# Significance of Carcinoembryonic Antigen (CEA) levels in colorectal carcinoma

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**Abstract**

**Background:** Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death globally. Though it is relatively less common in Indian sub continent, but now a days it is also identified as an important heath problem in Bangladesh. **Objectives :** To find out the clinico-demographic Characteristics of colorectal carcinoma. **Methods:** This descriptive cross-sectional study was conducted among 72 patients with colorectal carcinoma confirmed by histopathology attending at the department of Surgery, Rajshahi Medical College during the period of January 2009 to December 2010. Data regarding patient's age & gender, information about the tumour like, anatomic subsite, diameter, staging, histological pattern, and preoperative serum Carcinoembryonic Antigen (CEA) level were collected by a pretested questionnaire. Fisher exact probability test and One Way ANOVA test were applied to verify the associations among the variables. **Results:** A total of 72 CRC patients, 32 ((44.4%) patients had rectal, 27 (37.5%) had right colon and the rest 13 (18.1%) had left colon carcinoma. Male and female ratio among the study subjects was 2.6:1. Highest incidence (23, 31.9%) of the carcinoma was in the 30-39 years age group. Of the study subjects, 12 (16.7%) cases were Dukes' stage A (stage I), 16 (22.22%) were Dukes' stages B (stage II), 30 (41.66%) were Dukes' stage C (stage III) and 14 (19.44%) cases were Dukes' stage D (stage IV). Out of 72 cases, 63 (87.5%) cases had elevated preoperative CEA serum levels (>5ng/ml). Preoperative elevated CEA levels was significantly associated ($p<0.05$) with Dukes' stage of the carcinoma. The mean preoperative CEA serum level was significantly differed with the degree of tumor differentiation ($p<0.001$) **Conclusion:** Preoperative serum CEA level >5 ng/ml should not be used as a single screening test for colorectal carcinoma . Preoperative serum CEA concentration >5ng/ml correlating with the signs and symptoms of CRC may be used in multiphasic screening of CRC for further confirmation.

**Key words:** Carcinoembryonic Antigen(CEA), colorectal carcinoma.

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## Introduction

Colorectal carcinoma (CRC) is not an uncommon disease now a day. Colorectal cancer is predominantly a disease of Westernized countries, with about two-thirds of the world cases occurring in developed nations.[1] In Western countries, cancer of colon & rectum ranks second after cancer of lung in incidence & death rates.[2] In recent periods, there is an increasing incidence of carcinoma of right colon with an associated decrease in the incidence of carcinoma of sigmoid colon & rectum.[3] Rates in immigrants from low-risk areas to these high-risk areas are known to rapidly increase to the level of the host population (e.g., in Japanese immigrants to the United States).[4] Most colorectal carcinomas occur sporadically in the absence of well defined familial syndromes. The peak incidence for colorectal carcinoma is between ages 60 and 79 years. Fewer than 20% of cases occur before age of 50 years.[5] Though CRC incidence rates generally are higher among males, than females, at all anatomic subsites, the male-to-female incidence rate ratio (MF IRR) increases progressively across the colon from the cecum to the rectum.[6,7]

Some aspects of Western lifestyle, primarily a high caloric intake and little physical activity, resulting in a positive energy balance, weight gain and, ultimately, obesity, are suspected to play a role in the etiology of colorectal disease. Physical activity, both at work and during leisure time, has consistently been

inversely associated with this disease.[8,9] Several large cohort studies reported that smoking doubles the risk of colorectal polyps, known precursors for colorectal cancer.[10]

Carcinoembryonic antigen (CEA) was first described in 1965 by Gold and Freedman,when they identified an antigen that was present in both fetal colon and colon adenocarcinoma but that appeared to be absent from healthy adult colon. Because the protein was detected in only cancer and embryonic tissue, it was given the name carcinoembryonic antigen, or CEA. Subsequent work showed that CEA, or at least a CEA-like molecule, was also present in certain healthy tissues, although concentrations in tumors were on average 60-fold higher than in the nonmalignant tissues. Fifty years after its initial detection in serum, CEA is one of the most widely used tumor markers worldwide and certainly the most frequently used marker in colorectal cancer.[11] Carcinoembryonic antigen (CEA) is a glycocalix related antigen that has been detected in the serum of 42% to 79% of patients with colorectal carcinoma at the different tumor stages. It disappears after resection of the tumors and reappears in the event of recurrence or metastases. Higher values are found in advanced stage of tumors that have spread beyond the bowel wall, in well differentiated neoplasms, and in tumors associated with blood vessel, lymphatic, and perineural invasion.[5,12]

