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Serum YKL-40: a New Potential Marker of Prognosis and Location of Metastases of Patients With Recurrent Breast Cancer

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YKL-40 is a recently discovered glycoprotein which is related in amino acid sequence to the chitinase protein family, but has no chitinase activity. Although the function of YKL-40 is presently unknown, the pattern of its expression by some tissues suggests that YKL-40 could function in tissue remodelling. The diagnostic features and relation to survival of serum YKL-40 have not been examined previously in human malignancies. In the present study YKL-40 was measured in serum obtained from 60 patients at the time that breast cancer recurrence was suspected. The median serum YKL-40 in patients with visceral or bone metastases was 328 and 157 μg/l, respectively and significantly higher compared to controls (99 μg/l, $P < 0.001$). Kaplan–Meier survival curves demonstrated that survival rates after 18 months were 24% for patients with high serum YKL-40 (>207 μg/l = the 95 percentile of controls) and 60% for patients with normal serum YKL-40. The significance of the difference between the shorter survival of patients with high serum YKL-40 and the longer survival of patients with normal serum YKL-40 was high ($P < 0.0009$). When evaluated with other prognostic factors of survival after recurrence of breast cancer, serum YKL-40 and serum lactate dehydrogenase (LDH) were the most significant independent factors. The results indicate that determination of serum YKL-40 can be used as a prognostic marker related to the extent of disease and survival of patients with recurrence of breast cancer. In addition, the serum YKL-40 level may be of value in the follow-up of patients with breast cancer and in evaluating potential metastatic spread.

Key words: breast cancer, tumour marker, bone metastasis, survival, prognosis
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INTRODUCTION

BREAST CANCER is the most frequent malignant disease in women, with growing incidence and mortality rates in Western countries. In the follow-up of these patients the early detection of recurrence may be important for successful treatment and prognosis. A wide variety of substances has been evaluated for their possible use as markers for breast cancer and until now the most used biochemical markers are the carcinoembryonic antigen (CEA) and the tumour-associated antigen CA 15-3 [1–4]. No biochemical marker has been found for screening or the primary diagnosis of breast cancer, but determinations of serum CEA and CA 15-3 seem to be of some value in evaluating development of recurrence and also in monitoring the disease activity during treatment of patients with advanced breast cancer [1]. However, neither CEA nor CA 15-3 can be used to predict the prognosis of the patients with relapse of breast cancer or to determine whether the metastatic spread is mainly located to bone or viscera.

The skeleton is the main site of metastases in patients with breast cancer [5]. The most used biochemical markers for bone metastases have been serum total alkaline phosphatase, bone alkaline phosphatase [6] and bone Gla protein (BGP, osteocalcin) [7–9]. However, these markers show considerable variation in patients with metastatic breast cancer and an increased serum BGP level in patients with recurrence of breast cancer does not reflect the presence of bone metastases [9, 10].

YKL-40 is a recently discovered glycoprotein which is related in amino acid sequence to the chitinase protein family [11, 12], but has no chitinase activity. YKL-40 was initially discovered as a prominent protein in the whey secretions of non-lactating cows [13] and as a protein secreted in large amounts by the MG-63 human osteosarcoma cell line [14], by cultures of human synovial cells [15], and by cultures of human cartilage cells [11, 12]. Northern blot analyses have shown that YKL-40 mRNA is expressed strongly by liver, weakly by brain, kidney and pla-

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centa, and at undetectable levels by heart, lung and skeletal muscle [12].

Although the function of YKL-40 is presently unknown, the pattern of its expression by some tissues suggests that YKL-40 could function in tissue remodelling. High levels of YKL-40 have been found by radioimmunoassay in the synovial fluid and serum of patients with osteoarthritis and rheumatoid arthritis [11], which are both diseases characterised by accelerated cartilage degradation. Northern blot analyses have shown that YKL-40 mRNA is in fact undetectable in normal human articular cartilage, but is prominent in cartilage from patients with rheumatoid arthritis [12]. The YKL-40 protein is rapidly induced in normal human cartilage tissue following the transition to cell culture conditions [12], further supporting a YKL-40 function in the cartilage remodelling response. The pattern of expression in breast secretions [13] supports a possible function for YKL-40 in breast tissue remodelling, since the whey of non-lactating cows is a secretion of the mammary gland during the remodelling and involution of breast tissue which follows the cessation of lactation.

