# GSTP1-1 in Ovarian Cyst Fluid and Disease Outcome of Patients With Ovarian Cancer

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## Abstract

Detoxification enzymes, especially glutathione S-transferase P1-1 (GSTP1-1), have been implicated in resistance to platinum-based chemotherapy. We studied GSTP1-1 levels in ovarian cyst fluid (oCF), obtained during surgery before chemotherapy, of patients with epithelial ovarian cancer and clinical outcomes were correlated. GSTP1-1 was determined by ELISA in oCF of 56 patients with epithelial ovarian cancer and 109 noncancer controls (21 borderline and 88 benign ovarian tumors). Differences in median GSTP1-1 between clinicopathologic subgroups were studied using Mann-Whitney $U$ and Kruskal Wallis tests. Differences in disease-free (DFS) and overall survival (OS) between groups were analyzed by applying Kaplan-Meyer estimates and log-rank tests. Univariate and multivariate analysis were done using Cox proportional hazard model. Significantly higher levels of GSTP1-1 were found in the oCF of malignant (median, 383; range, 10-32,695 ng/mL) compared with benign (median, 20; range, 0-1,128 ng/mL) ovarian tumors ($P < 0.01$). Significantly higher GSTP1-1 levels were found in patients with advanced International Federation of Gynaecologists and Obstetricians stage ($P = 0.01$), high-grade tumors ($P = 0.44$), and/or high levels of preoperative CA 125 ($P = 0.01$). Of patients who received chemotherapy (stage, $\geq$Ic; $n = 30$), high GSTP1-1 levels were significantly associated with a poor DFS and OS (log-rank $P = 0.047$ and $P = 0.033$, respectively). International Federation of Gynaecologists and Obstetricians stage was the only independent predictor for DFS. GSTP1-1 was the only independent predictor for OS. (Cancer Epidemiol Biomarkers Prev 2009;18(8):2176–81)

## Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy world-wide. Approximately 70% of the patients are diagnosed with advanced stage of disease [International Federation of Gynaecologists and Obstetricians (FIGO) III and IV] with 5-year survival rates of only 10% to 20% (1, 2). Because the introduction of platinum-based chemotherapy into clinical practice, prognosis of patients with advanced EOC has markedly improved. However, this success is limited by the phenomenon of platinum-based chemoresistance. Platinum-resistant disease includes patients who do not respond to platinum-based chemotherapy at all and those who relapse within 6 months following primary chemotherapy. These patients have a poor prognosis, with an expected median OS of <10 months (3). Early identification of platinum-resistant disease will provide the opportunity to change usual regimens, which may improve the prognosis of this group of patients with EOC.

The mechanism of chemoresistance has been studied extensively in recent years, and today, it is generally accepted that the detoxification enzymes glutathione S-transferases (GST) play an essential role in this process (4). GSTs are enzymes that catalyze the phase II conjugation reaction with glutathione of highly reactive compounds that are formed during phase I modification of endogenous compounds and xenobiotics, such as anticancer agents. The human GST superfamily comprises cytosolic dimeric isoenzymes, which have been assigned to at least four generic classes: α (A), μ (M), π (P), and θ (T), each class consisting of one or more isoenzymes with a wide variety of substrate specificities (5). The π class GSTs (GSTP1-1) are believed to interact with platinum-based compounds and are frequently found to be overexpressed in a variety of neoplastic tissues, including ovarian cancer (5, 6). It has been shown that high GSTP1-1 activity results in an increased metabolism of several anticancer drugs, including platinum-based compounds, which subsequently results in a diminished cytotoxic effect on tumor cells (4, 6, 7). For ovarian cancer, some researchers found a relationship between overexpression of GSTP1-1 in malignant ovarian tissue and poor prognosis or bad response to chemotherapy (8-13), whereas others could not detect such an association (14-21).

Less attention has been paid to the analysis of GSTP1-1 in body fluids of patients with ovarian cancer. Ovarian cyst fluid (oCF) might provide a practical source of prognostic markers because it is in close contact with tumor tissue, it is readily available, and its components are homogeneously distributed. The purpose of the present study was to examine the relation between important

clinicopathologic variables and their association with GSTP1-1 levels in oCF of patients with EOC.

