive and diagnostic strategies against cancer. The cancer statistics need closer attention from all parts of health communities, such as oncology and related clinics, health ministry, and university biostatistics departments.

In conclusion, the apparent shift of colorectal cancers may require modifying current practices to include more frequent use of screening colonoscopy, particularly in women and in older people in our country. This study was based on a remarkable sample size over a relatively long time period providing information about the distribution of colorectal cancers according to subsite and in relation to gender and age in a region where there is very limited population-based epidemiological survey on cancer incidence. Time trends in CRC will need to be continually monitored and evaluated with more detailed data including all demographic, geographical and environmental, nutritional and lifestyle factors which are not recorded regularly up to date in most of the cancer registries. A high level of continuous vigilance is necessary to use these statistics to detect changes in risk factors.

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