We have recently developed a sensitive and specific radioimmunoassay (RIA) for the measurement of human YKL-40 in serum [11]. The diagnostic features and relation to survival of serum YKL-40 have not been examined previously in human malignancies. In the present study we have assessed whether the level of serum YKL-40 reflects disease activity, localisation of metastases and prognosis of survival in patients with recurrent breast cancer.

PATIENTS AND METHODS

YKL-40 was assayed in serum samples collected in a clinical investigation carried out between October 1987 and May 1991 for staging patients with recurrent breast cancer [10]. Hospital records were reviewed in June 1993. All patients were followed until death or June 1993.

Patients

The study included 60 women, aged 29–78 years (one was older than 69 years). They were all potential candidates for systemic antineoplastic treatment. The criteria of entry were (1) suspicion of distant metastases (i.e. suspicion of first recurrence) after primary treatment of localised breast cancer (n = 47); (2) locally advanced disease or distant metastases at the time of initial diagnosis of breast cancer (n = 6); or (3) suspicion of metastases to bone in patients who had been treated for their first recurrence of breast cancer 9–27 months earlier (n = 7; these patients had their first recurrence to soft tissue only). Patients with previous or concomitant cancers other than breast cancer were not eligible. A total of 39 patients (65%) had received adjuvant therapy (36 were in criterion 1 at entry, 1 was in criterion 2 and 2 were in criterion 3); 56% of these patients had received combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil. 12 patients (20%) received radiotherapy and 18 (30%) endocrine therapy.

Mastectomy specimens were macroscopically and microscopically evaluated according to uniform protocolled guidelines. The histological evaluation of primary tumour included histological typing according to WHO recommendations [16]. Ninety percent of the patients had ductal carcinomas and these were classifed as well (DA = I), medium (DA = II), and poorly (DA = III) differentiated according to the grading system of Bloom and colleagues [17] using the following histological factors: tubule formation, pleomorphism and mitotic nuclei.

Further details about the patients are given elsewhere [10]. The protocol was approved by the local Ethical Committee of Copenhagen County Hospitals. Informed consent according to the Helsinki II Declaration was obtained from all patients before entry into the study.

Methods

The staging programme included history, physical examination, blood test, ultrasound scanning of the liver, chest X-ray, radiological bone survey, ^{99m}Tc-dicarboxypropanediphosphonate (DPD, Tecos) bone scintigraphy, ^{99m}Tc nanocoll (Soleo Basle Ltd) bone marrow scintigraphy, and bilateral posterior iliac crest biopsy.

Laboratory analysis. Blood samples were taken at the time when recurrence of breast cancer was suspected (see the three criteria of entry into the study). The samples were either analysed immediately or stored at −20°C until analysis.

Serum YKL-40 was determined by RIA [11]. The antiserum was raised in rabbits immunised with purified intact human YKL-40, and homogeneous human YKL-40 was used for standard and tracer. The tracer was prepared by the iodogen method and antibody-bound and free ^{125}I-labelled YKL-40 were seperated by use of a donkey anti-rabbit antibody-coated cellulose suspension. The intra- and interassay variations were <6.5% and <12%, and the sensitivity 10 μg/l [11]. Reference intervals for serum YKL-40 concentrations in 120 healthy women (aged 18–69 years) were established in another study [18]. Serum YKL-40 levels in these control women did not show any variation with age, either in average level or in range.

Serum BGP was determined by an enzyme-linked immunosorbent assay (ELISA) using polyclonal rabbit antibody to bovine BGP [19]. Haemoglobin, leucocytes, thrombocytes, alkaline phosphatase (AP), lactate dehydrogenase (LDH), aspartate aminotransferase (ASAT), albumin, prothrombin and calcium were determined in blood or serum by routine methods.

The oestrogen receptor content was measured by a dextran-coated charcoal assay according to the methods recommended by the EORTC [20]. Tumours were considered positive when at least 10 fmol/mg cytosol protein were present. The oestrogen receptor content was in all cases measured in histologically verified malignant tissue from the primary tumour.

