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Clinical Cancer Research

Imaging, Diagnosis, Prognosis

Elevated Plasma Growth Differentiation Factor-15 Correlates with Lymph Node Metastases and Poor Survival in Endometrial Cancer

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Abstract

Purpose: The study objective was to investigate and validate plasma growth differentiation factor-15 (GDF-15) as a predictor of lymph node metastasis and a poor prognosis in primary endometrial cancer.

Experimental Design: Plasma samples from 510 women treated for endometrial cancer in a primary investigation cohort ($n = 44$) and a secondary validation cohort ($n = 466$) were analyzed for GDF-15. Plasma from healthy premenopausal ($n = 20$) and postmenopausal ($n = 20$) women, women with borderline ($n = 43$), benign ($n = 144$), and malignant ovarian tumors ($n = 125$) were used for comparison.

Results: Median plasma GDF-15 concentration for the endometrial cancer group was elevated (1,077 ng/L) as compared with pre- and postmenopausal controls (590 and 684 ng/L) and women with benign (591 ng/L) or borderline ovarian tumors (718 ng/L; all $P < 0.001$), but similar to the ovarian cancer group. In the large validation cohort of endometrial carcinomas, high plasma GDF-15 was significantly associated with International Federation of Gynecology and Obstetrics (FIGO) stage III/IV disease, nonendometrioid histology, high grade, older age, postmenopausal status, and lymph node metastases (all $P \leq 0.001$). High GDF-15 was also an independent predictor of poor disease-specific and recurrence-free survival.

Conclusions: Based on findings indicated in a primary investigation set and confirmed in the large secondary validation set, we report for the first time plasma GDF-15 as a biomarker for endometrial cancer phenotype, including presence of lymph node metastasis and reduced survival. Its applicability as a predictor of metastatic nodes and in monitoring treatment of endometrial cancer needs to be further studied. *Clin Cancer Res; 17(14); 4825–33. ©2011 AACR.*

Introduction

Endometrial cancer represents the most common pelvic gynecologic cancer form. The incidence of endometrial cancer is increasing worldwide. Several biomarkers have shown associations with clinical characteristics and prognosis in endometrial cancer (1–6), but currently none are implemented in routine clinical practice. There is a need for identification of new biomarkers improving our understanding, diagnosis, and follow-up of endometrial cancer (7). Ideally, novel biomarkers could also provide new targets and individualized therapy (8).

We have recently identified growth differentiation factor-15 (GDF-15) as a novel biomarker in ovarian carcinoma, with independent prognostic impact (9). GDF-15 overexpression has also been reported in malignant melanoma and prostate, thyroid, pancreatic, and colonic cancers (10–14). GDF-15 is a distant member of the transforming growth factor (TGF)-β superfamily, also named macrophage-inhibitory cytokine-1, and was originally identified in activated macrophages (15). GDF-15 regulates physiologic processes involved in tissue differentiation and maintenance (15). Furthermore, GDF-15 has been identified as a prognostic biomarker in patients with acute coronary syndrome (16), myocardial infarction (17), and chronic heart failure (18). Elevated levels have also been linked to higher risk of future cardiovascular disease in apparently healthy elderly women (19). GDF-15 is highly expressed in the placenta (20), and augmented circulating GDF-15 in pregnancies has been linked to preeclampsia and diabetes mellitus (21), both conditions associated with increased risk for cardiovascular disease (21).

Under physiologic conditions, placenta is the only tissue where GDF-15 is found in large amounts (20), but GDF-15 increases in acute injury, inflammation, and cancer

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Translational Relevance

The majority of patients with endometrial cancer are diagnosed at an early stage because of postmenopausal bleeding. Still, one third of patients dying from this cancer type were initially classified as early stage. Recurring endometrial cancers have limited response to conventional systemic therapy, and although biomarkers predicting survival or therapy response have been identified, none are routinely applied in the clinic. This article identifies and validates in an independent patient cohort plasma growth differentiation factor-15 (GDF-15) as a novel biomarker for aggressive endometrial cancer phenotype, including presence of lymph node metastasis and poor survival. The value of lymph node sampling is controversial in endometrial cancer and associated with short- and long-term complications. A biomarker improving risk stratification for tailoring surgical lymph node sampling would be useful in the clinical setting. Further implementation studies are needed to investigate the applicability of GDF-15 in a routine clinical risk stratification to guide individualized therapy and follow-up.

