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ORIGINAL ARTICLE

Plasma YKL-40, as a prognostic tumor marker in recurrent ovarian cancer

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Background. YKL-40, a member of family 18 glycosyl hydrolases, is secreted by cancer cells. The function of YKL-40 in cancer diseases is unknown, but it is a growth factor of connective tissue cells and probably has a role in inflammation and remodeling of the extracellular matrix, a process also involved in metastatic malignant diseases. High serum YKL-40 has been associated with poor prognosis for patients with colorectal and recurrent breast cancer.
Aim of the study. The purpose of the present study was to examine the prognostic value of plasma YKL-40 in patients presenting with recurring ovarian cancer.
Methods. YKL-40 was determined by ELISA in plasma samples from 73 patients with relapse of ovarian cancer shortly before start of second-line chemotherapy. The endpoint used was death because of ovarian cancer.
Results. Plasma YKL-40 was increased in ovarian cancer patients (median 94 μg/L, range 20–1970 μg/L) compared with age-matched controls (33 μg/L, range 20–130 μg/L) ($p < 0.001$). Fifty-five per cent of the patients had a plasma YKL-40 level above the upper normal 95th percentile of controls. Patients with high plasma YKL-40 (i.e. > 130 μg/L or > 160 μg/L) at the time of relapse had significantly shorter survival than patients with normal levels (respectively $p = 0.007$ and $p = 0.004$). Plasma YKL-40 proved to be an independent prognostic factor in a multivariate Cox analysis (YKL-40 > 160 μg/L; HR $= 2.27$) ($p = 0.006$), including serum CA-125 and clinical/histological parameters.
Conclusion. High plasma YKL-40 is related to short survival in patients with recurrent ovarian cancer.

Keywords: YKL-40; ovarian cancer; tumor marker; prognosis

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The incidence of ovarian cancer (OC) in Denmark has been very constant these last decades and was 13.24 per 100 000 women annually in 1997 (1). It is the fifth most frequent female cancer and accounts for a considerable number of cancer related deaths in women (2,3). Post-therapeutic relapse of OC augurs especially ill for the chance of survival, which is almost zero. It is not known if early intervention with second-line chemotherapy changes this critical survival overall. However, hypothetical identification of clinically useful tumor markers could augment an earlier diagnosis of recurrent cancer and, by their possible prognostic function, influence future treatment regimes. CA-125 is a well-established biochemical tumor marker of clinical use in OC, but diverging conclusions have been made concerning its prognostic value in this malignancy. Only in a few univariate analyses has preoperative or pre-chemotherapy CA-125 determination been found

to be of prognostic value (4,5). The prognostic value of pretreatment CA-125 determination disappears when FIGO stages are included in multivariate Cox analyses, indicating that the prognostic function of pretreatment CA-125 determination is merely a dependent reflection of the very strong prognostic stage (5,6). The high frequency and poor prognosis of OC emphasizes the need for both additional and better biochemical tumor markers.

YKL-40, a member of the mammalian family of 18 glycosyl hydrolases (7–9), is a heparin and chitin-binding lectin (9,10) without chitinase activity (7,10,11). The term YKL-40 originates from the one-letter code for its three N-terminal amino acids and the molecular weight (40 kDa) (12). YKL-40 is secreted in large amounts *in vitro* by the MG63 human osteosarcoma cell line (12) and is expressed selectively by murine mammary tumors initiated by neu/ras oncogenes but not by c-myc or int-2 oncogenes (8). The gene for YKL-40 has been sequenced (13) and a search of the YKL-40 protein sequence against the best database at the NCBI using the BLAST program has shown that YKL-40 is expressed by several types of cancer (colon, breast, ovarian, uterine, prostate, kidney, lung, oligodendroglioma, glioblastoma and germ cell tumors). YKL-40 is also secreted by macrophages (10,13,14), neutrophils (15) and arthritic chondrocytes (7,16). Ongoing immunohistochemical analyses of cancer tissue show that YKL-40 is not only produced by cancer cells but also by cells (macrophages) in the stroma (Julia S. Johansen and Paul A. Price, personal observation). The precise physiological function of YKL-40 is unknown, but recently it has been reported that YKL-40 is a growth factor which stimulates growth rates of fibroblasts (17), chondrocytes and synovial cells (18). It was found that YKL-40 is effective in a concentration range similar to IGF-1, and that both growth factors work synergistically in stimulating the growth of fibroblasts (17). Interestingly Malinda *et al*. have reported that YKL-40 is a potent migration factor for endothelial cells and modulates the morphology of these cells by promoting the formation of branching tubules, indicating that YKL-40 may also function in angiogenesis (19).