Survival rates for cancers of large bowel have steadily improved with the improvement in the diagnostic techniques and availability of better method of treatment.[13] Though the incidence of colorectal carcinomas in our country is no less than the Western world, there is no broad based study regarding this. So definitely it is highly important to carry out a study of these cancers in our country because the knowledge about age, gender, anatomic subsite, tumor st age, tumor grade (histological pattern) and preoperative serum Carcinoembryonic Antigen (CEA) level distribution in patients with colorectal carcinoma in our country will invariably strengthen our efforts to combat this killer disease.

## Methods

This was a cross sectional descriptive study conducted at Surgery department of Rajshahi Medical College Rajshahi, Bangladesh. The patients with colorectal carcinoma admitted in the above mentioned hospitals constituted the study population. Total 72 admitted patients with colorectal carcinoma confirmed histopathologically during the period of January 2009 to December 2010 were included in the study as sample with their consent to participate after explaining the purpose and procedure of the study. Data were collected with the help of a pre-tested questionnaire. The questionnaire was designed to record patient's age & gender, information about the tumour like, anatomic subsite, , diameter, staging, histological pattern of the tumour and preoperative serum Carcinoembryonic Antigen (CEA) level. The information were recorded from interview with the patients, the patients' treatment file/card, investigation reports, and consultation with the concerned doctors if necessary. Preoperative CEA level was determined by Enzyme - linked Immunosrbent Assay (ELISA) method. Data were analyzed by computer using SPSS for windows. Descriptive analytical techniques involving frequency distribution and computation of percentage were applied. Fisher exact probability test was applied to verify an association between anatomical subsite and size (diameter) of colon carcinoma, and Dukes' stage of the carcinoma and preoperative serum CEA level. One Way ANOVA test was also applied to check the correlation between histological pattern of colorectal carcinoma and preoperative CEA level.

## Results

A total of 72 CRC patients, 32 ((44.4%) patients had rectal, 27 (37.5%) had right colon and the rest 13 (18.1%) had left colon

carcinoma. Considering all the anatomical subsite of CRC, males were more than the females except in case of sigmoid colon. Over all Male and female ratio was 3.2:1 (Table 1). The highest number of the study subjects, 23 (31.9%) patients were in the age group of 30 to 39 years. Next common age group (17, 23.6%) was 20 to 29 years (Figure 1).

Weight loss and weakness was the most common (59, 81.9%) clinical presentation of the study subjects. Other common complaints were anorexia (56.9%), abdominal pain (52.7%), abdominal discomfort (48.6%), per rectum bleeding (47.2%), altered bowel habit (43.8%) and abdominal lump (43.8%). Abdominal discomfort was more common among the patients of colon carcinoma than rectal carcinoma. Per rectum bleeding was more common in rectal carcinoma than colon carcinoma (Table 2).

Out of 40 colon carcinoma, majority (28, 70.0%) were 3-5 cm in diameter, 7(17.5%) were < 3 cm and the rest 5 (12.5%) were >5cm in diameter. The percentage of carcinoma having diameter < 3cm in right colon was 42.8%. The percentage of the carcinoma with diameter 3-5 cm in right colon was increased to 71.4% . It was increased to 80.0% among the carcinoma having diameter >5cm. But there was no significant association between size and anatomic subsite of the carcinoma (Table 3).

Out of 72 CRC cases, 12 (16.7%) cases were Dukes' stage A (stage I), 16 (22.22%) were Dukes' stages B (stage II), 30 (41.66%) were Dukes' stage C (stage III) and 14 (19.44%) cases were Dukes' stage D (stage IV). Among them 63 (87.5%) cases had elevated CEA serum levels (>5ng/ml) before surgery. The proportion of the patients having preoperative elevated CEA levels was gradually increased in advanced stage (higher Dukes' stages) of carcinoma than in early. There was a statistically significant ($P < 0.05$) association between Dukes' stage of the carcinoma and preoperative elevated CEA levels ($p<0.05$)(Table 4).