Statistical analysis

The statistical analysis was performed using the SPSS Software and MedStat packages. Results are expressed as median and percentiles. Comparisons between groups were made using the non-parametric Mann–Whitney test and the Kruskal–Wallis test. A two-tailed P value of <0.05 was considered significant.

Survival was measured from the time of registration in the staging protocol to death or last follow-up. Survival analysis was performed using the Kaplan–Meier method. Univariate comparisons of survival were made using the log rank test [21]. The independent prognostic effect of serum YKL-40 together with other significant univariate prognostic factors were assessed using the Cox proportional hazards model [22]. Initially, univariate prognostic factors (P < 0.20, log rank test) were considered simultaneously. The cut-off of P = 0.20 at this stage of analysis ensured that variables which had some prognostic value were not disregarded prematurely. The final model was achieved using the maximum partial likelihood method with backward elimination (P value to remove, 0.10) and forward selection (P value to enter, 0.15). Cumulative hazard plots were made in order to assess the assumption of proportional death intensities.

Cut-off levels. For serum YKL-40 the 95 percentile value from the control group was used as the cut-off level (207 μg/l). The cut-off levels for the other biochemical analyses were chosen as the standard limit between normal and elevated values: ≤2.0, 2.1–2.9, >2.9 mmol/l for serum BGP; 7.0 mmol/l for haemoglobin; 275 U/l for serum AP; 400 U/l for serum LDH; 30 U/l for serum ASAT; 600 mg/l for serum albumin; 100% for serum prothrombin; and 1.35 mmol/l for serum ionised calcium.

RESULTS

Recurrence

All serum analyses reported here were made on blood samples obtained from each of 60 women at the time of entrance into the study. 47 of these women entered the study at the time that breast cancer recurrence was first suspected (criterion 1). Further tests revealed that six of these women did not in fact have breast cancer recurrence. Six women entered the study because they had locally advanced disease or distant metastases at the time of initial breast cancer diagnosis (criterion 2) and seven women entered the study because they were suspected to have bone metastases 9–27 months after their first recurrence of breast cancer (criterion 3). Of these 60 women, 30 (50%) had soft tissue recurrence; bone metastases (as detected by X-ray or bone biopsy) were found in 40 patients (67%); and visceral metastases (lung, pleura or liver) occurred in 19 (32%) patients.

Location of metastases

Figure 1 shows the level of serum YKL-40 in each of the 60 study participants when grouped into categories defined by the sites of metastasis. The Kruskal–Wallis test of the YKL-40 levels between the groups was significant ($P = 0.03$). The serum YKL-40 levels in the 6 study participants who proved not to have breast cancer recurrence were within the normal range. In the patients with breast cancer metastases, the highest YKL-40 levels were seen in patients with metastases to viscera (± bone metastases and ± soft tissue metastases). The median serum YKL-40 level in these 19 women, 328 μg/l, was significantly higher than the level in age-matched control women (99 μg/l, $P < 0.001$). The median YKL-40 level in the 25 women with metastases to bone but not to viscera, 157 μg/l, was also significantly above the level in the age-matched control women ($P < 0.001$), while the median serum YKL-40 level in women with soft tissues as the only metastasis site, 123 μg/l, was not significantly elevated. The percentage of patients with serum YKL-40 levels above the 95 percentile for control women varied somewhat with site of metastasis, 58% for viscera, 48% for bone. Only 2 patients with metastases to soft tissue had elevated serum YKL-40 and 1 of these patients had a very high serum YKL-40 concentration (904 μg/l) and died after 5 months. At the time of blood sampling this patient had pleural effusion but microscopy did not reveal malignant cells.

Figure 2 shows the individual serum YKL-40 concentrations in relation to the number of bone metastases detected on X-ray examination for the subset of patients who did not have visceral involvement ($n = 41$). 4 patients with a normal X-ray had a positive bone scanning and biopsies revealed bone marrow carcinosis, 2 of these patients had elevated serum YKL-40. If these 4 patients were removed from the statistical analysis, serum YKL-40 was significantly elevated in patients with two or more bone metastases (median 233 μg/l) compared with patients with only one (120 μg/l, $P < 0.03$) or no bone metastases (121 μg/l, $P < 0.01$) detected on X-ray.