Moderate to significant elevated serum concentrations of YKL-40 have been found in a variety of diseases characterized by inflammation and remodeling of the extracellular matrix such as active rheumatoid arthritis (16,20–23), osteoarthritis (16,24), bacterial pneumonia (25), and liver fibrosis (26,27). Interestingly, increased serum levels of YKL-40 have proved to be related to short survival in patients with recurrent breast cancer (20), and in patients with colorectal cancer a high preoperative serum YKL-40 level (28) or elevated serum YKL-40 during the follow up postoperatively is a predictor of short survival (29).

The purpose of the present study was to examine the relationships between survival, serum CA-125 and plasma YKL-40, as measured in pretherapeutic samples from patients presenting with recurring OC.

Materials and methods

Patients and clinical variables

The study included 73 women (mean age 55, range 25–76 years) with recurrent OC. Blood samples were obtained at the time of diagnosis of the recurrence and before initiation of second-line chemotherapy in the period from December 1993 to September 1998. Plasma YKL-40 and serum CA-125 concentrations were measured in samples collected at the same tapping by use of the Venoject system. The patients were treated according to treatment protocols in the Department of Oncology, Rigshospitalet, and were followed to death or to July 1999. As primary chemotherapy, 65 patients received platinum-based treatments, 28 of these 65 patients in combination with paclitaxel, three received melphalan treatment, two patients no treatment (FIGO stages IA and IB), and three patients received three other treatments. At the time of relapse, 49 patients received platinum-based treatments, five were treated with melphalan, eight with ifosfamide, eight with topotecan, and three patients received three other treatments. Time to death was measured from the date of starting chemotherapy at the time of recurrence. Additional clinical variables included in the analyses were: tumor recurrences detected by clinical examination, ultrasound and computed tomography, localization of the tumors (pelvis, peritoneum/retroperitoneum or liver), tumor size $> 1\,cm^3$ or $\leq 1\,cm^3$, primary treatment, second-line treatment, time interval from the end of primary (first-line) treatment to relapse, as relapse yes/no ≤ 6 months and ≤ 12 months, age, original FIGO stage (Table I), histology and performance score.

Ethics

Informed consent was obtained from all patients and the study was approved by the Ethics Committee for the municipalities of Copenhagen and Frederiksberg (No. KF01-78/93 and KF01-004/94).

Table I. Original FIGO stages for patients who died during the follow-up and patients still alive

	Alive	Dead	
FIGO stages	n (%)	n (%)	P
1	2 (25)	4 (6)	
2	1 (12,5)	11 (17)	
3	4 (50)	39 (60)	
4	1 (12,5)	11 (17)	
Total	8 (100)	65 (100)	0.33

P: two sample rank sum test for difference in FIGO stages between alive and dead patients.

Healthy controls

The normal range of plasma YKL-40 was determined in 102 apparently healthy women (mean age of 50 years, range 25–76 years). They were all healthy, were not taking any medicine, and had no clinical signs or symptoms of cancer, joints, liver, metabolic or hormonal disease (24).

Biochemical analysis

Blood samples were left on the clot or left on the blood cells at room temperature and separated by centrifugation at 2000 *g* for 20 min. Serum and plasma samples were stored in aliquots at −20 °C until assayed. All samples were processed into serum or plasma in less than 8 h after venipuncture.

Plasma YKL-40 concentrations were determined by a commercial ELISA (Quidel Corporation, Santa Clara, CA) (30). The intra- and interassay variations were 3.6% and 5.3%, respectively. The sensitivity of the assay was 10 μg/L.

Serum CA-125 levels were determined using a CA-125 immunoassay (EIA) system according to the manufacturer's instructions (IMX, Abbott CA-125, Abbott Laboratories, Chicago, IL). The intra- and interassay variations were 8.9% and 7.8%, respectively.

Statistical analyses

The statistical analyses were performed using SPSS version 9.0. Spearman Rank and Mann–Whitney tests were used to test for correlations and median differences, respectively. The two-sample rank-sum test was used for variables representing an ordinal scale. Life tables were established according to Kaplan-Meier and tested by the univariate log-rank test. To test for independent prognostic factors, the variables were entered in the multivariate Cox analysis.

Trends were established by actual values of plasma YKL-40, serum CA-125 and the time interval between the primary and second-line therapy to assure correlation between the variables and survival. Subsequently separate analyses were performed using plasma YKL-40, serum CA-125 and the time interval as dichotomy variables. The cut-off level for YKL-40 was set at 50, 94 and 160 μg/L corresponding to the lower quartile, median value and upper quartile of the plasma YKL-40 levels in the OC patients. Furthermore, we examined the cut-off level 130 μg/L for plasma YKL-40 corresponding to the upper normal level in healthy age-matched controls. For CA-125 the traditional cut-off at 35 U/mL was used. Furthermore, the patients were divided into groups according to the time interval between the primary treatment and relapse, as relapse yes/no ≤ 6 months and ≤ 12 months.

