



Prevalence of Colorectal Adenocarcinoma in Northern Regions of Pakistan: A Cross Sectional Study

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ABSTRACT

CRC is one of the leading malignancies worldwide but it shows significant international variations in its distribution. Pakistan is a country with its own peculiar environment. According to an estimate, the incidence of cancer in Pakistan is rising since its independence in 1947, particularly in northern province, Khyber Pakhtoonkhawa. The genetic set up and the effect of external factors in the people of Northern Pakistan, may not be the same like Americans or Europeans. Relatively little information is available about different aspects of CRC in Pakistan. Present study was aimed at determining the frequency and prevalence of CRC in Khyber Pakhtoonkhawa. A total of 181 cases of colorectal adenocarcinoma (CRA) who underwent intestinal resection were studied. Sections from both tumor and normal intestine for control were prepared. Among the samples, 75% were males and 25% females with 15 to 90 years of age (mean age 54.68±16.89 years). Higher average age was found to have high tendency to acquire colorectal adenocarcinoma and rectosigmoid was the most important site. Tumors were mostly exophytic, moderately differentiated with majority showing no lymphovascular invasion.

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Authors' Contribution

AQ and AHN conceived the idea of research. AQ conducted the experimental work and wrote the article. AHN supervised the work. ARS and BNM guided and helped in experimental work and writing the article.

Key words

Prevalence, CRC, colorectal cancer, adenocarcinoma

INTRODUCTION

Colorectal cancer (CRC) is a term applied to the cancer arising in colon and rectum. It shows significant international variation in its distribution. Globally it is the third most common cancer in males and second in females with markedly varying incidence and mortality rate (Jemal *et al.*, 2011). In a well-developed country like United States, about 148,300 new cases of CRC are registered leading to approximately 56,600 deaths each year (Vinay *et al.*, 2010). However, both the incidence and mortality in United States is slowly and steadily decreasing (Siegel *et al.*, 2012). In the last 15 years, the incidence has declined about 2 to 3 percent per year (Kohler *et al.*, 2011). The highest incidence of CRC has been reported in Australia and New Zealand (Ferlay *et al.*, 2010), Europe and North America, while the lowest in Africa and South-Central Asia (Jemal *et al.*, 2011). The reported cases rapidly increased in areas which were historically at low risk, like Spain and many countries within Eastern Asia and Eastern Europe (Center *et al.*, 2009). Westernization of diet as observed in Japan (Matsumara, 2001) has rapidly increased the incidence of

CRC (Center *et al.*, 2009). The migrants from low to high risk countries showed a rapid increase in the risk for CRC (Boyle and Langman, 2000). Indeed each death from colonic carcinoma should be viewed as a preventable tragedy (Vinay *et al.*, 2010).

A broad spectrum of colonic neoplasms range from benign lesions to invasive colorectal carcinoma. Histopathologically, CRC can be categorized into non-neoplastic polyps, neoplastic polyps (adenomas), and carcinomas (Christine *et al.*, 2010). The nonneoplastic polyps include hyperplastic, juvenile, hamartomatous, inflammatory, and lymphoid polyps. They are not generally thought as precursors of carcinoma. Adenomas are classified into three histological types, with increasing malignant potential: tubular, tubulovillous, and villous (Rostirolla *et al.*, 2009). The three characteristics of adenomas which are related with their potential to transform into carcinoma include large size, villous pathology, and the degree of dysplasia (Martinez *et al.*, 2009). The risk of CRC is related with personal history of colonic adenomas (Neugut *et al.*, 1993) as the adenocarcinomas are usually considered to take origin from adenomas (Shinya and Wolf, 1979; Fenoglio and Lane, 1974; Morson, 1974; Muto *et al.*, 1975; Stryker *et al.*, 1987). This observation is because of the finding of both benign and malignant lesion within colorectal tumors (O'Brien *et al.*, 1990) as well as 25% increased risk of CRC at the site of the adenoma (Winawer *et al.*,

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2000). It has been suggested by some studies that the risk of CRC in some families is related with the presence of hyperplastic polyposis, juvenile polyposis and Peutz-Jeghers syndrome (Howe *et al.*, 1998; Jeevaratnam *et al.*, 1996; Rashid *et al.*, 2000). Hereditary CRC has two forms, familial adenomatous polyposis (FAP) due to germline mutation in the gene APC (Soravia *et al.*, 1998; Pedemonte *et al.*, 1998; Sieber *et al.*, 2002) and hereditary nonpolyposis colorectal cancer (HNPCC), also called Lynch syndrome due to germline mutation in the DNA MMR genes (Nicolaidis *et al.*, 1994; Miyaki *et al.*, 1997). High fatty diets (Newcomb *et al.*, 1993; Meyer and White, 1993) and meat (Terry *et al.*, 2001; Michels *et al.*, 2000) are associated with development of both adenomatous polyps and CRC. Similar association has been noticed for cigarette smoking (Chao *et al.*, 2000; Terry *et al.*, 2001). Some studies also reported sedentary lifestyle as a risk factor for CRC (White *et al.*, 1996; Slattery *et al.*, 1988). The common metastatic sites are liver, lymph nodes, lungs and bones (Vinay *et al.*, 2010). Some drugs and supplements like NSAIDs, folic acid, estrogens, and calcium may prevent development of CRC (Tomeo *et al.*, 1999) but none has provided any convincing therapy. Even the antioxidant vitamins have shown no effect on CRC incidence (Greenberg *et al.*, 1994). The most common molecular markers for CRC are microsatellite instability (MSI), 5q and 17p allelic abnormalities, allelic loss at chromosome 18q and genetic mutations in some important genes *i.e.* *Kras* and *p53*.