(10, 22–24), and is induced rapidly by cytokines such as interleukin-1 (IL-1) and TGF-β (15, 20, 25). Hence, GDF-15 is suggested to regulate a wide variety of physiologic processes known to be relevant for cancer development, such as inflammation, growth inhibition, induction of apoptosis, cell detachment, and tumor invasiveness (26).

On this background, we have carried out a comprehensive study of GDF-15 in relation to an extensive panel of clinicopathologic variables including survival in endometrial cancer. A prognostic impact indicated in a primary investigation cohort has been validated in a large secondary validation cohort.

Materials and Methods

Study population

EDTA-plasma samples were collected from a total of 510 patients operated on for endometrial cancer at the 2 largest gynecologic departments in Norway: Oslo University Hospital, Ulleval (Oslo, $n = 44$), from 2003 to 2009 and at Haukeland University Hospital (Bergen, $n = 466$), from 2001 to 2009. None of the included patients had a prior diagnosis of endometrial cancer or had received chemotherapy for the present disease. The 1988 revision of the International Federation of Gynecology and Obstetrics (FIGO) stages was used.

Primary investigation cohort

In the small Oslo cohort of 44 patients with primary endometrial cancer, all blood samples were from fasting women prior to hysterectomy, and none of the patients had a prior cancer history.

Secondary validation cohort

In the large Bergen cohort of 466 patients, 27 patients had a previous history of another cancer type. Blood samples were collected during hospital admission in relation to primary treatment of the patients' endometrial cancer.

Study design

We compared the results from this study with previously published results from women operated on in Oslo between 2003 and 2009 for borderline ovarian tumor (BOT), ovarian cancer, or benign adnexal tumor and from 20 pre- and 20 postmenopausal healthy women (9). EDTA-plasma was collected and stored as previously described (27). Extensive clinical information was collected at patient inclusion from medical charts as well as directly from the patient. Follow-up information was retrieved from hospital medical records and correspondence with the primary physicians and cross-checked with the National Cancer Registry.

Women participating in this study gave informed written consent, and the biobank studies were approved by the Regional Committee of Medical and Health Research Ethics (REK) Eastern Norway (for Oslo) and by REK Western Norway (for Bergen, NSD 15501).

GDF-15 immunoassay

GDF-15 in plasma was measured by an immunoradiometric sandwich assay by using a polyclonal, affinity chromatography–purified goat anti-human GDF-15 IgG antibody (R&D Systems). All analyses were conducted in duplicate. Clinical data were blinded to the laboratory, which also had developed the assay (28). The assay has a detection limit of 20 ng/L, an intraassay imprecision of 10.6% or less, and an interassay imprecision of 12.2% or more (28).

Statistical analysis

Statistical analysis was conducted applying Statistical Program for the Social Sciences, version 15.0. Probability of less than 0.05 was considered statistically significant. The clinical characteristics are presented as median values and range, or percentage of patients, and the GDF-15 results as medians [and 95% confidence interval (CI) of the medians] as well as interquartile range for the main patient groups. A nonparametric Mann–Whitney *U* test was used for comparison of continuous data between study groups. For the categorical data, χ^2 test was used. Univariate survival analyses were conducted by using the Kaplan–Meier method and log-rank test, grouping low versus high concentration of GDF-15. Cutoff values for categorization were based on tertiles which were based on the frequency distribution of the marker, the size of subgroups, and number of events in each category. Groups with similar survival were merged, i.e., the 2 lower GDF-15 tertiles. Multivariate survival analyses were conducted with Cox regression. On the basis of results from other cancer types, we decided to test for the 1-sided hypothesis that high GDF-15 was associated with metastatic disease and poor survival in the small primary investigation cohort. Confirming this