The mean CEA serum level (16.2ng/ml) was highest in well differentiated carcinoma. It was 10.7 ng/ml and 6.1 ng/ml in moderately and poorly differentiated carcinoma respectively. The mean preoperative CEA serum level was significantly differed with the degree of tumor cell differentiation ($p<0.001$)(Table 5).

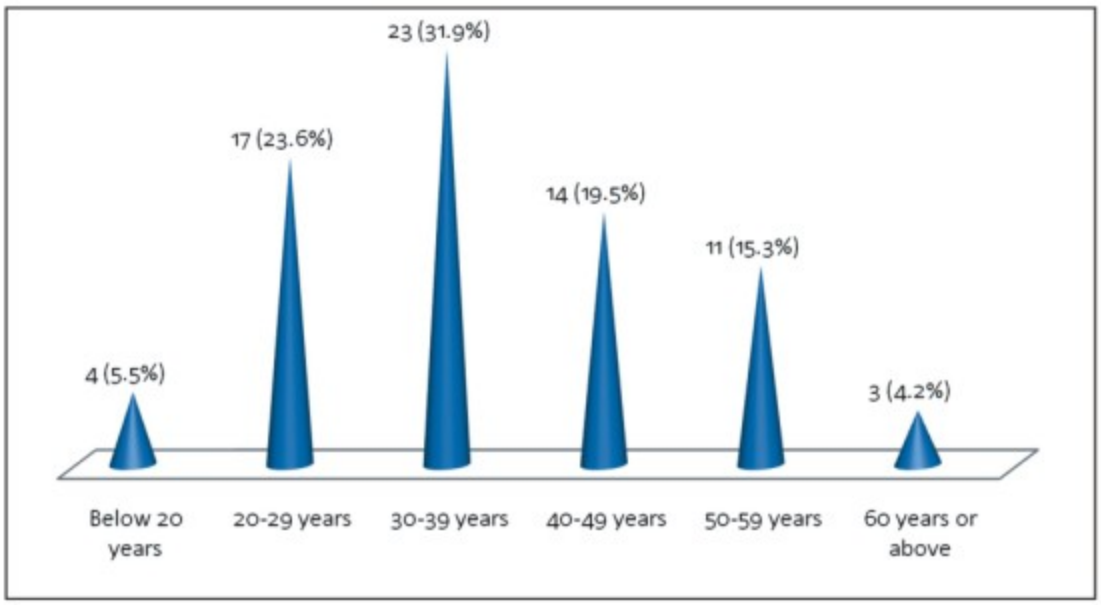


**Figure 1:** *Age distribution of the patients (n=72)*

**Table 1: Sex and site of lesion (n=72)**

| Site of lesion | | Gender | | Total | Male : Female |
|---|---|---|---|---|---|
| | | Male N (%) | Female N (%) | N (%) | |
| **Rights Colon** | Caecum | 13 | 2 | 15 | |
| | Ascending colon | 6 | 1 | 7 | |
| | Right colic flexure | 4 | 1 | 5 | |
| | Total | 23 (85.2) | 4 (14.8) | 27 (37.5) | 5.7:1 |
| **Left Colon** | Transverse colon | 1 | 0 | 1 | |
| | Left colic flexure | 3 | 0 | 3 | |
| | Descending colon | 1 | 1 | 2 | |
| | Sigmoid colon | 4 | 3 | 7 | |
| | Total | 9 (69.2) | 4 (30.8) | 13 (18.1) | 2.3:1 |
| **Rectum** | | 23 (71.9) | 9 (28.1) | 32 (44.4) | 2.7:1 |
| **Total** | | 55 (76.4) | 17 (23.6) | 72 (100.0) | 3.2:1 |