Survival after recurrence

At the time of analysis, 9 of the 60 patients were still alive. The median survival after recurrence in the 41 patients with first recurrence of breast cancer was 16 months (25–75 percentiles: 9–26 months). For the entire group of 60 patients, which includes 19 women who entered the study according to criteria other than the first recurrence of breast cancer (see Patients and Methods), the median survival measured from time of entry into

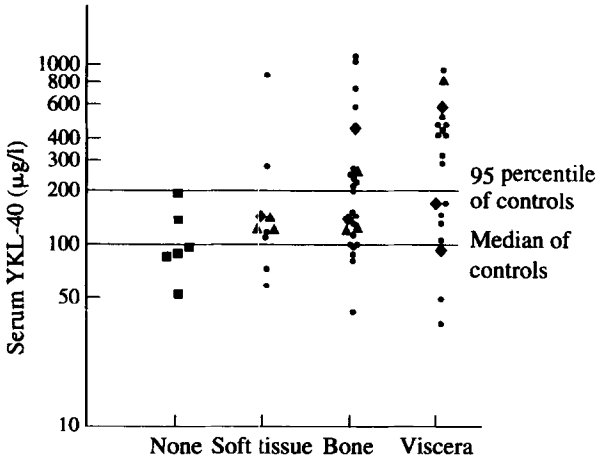

Figure 1. Serum YKL-40 concentrations (logarithmic scale) in patients staged for recurrence of breast cancer in relation to sites of metastases. None, the 6 women who proved not to have breast cancer recurrence; soft tissue, the 10 women with metastases to soft tissues only; bone, the 25 women with metastases to bone (± soft tissue); viscera, the 19 women with metastases to viscera (± soft tissue or bone). ● Patients who entered study at time of first breast cancer recurrence; ■ patients who entered at the time recurrence was suspected but proved not to have recurrence of breast cancer; ◆ patients who entered study at time of initial diagnosis and had locally advanced disease or distant metastases at the time of initial diagnosis; ▲ patients who entered the study 9–27 months after the first recurrence (to soft tissue only) (see Patients and Methods).

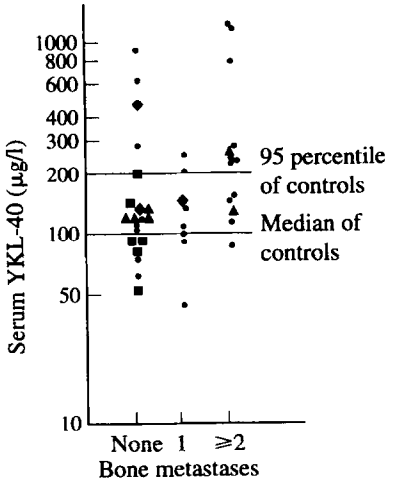

Figure 2. Serum YKL-40 concentrations (logarithmic scale) in patients staged for recurrence of breast cancer in relation to radiographically determined presence of bone metastases. None, the 6 women who proved not to have metastases plus the 10 women with soft tissue metastases only plus the four women who had metastases to bone verified by bone scintigraphy, bone marrow scintigraphy or bone biopsy, but not by X-ray; 1 and ≥2 bone metastases, the 21 patients who had one or more radiographically detectable bone metastases but no visceral metastases. Legend to symbols, see legend to Figure 1.

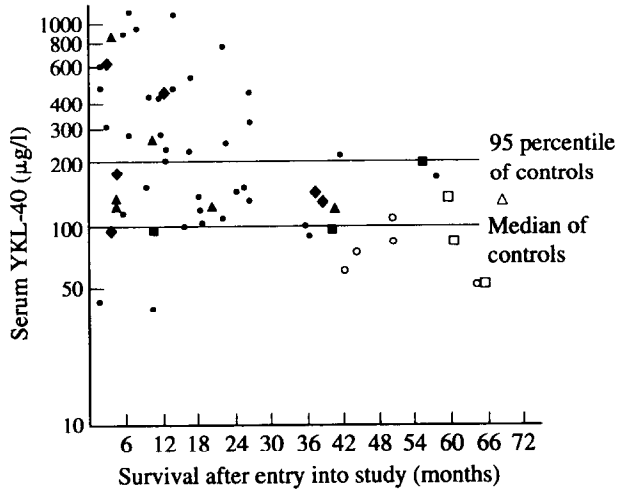

Figure 3. Relationship between YKL-40 levels (logarithmic scale) in serum from patients obtained at the time of entry into the study and months of survival after this time. Closed symbols, dead at time of data analysis; open symbols, alive. Legend to symbols, see legend to Figure 1.