## Materials and Methods

**Patients and Cyst Fluid Collection.** This study includes 165 patients diagnosed with primary ovarian tumors at the Radboud University Nijmegen Medical Centre in the period between 1988 and 2007. All these patients have undergone primary surgery. oCF was collected by aseptic fine needle aspiration at the Department of Pathology, immediately after surgical removal of the tumor. After cooled transport to the laboratory, the oCF samples were centrifuged at 3,000× *g* for 10 min and the supernatant was stored at −35°C in small portions until use. Determination of the levels of GSTP1-1 was carried out by ELISA, without prior knowledge of the histologic or clinical outcome. Histopathologic diagnosis was done by a pathologist specialized in gynecologic oncology and revealed 88 benign, 21 borderline, and 56 malignant epithelial ovarian tumors. Informed consent was obtained from all participants.

**ELISA Procedures.** ELISA for GSTP1-1 was done in microtiter plates as described previously (22, 23). In short, plates were coated overnight with anti–GSTP1-1 monoclonal antibody in PBS and were blocked with PBS-T supplemented with 1% bovine serum albumin. Between the incubations, plates were washed five times with PBS. Standards of GSTP1-1 diluted in PBS-T or diluted samples were then added to the wells. Plates were incubated overnight, washed, incubated with rabbit anti–GSTP1-1 antiserum, and subsequently incubated with peroxidase-labeled swine anti-rabbit. After the final wash, plates were incubated with o-phenylenediamine, $H_2O_2$ in

sodium citrate, and $Na_2HPO_4$. The reaction was stopped by adding $H_2SO_4$. All standards and samples were measured in duplicate. A four-parameter weight logistic regression model was used to calculate standard curves and unknowns.

**Clinicopathologic Characteristics.** From the medical and pathology reports of the patients diagnosed with EOC (*n* = 56), the following clinicopathologic characteristics were retrieved retrospectively: age at diagnosis, FIGO stage, histologic tumor subtype, histopathologic grade, residual tumor after surgery, presence of malignant cells in ascites, tumor recurrence, preoperative CA 125 levels, and chemotherapeutic treatment. Staging was done according to the criteria of the International Federation of Gynaecologists and Obstetricians (FIGO; ref. 24). Histopathologic tumor type and grade were classified according to the WHO criteria (25). Chemotherapeutic treatment was defined as complete adjuvant combination chemotherapy of six courses, always including a platinum-based agent and was started within 3 wk after surgery. Additional information regarding recurrence of disease was collected for patients who received chemotherapy. Recurrence of disease was defined as a measurable lesion detected by computed tomography, magnetic resonance imaging, and/or ultrasonography.

**Statistical Analyses.** For the purpose of statistical analysis, variables regarding patient characteristics were grouped in the following manner: FIGO stage, I, II versus III, IV; tumor grade, low-grade (grade 1) versus high-grade (grade 2 and 3; ref. 26); histology, serous versus mucinous versus endometrioid versus other; residual disease, <1 cm (definition of optimal cytoreductive surgery) versus ≥1 cm (definition of suboptimal debulking); ascites, presence of malignant cells versus no malignant cells;

**Table 1. Median (range) GSTP1-1 cyst fluid concentrations (ng/mL) by clinicopathologic parameters and of patients with EOC (*n* = 56)**

|  | *n* (%) | Cyst fluid median | GSTP1-1 (range) | P |
|---|---|---|---|---|
| FIGO stage |  |  |  | *0.010** |
| I + II | 27 (48) | 162 | (10-1,302) |  |
| III + IV | 28 (50) | 703 | (10-32,695) |  |
| *Unknown* | *1 (2)* |  |  |  |
| Tumor grade |  |  |  | *0.044** |
| Low-grade | 14 (25) | 89 | (10-1,302) |  |
| High-grade | 37 (66) | 448 | (10-32,695) |  |
| *Unknown* | *5 (9)* |  |  |  |
| Histology |  |  |  | *0.264*[†] |
| Serous | 24 (43) | 224 | (10-25,963) |  |
| Mucinous | 15 (27) | 114 | (10-32,695) |  |
| Endometrioid | 12 (21) | 447 | (28-3,583) |  |
| Other[‡] | 5 (9) | 881 | (362-2,384) |  |
| Residual tumor |  |  |  | *0.301** |
| <1 cm | 38 (68) | 299 | (10-3,583) |  |
| ≥1 cm | 18 (32) | 617 | (10-32,695) |  |
| Malignant cells in ascites |  |  |  | *0.101** |
| No | 25 (45) | 162 | (12-13,020) |  |
| Yes | 28 (50) | 535 | (10-32,695) |  |
| *Unknown* | *3 (5)* |  |  |  |
| Preoperative CA 125 |  |  |  | *0.010** |
| ≤126 U/mL | 27 (48) | 114 | (10-960) |  |
| >126 U/mL | 26 (47) | 594 | (10-32,695) |  |
| *Unknown* | *3 (5)* |  |  |  |
| Total | 56 (100) | 383 | (10-32,695) |  |