Table 1. Clinical characteristics and GDF-15 results for the endometrial cancer groups

	Primary investigation cohort, endometrial cancer Oslo $n = 44$ (%; min–max)	Secondary validation cohort, endometrial cancer Bergen $n = 466$ (%; min–max)	[a]Premenopausal healthy $n = 20$ (%; min–max)	[a]Postmenopausal healthy $n = 20$ (%; min–max)	[a]Benign ovarian tumor $n = 144$ (%; min–max)	[a]BOT $n = 43$ (%; min–max)	[a]Ovarian carcinoma $n = 125$ (%; min–max)
Age, y	66 (48–86)	65 (28–93)	32 (24–44)	57 (48–72)	54 (22–92)	55 (22–90)	65 (29–87)
Parity	1 (0–3)	2 (0–11)			2 (0–7)	1 (0–4)	2 (0–5)
BMI, kg/m^2	26.0 (18.0–41.5)	27.2 (15.2–73.0)[c]	21.1 (18.3–31.3)		24.2 (16.5–44.8)	25.1 (14.9–35.8)	23.5 (15.6–32.9)
Menopausal status							
Premenopausal	2 (5)	22 (5)	20 (100)		49 (34)	15 (35)	9/125
Perimenopausal	3 (7)	36 (8)			13 (9)	1 (2)	8/125
Postmenopausal	39 (89)	408 (88)		20 (100)	82 (57)	27 (63)	108/125
FIGO stage (1988)							
I	36 (82)	330 (71)				38 (88)	25/125
II	1 (2)	56 (12)				3 (7)	11/125
III	5 (11)	58 (12)				2 (5)	71/125
IV	2 (5)	22 (5)				0 (0)	18/125
GDF-15, ng/L	981	1,106	590	684	591	718	1,242
EDTA plasma	(850–1,076)	(1,047–1,181)	(473–640)	(580–776)	(530–675)	(629–976)	(1,063–1,453)
	$P < 0.001$[b]	$P < 0.001$[b]	$P = 0.06$		$P = 0.3$	$P = 0.4$	$P < 0.001$[b]
	IQR: 723–1,384	IQR: 776–1,710	IQR: 461–654	IQR: 561–804	IQR: 389–871	IQR: 480–1,123	IQR: 782–2,149

NOTE: The clinical data are presented as medians and range (minimum and maximum values) or numbers (and percentages) of patients in each group (for menopausal status and FIGO stage); The plasma GDF-15 results are presented as medians (and 95% CI for the medians) as well as interquartile ranges (IQR); *P* value was derived with the Mann–Whitney *U* test between GDF-15 median of the current study group and the postmenopausal group.

[a]Results from the other patient groups used for comparison, have been presented previously (9).

[b]$P < 0.05$.

[c]BMI (body mass index) data available from 377 of 466 women.

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hypothesis, we investigated the large validation cohort for correlation with a larger panel of clinicopathologic variables (all 2-sided *P* values). Receiver operating characteristic (ROC) curve was constructed for plasma GDF-15 as discriminator between women with endometrial cancer and healthy pre- or postmenopausal women, as well as for GDF-15 as discriminator between endometrial cancer patients with and without lymph node metastasis.

Results

Plasma GDF-15 is elevated in endometrial carcinoma patients

Clinical characteristics for the 2 endometrial cancer patient groups are presented in Table 1, together with the previously published clinical data from the healthy pre- and postmenopausal and patient groups used for comparisons (9). Median plasma concentration of GDF-15 was significantly elevated in both the primary investigation cohort and the secondary validation cohort ($n = 44$ and 466) of endometrial cancer patients as compared with the control groups of pre- and postmenopausal healthy women, patients operated on for BOT or benign adnexal tumor (Table 1). Median plasma GDF-15 concentration for the total endometrial cancer group did not differ significantly from the ovarian cancer group (1,077 vs. 1,242 ng/L; $P = 0.1$).

