



Research Article

Clinical Utility Of Serum CA19.9 And CEA Tumour Markers In The Diagnosis Of Colorectal Carcinoma

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ABSTRACT

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The present study was designed to investigate the efficiency of serum carcinoembryonic antigen (CEA) and carbohydrate cancer antigen (CA19-9) levels for diagnosing colorectal carcinoma (CRC) in Indian patients, as very limited data is available till date regarding the same. The Serum levels of tumour markers CEA and CA 19-9 were analyzed in Colorectal cancer patients and Controls by the ECLIA principle.

We observed significantly elevated levels of CEA / CA 19-9 tumour marker levels in the CRC patients as compared to the control subjects. This clearly reveals that the combination of CEA and CA-19.9 may contribute significantly to the diagnosis of CRC. Also, increased levels of CEA tumor markers were observed during the early stages of cancer, while CA-19.9 tumour marker levels were elevated towards the later stages of cancer development, it can be inferred that, the CEA marker can be used as an effective tumour marker for screening while CA19.9 tumor marker can be used to assess disease progression.

INTRODUCTION:

The incidence of cancer varies widely according to the geographic location ^[1,2]. The most common cancers observed in the Western world are those of the lung, colon & rectum and prostate in men; and breast in women. In India, the leading cancers are those of the oropharynx, stomach and esophagus in men and uterine cervix, breast and oropharynx in women ^[1,3].

The incidence of colorectal cancer in the Western countries have been observed to be almost eight times that of India ^[1,3]. However, the incidence of colorectal cancer is rapidly increasing, especially in Asia ^[4,5,6,7].

This has been attributed predominantly to the dietary pattern of the population. The low fat and high fruit / vegetable content in the Indian diet as well as the use of certain spices, such as turmeric (curcumin) may have an anti-oxidant role in cancer prevention ^[1,8].

Colorectal cancer (CRC) is caused due to various factors including genetic factors (accumulation of mutations) and environmental factors (e.g. composition of diet, obesity, diabetes mellitus, smoking, alcohol consumption). Of late, chronic inflammation has also been regarded as an important risk factor for the development of cancer. Recent data propose a direct effect of inflammation on tumor growth. Several pro-inflammatory cytokines released by innate and adaptive immune cells have been shown to regulate cancer cell growth and thereby contribute to tumor promotion and progression ^[9].

Chronic inflammation is especially apparent in patients with inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), and have an increased risk for the development of colitis-associated CRC depending on the duration and severity of intestinal inflammation ^[10].

There are also genetic influences in different ethnic groups leading to the development of hereditary CRC ^[1]. The contribution of chronic inflammation to tumour development has been widely attributed to its ability to induce mutations (e.g. through reactive oxygen or

nitrogen species) ^[11].

In general, most cases of CRC are sporadic worldwide and hereditary CRC accounts for up to 15% of all cases ^[1,12]. Hereditary cancers usually occur in the younger age group. Although CRC in the young population may be more aggressive, if detected during early stages, young patients can have better overall 5-year survival rates ^[1,13].

The early, reliable diagnosis of CRC is essential, so that the morbidity and mortality associated with this condition could be reduced. Limited data are available regarding the association between colorectal cancer and the circulating serum tumour marker concentrations, namely, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) ^[4]. CEA is the most widely used tumor marker for CRC, because it is expressed at low levels in normal intestinal epithelia but markedly upregulated in most CRC ^[14,15]. CEA affects tumorigenesis by enhancing tumor cell survival and inducing tumor angiogenesis [16]. Serum CEA is recommended as a prognostic biomarker for monitoring recurrence of CRC following curative resection, and it can be ordered preoperatively for assistance in staging, surgical planning, and predicting prognosis ^[4,17].

CA 19-9 is an antigen defined by monoclonal antibody binding to CA 19-9, the tumor surface marker, Sialyl-Lewis A ^[18]. Serum CA 19-9 is known to be elevated in subjects with various gastrointestinal cancers, such as pancreatic, gastric, hepatic, and biliary tract carcinomas, and it has also been used as a tumor marker of CRC in clinical practice, usually accompanied by CEA ^[19].

