Present and Probable Uses of CEA

The Editor interviews:
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Editor: Are any of the assays for carcinoembryonic antigen (CEA) clinically useful now?

Dr. Holyoke: Yes, we think so. However, this is a qualified "yes," since no clinical trials have shown clearly and conclusively that CEA measurement ultimately improved the quality, or length, of survival. But data indicate several situations in which monitoring CEA levels in plasma or serum will probably prove clinically valuable.

Editor: Would screening for cancer be one of those clinical situations?

Dr. Holyoke: Dr. T.M. Chu and I are trying to find the answer to this question, primarily by studying colon cancer patients. In one study conducted by many institutions, including the National Cancer Institute of Canada and the American Cancer Society, patients with colon cancer were tested for elevated CEA levels by Hansen's method in plasma or Thomson's method in serum. As a result of this study, it was initially felt that CEA was not useful for screening colon cancer. However, this was probably an overly simplistic response.

Recently, Dr. Chu and I completed a study at Roswell Park of 1,800 older men at somewhat high risk for cancer. Positive CEA values in two of these patients identified previously undetected cancers of the pancreas and the lung. In two additional cases, CEA elevations indicated cancer recurrence and in a third, preceded the reappearance of a lung cancer by three months.

Further study of high-risk groups with semi-annual or yearly monitoring could provide additional information.
CEA records is necessary to evaluate whether CEA assay is beneficial in screening programs. At present, we do not recommend it.

Editor: *What are the drawbacks to CEA screening for cancer?*

Dr. Holyoke: CEA has a limited sensitivity and specificity for cancer, i.e., a significant number of false negatives and false positives are encountered. A high rate of false positives is associated with emphysema, alcoholism, ulcerative colitis, ileitis, pancreatitis, diabetes, hypertension as well as smoking.

However, we do feel that the CEA test should prove worthwhile as a diagnostic adjunct in patients with gastrointestinal symptoms, since less than two in 100 young, healthy individuals without malignant or serious benign disease have elevated CEA levels—above 2.5 ng./ml. as measured by the Hansen assay.

Editor: *How does the CEA test compare with alkaline phosphatase in tumor detection?*

Dr. Holyoke: A rise in CEA was noted in 54 of 87 patients with colon cancer as against 24 elevations of alkaline phosphatase. By contrast Dr. Schott of the Mayo Clinic has data indicating that CEA is not that much more sensitive than alkaline phosphatase; further study is required to clarify the situation.

Editor: *What percentage of colon tumors will be detected by CEA?*

Dr. Holyoke: Using Duke’s Staging, the following percentages of colon cancer patients had elevated CEAs: Stage A, 18 percent; Stage B, 53 percent; Stage B2, 62 percent; Stage C1, 65 percent; and Stage C2, 79 percent.

Tumors larger than about 15–30 grams are detectable by CEA measurements. This is not a precise figure, of course, but cancers smaller than a critical size will usually escape detection. In addition, about 10 percent of patients with even large tumors will never show an elevated CEA, partly because some colon cancers simply lack significant amounts of CEA which can be released into the serum.

Editor: *How should one proceed in the face of an elevated CEA?*

Dr. Holyoke: If the cause cannot be found, repeating the assay at 10-day to two-week intervals times two is recommended. One repeat is required in any case. If the values remain positive, a clinical investigation for suspected cancer is justified. Continued CEA elevation without demonstrable disease necessitates quarterly tests until resolution of the problem.

Editor: *Following surgery or during adjuvant treatment, is CEA an effective monitor of the disease course?*
Dr. Holyoke: Yes, in colon cancer patients. CEA levels changed appropriately in 90 percent of the patients who had progression or regression of disease and fell in response to successful chemotherapy. It has been reported that CEA may fall even when there is no clinical evidence of response. In addition, Mach reported that a rise in CEA value often appears "weeks or months" before clinical or laboratory evidence of progression. However, Meeker has suggested that the test for CEA is too irregular to be generally useful. We feel that about five weeks postoperatively, when the effects of surgery are past, CEA monitoring can indicate disease progression in about a third of patients six or more months before it is ordinarily detectable.

One serious problem remains. CEA monitoring has given false positive results in two of our 22 patients who are presently disease free even when two consecutive elevated CEA levels is the criteria of positivity. This is approximately a 10 percent false positivity, a troublesome problem for clinicians. Obviously considerably more data is necessary.

Editor: Is the CEA test an accurate prognostic aid?