*Mann-Whitney *U* test.
[†] Kruskal-Wallis test.
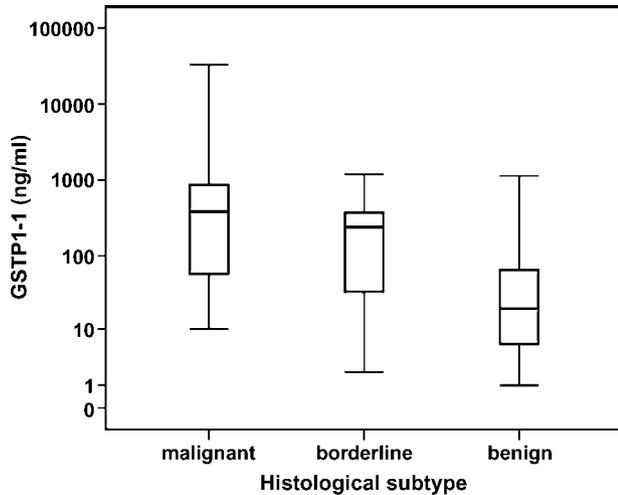[‡] Clear cell, *n* = 4; undifferentiated, *n* = 1.

**Figure 1.** The boxplots of the GSTP1-1 (ng/mL) concentrations in oCF by histologic subtype of patients with malignant ($n = 56$), borderline ($n = 21$), and benign ($n = 88$) ovarian tumors.

preoperative CA 125, ≤126 U/mL versus >126 U/mL (median value).

GSTP1-1 samples were measured in duplicate and in the analysis the values were averaged.

Differences in concentrations of GSTP1-1 between groups of patients were tested for statistical significance using the Mann-Whitney $U$ test in case of two groups and the Kruskal Wallis test in case of more than two groups, respectively.

Survival analysis was done with the subgroup of patients with EOC that received chemotherapy after primary surgery ($n = 30$). Survival techniques were used to study the time to recurrence and to study the time to death. Disease-free survival (DFS) was defined as the time interval from the date of the last course of chemotherapy to recurrence or last follow-up. Overall survival (OS) was defined as the time interval from the date of surgery to the date of either death or last follow-up. The GSTP1-1 oCF value of 160 ng/mL was used for dividing patients into two groups after a statistically significant difference in DFS and OS was found with logistic regression analysis. The Kaplan-Meyer estimates were calculated of the patients with GSTP1-1 oCF values below 160 ng/mL and above 160 ng/mL, respectively. Subsequently, the log-rank test was used to test their difference for statistical significance. Univariate proportional hazards model was used to study the influence of the clinicopathologic parameters on DFS and OS separately. Histology was not studied because of the small number of patients within the different subgroups (serous $n = 18$, mucinous $n = 3$, endometrioid $n = 5$, other $n = 4$). Tumor grade was not studied because of the small number of patients with low-grade carcinomas ($n = 3$). The hazard ratios (HR) with the corresponding 95% confidence interval (CI) are presented. Multivariate proportional hazards model with selection procedures was used to find the clinico-pathologic parameters that independently contribute to a decreased time to recurrence (or death). The adjusted HRs with the corresponding 95% CI of the final model are presented.

$P$ values less than <0.05 were considered statistical significant. All statistical analyses were done using the software package SPSS 14.0 for Microsoft Windows (SPSS, Inc.).