The underlying biologic mechanisms for increased CEA and CA 19-9 in colorectal adenoma are not yet fully understood. Fischbach and Mössner ^[20] revealed an increase in tissue concentrations of CEA and CA 19-9 progressing from normal colonic mucosa through colorectal adenomas to carcinomas. They also showed that, in the adenoma group, CEA concentrations increase with increasing

villous component and with the extent of cellular atypia present, reflecting their special position in the adenoma-carcinoma sequence. These results supported the biological significance of CEA and CA 19-9 in carcinogenesis of CRC and its precursors. They also suggested that the release of tumor antigens out of tumor tissue may be associated with tumor vascularity, extent of tumor necrosis, the activity of tumor cells as measured by the number of mitotic figures, or tumor differentiation.

Increases in vascularity, the extent of necrosis, and the degree of cellular atypia in malignant transformation process may explain the noted increase in serum CEA and CA 19-9 in colorectal adenoma. Given that the risk of malignant transformation is associated with size, the extent of villous component, and the degree of cellular atypia of adenoma, serum CEA and CA 19-9 levels may be also associated with these factors [21]. Several previous studies have shown that significantly higher concentrations of CEA or CA 19-9 are found in adenoma tissue (which is a precursor of CRC), as well as CRC tissue, in comparison to normal mucosa [4,20,22,23]. However, there have been limited studies so far with respect to Indian patients. The present study was designed to investigate the efficiency of serum carcinoembryonic antigen (CEA) and carbohydrate cancer antigen (CA19-9) levels for diagnosing colorectal carcinoma (CRC) in Indian patients, and to determine whether the levels of these antigens vary according to CRN severity.

MATERIALS AND METHODS

SUBJECTS:

A total of 57 Colorectal cancer patients diagnosed at Delhi State Cancer Institute, Delhi, India, were included in this study. The Serum levels of tumour markers CEA and CA 19-9 were analyzed. The clinical details of the patients were obtained prospectively from the medical records. Thirty Seven healthy individuals served as controls for the study. The study was approved by the Institutional Review Board. Informed consent was obtained from all the subjects.

METHODS:

Tumor markers were measured with an electrochemiluminescent (ECLIA) assay on Cobas e411, Roche Diagnostics, Mannheim, Germany. The reference values were 0 – 4.7 ng/ml for CEA and 0 – 39 u/ml for Ca19-9.

RESULTS:

Of the 57 Colorectal cancer patients included in the study, elevated CEA and CA 19.9 levels were observed in 51 % and 25 % of patients respectively (Table 1). Tumor staging is performed based on the sixth edition of the TNM system, published by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/ UICC) [24]. Depending on the tumor staging, patients were divided into four groups: Stage I, Stage II, Stage III and Stage IV. The staging of the patients showed a total number of 29 patients in Stage II, 13 patients in Stage III and 15 patients in Stage IV. None of the patients belonged to stage I (Table 1).

Table 1: Total number of patients on the basis of staging and elevated tumour marker levels

Tumour Stage	Total no. of patients	No. of patients with elevated CEA levels	No. of patients with elevated Serum CA-19.9 levels
Stage II	29	11	02
Stage III	13	05	02
Stage IV	15	13	10
Total	57	29 (51%)	14 (25%)

Table 2 shows the total number of samples in various tumour stages with elevated serum CEA and serum CA19.9 levels. The average levels of both CEA and CA-19.9 tumour markers in stages II, III and IV are depicted in Table 2. While, in case of healthy controls, the average CEA and CA19.9 levels were observed to be 2.4 ng/ml and 11.7 U/ml respectively. This clearly indicates that patients with Colorectal cancer exhibit high levels of both CEA and CA19.9 tumour markers, when compared to healthy controls. Thus, both CEA and CA-19.9 tumour markers show high positive rate among the CRC patients.

