Serum CA19-9 Is Significantly Upregulated up to 2 Years before Diagnosis with Pancreatic Cancer: Implications for Early Disease Detection

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Abstract

Purpose: Biomarkers for the early detection of pancreatic cancer are urgently needed. The primary objective of this study was to evaluate whether increased levels of serum CA19-9, CA125, CEACAM1, and REG3A are present before clinical presentation of pancreatic cancer and to assess the performance of combined markers for early detection and prognosis.

Experimental Design: This nested case–control study within the UKCTOCS included 118 single and 143 serial serum samples from 154 postmenopausal women who were subsequently diagnosed with pancreatic cancer and 304 matched noncancer controls. Samples were split randomly into independent training and test sets. CA19-9, CA125, CEACAM1, and REG3A were measured using ELISA and/or CLIA. Performance of markers to detect cancers at different times before diagnosis and for prognosis was evaluated.

Results: At 95% specificity, CA19-9 (>37 U/mL) had a sensitivity of 68% up to 1 year, and 53% up to 2 years before diagnosis. Combining CA19-9 and CA125 improved sensitivity as CA125 was elevated (>30 U/mL) in approximately 20% of CA19-9–negative cases. CEACAM1 and REG3A were late markers adding little in combined models. Average lead times of 20 to 23 months were estimated for test-positive cases. Prediagnostic levels of CA19-9 and CA125 were associated with poor overall survival (HR, 2.69 and 3.15, respectively).

Conclusions: CA19-9 and CA125 have encouraging sensitivity for detecting preclinical pancreatic cancer, and both markers can be used as prognostic tools. This work challenges the prevailing view that CA19-9 is upregulated late in the course of pancreatic cancer development. 

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related death and has the lowest survival rate for any solid cancer (~2%; refs. 1, 2). Surgical resection is the only chance of cure, but due to advanced stage at presentation only 20% of patients have resectable tumors (3). Of these, only 15% will have early-stage cancers (4, 5). When resection is possible followed by adjuvant therapy, the 5-year survival is better at 20% to 30% (6). It is clear that early detection of smaller tumors is necessary to improve resectability rates and survival. Indeed it was shown that if tumor size at detection can be reduced from 3 to 2 cm, then there is an increase in resectability from 7% to 83% with increased median survival from 7.6 to 17.2 months (7).

The serum marker CA19-9 (8–10) is the only biomarker used routinely in the management of PDAC. It has a 79% to 81% sensitivity and 82% to 90% specificity for diagnosis (11), with false-positive results observed in benign pancreaticobiliary diseases such as pancreatitis, cholangitis, and obstructive jaundice (12–14). Furthermore, CA19-9 is not expressed in 8% to 10% of the Caucasian population with the Lewis a-b-genotype, as the CA19-9 epitope is the sialylated Lewis A blood group antigen (14, 15). Despite this, CA19-9 has proved useful for disease management, in which increased posttherapy levels indicate poor prognosis and poor therapy response (16, 17). Moreover, the levels of CA19-9 in the months and years before PDAC diagnosis have not been examined, leaving its capacity to contribute to early diagnosis untested. Other reported noninvasive diagnostic and/or prognostic markers of pancreatic cancer that have been tested alone or in combination, include CA125 (18–21), CEA (22), CEACAM1 (23), MUC1 (24), OPN/SPP1 (25), MUC1/GDF15 (26), REG3A/PAP1 (27, 28), and PKM2 (29). As yet, the clinical utility of these markers remains to be determined and most require further multicenter validation.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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A major shortcoming of cancer biomarker studies aiming to address early detection is a lack of appropriate samples. Biomarkers tested in samples taken from patients diagnosed with cancer and benign or healthy controls only address potential use for differential diagnosis. Samples collected before diagnosis are preferential, enabling early changes to be detected, with consistent rising levels in the lead up to diagnosis adding confidence to the discovery. The serum samples used in this study come from a repository collected as part of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomized controlled trial of ovarian cancer assessing impact of screening on mortality using transvaginal ultrasound and serum CA125 interpreted using the Risk of Ovarian Cancer Algorithm (ROCA). Preclinical samples from participating women who subsequently developed PDAC were available for evaluating CA19-9, CA125, CEACAM1, and REG3A for early diagnosis.