## Results

**Patient's Characteristics.** Median age at diagnosis was 56 years (range, 31-89 years) for patients with EOC ($n = 56$), 53 years (range, 15-82 years) for patients with border-line tumors ($n = 21$), and 46 years (range, 19-77 years) for patients with benign epithelial tumors ($n = 88$). Age differed significantly between patients with EOC and patients with benign ovarian tumors ($P < 0.01$, Mann-Whitney $U$ test). No significant differences in age were
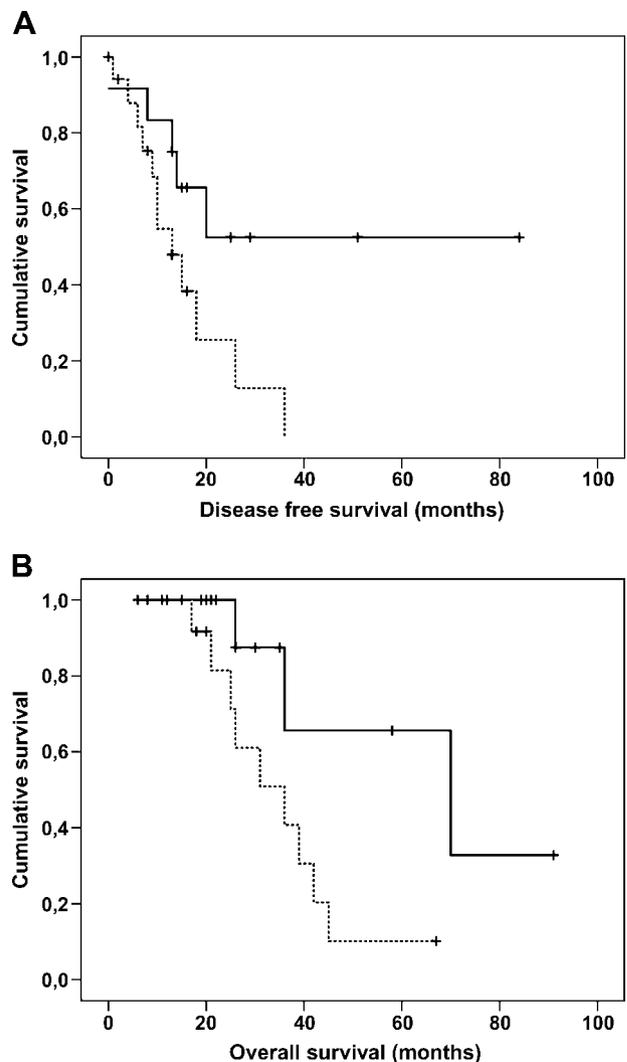


**Figure 2.** Kaplan-Meier estimates of DFS (**A**) and of OS (**B**) of patients who received chemotherapy ($n = 30$). The group with low GSTP1-1 values (≤160 ng/mL; *solid line*) and the group with high GSTP1-1 values (>160 ng/mL; *broken line*) include 12 and 18 patients, respectively. *Vertical bars,* patients with censored data.

**Table 2. HR with 95% CI of DFS and of OS by clinicopathologic parameters of patients with EOC who received six courses of adjuvant platinum-based chemotherapy ($n$ = 30), using univariate Cox Regression**

| | $n$ | DFS HR | (95% CI) | $P$ | OS HR | (95% CI) | $P$ |
|---|---|---|---|---|---|---|---|
| GSTP1-1 | | | | | | | |
| Low (≤160 ng/mL) | 12 | 1.00 | (Reference) | | 1.00 | (Reference) | |
| High (>160 ng/mL) | 18 | 2.79 | (0.97-8.04) | 0.058* | 4.50 | (0.97-20.92) | 0.055* |
| FIGO stage | | | | | | | |
| I + II | 11 | 1.00 | (Reference) | | 1.00 | (Reference) | |
| III + IV | 19 | 10.17 | (2.25-45.99) | 0.003* | 3.12 | (0.84-11.59) | 0.089* |
| Residual disease | | | | | | | |
| <1 cm | 18 | 1.00 | (Reference) | | 1.00 | (Reference) | |
| ≥1 cm | 12 | 1.56 | (0.52-4.67) | 0.424 | 1.06 | (0.28-4.03) | 0.935 |
| Malignant cells in ascites | | | | | | | |
| No | 9 | 1.00 | (Reference) | | 1.00 | (Reference) | |
| Yes | 20 | 5.07 | (1.14-22.65) | 0.033* | 2.30 | (0.61-8.67) | 0.218 |
| Preoperative CA 125 | | | | | | | |
| ≤126 U/mL | 11 | 1.00 | (Reference) | | 1.00 | (Reference) | |
| >126 U/mL | 18 | 2.65 | (0.82-8.60) | 0.104 | 4.97 | (1.06-23.20) | 0.041* |