Figure 1 illustrates the individual and median GDF-15 plasma concentrations for all patient groups and control groups of healthy women.

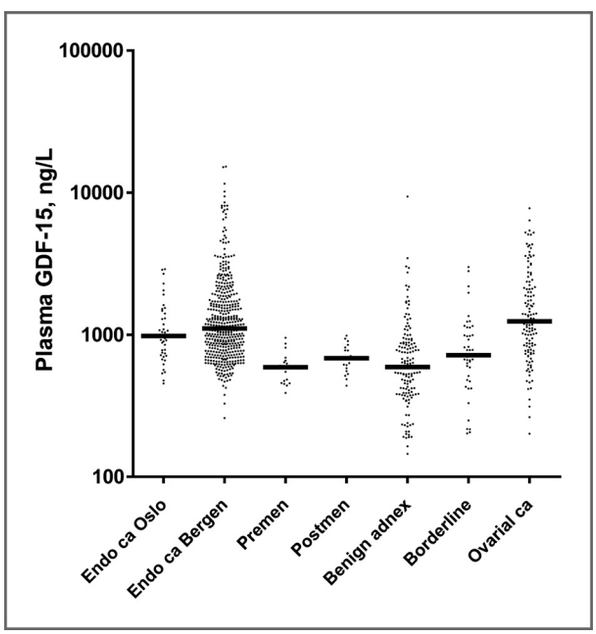

Figure 1. Individual plasma GDF-15 concentrations for the study groups. Horizontal bars represent median values. Endo ca, endometrial cancer ($n = 44$ for the primary investigation cohort, Oslo, and $n = 466$ for the secondary validation cohort, Bergen). Previously published data from the other patient (benign ovarian tumor, borderline, and invasive ovarian cancer) and control (premenopausal and postmenopausal) groups are shown as comparison for the endometrial cancer groups (9).

Primary investigation cohort: high plasma GDF-15 is associated with metastatic disease and poor survival

In the primary investigation cohort, 7 of 44 patients presented with FIGO stage III/IV disease. FIGO stage III/IV had a higher median GDF-15 of 1,092 compared with 920 ng/L for patients with stage I/II disease (1-sided $P = 0.04$). Patients with high GDF-15, defined by the upper tertile, had a shorter median disease-specific survival time as compared with the rest (1-sided $P = 0.05$; log-rank test).

Secondary validation cohort: plasma GDF-15 is associated with clinicopathologic findings

On the basis of the findings suggesting a link between phenotype and plasma GDF-15 levels in endometrial carcinoma, we investigated a secondary validation cohort for a larger panel of clinicopathologic variables. As listed in Table 2, we found that high plasma GDF-15 was highly significantly associated with FIGO stage III/IV disease, nonendometrioid histology, high grade, older age, postmenopausal status, and presence of lymph node metastases (all $P \leq 0.001$).

High GDF-15 is associated with poor survival

The validation cohort had a follow-up time from 1 to 96 months after primary treatment for clinical relapse and survival (median, 43 months for survivors). High plasma GDF-15 correlated significantly with shorter disease-specific survival time and shorter time to disease recurrence as illustrated in Fig. 2.

Women with high plasma GDF-15 levels had a 5-year disease-specific survival of 70% compared with 89% for patients with low GDF-15 (log-rank test; $P < 0.001$). Corresponding 5-year recurrence-free survival was 62% versus 84% for high versus low GDF-15 (log-rank test; $P < 0.001$). In an unadjusted analysis of disease-specific survival, high plasma GDF-15 predicted poor prognosis with an HR of 3.7 (95% CI, 2.3–6.1). Adjusting for age, FIGO stage, histologic subtype, and grade, high plasma GDF-15 still predicted poor survival independently, although with a lower HR of 1.8 (95% CI, 1.1–3.0; Table 3).