Materials and Methods

Serum samples

This nested case–control study was approved by the Joint UCL/UCLH Research Ethics Committee A (ref. 05/Q0505/57). Written informed consent was obtained from donors and no data allowing identification of patients were provided. The study set comprised serum from women recruited to UKCTOCS between 2001 and 2005 and collected according to a standard operating procedure (30, 31). Trial participants at enrollment were postmenopausal women ages 50 to 74 who had no family history of ovarian cancer. All participants were “flagged” with the national agencies for cancer registrations and deaths using their NHS number. Women subsequently diagnosed with pancreatic cancer (cases) were identified by cross-referencing with the Health and Social Care Information Centre cancer registry codes and death codes (ICD 10 C25.0/1/2/3/9). Initially, 171 cases were identified (with 304 associated samples) that had not been registered as having any other cancer since randomization. Matched noncancer controls (i.e., with no cancer registry code) from individual women (1/case sample; n = 304) were selected on the basis of collection date and center to minimize variation due to handling. For the 171 cases, confirmation of diagnosis was sought from general practitioners and consultants through questionnaire and from the Hospitals Episode Statistics database. As a result, 17 cases were excluded that did not have a confirmed diagnosis of PDAC. The resulting study set was 261 serum samples from 154 women subsequently diagnosed with PDAC up to 6.5 years later and 304 matched control sera from 304 women. Of note, 119 cases provided single samples and 35 provided two or more serial samples.

Statistical analysis

GraphPad Prism and MedCalc software were used for statistical analyses. For normally distributed data, the Student t test was used to assess significance of differences, otherwise the Mann-Whitney U test was used. The Fisher exact test was used to assess significance of associations for noncontinuous variables. Correlation analysis used the Spearman rank test. All P values <0.05 were considered significant. Receiver operating characteristic (ROC) curves were constructed for each marker and combinations to assess diagnostic accuracy. Kaplan–Meier analysis was used to examine biomarker levels in relation to survival using time from sample collection to death.

Results

Study set characteristics

There was no significant difference in time to centrifugation between case and control samples, whereas there was a difference...
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the majority of cases (Supplementary Data and Supplementary Fig. S2), whereas none showed increasing CEACAM1 or REG3A.

Markers were analyzed according to time to diagnosis (grouped as 0–0.5, 0.5–1, 1–2, 2–3, 3+, 0–4+ (all samples), 0–1, and 1–4 years). In cases in which serum was obtained <12 months before diagnosis, median CA19-9 was 43.2 U/mL [interquartile range (IQR) 5.7–136.2 U/mL] compared with 3.1 U/mL (IQR 0.6–6.9 U/mL) in controls (P < 0.0001; AUC = 0.82; Fig. 2). For CA125, median values were 24.1 U/mL (IQR 12.9–47.9) for cases and 12.8 U/mL (IQR 9.3–14.5) for controls (P < 0.0001; AUC = 0.78).

CEACAM1 (P = 0.045; AUC = 0.71) and REG3A (P = 0.022; AUC = 0.73) were only significantly elevated in the 6 months before diagnosis. CA19-9 and CA125 were also raised in the 0.5- to 1-year prediagnosis group (P = 0.0016; AUC = 0.80 and P = 0.0167; AUC = 0.73, respectively), but not >1 year. There were no significant associations for any of the markers with respect to time to centrifugation, age, BMI, smoking, alcohol consumption, HRT, or oral contraceptive pill (OCP) use, except REG3A, which correlated with age (p = 0.31; P < 0.001) in the controls.