Table 2: Average levels of serum tumor markers at various tumor stages

Tumour stages	Average serum CEA levels	Average serum CA19.9 levels
Stage II	81 ng/ml	121 U/ml
Stage III	35 ng/ml	31 U/ml
Stage IV	1420 ng/ml	6614 U/ml

DISCUSSION

As per the available literature data, elevated CEA concentrations are associated with higher rate of any adenoma, advanced adenoma, high-risk adenoma, advanced Colorectal Neoplasia (ACRN), overall Colorectal Neoplasia, and colorectal cancer (CRC) [4]. Elevated CA 19-9 concentrations are also reported to be associated with higher rate of advanced adenoma, high-risk adenoma, ACRN, and CRC [4]. Elevated levels of both these tumour markers have been identified as independent predictors of ACRN [14,15,25].

A literature survey of other studies associated with serum CEA, CA 19-9, and colorectal adenoma was carried out. A German study including 32 patients with colorectal adenoma and 119 healthy subjects showed that neither the size of colorectal adenomas nor their histologic severity influences serum CEA concentration [26]. However, a Croatian study including 46 patients with colorectal adenoma reported that elevated serum CEA concentrations were associated with larger adenomas, although they were not associated with multiplicity or degree of dysplasia [22]. An

Israeli study involving 93 patients with colorectal adenoma also demonstrated an increased association of elevated serum CEA with larger tumor size (>2.3 cm in diameter) and adenoma with villous component, but not with severe dysplasia or carcinoma in situ [26]. In Nam HK, et al [4], both elevated serum CEA and CA 19-9 levels were reported to be significantly associated with larger lesion size and multiplicity of adenomas. CEA and CA 19-9 have not been recommended as screening tests for CRC, as the sensitivities of these tumour markers for detecting CRC have been reported to be very low [17, 28, 29, 30]. However, according to Nam HK et al [4], elevated serum CEA and CA 19-9 levels were independent predictors of ACRN. And, although CEA alone or CA 19-9 alone may be inappropriate as screening tests for CRC, they may be useful as an adjunct to other screening methods, such as fecal immunochemical test or clinical risk scoring. Further studies are needed to determine whether serum CEA and/or CA 19-9 are useful as an adjunct to cancer or ACRN detection. In the present study, we observed significantly elevated levels of CEA / CA 19-9 tumour

marker levels in the Colorectal cancer patients as compared to the control subjects. A high statistically significant difference in the levels of serum CEA and CA19-9 between different disease stages of CRC ($P < 0.001$) have been reported [31]. In the present study as well, patients in stages II and III were observed to possess elevated levels of both CEA and CA19.9 tumour marker levels, as compared to the control subjects. However, the stage III patients exhibit abnormally high levels of both the markers. Average CA19.9 levels were observed to be higher as compared to average CEA levels in stage III patients.

Studies have also shown that the mean CEA and CA19-9 serum levels are significantly higher in patients with regional lymph nodes involvement and in liver metastases, as compared to patients without lymph node involvement and liver metastases. Thus, CEA and CA19-9, could be used as diagnostic factors, predicting the severity of CRC and metastatic status. Both the markers showed significant sensitivity for the malignant state when used alone. Also, in this study, the average age of the subjects included was 45 years. This indicates the incidence of CRC to be increasing in younger individuals aged < 50 years [32,33]. This is again of serious concern, as the patients need to undergo colonoscopy with low cost-effectivity, for primary screening. The screening of tumour markers such as CEA and/or CA 19.9, can be highly advantageous in such instances as an adjunct to CRC screening for young adults at high risk for ACRN.

CONCLUSION

Our observations clearly reveal that the combination of CEA and CA-19.9 may contribute significantly to the diagnostic potential. Though both the markers show significant sensitivity for diagnosis of colorectal carcinoma, when used alone; the complementation of both CEA with CA 19.9 can increase the sensitivity in the diagnosis of CRC. Combination of positive information from both the sources is likely to lead to a more accurate diagnosis and may therefore improve

the efficiency of the follow-up and therapeutic response.

Also, since, increased levels of CEA tumor markers are observed during the early stages of cancer, while CA-19.9 tumour marker levels are elevated towards the later stages of cancer development. We could predict that CEA marker can be used as an effective tumour marker for screening while CA19.9 tumor marker can be used to assess disease progression. Therefore, the combination of these markers will aid in more accurate diagnosis, which would eventually improve the efficiency of follow up and therapeutic response.

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