GDF-15 in endometrial cancer is predictive of lymph node metastasis

Lymph nodes were sampled routinely as part of the primary surgery in 80% (374 of 466), and metastasis was detected in 12% ($n = 46$). Patients with lymph node metastasis had higher median GDF-15 (1,520 ng/L; 95% CI, 1,116–2,022 ng/L) compared with patients without lymph node metastasis (1,006 ng/L; 95% CI, 933–1,095 ng/L; $P = 0.001$).

Women with high GDF-15 had a significantly higher risk of lymph node metastasis compared with patients with low plasma GDF-15 (OR = 3.1, 95% CI, 1.6–5.8; $P < 0.001$). The predictive value of high GDF-15 was still significant in a multivariate model, after adjusting for age and preoperative classification into high- and low-risk patients according to histologic subtype and grade in curettage specimens with an adjusted OR of 2.8 (95% CI, 1.4–5.5; $P = 0.003$) for

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Table 2. GDF-15 estimated in prospectively collected blood samples from 466 endometrial carcinoma patients in relation to clinicopathologic factors

Variable	*N*	Median	*P*
FIGO stage (1988)			<0.001
I/II	386	1,034.5	
III/IV	80	1,652.5	
Histologic type			<0.001
Endometrioid	379	1,037.0	
Nonendometrioid	87	1,474.0	
Nonendometrioid subtypes			0.803[d]
Clear cell	20	1,377.5	
Serous papillary	39	1,336.0	
Carcinosarcoma	21	1,617.0	
Undifferentiated	7	1,506.0	
Histologic grade			<0.001
1/2	313	1,000.0	
3	153	1,336.0	
Age, y			<0.001
<66	250	893.0	
≥66	216	1,347.0	
Parity			0.467
0[a]	69	1,187.0	
≥1	395	1,095.0	
Menopausal status			<0.001
Pre/perimenopausal	58	777.0	
Postmenopausal	408	1,152.5	
BMI[b]			0.578
<25	130	1,131.0	
≥25	247	1,048.0	
Lymph node metastases[c]			0.001
Neg	328	1,006.0	
Pos	46	1,520.0	

Abbreviation: BMI, body mass index.
[a]Parity information missing for 2 patients.
[b]BMI missing in 89 cases.
[c]Lymph node sampling not carried out in 92 cases.
[d]Kruskal–Wallis test.

