Serum YKL-40 in Risk Assessment for Colorectal Cancer: A Prospective Study of 4,496 Subjects at Risk of Colorectal Cancer

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Abstract

The aim of the present study was to test the hypothesis that high serum YKL-40 associates with colorectal cancer in subjects at risk of colorectal cancer. We measured serum YKL-40 in a prospective study of 4,496 Danish subjects [2,064 men, 2,432 women, median age 61 years (range, 18–97)] referred to endoscopy due to symptoms or other risk factors for colorectal cancer. Blood samples were collected just before large bowel endoscopy. Serum YKL-40 was determined by ELISA. Serum YKL-40 was higher (P < 0.0001; unadjusted for confounding covariates) in subjects diagnosed with colon cancer (median 126 μg/L, 25%–75%: 80–206 μg/L) and rectal cancer (104, 72–204 μg/L) compared with subjects with adenoma (84, 53–154 μg/L), other nonmalignant findings (79, 49–138 μg/L), and no findings (62, 41–109 μg/L). Serum YKL-40 independently predicted colorectal cancer [OR, 1.53; 95% confidence interval (CI), 1.40–1.67; AUC = 0.68, P < 0.0001]. Restricting the analysis to subjects with no comorbidity increased the OR for serum YKL-40 to predict colorectal cancer (OR, 1.82; 1.58–2.08; AUC = 0.73, P < 0.0001). Combining serum YKL-40 and CEA demonstrated that both were significant [(YKL-40, OR, 1.27; 95% CI, 1.16–1.40); (CEA, OR, 1.92; 1.75–2.10; AUC = 0.75, P < 0.0001; OR for a 2-fold difference in marker level)]. Multivariable analysis (YKL-40, CEA, age, gender, body mass index, and center) showed that serum YKL-40 was a predictor for colorectal cancer in individuals without comorbidity (OR, 1.25; 95% CI, 1.05–1.40; P = 0.012), whereas this was not the case for those with comorbidity (OR, 0.98; 95% CI, 0.84–1.14; P = 0.80). In conclusion, high serum YKL-40 in subjects suspected of colorectal cancer and without comorbidity associates with colorectal cancer. Determination of serum YKL-40 may be useful in combination with other biomarkers in risk assessment for colorectal cancer.

Introduction

Colorectal cancer is one of the most common and serious malignant diseases of the Western world with approximately 1.2 million new cases and 610,000 deaths worldwide. It has been shown that screening may reduce cancer-specific mortality by approximately 15% (1), but as of today, colorectal cancer screening rests on either analysis of stool samples with follow-up endoscopy or endoscopy alone, both potentially invasive, and both considered highly unpleasant for the individual. Replacing one or the other with a routine blood samples would seem attractive. At present, however, no single plasma biomarker has sufficient sensitivity and specificity to accomplish this (2). Studies are ongoing to test whether combinations of several serum and/or plasma biomarkers are useful to select subjects for subsequent endoscopy.

Soluble concentration of YKL-40 (Chitinase 3-like 1 and CHI3L1) is emerging as a new biomarker in patients with cancer (3). High plasma YKL-40 levels in subjects from the general population associate with increased risk of developing (4) and death from gastrointestinal cancer (5). In this study population, we also examined plasma C-reactive protein (CRP) and YKL-40 levels simultaneously and observed that elevated YKL-40 levels were associated with an increased risk of gastrointestinal cancer, independently of CRP levels (6). In addition, high serum YKL-40 levels before (7) and after operation (8) for colorectal cancer are independent prognostic biomarkers of short overall survival. YKL-40 is a highly conserved glycoprotein produced by cancer cells (including colorectal cancer cells), macrophages and neutrophils (3) and by fetal and embryonic stem cells (9, 10). IL6 and hypoxia stimulate YKL-40 synthesis (11, 12). YKL-40 regulates VEGF and plays a role in angiogenesis.

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YKL-40 and inflammation (3, 16), including inflammation-associated carcinogenic changes of colonic epithelial cells (17, 18). Furthermore, YKL-40 participates in activation of Akt signaling pathways in these cells (19), in apoptosis (20), in cell proliferation and differentiation (9, 10), and in regulation of extracellular tissue remodeling (3), all processes that are important for cancer growth and dissemination (21). Recently, it has been demonstrated that YKL-40 regulates cellular and tissue responses via IL13 receptor α2 (22).

In the present study, we tested the hypothesis that high serum concentration of YKL-40 associates with colorectal cancer. For this purpose, serum YKL-40 was determined in a prospective study of 4,496 Danish subjects referred to large bowel endoscopy.