Sensitivities for detection of PDAC were calculated using selected cutoffs (Table 3). CA19-9 (>25 U/mL) was the best performing marker, discriminating cases from controls with sensitivity/specificity (SN/SP) of 70.6%/95.9% and 64.7%/95.5% in the 0 to 0.5 and 0.5 to 1 years before diagnosis (Table 3). The SN/SP for detection of PDAC with CA125 (>20 U/mL) in these time periods was somewhat poorer at 70.6%/90.0% and 52.9%/86.4%, respectively. CEACAM1 and REG3A were poor at detecting cancer compared with CA19-9 or CA125; for the 0 to 0.5 years group, the SN/SP for CEACAM1 was 53.3%/83.3% (>50 ng/mL), whereas for REG3 it was 29.4%/90% (>13 ng/mL). Combining markers showed the model “CA19-9>37 U/mL or CA125>30 U/mL” provided the highest sensitivities at >90% specificity; 57.1% for...
Table 3. Performance of cutoff models for the discovery set

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NOTE: Darker shading denotes higher values. Values in the box indicate the best-performing early-detection model. See Supplementary Data and Supplementary Table S1 for numbers of test-positive cases and controls for using the CA19-9 >37 U/mL and CA125 >30 U/mL models.
Table 4. Performance of cut-off models for restricted validation set

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</table>

NOTE: Darker shading denotes higher values. Values in the box indicate the best-performing early-detection model. See Supplementary Data and Supplementary Table S1 for numbers of test-positive cases and controls for using the CA19-9 >37 U/mL and CA125 >30 U/mL models.
the 0- to 1-year group [positive predictive value (PPV) 90.9%; OR = 26.67, 95%CI 5.6–128.2] and 44.2% for the 0- to 2-year time group (PPV 92.0%; OR, 24.59; 95%CI 5.4–111.4), but were only marginally better (and not significantly so) than using CA19-9 alone (Table 3). Adding CEACAM1 and/or REG3A into models decreased specificity with little improvement in sensitivity (data not shown). Logistic regression showed the best combined model (CA19-9, CA125, and CEACAM1) had an AUC of 0.88 (SE, 0.042; 95% CI, 0.79–0.95) for the 0- to 1-year group, but was not significantly higher than using CA19-9 alone (AUC = 0.82). Together, these data indicate that CA19-9, and possibly CA125, may be useful in predicting PDAC up to 24 months in advance of diagnosis.

Validation of CA19-9 and CA125 as early detection biomarkers

CA19-9 and CA125 were further assessed in a validation set comprising 168 samples from 101 cases. This was subsequently restricted to 138 samples by removing all but one serial samples (at random) from the same case/woman that fell within the same time group (Table 2). In this restricted set, CA19-9 was significantly higher in cases than controls for the 0–0.5, 1–2, 2–3, and 3+ year time groups, though failed significance for the 0.5- to 1-year group (Supplementary Data and Supplementary Fig. S3). CA125 was significant for the 0 to 0.5 and 3+ year time groups. The simple cutoff model “CA19-9 >37 U/mL or CA125 >30 U/mL” applied to this dataset gave 56.7% sensitivity and 90.6% specificity for the 0- to 1-year group (PPV = 77.3%; OR, 12.55; 95% CI, 3.89–40.48), compared with 50% sensitivity and 94.3% specificity using CA19-9 alone (PPV = 83.3%; OR, 16.67; 95% CI, 4.25–65.43; Table 4). For the 0- to 2-year group, sensitivity was 40.6% and specificity 90.5% (PPV = 74.3%; OR, 6.54; 95% CI, 2.80–15.28). Logistic regression combining CA19-9 and CA125 gave AUCs of 0.90 and 0.76 for the 0 to 0.5 and 0 to 1 year groups, respectively, but was not significantly higher than using CA19-9 alone. Thus, CA125 adds little discriminatory power in combined models. Despite this, 13 of 53 positive cases in the validation set were detected solely using CA125.