Present study is a cross-sectional study of incidence of colorectal adenocarcinoma in northern regions of Pakistan.

MATERIALS AND METHODS

A cross-sectional study (approved by the Commandant of AFIP) was carried out in the Departments of Histopathology and Molecular biology at Armed Forces Institute of Pathology (AFIP), Rawalpindi (the tertiary referral centre situated in northern area of Pakistan) and in the Molecular Biology Department, University of Health Sciences Lahore.

Patients' selection and sampling

A total of 181 patients of all age group were enrolled in current study after the informed consent (both in English and Urdu languages). All patients were Pakistani, resident of northern area coming to AFIP, presenting CRC. Patients interviewed and complete information about age, gender, nationality, life style, economic condition, dietary habits, family history, smoking habit, presence of any type of addiction, presence of any type of tumor and other health problems

were recorded. No authenticated prevalence data of colorectal cancer of Pakistani patients was available from any authenticated source. However, the prevalence rate was calculated according to the data available in a study from Kashmir which is a neighboring country with Northern area of Pakistan (Sameer *et al.*, 2009).

Patients diagnosed with any other malignancy in the past or under anticancer treatment were excluded. All the information was kept confidential.

Histology

Intestinal tumor tissue and its adjacent normal intestine (minimum 3cm. away from the tumor) were taken for further analysis. Histological features of all the selected cases were reviewed from H & E slides and a new diagnosis was made, regardless of the previous diagnosis. The tumor samples and the un-involved tissue, at least 3cm away from the tumor margin were fixed in. Histological sections were cut at a thickness of 4 µm after paraffin embedding and stained with hematoxylin and Eosin stains (H & E). The tumor was graded and was classified according to the standard Dukes' staging system. Tumor was considered as mucinous carcinoma if the mucin lakes represented more than 50% of the tissue.

RESULTS

Gender wise prevalence of CRCs

Out of total hundred and eighty one CRC patients, 136 (75.1%) were males and 45 (24.9%) were females (Table I).

Table I.- Prevalence of CRC in different age groups of male and female patients of the study.

Age groups	Male	Female	Total
< 40 years	24 (13.25%)	12 (6.62%)	36 (19.88%)
40-59 years	40 (22.09%)	13 (7.18%)	53 (19.88%)
≥ 60 years	72 (39.77%)	20 (11.04%)	92 (50.82%)
Total	136 (75.1%)	45 (24.9%)	181 (100%)

Relationship between age, gender and CRC

Samples in this study were divided into three age groups, <40 years of age, between 40 to 59 years and ≥60 years (Table I). Our results indicated that Pakistani CRC patients, both male and females, with higher average age had high tendency to acquire CRC. The risk factor to get CRC was higher in age group ≥ 60 yrs. In total 181 CRC samples, 36 (19.88%) were found to be < 40 years of age and 53 (29.28%) were found to be within 40 to 59 years

age. In the ≥ 60 years group, 92 (50.82%) were found to be involved with CRC. The maximum age of the CRC patient was 90 years. The patient was a female having a sigmoid tumor of 6.5cm and reported as moderately differentiated adenocarcinoma without any nodal metastasis. The minimum age of the patient was 15 years boy having 8cm rectal tumor and was diagnosed as moderately differentiated adenocarcinoma with 4 nodal metastasis and lymphovascular invasion.

Table II.- Prevalence of location of tumors, histopathological type, different grades of tumours, lymphovascular and perineural invasions in the colon.

Parameters	Frequency
Location in Colon	
Anorectal	7 (3.87%)
Ascending colon and cecum	47 (25.97%)
Hepatic flexure	3 (1.66%)
Descending colon	10 (5.52%)
Rectosigmoid	97 (53.59%)
Splenic flexure	6 (3.31%)
Transverse colon	11 (6.08%)
Histological Types	
Simple Adenocarcinomas	143 (79.01%)
Adenocarcinoma (Signet ring)	5 (2.76%)
Adenocarcinoma (With mucin)	5 (2.76%)
Mucinous adenocarcinoma	28 (15.47%)
Grades of tumor	
Moderately differentiated	85 (46.96%)
Well differentiated	78 (43.07%)
Poorly differentiated	15 (8.3%)
Undifferentiated	3 (1.7%)
Lymphovascular and perineural invasions	
Tumors without any invasion	117 (64.6%)
Lymphatic	3 (1.7)
Lymphatic and perineural	2 (1.1)
Lymphovascular	43 (23.8%)
Lymphovascular & Perineural	10 (5.5)
Perineural	1 (0.6%)
Vascular	4 (2.2%)
Vascular and perineural	1 (0.6%)