Materials and Methods

Study design

A prospective study of 4,496 subjects [2,432 males and 2,064 females, median age 61 years (18–97 years)] referred to endoscopy [(complete colonoscopy n = 2,738, flexible sigmoidoscopy n = 1,701 (including incomplete colonoscopies), rigid proctoscopy n = 52, unknown n = 5] due to symptoms or other risk factors for colorectal cancer, excluding individuals with hereditary disposition. Incomplete colonoscopies were recorded as flexible sigmoidoscopies. Six Danish Hospitals participated in the study and consecutively recruited individuals as they were referred to the out-patient clinics during the period January 2004 to December 2005. The compliance was 96.8%. Baseline variables included age, gender, body mass index (BMI), alcohol and smoking habits, current medication, and comorbidity, including malignant disease (registered using ICD-10 codes) within the last 5 years. On the basis of the results of the endoscopy, the included subjects were separated into five categories: colon cancer (CC), rectal cancer (RC), adenoma, other nonmalignant bowel lesions, and no findings. Using available data registries, the patients included were observed for 3 months after their endoscopy to verify additional diagnoses within that period. Further details of the study are given elsewhere (23).

YKL-40 analysis and reference intervals

Blood samples were collected at the day of endoscopy, just before the procedure according to a standard operating procedure; every single included individual was fasting at the time of collection. The procedure was similar among the groups of colorectal cancer cases and noncases. Whole blood was collected in tubes without gel separator (Vacutainers; B&D), and were within 2 hours centrifuged at 3,000 × g for 10 minutes at room temperature. Serum was transferred into cryotubes and stored at −80°C under 24/7 electronic surveillance. The processed serum samples were stored at −80°C to hinder protein degradation.

The measurement of YKL-40 was performed blinded in a randomized order at the completion of the study. Serum concentrations of YKL-40 were determined in duplicates, in samples stored frozen for up to 3 years at −80°C, by a commercial ELISA (Quidel). The detection limit was 20 μg/L. The intraassay coefficient of variation (CV) was <5% and the interassay CV was <6%.

Plasma concentrations of CEA were determined using the Abbott Architect i2000 automated immunoassay system at the Abbott Center of Excellence in Amsterdam (the Netherlands). The on-market Architect CEA reagents were used for the determination. The day-to-day variation was <1.5%.

Statistical analysis

The statistical analyses used were all predefined and described in the statistical analysis plan in the study protocol. Descriptive statistics are presented by the median, minimum, and maximum for continuous variables. The initial analysis grouped all individuals by the observed finding: colorectal cancer, adenoma, nonmalignant finding, and those without any finding. These groups were compared using logistic regression analysis with YKL-40 or CEA as the explanatory variables and adjusting each by age, gender, and comorbidity. The estimation of differences between levels of YKL-40 and CEA for individuals with or without comorbidity was done using a linear model with the biomarkers log transformed and adjusted for gender and age. The probability of colorectal cancer was estimated using logistic regression analysis modeling the probability for colorectal cancer. Goodness of fit was assessed using the Hosmer-Lemeshow test. Serum concentrations of YKL-40 were scored as a continuous variable using the log-transformed values (log-base 2) and CEA (log-base 2). ROC curves were estimated and the areas under the ROC curves (AUC) were calculated. Multivariable analyses (serum YKL-40, CEA, gender, comorbidity, and BMI) were performed on the entire set as well as subsets using logistic regression analysis. A clustering effect for center was included in the model. Model selection was done, including tests for possible interactions, and the final multivariable model only included significant covariates. Correction for multiple testing was assessed by the Bonferroni adjustment.

A 10-fold internal cross-validation was done for the multivariable models and demonstrated validity of the final model. P values less than 5% were considered significant. The database was managed and calculations performed using the SAS system (SAS v9.2; SAS Institute) and R (URL, http://www.R-project.org).

Results

Clinical characteristics and serum YKL-40

The most frequent reasons for individuals to be referred to the study were abdominal pain (46.0%), rectal bleeding (37.2%), and weight loss (18.1%). Some patients had more than one symptom. Of note, 184 subjects (4.1%) had CC, 109 (2.4%) had RC, 854 (19.0%) had adenomas, 1,176 (26.2%) had other nonmalignant findings (≥98% had diverticula), and 2,173 (48.3%) had no findings.