Our intention was also to build algorithms based on available serial/longitudinal data. ROCA used in UKCTOCS (32, 33) could not be developed for CA19-9 due to lack of serial control samples. A Parametric Empirical Bayes algorithm (34) applied to the combined dataset gave sensitivities of 19% and 17% (at 0.5- to 1-year group, respectively, but twofold higher using combined models versus CA19-9 alone, differences were not significant.

Prognosis

The four markers were investigated as prognostic factors using time from sample collection to death in cases in which pancreatic cancer was cited as the primary or contributory cause of death. First, poor and good prognosis case samples were, respectively, defined as falling below and above the median time from sample collection to death (30.5 months). Both CA19-9 and CA125 were significantly elevated in the poor prognosis group, whereas CEACAM1 and REG3A were not (data not shown). Kaplan–Meier analysis confirmed a significant difference in survival curves for CA19-9 (cutoff 40 U/mL; log-rank test P < 0.0001; HR, 2.69; 95% CI, 1.84–3.91) and CA125 (cutoff 25 U/mL; log-rank test P < 0.0001; HR, 3.15; 95% CI, 2.11–4.69), confirming them as prognostic markers (Fig. 3). Median survival times from collection were 14.5 versus 36.0 months for CA19-9 and 14.0 versus 35.0 months for CA125.

Discussion

To our knowledge this is the first study to show that serum CA19-9, CA125, CEACAM1, and REG3A are significantly elevated before PDAC diagnosis. To our surprise, in 16% of cases, CA19-9
was elevated (>37 U/ml) 2 to 3 years before diagnosis, with sensitivity increasing toward diagnosis. The PPV of CA19-9 was 90% up to 1 year before diagnosis and >80% up to 2 years, depending on the cutoff level used. CA125 also increased in preclinical disease, and although combined models gave only modest increases in performance versus CA19-9 alone, CA125 detected 13% of CA19-9-negative cases; some of which are likely to be Lewis antigen negative. Notably, combined models gave average lead times up to 23 months. Together, our data support the notion that a panel of markers, including CA19-9, may be beneficial for earlier detection of pancreatic cancer with potential use in screening.

Three studies have explored the utility of serum CA19-9 levels as a screening tool for pancreatic cancer (35–37). Kim and colleagues assessed CA19-9 in 70,940 asymptomatic individuals identifying four cancers among 1,063 individuals with elevated CA19-9 (>37 U/ml; PPV = 0.9%; sensitivity 100%; specificity 98.5%). Notably, a higher proportion of women (2.5%) compared with men (0.5%) had elevated CA19-9. This did not increase with age in women, as was observed here. Given the low predictive value of CA19-9 and low prevalence of pancreatic cancer in the general population, it was concluded from these studies that CA19-9 testing alone has no utility as a screening tool. However, here CA19-9 elevations were noted up to 36 months before diagnosis, indicating its potential as a first-line test for early detection that may increase the number of patients with resectable disease. These results need to be independently validated. Annual CA19-9 blood testing may also benefit high-risk populations such as those from kindred with family history of pancreatic cancer. Guidelines for the surveillance of these family members are not established, although there are recent studies assessing outcomes of screening these high-risk populations (38, 39).

Serum CA125 has been evaluated as a marker for detecting malignant versus benign pancreatic tumors with a reported sensitivity of 60.8% and specificity of 83.3% (21). Combining CA19-9 and CA125 gave values of 87.8% and 77.8%, respectively, with the authors concluding that test results should be interpreted in reference to imaging. A similar study reported a sensitivity of 56.9% and specificity of 77.6%, with CA125 providing a limited contribution in jaundiced patients (40). Herein, in the prediagnostic setting we show that CA125 performed with higher specificity, providing additional sensitivity in combination with CA19-9.