the study was also 16 months (25–75 percentiles: 7–40 months). Figure 3 shows the YKL-40 level in serum obtained at the time of entry into the study in relation to months of survival after this time for all 60 women. As can be seen from this figure there is a striking relationship between high serum YKL-40 levels at the time of entry into this study and reduced survival. This correlation holds even if attention is focussed on the subset of 41 women who in fact entered the study at the time of first breast cancer recurrence (symbols ● and ○ in Figure 3).

Figure 4 shows the Kaplan–Meier plot for the survival time from first breast cancer recurrence for the subset of 41 women whose serum YKL-40 levels were determined at this time.

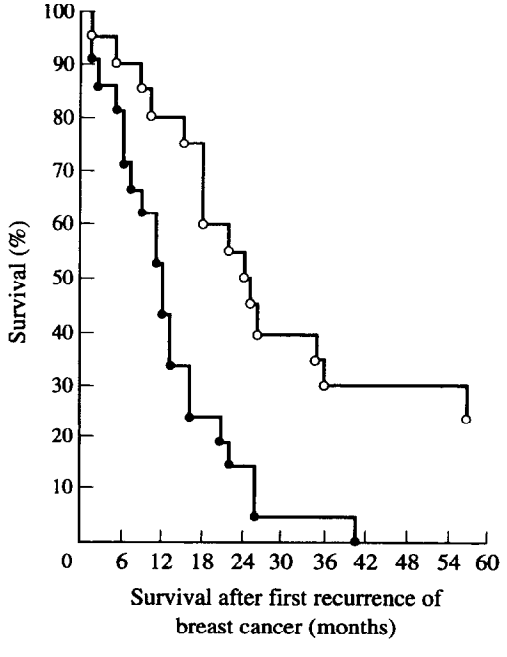

Figure 4. Kaplan–Meier plot of survival from the date of first cancer recurrence according to the level of YKL-40 in serum obtained at the time of recurrence of breast cancer. The survival curves are shown for the 20 patients with normal serum YKL-40 (○ ≤ 207 µg/l) and 21 patients with elevated serum YKL-40 (● > 207 µg/l).

Although the number is small, the survival time for the 21 patients whose serum YKL-40 levels were above the 90 percentile of age-matched control women is dramatically shorter than for the 20 patients with a normal serum YKL-40 level. The survival rate at 18 months after recurrence was 60% for patients with normal and only 24% for patients with high serum YKL-40 ($P < 0.0009$).

The univariate survival data for 17 variables in all 60 patients is summarised in Table 1. Age, degree of anaplasia, serum LDH, serum AP, serum albumin and serum YKL-40 were all significant univariate prognostic factors.

Cox regression analysis

The initial Cox model included univariate significant blood tests and duration of recurrence-free interval. Serum albumin was not included because the value was only recorded for 40% of the patients. The initial model showed that only serum YKL-40 and serum LDH were independent prognostic factors on survival after recurrence in the 41 patients with first recurrence of breast cancer (Table 2). Backward and forward elimination procedures eliminated all covariates except serum YKL-40 ($P = 0.004$) and serum LDH ($P = 0.037$). If all 60 patients were included in the calculations, backward and forward elimination procedures again eliminated all covariates except serum YKL-40 ($P = 0.001$) and serum LDH ($P = 0.01$). Based on the estimated survival pattern for the four combinations of the two serum YKL-40 levels and the two levels of serum LDH, the calculated survival rate after 12 months for patients with normal serum LDH and normal and elevated serum YKL-40 was 83 and 56%, respectively. Among patients with increased serum LDH levels the 12 months survival rate was 67% for patients with normal and 28% for patients with high serum YKL-40.

DISCUSSION

Although this study was initiated because of our expectation that YKL-40, an abundant secretory protein of MG-63 human osteoblastic osteosarcoma cells, could be a marker for breast cancer metastases to bone, serum YKL-40 proved to be a marker for an aspect of breast cancer itself rather than for bone metastasis.