Results

The median plasma YKL-40 level in the OC patients at the time of the first recurrence after the operation was 94 μg/L (range 20–1970 μg/L): significantly higher ($p < 0.001$) compared with the plasma YKL-40 level in the age-matched healthy women (median 33 μg/L, range 20–130 μg/L). Fifty-five percent (40/73) of the OC patients had a plasma YKL-40 level above the upper 95th percentile of the healthy age-matched women (83 μg/L), and 29% (21/73) had a plasma YKL-40 level above the upper normal range of the healthy women (130 μg/L). Figure 1 illustrates the individual plasma YKL-40 concentrations in the patients with recurrent OC and the healthy women according to age. In the OC patients significant positive correlations were found between plasma YKL-40 and serum CA-125 ($R^S = 0.352$, $p = 0.002$) and between YKL-40 and age ($R^S = 0.368$, $p = 0.001$).

Plasma YKL-40 levels in relation to survival

At the time of follow up, 65 patients (89%) had died of OC (median survival time after first recurrence was 15.2 months, range 0.4–64.6 months, quartiles 7.4–22.2 months). Eight patients were still alive (median follow-up time: 20.5 months, range 3.4–42.1 months, quartiles 10–36.9 months). There was no significant difference in the median plasma YKL-40 levels at the time of the first recurrence between the patients who died during the follow up and those still alive (Table II).

Patients with a high plasma YKL-40 level, > 160 μg/L, had significantly ($p = 0.004$) shorter

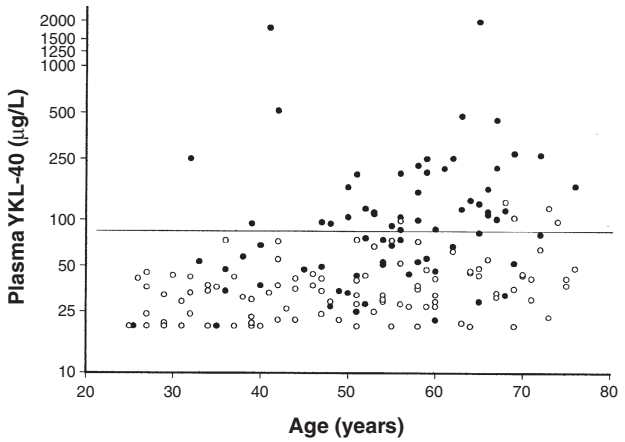

Fig. 1. Scatter plot of age and plasma YKL-40 levels (logarithmic scale) for the patients with recurrent ovarian cancer (•, $n = 73$) and the age-matched healthy women (○, µ, $n = 102$). The solid line indicates the upper 95% limit of the healthy women. Fifty-five per cent of the patients had elevated plasma YKL-40.

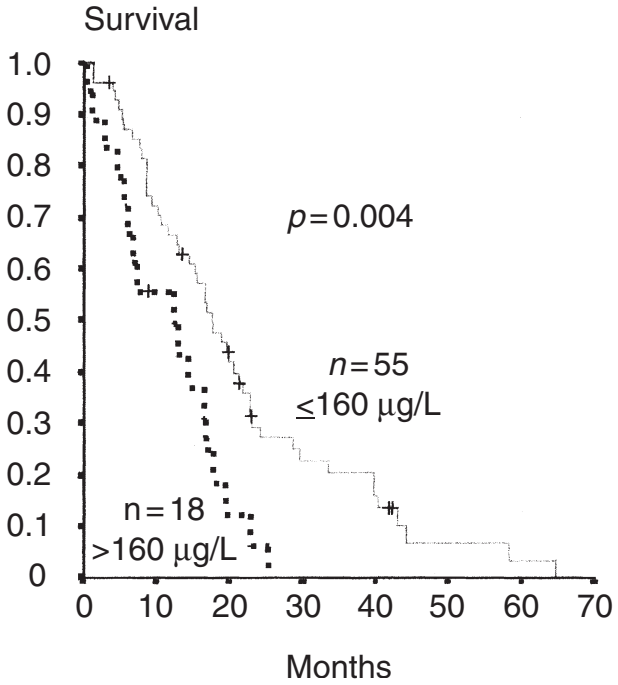

Fig. 2. Kaplan-Meier survival curves. Ovarian cancer patients with high plasma YKL-40 (> 160 µg/L, $n = 18$) and ovarian cancer patients with normal/slightly elevated plasma YKL-40 (≤160 µg/L, $n = 55$).