CEACAM1 is expressed in pancreatic carcinoma in situ lesions, and, thus, has early-stage marker potential (23). It was further shown in this previous study that serum CEACAM1 had superior accuracy to CA19-9 in clinical samples from patients with PDAC. Although the function of CEACAM1 remains unclear, several studies have identified its aberrant expression in a variety of cancers often with conflicting reports (41–43). Herein, CEACAM1 seems to be upregulated in pancreatic adenocarcinoma, although is elevated in serum closer to diagnosis as compared with CA19-9. CEACAM1 did not significantly improve classification in combined models and it was not a prognostic factor. We conclude that serum CEACAM1 is not an early marker of pancreatic cancer.

REG3A expression has been associated with pancreatic inflammation (44) and cancer (27, 28, 45). In the latter study, REG3A had 90% sensitivity and 82.8% specificity for discriminating PDAC cases from healthy controls and was not correlated with the CA19-9 level or associated with concomitant pancreatitis or jaundice. In the present study, REG3A was discriminatory within 6 months of diagnosis, but was rarely elevated independently of CA19-9. In summary, REG3A is a poor early marker, adding little in combined models.

Our data also confirm CA19-9 as a prognostic marker, as we show that prediagnosis cases with levels <40 U/ml had a prolonged median survival (from 14.5 to 36 months using time from blood draw), and is in agreement with published data (reviewed in ref. 11). CA125 was similar in predicting overall survival, and, thus, also seems to be a prognostic factor in pancreatic cancer. This is supported by the notion that CA125 plays a direct role in the progression and dissemination of pancreatic tumor cells (46).

Our study has several limitations. First, only postmenopausal women were studied, and hence may not reflect the utility of pancreatic tumor markers in the general population. Second, there was insufficient information on grading, staging, tumor size, and treatment to be able to examine correlations with the markers. Indeed, it is likely that many of the test-positive cases were at an advanced stage of disease when tested, in agreement with observed correlations between serum CA19-9 levels and pancreatic tumor burden (47); although this may not always hold true (48). Third, the number of cases (and controls) with serial samples was insufficient to accurately build and assess longitudinal algorithms. Fourth, there was a lack of data on benign morbidity in both the case and control groups for which CA19-9 may be elevated. Despite these limitations, the study is unique in that preclinical samples were investigated, allowing an objective assessment of how serologic markers change during disease progression. Indeed, our findings suggest that raised CA19-9 can be detected early in the course of PDAC development when tumor size is likely to be smaller and when survival outcomes are improved (7). Importantly, although the majority of test-positive cases in our study had elevated CA19-9 (and/or CA125) within 1 year of diagnosis, likely indicating advanced disease, these patients still went undiagnosed. This alludes to the nonspecific nature of the symptoms of pancreatic cancer, but also raises the possibility of an earlier diagnosis that may improve outcome. Although one recent study has assessed prediagnostic PDAC samples (from the prospective EPIC cohort), reporting that autoantibodies against ezrin seem early in PDAC development, CA19-9 levels were unfortunately not reported in the 16 cases examined (49).

Our data also suggest that that HRT use at randomization was associated with lowered risk of pancreatic cancer. The apparent protective effect of HRT use is at odds with two large prospective cohort studies showing no association (50, 51). The reason for this discrepancy is unclear, but may be a chance association given the much lower number of controls used in the present study.

In conclusion, CA19-9 may have clinical utility in screening for pancreatic cancer as a first-line test, particularly if used longitudinally in higher risk or symptomatic populations, whereas CA125 measurements may improve its performance and increase its prognostic value. It is unclear whether the use of other screening investigations (endoscopic ultrasound scan, CT scan) would have allowed earlier diagnosis (i.e., at a still resectable state) when applied at the time of a CA19-9 or CA125 rise and this would need to be trialed in future studies.
Disclosure of Potential Conflicts of Interest

I.J. Jacobs reports receiving other commercial research support from Becton Dickinson, has ownership interest (including patents) in Abcodia and ROCA ALGORITHM, and is a consultant/advisory board member for Abcodia and Becton Dickinson. No potential conflicts of interest were disclosed by the other authors.

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Serum CA19-9 Is Significantly Upregulated up to 2 Years before Diagnosis with Pancreatic Cancer: Implications for Early Disease Detection


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