Of note, 184 subjects (4.1%) had CC, 109 (2.4%) had RC, 854 (19.0%) had adenomas, 1,176 (26.2%) had other nonmalignant findings (≥98% had diverticula), and 2,173 (48.3%) had no findings. Comorbidity was registered in 2,624 subjects, and the most frequent included previous adenoma (n = 324), arthrosis (n = 298), diabetes (n = 270), bronchitis (n = 227), and previous malignant disease >5 years ago (n = 138). The frequency of inclusion of subjects into the five different groups was not different over the 2 years inclusion period.

Serum YKL-40 was associated with age (Spearman-rank correlation, r = 0.48, P < 0.0001) and serum CEA (r = 0.22, P < 0.0001). Men had significantly higher serum YKL-40 levels than women (77 vs. 70 μg/L, P = 0.0002). Serum YKL-40 was higher (P < 0.0001) in subjects diagnosed with CC (median 126, 25%–75% 80–206 μg/L) and RC (104, 72–204 μg/L) compared with subjects with adenoma (84, 53–154 μg/L), other nonmalignant findings (79, 49–138 μg/L) and no findings (62, 41–109 μg/L). In patients

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with colorectal cancer serum YKL-40 increased with stage ($P < 0.0001$). There was no difference in serum YKL-40 between patients with right-sided CC ($n = 67$, median 115 μg/L) and left-sided CC (all left-sided combined $n = 117$, median 134 μg/L; sigmoid $n = 90$, median 130 μg/L; other left-sided $n = 27$, median 186 μg/L), but lowest values were found in patients with tumor localized to the rectum ($n = 109$, median 104 μg/L). The difference between patients with CC combined and RC was insignificant for serum YKL-40 and CEA.

Serum YKL-40 was higher in subjects with no finding, but with registered comorbidity compared with those not having registered comorbidity [19% higher, 95% confidence interval (CI), 12–17, adjusted for age and gender, linear modeling].

Serum YKL-40 and Risk of Colorectal Cancer

Pairwise univariate comparisons of serum YKL-40 and CEA levels (logistic regression) between the diagnostic groups are shown in Table 1. In addition, the same analyses are presented adjusted by age, gender, and comorbidity. The AUC under the ROC curve and the $P$ value (in parentheses) are presented. CC and RC are not significantly different whereas the malignant findings are significantly and substantially higher than the nonmalignant findings. The results were similar if the same calculations were performed, including only patients examined by colonoscopy (Table 1).

Serum YKL-40 and CEA levels in patients with colorectal cancer were also compared with the “healthy” individuals examined in this study, defined as having no endoscopy findings, no comorbidity, and were not using any prescribed drugs (logistic regression analysis). The AUC between patients with colorectal cancer and this “healthy group” was 0.77, and the AUC between patients with adenomas to this “healthy group” was 0.67. The corresponding AUC for serum YKL-40 and CEA were 0.56 and 0.72, respectively.

ROC curves comparing colorectal cancer with the remaining diagnostic groups for analyses unadjusted for confounding variables are shown in Fig. 1 for serum YKL-40 and CEA. Serum YKL-40 independently predicted colorectal cancer (OR, 1.53; 95% CI, 1.40–1.67; AUC = 0.68, $P < 0.0001$, logistic regression analysis). Restricting the analysis to subjects with no comorbidity increased the OR for serum YKL-40 to predict colorectal cancer (OR, 1.82; 95% CI, 1.58–2.08; AUC = 0.73, $P < 0.0001$). Combining serum YKL-40 and CEA demonstrated that both markers were significant (YKL-40; OR, 1.40; 95% CI, 1.16–1.40; CEA; OR, 1.92; 95% CI, 1.75–2.10; AUC = 0.75; the OR for a 2-fold difference in marker level).

### Table 1. Pairwise univariate comparisons of serum YKL-40, adjusted YKL-40, serum CEA, and adjusted CEA between the five diagnostic groups