Dr. Holyoke: Yes, at least for colon cancer. Dr. Chu and I followed 41 patients who had clinically or microscopically complete resections. We divided the patients into three groups, according to their preoperative CEA determinations: less than 2.5 ng./ml.; between 2.6 and 7.0 ng./ml.; and greater than 7.0 ng./ml. To date only one of 20 patients who had CEA levels less than 2.5 ng./ml. developed a recurrence after 18 months. Six of the 11 patients with an intermediate CEA level had tumor reappearance after an average of 11 months, while seven of nine cases with a CEA greater than 7.0 had recurrence on an average of 8.4 months after surgery. These findings indicate that preoperative CEA measurement would probably be prognostically valuable in colon cancer patients. Whether our initial study will be confirmed is impossible to say; however, the only known bias in the selection of our group was that all patients were macroscopically free of disease following surgery.

Mach et al., in a recent Lancet publication (Sept. 1974), published a follow-up of 22 similar patients. Their value scale or patient group must have been different; there were no patients in their series reported at < 5.0 ng./ml. However, above 5.0 ng./ml. they found eight of 22 with evidence of tumor return. We would expect 50-60 percent recurrence. In addition, the average pre-surgical value in this group was 60 ng./ml. If we look at the 14 patients with no evidence of clinical recrudescence to date, the mean is about 15 ng./ml., a statistically significant difference that lends support to our findings.

Thus we are convinced that CEA is a valuable prognostic test prior to surgery for colon cancer. We can assure most colon cancer patients with preoperative CEA levels of less than 2.5 ng./ml. that they have an excellent prognosis and recommend adjuvant therapy for those with a CEA in plasma of greater than 5.0 or 6.0 ng./ml.
Editor:  

Is CEA more accurate than the usual methods of assessing prognoses?

Dr. Holyoke:  

Careful clinical staging particularly with relation to size and invasiveness of the primary lesion and quantitation of lymph node involvement is probably equally accurate, but also expensive and time consuming. To date lymphoblastogenesis studies, skin antigen tests, with the possible exception of DNCB sensitization, and M.I.F. have all proved less predictive than we hoped and certainly less so than CEA.

Editor:  

Have CEA measurements been evaluated in patients with gastro-intestinal cancers other than colon cancer?

Dr. Holyoke:  

Yes. Presently, CEA is the best test we know for pancreatic cancer. In 1971 Dr. Zamcheck reported in American Journal of Digestive Diseases 100 percent positivity in his first 13 patients with pancreatic carcinoma. This response has been widely confirmed. In our early series, CEA was elevated in 12 of 13 patients with unresectable pancreatic cancer and also in the only two patients with operable diseases. For the inoperable patients the average plasma level was 17.9 ng./ml.; for the two resectable patients, 3.7 ng./ml. To date the CEA level has been only marginally elevated in resectable lesions. Elevations due to pancreatitis are a major problem.

Dr. Zamcheck has reported that 18 of 42 patients with pancreatitis had an elevated CEA in their plasma. On further examination, 11 had evidence of cirrhosis. Yet, the CEA levels were generally lower than those seen in patients with disseminated cancer. Several studies are under way to monitor CEA in pancreatic juice, but the clinical usefulness of this approach remains to be determined.

Editor:  

Is CEA also a useful assay for gastric carcinoma?

Dr. Holyoke:  

The Mayo Clinic group has reported that only nine of 37 patients, or 24 percent, with metastatic gastric cancer had CEA elevations; alpha fetoprotein showed a slightly better response with 12 elevations. Interestingly, CEA and alpha fetoprotein together detected metastatic gastric cancer 50 percent of the time. This percentage is probably still too low to be useful, but suggests the direction that we should pursue in the future, multiple antigen assay.

Editor:  

Does CEA have a place in the diagnosis and management of other carcinomas?

Dr. Holyoke:  

The Table lists our evaluation of the present and probable usefulness of the CEA assay. It definitely has a role to play in colon and pancreatic cancer and has been specifically indicated in neuroblastoma. In patients with bronchogenic cancer its usefulness is controversial. I don’t think it will be useful for breast cancer despite a report from Dr. Zamcheck’s group suggesting otherwise. I can’t
foresee any general application of CEA for sarcomas, gynecological or urological cancers since, in most patients, plasma or urine measurements of CEA relate poorly to tumor presence and have a very high percentage of false negatives.

**Editor:** What lies ahead in this area?

**Dr. Holyoke:** We are developing more precise information about patients with colon cancer as well as more specific assay techniques using the primary tumor as an antigen source. The combination of the CEA test with other antigen marker assays may be helpful. Finally, new specific tumor tissue antigen markers are awaited.

**Editor:** Thank you, Dr. Holyoke.