The sensitivity and specificity of a potential biochemical marker may vary considerably according to different cut-off values. We have selected the cut-off for serum YKL-40 to the 95 percentile of healthy age-matched women. We found that the sensitivity of serum YKL-40 in detecting metastatic disease seems to vary with the localisation of metastases. Elevated serum YKL-40 levels (>207 µg/l) were seen in 46% of the patients with breast cancer recurrence and serum YKL-40 elevations seem to be more frequent in patients with higher tumour burden, i.e. 58% in patients with metastases to viscera, 48% for bone and only 20% for metastases to soft tissue. The median serum YKL-40 levels were significantly higher in patients with bone or visceral involvement compared with patients with soft tissue recurrence and with healthy subjects. Thus, in a woman suspected of recurrence of breast cancer, a very high level of serum YKL-40 might indicate the spread of cancer to viscera or bone. In standard programmes for staging of patients with recurrent breast cancer, serum AP is recommended as a screening test for bone metastases in asymptomatic patients [23]. In the case of elevated serum AP values, further diagnostic procedures include bone scintigraphy and bone marrow examination [24]. Future studies should focus on the role of serum YKL-40 as a supplement to serum AP. Local recurrence, skin metastases and

Table 1. Univariate survival analyses in the 60 patients

Variable	No. of patients (no. alive)	Median survival, months (25–75%)	*P* (log rank)
Age (years)			
≤50	30 (8)	18 (10–55+)	
>50	30 (1)	16 (6–26)	0.04
Menopausal status			
Pre-	30 (7)	18 (10–55+)	
Post-	29 (2)	16 (6–26)	0.07
Size of primary tumour (cm)			
≤2	25 (5)	22 (10–37)	
3–4	16 (1)	16 (10–37)	
>4	17 (2)	12 (5–21)	0.46
Axillary node status			
Negative	18 (5)	22 (10–41+)	
Positive	34 (3)	18 (10–41)	0.29
Degree of anaplasia			
Low	13 (0)	12 (4–18)	
High	15 (3)	26 (11–56)	0.01
Oestrogen receptor status			
Negative	10 (2)	10 (6–18+)	
Positive	18 (2)	21 (11–37)	0.99
Recurrence free interval (months)			
≤24	32 (4)	13 (5–26)	
>24	28 (5)	21 (10–41)	0.18
Dominant site of metastasis			
Soft tissue	10 (4)	18 (6–50)	
Bone	25 (1)	18 (12–26)	
Viscera	19 (1)	9 (3–16)	0.24
Blood haemoglobin (mmol/l)			
≤7.0	11 (8)	9 (2–16)	
>7.0	49 (1)	20 (10–41)	0.24
Serum ASAT (U/l)			
≤30	38 (7)	20 (10–47)	
>30	20 (2)	12 (4–26)	0.38
Serum LDH (U/l)			
≤400	29 (8)	25 (15–53+)	
>400	31 (1)	10 (5–21)	0.00
Serum AP (U/l)			
≤275	40 (9)	22 (11–56)	
>275	20 (0)	10 (3–18)	0.00
Serum albumin (mg/l)			
≤600	8 (0)	7 (3–11)	
>600	16 (1)	23 (18–41)	0.00
Serum prothrombin (%)			
≤100	16 (2)	9 (2–16)	
>100	33 (4)	20 (10–35)	0.13
Serum Ca^{++} (mmol/l)			
≤1.35	13 (1)	12 (7–35)	
>1.35	5 (0)	12 (2–18)	0.24
Serum BGP (mmol/l)			
≤2.0	23 (5)	13 (4–56)	
2.1–2.9	19 (1)	18 (7–37)	
>2.9	18 (3)	24 (12–47)	0.67
Serum YKL-40 (μg/l)			
≤207	35 (9)	24 (15–53+)	
>207	25 (0)	11 (6–21)	0.00
All	60 (9)	16 (7–40)	

ASAT, aspartate aminotransferase; LDH, lactate dehydrogenase; AP, alkaline phosphatase; BGP, bone Gla protein.

solitary lymph gland metastases do not tend to be detected with this marker, but these recurrences may easily be detected by the physical examination. The number of patients in the present study is relatively small and further studies are needed to evaluate whether the sensitivity and specificity of serum YKL-40 is high enough to be used routinely in screening programmes for recurrence of breast cancer.