<table>
<thead>
<tr>
<th>All patients</th>
<th>Adenoma</th>
<th>Nonmalignant</th>
<th>No finding</th>
<th>Colon cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum cancer</td>
<td>0.60* (0.0013)</td>
<td>0.63* (0.0001)</td>
<td>0.71* (0.0001)</td>
<td>0.54* (0.42)</td>
</tr>
<tr>
<td>0.68* (0.10)</td>
<td>0.72* (0.007)</td>
<td>0.81* (0.007)</td>
<td>0.61* (0.41)</td>
<td></td>
</tr>
<tr>
<td>0.71* (&lt;0.0001)</td>
<td>0.76* (&lt;0.0001)</td>
<td>0.75* (&lt;0.0001)</td>
<td>0.50* (0.60)</td>
<td></td>
</tr>
<tr>
<td>0.77* (&lt;0.0001)</td>
<td>0.82* (&lt;0.0001)</td>
<td>0.85* (&lt;0.0001)</td>
<td>0.61* (0.89)</td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>0.53* (0.060)</td>
<td>0.61* (&lt;0.0001)</td>
<td>0.63* (&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>0.56* (0.020)</td>
<td>0.67* (0.005)</td>
<td>0.67* (0.004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.56* (&lt;0.0001)</td>
<td>0.56* (&lt;0.0001)</td>
<td>0.69* (&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmalignant</td>
<td>0.58* (&lt;0.0001)</td>
<td>0.65* (&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66* (0.83)</td>
<td>0.68* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50* (0.90)</td>
<td>0.72* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66* (0.0009)</td>
<td>0.76* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No finding</td>
<td>0.72* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.78* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.72* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.82* (&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Values are the AUC under the ROC curve ($P$ value). The upper values are for all patients and the lower values are only patients examined by colonoscopy to caecum.
Multivariable analysis was done, including serum YKL-40, CEA, age, gender, BMI, comorbidity, and center. BMI was not significant \((P = 0.21)\), and therefore excluded from further analysis. Comorbidity was not a significant predictor of colorectal cancer \((P = 0.68)\). However, a significant interaction between comorbidity and serum YKL-40 was shown when comorbidity was included in the multivariable model \((P = 0.049)\). Serum YKL-40 was a predictor for colorectal cancer for those individuals not having comorbidity, whereas this was not the case for those with comorbidity, Table 2 (model 1).

This pattern was not seen for serum CEA, Table 2. Excluding patients with adenoma from the analysis resulted in improved discrimination, Table 2 (model 2). For model 1, the sensitivity was 65\% at 80\% specificity for the combination of serum YKL-40 and serum CEA restricted to patients without comorbidity. For model 2, the sensitivity was 68\% at 80\% specificity. A similar analysis, but only including CEA, showed a 62\% sensitivity at 80\% specificity and in a model with YKL-40 had a 58\% sensitivity at 80\% specificity. In both models, the Wald \(\chi^2\) statistic was much higher for CEA compared with YKL-40, suggesting that CEA contributes more to the data fit than YKL-40, although YKL-40 is significant. All primary endpoints that were significant remained significant when adjusted for multiple testing. Testing those undergoing a complete colonoscopy versus sigmoidoscopy demonstrated almost similar results \((P = 0.71)\).

**Discussion**

The main finding of the study is that high serum YKL-40 was associated with increased risk of colorectal cancer in subjects without comorbidity, and that elevated serum YKL-40 is a biomarker of increased risk of colorectal cancer and independent of serum CEA. Adjusting the risk estimate for potential confounders such as gender, age, BMI, and serum CEA did not change the risk estimate substantially.

Serum- and plasma-based biomarkers for early detection of individuals with colorectal cancer are attractive as they could be integrated into regular health check-up without the need for additional stool sampling, thereby increasing screening acceptance. Serum YKL-40 could be an alternative approach for the early detection of colorectal cancer. If the results are validated a high serum YKL-40 in an otherwise healthy individual could trigger a follow-up colonoscopy for a final diagnosis. Screening is defined as the early detection of disease in asymptomatic individuals. Our study population was selected because of clinical symptoms or risk factors associated with colorectal cancer, and this includes a selection bias. Finally, as we studied Caucasians only, our results may not necessarily apply to other ethnic groups. Misclassification of serum concentrations of YKL-40 will always occur to some extent even though we measured all samples in duplicate and had CVs of 4\% to 6\%. The YKL-40 measurements in serum were determined blindly, that is, without knowledge of clinical data and diagnosis. Serum YKL-40 is stable for more than 15 years if stored at minus 80˚C. The distribution of storage time was similar among the groups of colorectal cancer cases and noncases being compared.

YKL-40 is not specific for colorectal cancer and increased YKL-40 levels in blood are found in patients with other types of cancer and inflammatory diseases, such as cardiovascular diseases, inflammatory bowel diseases, diabetes, chronic obstructive lung disease, asthma, infections, and rheumatoid arthritis (3). As a consequence, the burden and severity of comorbidity of the subjects included in the present study may have a major role associated with interpretation of the results of serum YKL-40 determination. YKL-40 is not exactly similar to another biomarker of inflammation, serum CRP, because CRP and YKL-40 are produced by different cell types and in different parts of the body. CRP is produced in the liver by hepatocytes in response to elevated cytokine levels after an inflammatory stimulus, whereas YKL-40 is produced in tissues by

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**Table 2.** Multivariable analysis modeling the probability for colorectal cancer compared with those individuals with adenomas, nonmalignant findings or no findings (model 1), and excluding adenomas from the control group (model 2).