**Table 2 : Presenting symptoms of colorectal carcinoma in relation to sites.**

| Symptoms | Rt colon (n=27) N(%) | Lt colon (n=13) N(%) | Rectum (n=32) N(%) | Total (n = 72) N(%) |
|---|---|---|---|---|
| Weight loss & weakness | 20(74.5) | 11(84.6) | 28(87.5) | 59 (81.9) |
| Anorexia | 15(55.5) | 9(69.2) | 17(53.2) | 41(56.9) |
| Abdominal pain | 15(55.5) | 6(46.15) | 17(53.15) | 38 (52.7) |
| Abdominal discomfort, dyspepsia | 20(74.5) | 8(61.5) | 7(21.8) | 35(48.6) |
| Bleeding P/R | 00(0.0) | 6(46.2) | 28(87.5) | 34 (47.2) |
| Altered bowel habit | 6(22.2) | 9(69.2) | 16(50.0) | 31(43.8) |
| Abdominal lump | 18(66.6) | 9(69.2) | 4(12.3) | 31(43.8) |
| Diarrhoea | 6(22.2) | 3(23.1) | 7(21.9) | 16 (22.2) |
| Constipation | 01(5.0) | 04(44.0) | 11(52.0) | 15 (20.8) |
| Nausea/Vomiting | 6(22.2) | 6(46.15) | 00 (0.0) | 12 (16.6) |
| Intestinal obstruction | 06(22.2) | 03(23.1) | 00 (0.0) | 09 (12.4) |
| intestinal perforation | 01(5.0) | 04(44.0) | 01(4.0) | 06 (8.3) |
| Painful defaecation | 00 (0.0) | 00 (0.0) | 04(19.0) | 04 (5.5) |

**Table 3: Distribution of patients by site and size of the colon carcinoma.**

| Size | Right side N (%) | Left side N (%) | Total N (%) |
|---|---|---|---|
| <3cm | 3 (42.8) | 4 (57.2) | 7 (17.5) |
| 3-5cm | 20 (71.4) | 8 (28.6) | 28 (70.0) |
| >5cm | 4 (80.0) | 1 (20.0) | 5 (12.5) |
| Total | 27 (67.5) | 13 (32.5) | 40 (100.0) |

P = 0.381 (Fisher exact probability test)

**Table 4: Dukes' stage of colorectal carcinoma and serum CEA Level.**

| | Serum CEA level | | |
|---|---|---|---|
| Dukes' Stage | ≤ 5ng/ml N (%) | >5ng/ml N (%) | Total N (%) |
| A | 4 (33.3) | 8 (66.7) | 12 (16.6) |
| B | 3 (18.7) | 13 (81.3) | 16 (22.2) |
| C | 2 (6.7) | 28 (93.3) | 30 (41.7) |
| D | 0 (00.0) | 14 (100.0) | 14 (19.5) |
| Total | 9 (12.5) | 63 (87.5) | 72 (100.0) |

p = 0.033 (Fisher exact probability test)

**Table 5: Tumor grade of colorectal carcinoma and preoperative serum CEA level.**

| Cell Differentiation | Number n | Mean CEA (ng/ml) serum level | F | significance between groups |
|---|---|---|---|---|
| Well Differentiation | 22 | 16.2[a] | 11.92 | 0.001 |
| Moderate Differentiation | 36 | 10.7[b] | | |
| Poor Differentiation | 14 | 6.1[c] | | |

Values in the same column not sharing common superscript letter are significantly ($p<0.05$) difference

## Discussion

The present study findings revealed that majority of colorectal carcinoma occurred in rectal area (44.4%) followed by right colon (37.5%) and then left colon (18.1%). This study corresponds with the previous studies[14,15] as 36.9% to 40.3% of the total number of the lesions occurred in rectum and recto - sigmoid area.

Colorectal carcinoma (CRC) incidence rates in males is notably higher than females, at all anatomic subsites.[6,7] In the present study, the same pattern of sex differences was also observed. This pattern is unexplained and may be a result of a combination of better awareness of screening in women, more exposure of males to risk factors like high body mass index/body fatness, alcohol intake, smoking , and protective effects of both endogenous and exogenous hormones in female.[16] There is a space to explore the different aspects of this sex differences in Bangladeshi perspectives.

The peak incidence for colorectal carcinoma is between ages 60 and 79. Fewer than 20% of cases occur before age of 50 years.[5] But recent reports have demonstrated an alarming increase in incidence of CRC among young adults aged 2049 years in the US.[17] The present study findings is consistent with the recent US reports. This shift of the incidence towards the younger age group may be due to increasing obesity, the consumption of lots of fast food, alcohol and highly processed meat in young adults. At the same time, eating little fiber and a sedentary lifestyle are also may be linked to a higher risk of colorectal cancer in young adults.