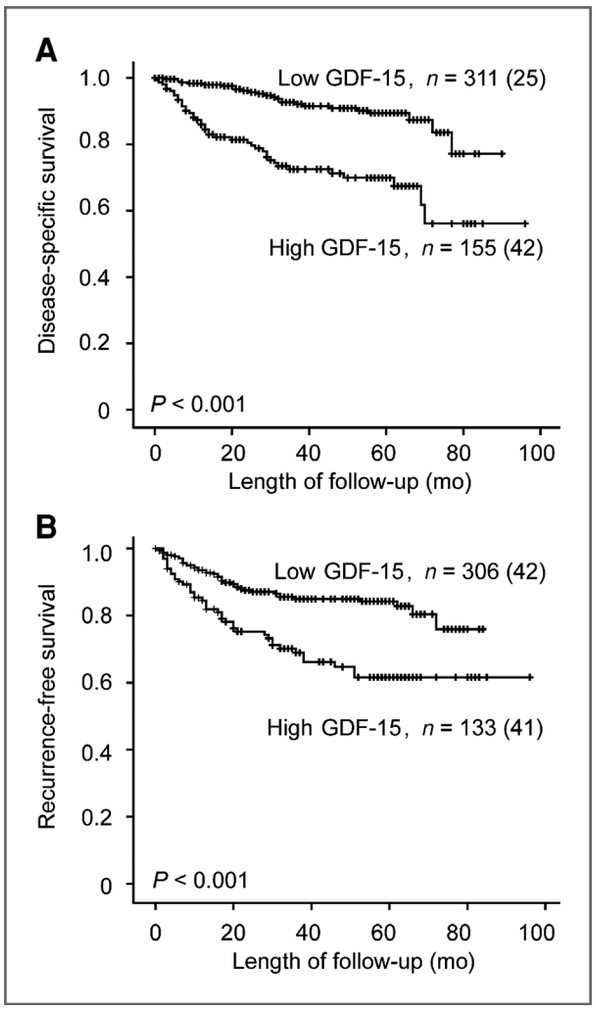

Figure 2. Disease-specific survival (A) and relapse-free survival (B) for the large secondary validation study cohort ($N = 466$) of endometrial cancer patients according to plasma GDF-15 concentration (divided according to the upper tertile). All patients had complete follow-up information. High concentration of GDF-15 was associated with shorter disease-specific and recurrence-free survival, both $P < 0.001$ (log-rank test).

lymph node metastasis among women with high GDF-15 (Table 4). Patient age was not a significant predictor of lymph node metastasis.

For the subgroup of patients with endometrioid grade 3 curettage, 44% with high GDF-15 had lymph node metastasis as compared with none in the low GDF-15 group ($P = 0.007$). Similarly, for the nonendometrioid subgroup based on curettage evaluation, 38% compared with 14% had lymph node metastases for high versus low GDF-15 values ($P = 0.03$).

ROC curves for GDF-15

A ROC curve for GDF-15 as a discriminator between women with endometrial carcinoma (for both patient cohorts; $n = 510$) and healthy pre- and postmenopausal controls ($n = 40$) gave an area under the curve (AUC) of 0.86 (95% CI, 0.82–0.91); $P < 0.001$ (Fig. 3A).

A ROC curve for GDF-15 as a discriminator between women with endometrial carcinoma (from the larger validation cohort) with lymph node metastasis ($n = 46$) and women with endometrial carcinoma without lymph node metastasis ($n = 328$) gave an AUC of 0.65 (95% CI, 0.56–0.74); $P = 0.001$ (Fig. 3B).

Discussion

Our present study is, to the best of our knowledge, the first report on plasma GDF-15 in endometrial cancer patients. We find that plasma GDF-15 is higher in endometrial cancer patients as compared with healthy pre- and

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Table 3. Multivariate survival analyses of 466 endometrial cancer patients according to the Cox proportional hazards regression model (forward stepwise likelihood ratio)

Variable	*N*	Unadjusted HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Age	466	1.06	1.04–1.08	<0.001	1.04	1.02–1.07	0.001
FIGO stage				<0.001			<0.001
I/II	386	1	—		1	—	
III/IV	80	10.16	6.22–16.59		6.27	3.71–10.61	
Histologic type				<0.001			<0.001
Endometrioid	379	1	—		1	—	
Nonendometrioid	87	7.13	4.40–11.58		3.46	2.07–5.78	
GDF-15				<0.001			0.03
Low	311	1	—		1	—	
High tertile	155	3.72	2.26–6.10		1.78	1.06–3.00	
Histologic grade				<0.001			
1/2	313	1			—	—	ns
3	153	6.53	3.86–11.05				

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics (1988 criteria applied); ns, not significant.

postmenopausal women and women with benign adnexal or BOTs. A biologic importance of GDF-15 in endometrial cancer was suggested by the association found between high plasma GDF-15 and poor survival in a primary investigation cohort. This association was clearly confirmed in our large, population-based secondary validation cohort, also showing a clear link between high plasma GDF-15 and aggressive histologic subtypes, lymph node metastases, short time to recurrence, and death due to endometrial cancer. Further studies are needed to explore the applicability of GDF-15 measurements for stratification for lymph node sampling and in routine follow-up. Because some of the plasma samples had been stored up to 9 years before analysis, with uncertain effect on GDF-15 protein degradation, confirming studies on fresh patient samples would be useful.