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Model 1 OR (95% CI)</th>
<th>P</th>
<th>Model 2 OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum YKL-40(^a) no comorbidity</td>
<td>1.25 (1.05-1.49)</td>
<td>0.012</td>
<td>1.30 (1.08-1.55)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum YKL-40(^a) with comorbidity</td>
<td>0.98 (0.84-1.14)</td>
<td>0.80</td>
<td>1.00 (0.85-1.17)</td>
<td>0.99</td>
</tr>
<tr>
<td>Serum CEA(^b)</td>
<td>2.48 (1.53-4.00)</td>
<td>&lt;0.0001</td>
<td>2.50 (1.51-4.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age(^c)</td>
<td>1.62 (1.44-1.83)</td>
<td>&lt;0.0001</td>
<td>1.67 (1.48-1.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (F vs. M)</td>
<td>0.47 (0.36-0.67)</td>
<td>&lt;0.0001</td>
<td>0.40 (0.30-0.53)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\)OR for 2-fold difference in serum YKL-40 level.

\(^b\)OR for 2-fold difference for serum CEA > 5 ng/mL.

\(^c\)OR for a 10-year difference in age.
different cells, including leucocytes, cancer cells, and cancer-associated macrophages. In severe infections, increases in plasma YKL-40 are observed before increases in plasma CRP. Thus, changes in plasma YKL-40 is independent of changes in plasma CRP.

If the serum YKL-40 concentrations in the patients included in the present study were compared with a large cohort of more than 3,000 healthy subjects from the general population (24), we found that patients with colorectal cancer had significantly higher (P < 0.0001) serum YKL-40 compared with these age-matched healthy subjects and that serum YKL-40 was higher than the normal age-matched 95% percentile in 20% of the patients with CC, in 15% with RC, in 11% with adenoma, in 9% with other findings, and in 8% of the patients with no finding. However, considerable potential sources of bias exist in comparisons of results from a case series (the present study) with an "external" control group (24), collected in another study with different admission criteria, under different conditions (i.e., not fasting) and with the presence of confounding.

At present the cutoff value for serum YKL-40 recommending colonoscopy cannot be answered in detail. We would recommend analysis of YKL-40 levels in a subsequent study, in which all subjects were offered colonoscopy as the only bowel examination. In that study, serum YKL-40 as a single marker or in combination with other markers would be validated and subsequently guidelines for recommending colonoscopy could be established.

Studies are required to better understand the functions of YKL-40 in cancer development and progression. YKL-40 plays several roles in different biologic processes such as inflammation, cell proliferation, differentiation, angiogenesis, apoptosis, and regulation of extracellular tissue remodeling (3, 9–20), processes important for the progression of cancer growth and metastatic potential (21). YKL-40 upregulates VEGF expression and blockade of YKL-40 activity decreases tumor growth, angiogenesis, and metastasis in xenografted SCID mice (13–15).

Chronic inflammation is a risk factor for development of colorectal cancer. IL6 stimulates YKL-40 secretion in healthy subjects (11). The expression of YKL-40 is highly induced in colonic epithelial cells and macrophages in areas with intestinal inflammation and enhances potentially pathogenic, but not nonpathogenic, bacterial adhesion, and invasion into colonic epithelial cells (17, 18). It has been suggested that growth-stimulating effects of epithelial YKL-40 in response to inflammatory or stressful stimuli are a critical and physiologic function in remodeling and maintaining the basic architecture of intestinal epithelium (25). Furthermore, the chitin-binding motif of YKL-40 is specifically associated with activation of Akt signaling in colonic epithelial cells, enhances the secretion of the proinflammatory cytokines IL8, and TNFα, and promotes proliferation of colonic epithelial cells (19).

In conclusions, serum concentrations of YKL-40 may be useful in the assessment of risk of colorectal cancer. However, serum YKL-40 cannot stand alone, but could be used in combination with other biomarkers, to initiate a follow-up colonoscopy for a definite diagnosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The study sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the article. The authors had full access to all the data in the study and had the final responsibility for the decision to submit the article for publication.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. Johansen, I.J. Christensen, L.N. Jørgensen, N. Brünner, H.J. Nielsen

Writing, review, and/or revision of the manuscript: J.S. Johansen, I.J. Christensen, L.N. Jørgensen, S. Laurberg, N. Brünner, H.B. Rahrt, K.T. Nielsen, H.J. Nielsen

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.S. Johansen, I.J. Christensen, K.T. Nielsen, H.J. Nielsen


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