Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) has been cited as being a more sensitive marker of colorectal cancer than carcinoembryonic antigen (CEA). The goal of this study was to determine the clinical sensitivity and specificity of TIMP-1 in subjects with colorectal cancer and controls undergoing colonoscopy. In addition, we wanted to determine if smoking had an effect on both TIMP-1 and CEA, or only CEA as already determined. For this reason, patients whose smoking history was known were selected for this study. Upper reference limits (95th percentiles) were determined for smokers and non-smokers for both markers.

EDTA plasma samples were collected from 2003 subjects prior to their colonoscopy, 12 of whom had colorectal cancer. Fourteen additional plasma samples were collected from subjects before undergoing colorectal cancer resection. Of the 2003 subjects, the smoking status of 74 subjects was not known and they were consequently excluded from data analysis. There were 26 total cancer patients: 18 with stage I or II disease and 8 with stage III or IV disease.

Concentrations of TIMP-1 and CEA were determined using the ARCHITECT i2000 analyzer. The 95th percentiles for TIMP-1 and CEA in non-smokers with no colorectal cancer were 172.1 ng/mL and 3.3 ng/mL, respectively. In smokers, we observed an elevation in both TIMP-1 and CEA 95th percentiles concentration which were 190.4 ng/mL and 7.4 ng/mL, respectively. Eight cancer subjects showed elevated concentrations of TIMP-1 and/or CEA, there were only 2 subjects with both markers elevated. Three of the stage II and IV colon cancer subjects had elevated TIMP-1; whereas, only 2 had elevated CEA levels. The overall sensitivity of TIMP-1 and CEA in colon cancer was the same, at 19.23% and the specificity was 95.0%. Combining both markers, the sensitivity increased to 30.8% with a specificity of 90.6%.

Although TIMP-1 has been shown by others to be more sensitive than CEA for colorectal cancer, our study demonstrates that TIMP-1 and CEA are indeed complementary. Both markers in combination increase the sensitivity in colon cancer by 1.6-fold. Additional research is needed to identify and validate biomarkers for colorectal cancer screening that are more sensitive for stage I and II disease.

Introduction

The National Cancer Institute estimates that there will be 106,100 and 40,870 new cases of colon and rectal cancer, respectively, and 49,920 deaths from the two cancers combined in 2009. Colorectal cancer (CRC) is more common in men than women. The prevalence increases with age, especially after 50 years old. For this reason, current screening recommendations for the general population commence at age 50. Tumor size, lymph node involvement and metastasis are used for staging and prognosis. Hyperplastic polyps and tubular adenomas also affect the colon, and can increase the risk of developing CRC.

Diagnosis of CRC

Screening tests include the Fecal Occult Blood Test, Fecal DNA, Immunochromatographic Fecal Test, Double Contrast Barium Enema, Flexible sigmoidoscopy, CT colonoscopy, and conventional colonoscopy. These methods have a low patient compliance, may not be readily accessible, and can become quite costly. Currently, the carcinoembryonic antigen (CEA) is recommended only for monitoring of CRC recurrence. There is a need for a more sensitive blood test for diagnosis of CRC in the general population.

Study objective

Tissue inhibitor of metalloproteinase-1 (TIMP-1) has been cited as being a more sensitive marker of colorectal cancer than CEA. The goal of this study was to determine the clinical sensitivity and specificity of TIMP-1 in subjects with colorectal cancer and controls undergoing colonoscopy.

Study Overview

EDTA plasma samples were collected from 2,003 subjects prior to their colonoscopy, 12 of whom had colorectal cancer. Fourteen additional plasma samples were collected from subjects before undergoing colorectal cancer resection. Of the 2,003 subjects, the smoking status of 74 subjects was not known and they were consequently excluded from data analysis. There were 26 total cancer patients: 18 with stage I or II disease and 8 with stage III or IV disease.

TIMP-1 Assay

The assay was performed using the ARCHITECT i2000 TIMP-1 assay; a two-step, sandwich format whereby capture is via anti-TIMP-1 coated paramagnetic microparticles to form a complex with TIMP-1 analyte originating from the sample. Detection is by an acid-labeled labeled monoclonal antibody conjugate that binds to the TIMP-1 analyte-microparticle complex. Exposing the reaction mixture to on-board trigger reagents containing peroxide at alkaline pH causes the release of light that is proportional to the TIMP-1 concentration in the specimens, calibrators, or controls.

CEA Assay

Performed using ARCHITECT i2000 CEA Assay

Results

The 95th percentiles for TIMP-1 and CEA in non-smokers with no colorectal cancer were 172.1 ng/mL and 3.3 ng/mL, respectively. In smokers, we observed elevations in both TIMP-1 and CEA 95th percentiles concentration which were 190.4 ng/mL and 7.4 ng/mL, respectively. Eight cancer subjects showed elevated concentrations of either TIMP-1 and/or CEA, and there were only 2 subjects with both markers elevated. Three of the stage III and IV colon cancer subjects had elevated TIMP-1; whereas, only 2 had elevated CEA levels. The overall sensitivity of TIMP-1 and CEA in colon cancer was the same, at 19.23%; whereas, the specificity was 95.0%. Combining both markers, the sensitivity increased to 30.8% with a specificity decreased to 90.8%.

Conclusions

• Although TIMP-1 has been shown by others to be more sensitive than CEA for CRC, our study demonstrates that TIMP-1 and CEA are complementary; both markers in combination increase the sensitivity for colon cancer detection by 1.6-fold over either one alone.
• The ROC in figure 5 shows that the AUC for TIMP-1 is 10% greater than that of CEA. In adding CEA to TIMP-1 there is little improvement in the AUC over TIMP-1 alone.
• Additional research is needed to identify and validate biomarkers for colorectal cancer screening that are more sensitive for stage I and II disease.
• It is well known that smokers have higher CEA concentrations compared to the normal non-smoking population. In our study, TIMP-1 was also increased in smokers by ~20%.

References