High plasma concentration of GDF-15 has been associated with cardiovascular disease. Also, a recent epidemiologic study indicates that circulating GDF-15 could be a predictor of all-cause mortality in apparently healthy elderly women, also after adjusting for inflammation markers such as IL-6 and C-reactive protein (29). Obesity, linked to high risk for cardiovascular disease, is known to increase the risk of endometrial carcinoma (7). In the primary investigation cohort, 10 of 44 endometrial cancer patients had some form of cardiovascular disease, mainly hypertension. However, a similar prevalence was found in the benign and borderline as well as invasive ovarian cancer groups. Also, we applied disease-specific survival in our analyses; it is therefore unlikely that cardiovascular disease represents an important bias in our study.

We find a strong association between tumor characteristics and plasma concentrations for GDF-15. On the basis of other studies, GDF-15 is induced by inflammatory

Table 4. Prediction of lymph node metastases in 370 patients with endometrial carcinoma, univariate and multivariate logistic regression

Variable	*N*	Univariate OR	95% CI	*P*	Multivariate OR	95% CI	*P*
Age	370	1.02	0.99–1.05	0.161	1.00	0.97–1.03	0.790
Curettage histology				0.002			0.010
Low risk[a]	279	1	—		1	—	
High risk[b]	91	2.74	1.45–5.20		2.43	1.24–4.75	
GDF-15				< 0.001			0.003
Low	260	1	—		1	—	
High tertile	110	3.07	1.64–5.76		2.78	1.41–5.47	

NOTE: When carrying out same multivariate logistic regression, but by using LnGDF-15 as a continuous variable instead of categorized GDF-15 into high (upper tertile) and low (lower 2 tertiles) GDF-15, GDF-15 remained predictive for lymph node metastasis (adjusted OR of 2.3; 95% CI, 1.4–3.9; $P = 0.001$).

[a]Hyperplasia and endometrioid grades 1–2.

[b]Nonendometrioid and endometrioid grade 3.

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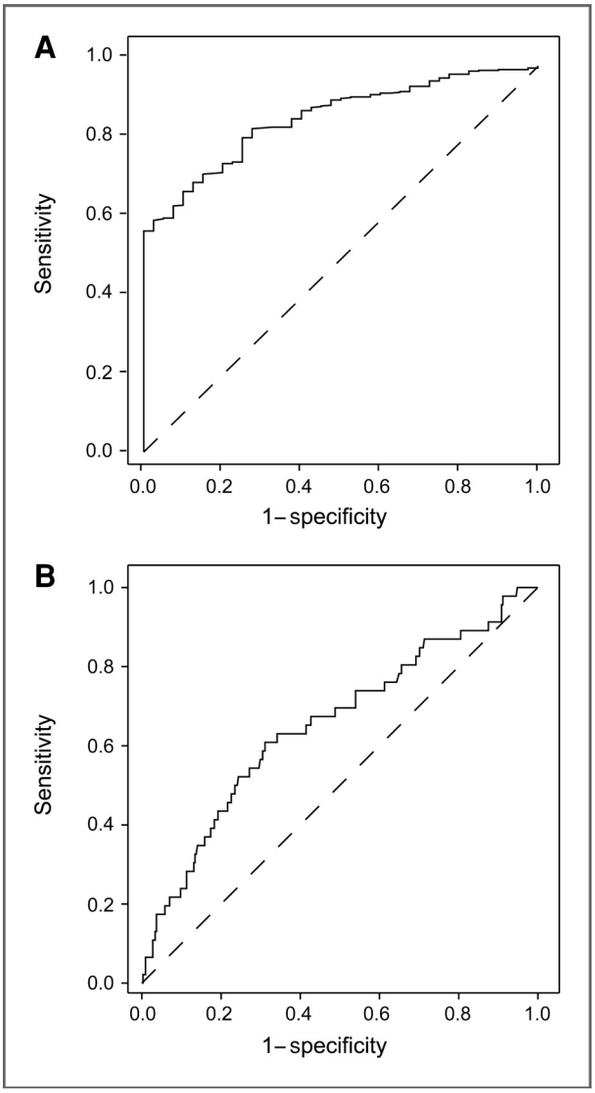