*Parameters with a $P$ value of ≤0.10 were selected for multivariate analysis.

found between patients with EOC and borderline tumors and between patients with benign and borderline tumors. Of the 56 patients with EOC, 22 had FIGO stage I (39%), 5 had FIGO stage II (9%), 21 had FIGO stage III (38%), and 7 FIGO had stage IV (13%). The remaining clinicopathologic data are listed in Table 1. For some patients, information about clinicopathologic parameters was incomplete (Table 1). Of the subgroup of EOC patients that received complete adjuvant chemotherapeutic treatment ($n$ = 30), recurrence of disease was observed in 17 patients (57%) of whom 5 (17%) showed recurrence within 6 months after completing chemotherapeutic treatment. DFS ranged from 1 to 84 months, with a median of 13 months. OS ranged from 6 to 91 months, with a median of 26 months. Twelve patients (40%) died within the follow-up period.

**Histopathologic Diagnosis.** Figure 1 shows the boxplots of the GSTP1-1 concentrations (ng/mL) in oCF of patients by histologic subtype. Median (range) concentrations were 383 (10-32,695) ng/mL, 240 (2-1,193) ng/mL, and 20 (0-1,128) ng/mL for malignant ($n$ = 56), borderline ($n$ = 21), and benign ($n$ = 88) oCF samples, respectively. Significantly higher concentrations of GSTP1-1 were

found in oCF from malignant ovarian tumors compared with benign tumors and in oCF from borderline tumors compared with benign tumors (both $P$ < 0.01, Mann-Whitney $U$ test). No significant differences in GSTP1-1 levels were found between patients with malignant and patients with borderline ovarian tumors ($P$ = 0.114).

**GSTP1-1 and Clinicopathologic Characteristics.** Table 1 shows the clinicopathologic outcomes and median (range) concentration of GSTP1-1 (ng/mL) for the 56 patients with EOC. Significantly higher GSTP1-1 concentrations were found in patients with FIGO stage III and IV disease compared with patients with FIGO stage I and II ($P$ = 0.01). Patients with high-grade carcinomas had significantly higher levels of GSTP1-1 compared with patients with low-grade carcinomas ($P$ = 0.044). High CA 125 levels were correlated with high GSTP1-1 levels ($P$ = 0.01; all Mann-Whitney $U$ test).

**DFS and OS.** Of the 56 patients with epithelial ovarian cancer, 5 patients received neoadjuvant chemotherapy before surgery and 21 patients did not receive chemotherapy at all or received less than six courses. These patients were therefore excluded and the remaining 30 patients were included for survival analysis. Surgery dates for this

**Table 3. Published reports on outcomes of the relationship between GSTP1-1 levels and response to chemotherapy and survival including the methods used for tissue analysis of GSTP1-1**

| Reference | $n$ | Method used for analysis of GSTP1-1 | Correlation between GSTP1-1 and response to chemotherapy | Correlation between GSTP1-1 and survival |
|---|---|---|---|---|
| Van der Zee et al. | 17 | High performance liquid chromatography | No | — |
| Green et al. | 78 | Immunohistochemistry | Yes | Yes |
| Hamada et al. | 61 | Immunohistochemistry | Yes | Yes |
| Van der Zee et al. | 89 | Immunohistochemistry | No | No |
| Hirazono et al. | 36 | Immunohistochemistry | — | Yes |
| Wrigley et al. | 66 | Immunohistochemistry | No | No |
| | | Western blotting | No | No |
| Ghazal-Aswad et al. | 39 | Immunohistochemistry | No | — |
| Cheng et al. | 20 | Immunohistochemistry | Yes | — |
| | | Western blotting | — | No |
| Kase et al. | 87 | Immunohistochemistry | Yes | — |
| Satoh et al. | 67 | Immunohistochemistry | — | Yes |
| Ikeda et al. | 93 | Immunohistochemistry | — | No |
| Howells et al. | 77 | Immunohistochemistry | No | No |
| Saip et al. | 55 | Immunohistochemistry | No | No |