In previous studies[18,19] abdominal pain, anorexia, weight loss and weakness, per rectum bleeding, altered bowel habit and abdominal lump were identified as the common complaints of the patients having colorectal carcinoma. The present study also agreed with them. In this study, per rectum bleeding was the most common specific symptoms in case of rectal carcinoma. So per rectum bleeding may be suggestive for rectal carcinoma.

Several studies emphasized that larger tumors are more frequent in the right colon than left.[20-22] Similar finding also found in this study. Right-sided tumors mostly do not cause any signs or symptoms in the early stages, and they are generally diagnosed when they attain a large size. This may be one of the reasons to have larger tumor in right colon than left. These tumors are diagnosed in the early stages with the technological improvement and common use of colonoscopy, but the present study findings suggest that the problem is still going on.

Many investigators have shown that preoperative serum CEA levels correlate with the extent of colorectal cancer.[12, 23] In 1994, Wang et al. reported, a total of 318 patients with colorectal cancer, 133 (42%) had preoperative CEA level >5 ng/ml (9). In this study, it is quite double (87.5%). Wang et al also reported that the incidence of preoperative CEA levels of >5 ng/ml in Dukes stages A, B, C and D diseases were 0, 32, 48 and 79%, respectively. Similarly, in a report by Ladenson et al.[23], a total of 203 patients with colorectal cancer, the incidence of preoperative CEA >5 ng/ml in Dukes' A, B,C and D stages were 3, 25,45 and 65%, respectively. The current study confirmed this trend, but the percentage of preoperative CEA >5ng/ml among the patients of the respective stages comparatively higher than the previous studies. In this study, the incidence of preoperative CEA >5ng/ml in Dukes'A, B, C and D stages were 66.7, 81.3, 93.3 and 100.0%, respectively. Besides malignant diseases like colorectal cancer, elevated serum CEA levels >5 ng/ml are frequently found in other benign disorders, like smoking, peptic ulcer, inflammatory bowel disease and a variety of benign liver diseases, including hepatitis, cirrhosis, cholelithiasis, obstructive jaundice and cholangitis.[24] There is a high prevalence of

smokers, peptic ulcer, inflammatory bowel disease, hepatitis B virus infection and cholelithiasis in Bangladesh. So these were the possible enhancing factors for high percentages of serum CEA levels >5 ng/ml among the study subjects in the different Dukes' stages. It suggests that serum CEA levels >5 ng/ml is nonspecific test for the screening of CRC. But in benign diseases/conditions, it is rare to rise serum CEA values >10 n g/L. A well designed study is needed considering all the confounding factors to identify the independent effect of CRC on serum CEA level in Bangladeshi people.

Several studies have shown that well differentiated colorectal cancer produce more CEA per gram of total protein than poorly differentiated specimens.[25] Bhatnagar et al.[25] 1999 observed that tissue CEA levels were highest for well differentiated adenocarcinomas (5.2-37.0 micrograms/g protein) with progressively lower levels seen in moderately differentiated and poorly differentiated tumors, and in normal. Mean serum CEA levels were 1.5 ng/ml for normal and 4.2, 6.4, 23, and 102 ng/ml for Dukes' A, B, C and D stage tumors, respectively. In their report mean concentration of CEA in well differentiated, moderately differentiated and poorly differentiated colorectal neoplasm were 18.0, 5.5 and 2.2ng/ml of protein, respectively. Similarly, serum concentration of CEA tends to be higher in patients with well differentiated tumors compared with those with poorly differentiated tumors.[26] The present study findings agreed with the this findings.

This study has some limitations that must be taken into consideration. First, sample size was small. Secondly, there was no option of controls (healthy, without CRC) in the study design, that is why the sensitivity and specificity of preoperative serum CEA level >5 ng/ml were not calculated for the screening of CRC. Third, serum CEA enhancing factors other than CRC were not considered as confounding variables in this study. Finally, it is not clear whether the analysis of this restricted patient group introduced a selection bias, and these findings may or may not reflect the situation in the overall population.

Preoperative serum CEA level >5 ng/ml should not be used as a single screening test for colorectal carcinoma . Preoperative high serum CEA concentration (>10ng/ml) correlating with the signs and symptoms of CRC may be used in multiphasic screening of CRC for further confirmatory diagnostic test.

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