survival than patients with a plasma YKL-40 level ≤ 160 µg/L (Fig. 2). Eighty-two per cent of the patients with high plasma YKL-40 (> 160 µg/L) had died within 18 months compared with 52% of the patients with a plasma YKL-40 ≤ 160 µg/L. When cut-offs for plasma YKL-40 were set at 50 or 94 µg/L, survival was not significantly better for the patients with YKL-40 values below the cut-off levels (data not shown; $p = 0.1$ and $p = 0.056$, respectively). Significantly poorer survival was found for OC patients with plasma YKL-40 levels > 130 µ/L compared with patients with plasma YKL-40 levels ≤ 130 µg/L ($p = 0.007$, life table not shown because it is all most identical to Fig. 2).

Regarding CA-125, no significant difference in survival was revealed between the patient groups divided by cut-off 35 U/mL (data not shown).

In the multivariate analysis using actual values of YKL-40, only YKL-40 and the time interval were found to be independent prognostic variables. When the time interval between the primary treatment and the relapse was set to ≤ 6 months, YKL-40 (cut-off = 160 µg/L) was the only independent prognostic variable in the multivariate Cox analysis. However, if the time interval was set to ≤ 12 months, plasma YKL-40 (cut-off = 160 µg/L) had no independent prognostic value ($p = 0.078$). The only independent prognostic factor in this test-frame was the time interval (Table III). When the cut-offs for plasma YKL-40 were set to 50 and 94 µg/L (the lower quartile and median value of the OC patients, respectively), YKL-40 proved nonsignificant as an independent prognostic variable and was excluded from the multivariate Cox analysis (data not shown). Using the cut-off 130 µ/L for YKL-40, only plasma YKL-40 and a time interval ≤ 12 months were found to be independent prognostic variables (Table III). Serum concentration of CA-125 showed no independent prognostic function in any of the performed Cox analyses.

Table II. Comparisons in plasma YKL-40 and serum CA-125 at time of recurrence between patients who died during the follow-up and patients still alive

	Alive (n = 8)			Dead (n = 65)			
	Median	Range	Quartiles	Median	Range	Quartiles	P
YKL-40 µg/L	88	20–476	40–138	94	20–1970	50–164	0.704
CA-125 U/ml	97	7–5532	68–258	136	2–1535	48–692	0.757
Interval months	23.5	1.0–72.0	1.3–34.8	6	1.0–42.0	3.0–12.0	0.239
Follow-up time	20.5	3.4–42.1	10.0–36.9	15.2	0.4–64.6	7.4–22.2	0.262
Performance	0.0	0–2	0.0–1.0	1.0	0–2	0.0–1.0	0.204

Interval = time interval from end of primary (first-line) treatment to relapse. Follow-up time = time from the date of starting chemotherapy for relapse to death or July 1999. Performance = performance score (0–4).

Table III. Independent prognostic variables of survival from the multivariate Cox analyses

	Variable	RH	95% CI	P
Actual values of CA 125, YKL-40 and interval	CA-125 U/ml	–	–	NS
	YKL-40 μg/L	1.003	(1.002–1.004)	< 0.001
	Interval	0.964	(0.94–0.99)	0.006
Dichotomy values	CA-125 > 35 U/ml	–	–	NS
	YKL-40 > 160 μg/L	2.27	(1.27–4.06)	0.006
	Interval ≤ 6 months	–	–	NS
Dichotomy values	CA-125 > 35 U/ml	–	–	NS
	YKL-40 > 160 μg/L	–	–	NS
	Interval ≤ 12 months	0.317	(0.17–0.59)	< 0.001
Dichotomy values	CA-125 > 35 U/ml	–	–	NS
	YKL-40 > 130 μg/L	2.218	(1.25–3.92)	0.006
	Interval ≤ 6 months	–	–	NS
Dichotomy values	CA-125 > 35 U/ml	–	–	NS
	YKL-40 > 130 μg/L	1.805	(1.02–3.18)	0.04
	Interval ≤ 12 months	0.342	(0.18–0.64)	0.001

RH = relative hazard; CI = confidence interval; NS = non-significant; Interval = time interval from end of primary (first-line) treatment to relapse.