group of patients ranged between January 1996 and November 2007, and the follow-up period was at least 6 months after completing chemotherapeutic treatment (median, 26 months). Figure 2 shows the Kaplan-Meier curves of the patients with GSTP1-1 values above 160 ng/mL and below 160 ng/mL of both DFS (Fig. 2A) and of OS (Fig. 2B). In the first group (GSTP1-1, >160 ng/mL), histologic subtypes were serous ($n = 9$), mucinous ($n = 1$), endometrioid ($n = 4$), clear cell ($n = 1$), mixed ($n = 1$), and not otherwise specified ($n = 2$). Tumor grade was 1 ($n = 1$), 2 ($n = 6$), 3 ($n = 8$), and unknown ($n = 3$). In the second group (GSTP1-1 ≤160 ng/mL), histologic subtypes were serous ($n = 9$), mucinous ($n = 2$), and endometrioid ($n = 1$). Tumor grade was 1 ($n = 2$), 2 ($n = 4$), 3 ($n = 4$), and unknown ($n = 2$). Higher levels of GSTP1-1 were related with both shorter DFS and shorter OS (logrank test, $P = 0.047$ and $P = 0.033$, respectively). Of the group of patients with a high level of GSTP1-1, 45% (95% CI, 32-58) had recurrence of disease within 12 months compared with 17% (95% CI, 6-28) of the group of patients with a low level of GSTP1-1. After 24 months, this was 74% (95% CI, 60-88) and 47% (95% CI, 31-63), respectively. Similar results were found regarding the time to death. Two-year survival and 3-year survival were 82% (95% CI, 70-93) and 41% (95% CI, 25-57) for the group of patients with a high level of GSTP1-1 and 100% and 66% (95% CI, 45-87) for the group of patients with a low level of GSTP1-1, respectively.

Table 2 shows the HR with 95% CI, using the univariate proportional hazard model. For the variables "Malignant cells in ascites" and "Preoperative CA 125," in one case each, data were missing. GSTP1-1, FIGO stage, and presence of malignant cells in ascites were regarded as significant predictors of DFS. However, using the multivariate proportional hazard model with selection procedure, FIGO stage was the only independent predictor that had impact on DFS (HR, 9.8; 95% CI, 2.2-44.6; $P < 0.01$). As a result, the other factors did not contribute additionally to FIGO stage to predict the time to recurrence. Regarding the time to death, we found that GSTP1-1, FIGO stage, and preoperative CA 125 level could be regarded as significant predictors of OS in univariate analysis. Now, we found, after the model selection procedure, that GSTP1-1 seemed to be the only independent prognostic factor that had impact on OS (HR, 8.3; 95% CI, 1.1-66.1; $P = 0.045$).

## Discussion

In this study, levels of GSTP1-1 were significantly higher in patients with EOC compared with patients with benign ovarian tumors. In patients with EOC, levels of GSTP1-1 were correlated positively to FIGO stage, tumor grade, and preoperative CA 125 levels. For the subgroup of patients that received six courses of chemotherapy, higher levels of GSTP1-1 were significantly associated with a poorer DFS. Although GSTP1-1 was not an independent predictor for DFS, it was the most important factor after FIGO stage, which was the only independent prognostic factor. Therefore, determination of GSTP1-1 in surgically obtained oCF might be of value to predict relapse of disease and response to chemotherapy at the time of diagnosis. In addition, GSTP1-1 seemed to be the only independent predictor of OS in multivariate analysis and, therefore, might be of value to serve as a marker for survival.