The most salient feature of serum YKL-40 as a breast cancer marker is its ability to identify a subset of women who will die sooner. The subset of women with elevated serum YKL-40 at the time that breast cancer recurrence was first suspected have a median survival of 12 months and 20 of these 21 patients were dead by 26 months. In dramatic contrast, the subset of 20 women whose serum YKL-40 values were within the normal 95 percentile value of healthy age-matched controls at the first time of breast cancer recurrence have a median survival of 24 months and 6 of these women survived longer than 3 years. These survival rates were significantly different ($P < 0.0009$). These observations clearly demonstrate that serum YKL-40 levels determined at the time of breast cancer recurrence have the potential to define a subset of breast cancer patients with a very poor prognosis. Since serum YKL-40 levels in these women were well above the normal value at the time that breast cancer recurrence was first suspected, it is also apparent that periodic evaluation of serum YKL-40 after the initial breast cancer would have led to earlier diagnosis of breast cancer recurrence in the subset of women with the poorest prognosis. Both the potential to identify women with poor prognosis of survival and the prospect of recognising recurrence in these women earlier could be useful in the clinical management of patients with breast cancer. We also examined the relative importance of serum YKL-40 as a prognostic factor of survival compared with other biochemical parameters normally used to monitor disease activity in our department (blood haemoglobin, serum LDH, serum ASAT, serum AP and serum BGP). We found that serum YKL-40 and serum LDH were the most significant independent prognostic factors. These results indicate that serum YKL-40 level may reflect factors such as tumour burden and disease progression.

Colomer and coworkers [1] evaluated the value of serum CA 15-3 and serum CEA as prognostic markers of survival in 173 patients with advanced breast cancer. Patients with elevated serum CA 15-3 had significantly ($P = 0.04$) shorter survival than patients with normal serum CA 15-3 levels whereas determination of serum CEA did not have any prognostic value of patient survival.

Although the function of YKL-40 is not yet known, its sequence is related to the chitinase family of glycosidic bond hydrolases [11, 12] and it is possible that YKL-40 is itself a glycosidic bond hydrolase. If YKL-40 is indeed a glycosidase, its normal function during breast tissue involution could be to turn over its as yet unidentified substrate in the extracellular matrix of breast cells. This putative YKL-40 activity could contribute directly to the invasive pathophysiology of the subset of breast cancer cells which secrete the protein by cleaving glycosidic bonds in the extracellular environment which, when broken, allow the cellular mobility which is critical to cancer cell invasion of normal tissues.

In summary, the study shows for the first time that determination of serum YKL-40 may play an important role in the early detection of metastatic spread and for the prognosis of survival in patients suspected of breast cancer recurrence. Longitudinal studies relating serum YKL-40 to progression of breast cancer

Table 2. Cox model for survival of patients entering staging of recurrent breast cancer. The analyses are based on 39 patients with first recurrence of breast cancer and a complete data set

Covariate	Categories	Coefficient (β)	S.E.	P (Wald's test)
Initial model				
Serum YKL-40 (μg/l)	≤207, >207	1.00	0.42	0.02
Serum BGP (mmol/l)	≤2, 2.1–2.9, >2.9	−0.28	0.24	0.24
Serum ASAT (U/l)	≤30, >30	−0.43	0.44	0.31
Serum LDH (U/l)	≤400, >400	0.58	0.47	0.22
Serum AP (U/l)	≤275, >275	0.33	0.51	0.52
Haemoglobin (mmol/l)	≤7.0, >7.0	−0.25	0.56	0.66
Recurrence-free interval (months)	≤24, >24	−0.19	0.39	0.63
Final model*				
Serum YKL-40 (μg/l)	≤207, >207	1.08	0.38	0.00
Serum LDH (U/l)	≤400, >400	0.75	0.37	0.04

*After backward elimination (*P* value to remove: 0.10; *P* value to enter: 0.15). See Table 1 legend for abbreviations.

as well as in other cancer diseases and during different treatment procedures are required. It is likely that serum YKL-40 determination can be useful in monitoring patients with advanced cancer, especially regarding visceral or bone metastases.

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