Discussion

This is the first report of plasma concentrations of YKL-40 in patients with recurrent OC. The study showed that the OC patients with high plasma YKL-40 at the time of the first recurrence had significantly shorter survival than the OC patients with normal or slightly elevated plasma YKL-40. Eighty-two per cent of the patients with high plasma YKL-40 had died within 18 months after the first recurrence compared with 52% of the patients with normal or slightly elevated plasma YKL-40. We also found that YKL-40 levels measured in a plasma sample at the time of relapse was an independent prognostic marker of survival, especially in early relapse (≤ 6 months after first-line chemotherapy) for patients presenting with first recurrence of OC. One explanation may be that tumors in patients with early relapse are biologically more aggressive, with a higher rate of degradation and remodeling of extracellular matrix than tumors in patients with a later relapse. Our study supports previous findings of an association between elevated serum YKL-40 levels and poor survival in colorectal and recurrent breast cancer patients (20,28,29). Furthermore, our observations support the hypothesis that YKL-40 is an important factor in the progression of malignant diseases, possibly through remodeling and degradation of the extracellular matrix. Although the plasma levels of YKL-40 may be prognostic in patients with recurrent OC, the mechanism by which plasma YKL-40 reflects disease status is not known. A search of the YKL-40 protein sequence against the best database at the NCBI using the BLAST program has shown that the protein is expressed by several types of cancer, including some OC. We speculate that YKL-40-positive cancer cells may have a different phenotype than YKL-40-negative cancers, and thereby YKL-40 may reflect differences in the biology of various cancer cells. The elucidation of YKL-40 function will be an important objective of future studies, as it seems likely that YKL-40 will prove to have an important role in cancer invasiveness.

In our study, we measured plasma YKL-40 in OC patients using an ELISA method. Earlier studies have performed measurements on serum samples from breast and colorectal cancer patients using a RIA system (20,28,29). We found that the plasma levels of YKL-40 are lower in OC patients compared with the reported serum levels in samples from breast and colorectal cancer patients. The median serum YKL-40 levels in patients with recurrent breast cancer with visceral metastases was 328 μg/L (58% had elevated serum YKL-40 compared with controls) and in patients with bone metastases the median serum YKL-40 was 157 μg/L (48% had elevated serum YKL-40), whereas patients with soft tissue metastases had normal serum YKL-40 levels (127 μg/L). The median preoperative serum YKL-40 level in 603 patients with colorectal cancer was 180 μg/L (range 56–2709 μg/L), and 16% of

the Dukes' A patients, 26% with Dukes' B, 19% with Dukes' C and 39% with Dukes' D had elevated serum YKL-40 (adjusted for age) (28). Furthermore, the normal range of plasma YKL-40 levels in the present study using the ELISA was lower compared with the normal range of serum YKL-40 levels (the same controls were used) using the RIA (24). The reason for this difference is mainly the result of different calibrations of the standards used in the two methods, but it has also been shown in an earlier study that the mean serum/plasma levels in healthy controls taken under optimal handling and determined by the same ELISA procedure are 56/39 μg/L, respectively, giving size to a serum/plasma ratio of 1.4 (31).

Nothing is known about a possible relation between the YKL-40 levels and menstrual cycle. The possibility exists that the reported plasma YKL-40 levels in healthy nonmenopausal controls may be influenced by the cycle day of blood sampling. In the present study the nonmenopausal women with recurrent OC had been treated with primary bilateral oophorectomy, hysterectomy and first-line chemotherapy (except two operated stage I patients). Therefore, none of the present OC patients had any menstrual cycle that could influence our prognostic results and conclusions.

Serum CA-125 levels showed no independent prognostic function, and no difference in survival could be detected between the patient groups divided by a CA-125 cut-off level at 35 U/mL. This finding is not surprising, because no previous independent prognostic function has been demonstrated for CA-125 measured in a blood sample before surgery for primary OC, or measured in a blood sample before start of chemotherapy for recurrent OC (32). However, CA-125 levels obtained after the first, second and third course of chemotherapy have been found to be significantly correlated to survival, with improving correlation with each course (33). Also, the CA-125 half-times measured in serial samples have been found to be of prognostic significance following the start of treatment for advanced OC (34). CA-125 determined in a pre-chemotherapy serum sample, therefore, only has prognostic value as the point of reference for subsequent samples.

In conclusion, we showed that an elevated plasma level of YKL-40 was associated with high risk of short survival in patients with recurrent OC. In an effort to treat cancer patients more selectively, many investigators have searched for prognostic markers. Successful identification of high-risk patients could focus on more selective treatments and spare a significant number of patients from the side-effects of ineffective chemotherapy, which will be even more important when effective second-line treatments are developed. We find that YKL-40 deserves further evaluation as a prognostic marker in future research studies of new treatments for OC and in follow up after operation of OC.

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