Up until now, the only other study investigating GSTP1-1 levels in oCF of ovarian tumors was published by our own research group (23). At that time, we also found higher levels of GSTP1-1 in oCF of malignant tumors compared with their benign counterparts. The present study included more patient samples, a longer follow-up, and focused on the role of oCF GSTP1-1 as a prognostic marker for the response to chemotherapy of patients with EOC. All other studies that investigated the relationship between GSTP1-1 and clinical outcomes and/or response to chemotherapy in patients with EOC were done on ovarian cancer tissue. In Table 3, we summarized published studies in which GSTP1-1 was determined in ovarian cancer tissue and related to the clinical outcomes of patients with EOC. Some researchers found a relationship between overexpression of GSTP1-1 in malignant ovarian tissue and poor prognosis or bad response to chemotherapy (8-13), whereas others could not detect such an association (14-21). These conflicting results might be explained by differences in techniques used to quantify GSTP1-1 (Table 3). It has been shown that immunohistochemical quantification of GSTP1-1 did not always correlate with the concentrations of GSTP1-1 as measured in the tissue cells by other methods, such as Western blot analysis (9, 14). Wrigley et al. (14) concluded that the Western blotting technique was more sensitive than immunohistochemistry because it detected GSTP1-1 that had been missed by observer examination of stained sections. In addition, different scoring systems to quantify GSTP1-1 by immunohistochemistry, observer variation in identifying positively stained cells, different cutoff points for discriminating high from low values, and different types of tissue, i.e., fresh versus formalin fixed and paraffin embedded may also be responsible for the conflicting findings. In two studies, researchers classified their results as either positive or negative, which resulted in a majority of GSTP1-1–positive samples, and consequently, no correlation of GSTP1-1 expression with response to chemotherapy or survival could be achieved (15, 20). In addition, immunohistochemical GSTP1-1 expression in ovarian tumor sections was found to be heterogeneous and not uniform (16), which means that the tumor biology will probably not be optimally reflected by analyzing one tissue biopsy. Therefore, the analysis of GSTP1-1 concentrations in body fluid samples, in which components are distributed homogeneously, might provide a valuable alternative. Ovarian CF has a direct relationship with the tumor tissue and compounds are homogeneously distributed. We believe that oCF might provide possible new prognostic markers. In addition, measurement of GSTP1-1 by ELISA is an uncomplicated, sensitive, and reliable method compared with immunohistochemistry, which at best is only semiquantitative.

Our findings are consistent with our hypothesis that women with decreased levels of oCF GSTP1-1 would have a better survival due to improved response to chemotherapy. We are aware of the fact that we have only studied 30 patients who received chemotherapy and we therefore suggest that larger studies with more uniform samples and increased power are required to replicate our findings. In addition, little is known about the mechanism of release of GSTP1-1 from tumor tissue into ovarian oCF. Because GSTP1-1 enzymes are predominantly expressed in the cytosol of living cells, it might be possible that an increased release into the oCF occurs in case of

tumor necrosis. Necrosis is often associated with the differentiation grade of the tumor, the latter of which was found to be a prognostic factor for survival (26). In our study, high-grade tumors contained significantly higher oCF levels of GSTP1-1 compared with low-grade tumors. However, we believe that tumor grade was not a confounding factor for survival in the group of patients that received chemotherapy because almost all patients in this subgroup had high-grade tumors. We therefore conclude that assessment of GSTP1-1 level in ovarian oCF, obtained during primary debulking surgery, could provide information about future response to chemotherapy and therefore might be of clinical value as a prognostic tumor marker.

In summary, to the best of our knowledge, this is the first study in which the relationship between GSTP1-1 in oCF and treatment outcomes in patients with EOC was analyzed. We focused on the group of patients who received chemotherapy to assess if GSTP1-1 could be a marker that can be used for the early identification of platinum resistant disease. We found a significant association between high GSTP1-1 levels in oCF and poor DFS and OS. Moreover, GSTP1-1 seemed to be the only independent predictor for OS in multivariate analysis. Although GSTP1-1 did not seem to be an independent predictor of early recurrence, after FIGO stage, it was the most important factor for prediction of DFS. In addition, high GSTP1-1 values were found more often in patients with chemoresistant EOC compared with patients with chemsensitive disease. Therefore, a combination of FIGO stage and GSTP1-1 level might be of value in identifying patients with chemoresistant EOC in an early phase of the disease to change therapy and improve prognosis.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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