Location wise prevalence of CRCs

The clinico-pathological data for this study was supplied by the clinicians. According to the site of tumor or anatomical part involved, all CRC tumors were divided into specified sections of colon. Tumors of ascending colon and cecum were grouped together. They were 47 in number *i.e.* 25.9%. Tumors of descending colon were less in number *i.e.* 10 with a percentage of 5.5%. Tumors of rectum, rectosigmoid junction and sigmoid were grouped together. They were 97 in total *i.e.* 53.6%. The most common location of CRC in our study group was rectum *i.e.* 45 (24.9%). This location was followed by Sigmoid 28 (15.5%) and then by the ascending colon 26 (14.4%). The least common site involved was hepatic flexure where the number of CRCs was only 3 (1.7%). Splenic flexure and transverse colon tumors were 6 and 11 with 3% and 6% respectively (Table II).

Prevalence of different histological type of adenocarcinomas of colon

Out of total 181 registered patients 79% (143/181) were having simple adenocarcinomas, 2.76% (5/181) having adenocarcinoma (Signet ring), 2.76% (5/181) having adenocarcinoma with mucin and 15.47 % (28/181) having mucinous adenocarcinoma (Table II).

Gross morphological prevalence of CRCs

Grossly 96 (53%) were exophytic adenocarcinomas. They were causing colonic obstruction due to a protruding growth. 85 (47%) tumors were found to be infiltrative in nature causing stricture formation.

Prevalence of different grades of CRCs

Out of the total of 181 cases, 85 (46.96%) carcinomas were moderately differentiated while 78 (43.07%) showed well differentiation. Fifteen cases were poorly differentiated *i.e.* 8.3%. Only 3 cases were quite undifferentiated *i.e.* 1.7% (Table II).

Prevalence of lymphovascular and perineural invasions of CRCs

Out of 181, 43 (23.8%) cases showed lymphovascular invasions while 10 (5.5%) showed both lymphovascular and perineural invasions. No invasion was seen in 117 (64.6%) (Table II).

TNM distribution of tumor samples

TNM classification method was followed to classify the tumors. Tumor stage was available for 143 patients included in the study. 117 patients were found to be in T3 stage followed by 14 patients in T4, 8 in T2 and 4 in T1 stage.

DISCUSSION

Both genetics and environmental triggers play an important role in pathogenesis of many common tumors like colorectal carcinoma. However the remarkable differences in the incidence and prevalence of these tumors in various parts of the world suggest a key role of the environment. The reported rate of CRC varies among different populations and it has been observed to be associated with factors like diet composition (MacLennan, 1997). In Iran, the reported incidence rate of CRC was very low *i.e.* 6–8 persons/100,000 total individuals/year (Ansari *et al.*, 2006; Hosseini *et al.*, 2004), while in Western countries, a comparatively higher incidence of 20 to 40/100 000 persons/year has been reported (Parkin, 2001).

There has not been any clear data published about CRC in Pakistani population (Murtaza *et al.*, 2012). In current study out of the total of hundred and eighty one CRC patients, 136 (75.1%) were males and 45 (24.9%) were females. Male predominance has also been reported from central Pakistan (Murtaza *et al.*, 2014) but this observation is different with respect to some studies (Okulezyk *et al.*, 2004; Jaw *et al.*, 2004). Majority of the patients had tendency to get CRC in the older age. Categorization of CRC according to the various segments of colon showed that the frequency of rectosigmoid tumor was higher (54.7%), as compared to other CRC tumor types like ascending colon/cecum (25.97%), descending colon (5.52%), and transverse colon (6%).

Cases included in our study, were mostly showing tumor in the ascending colon while few cases were seen in descending colon. Some studies have tried to explain the differences in tumor location due to the role of diet with respect to bowel transit timings and fermentation of carbohydrates (Brink *et al.*, 2003), production of volatile fatty acids or may be the exposure of colonic epithelium to potentially dietary carcinogens (Brink *et al.*, 2003). However more etiological insight is required to clarify the increased preference of tumor formation at particular sites. Similarly no relation has been seen between the tumor and Dukes or TNM clinical advancement (Okulezyk *et al.*, 2004). There is quite difference in the grading of CRC in different studies. In our study most of the adenocarcinomas were moderately differentiated. Similarly, in cohort study of Netherlands the tumors were mostly moderately differentiated (Brink *et al.*, 2003). The difference between well and moderately differentiated tumors is often ambiguous because of subjective reasons.

CONCLUSION

It is concluded that majority of the northern area

patients, males or females have tendency to get CRC in the older age. The frequency of rectosigmoid tumor is higher as compared to other sites. Most of these CRC cases present as exophytic growths with moderately differentiated adenocarcinomas. As this study was comprised limited number of cases, it cannot be concluded that males of northern areas have more chances to get this disease. Certainly this needs a much wider scale epidemiological study of this region.

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Statement of conflict of interest

Authors have declared no conflict of interest.

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