Figure 3. A, ROC curve for GDF-15 as a discriminator between women with endometrial carcinoma (for both patient cohorts, $n = 510$) and healthy pre- and postmenopausal controls ($n = 40$). B, ROC curve for GDF-15 as a discriminator between women with endometrial carcinoma (from the larger validation cohort) with lymph node metastasis ($n = 46$) and women with endometrial carcinoma without lymph node metastasis ($n = 328$).

cytokines such as IL-1 and TNF-α, and produced by activated macrophages (15). Cancer and inflammation are clearly related (30), and our finding of elevated plasma GDF-15 levels in cancer patients compared with controls may be because of cancer-related activation of inflammatory processes. Also, GDF-15 is induced by the tumor suppressor gene *p53* and other antitumorigenic agents, such as the nonsteroidal anti-inflammatory drugs and peroxisome PPARγ, suggesting that GDF-15 may be a downstream target of pathways regulating cell-cycle arrest and apoptosis (26, 31–33). In addition to being overexpressed in many cancer types, GDF-15 has also been proposed to have anticancer effects, with antitumorigenic and proapoptotic properties (12, 26). GDF-15 exerts pleiotropic roles in the early and late stages of carcinogenesis and seems to contribute to proliferation, migration, invasion, metastases, and treatment resistance in cancer (34). Overall, there are clear indications for a strong link between augmented GDF-15 expression and tumor development and metastasis, in line with our findings for endometrial carcinomas.

Serum GDF-15 has previously been identified as a biomarker associated with pancreatic (12), prostatic (11), and colorectal carcinomas (35). We have shown that GDF-15 is elevated in women with ovarian carcinoma, and that it is associated with poor prognosis (9). Interestingly, earlier reports have linked GDF-15 concentrations in ascites and pleural fluid to prognosis for ovarian cancer (9), but not in breast carcinoma (36), indicating some biological diversity for different epithelial cancer types. From the present and previous studies of GDF-15 in cancer, it is clear that elevated GDF-15 is not specific for a certain cancer type. GDF-15 is unlikely to represent a primary screening biomarker for endometrial cancer to discriminate between healthy women and women with endometrial cancer, as illustrated in the ROC curve of Fig. 3A. The results from our large validation cohort, however, seem promising in selecting women with endometrioid endometrial cancer for lymph node removal at time of hysterectomy. The highly significant correlation between high plasma GDF-15 and lymph node metastases identified in our large cohort of endometrial cancer patients indicates clinical relevance. In endometrial cancer, the value of lymph node sampling is controversial (37), with no survival benefit from lymphadenectomy shown in randomized clinical trials (38, 39). Surgical lymph node sampling has both short- and long-term complications for the patients, and a biomarker identifying which patients in whom surgical lymph node sampling is justified would be useful in the clinical setting. Whether inclusion of plasma GDF-15 will improve preoperative prediction models for lymph node metastasis in the routine clinical handling of endometrial cancer patients needs to be further studied (40).

On the basis of our results in a primary investigation cohort, clearly confirmed in a secondary validation cohort, we conclude that plasma GDF-15 is elevated in patients with endometrial cancer and is a marker for phenotype, including lymph node metastasis and disease-specific survival. Further studies are needed to explore the applicability of GDF-15 measurements for stratification for lymph node sampling and in routine follow-up.

Disclosure of Potential Conflicts of Interest

T. Kempf and K.C. Wollert have filed a patent and have a contract with Roche Diagnostics to develop a GDF-15 assay for cardiovascular applications. No products/companies are discussed in the article in which any author has an interest. There are therefore no potential conflicts of interest. The remaining authors indicated no potential conflicts of interest.

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