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REVIEW ARTICLE

Can Nidogen-1 and Nidogen-2 improve our preoperative cancer detection rate?

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Abstract

Introduction and objective. Ovarian cancer (OC) is the third most commonly diagnosed gynecological cancer among women worldwide and the second most common in Poland. Early-stage ovarian cancer is still very difficult to diagnose and concerns only about 20–30% of all ovarian cancers. Most cases (approximately 70%) of ovarian cancer are diagnosed at more advanced stages (III and IV). The aim of the review is to bring closer new potential biological markers – Nidogen-1 and Nidogen-2 in the diagnosis of ovarian cancer.

Brief description of the state of knowledge. To date, the best serum marker for ovarian cancer is Ca-125, but its use as a screening marker is limited due to high false positive rates. Ca-125 could be elevated in other benign and malignant conditions. Serum concentrations of Nidogen-1 and Nidogen-2 are higher in the advanced stagegroup (Stage III and IV), in comparison to the early stage group (Stage I and II) in serous ovarian cancer, and can reflect the tumour burden. Analysis showed that Nidogens discriminate against patients with serous ovarian carcinomas from healthy controls. The concentrations of both of them correlate with concentration Ca-125, especially Nidogen-2. The above biomarkers were compared with the results of the preoperative detection of ovarian cancer that are often used in clinical practice – IOTA Simple Rules, Risk of Malignancy Index and Risk of Ovarian Malignancy Algorithm.

Conclusions. Nidogen-1 and Nidogen-2 are new promising biomarkers for ovarian cancer, especially for the serous type, although there is still a need for prospective studies proving their good diagnostic value.

Key words

ovarian cancer, serous ovarian cancer, Nidogen-1, Nidogen-2

INTRODUCTION

Epithelial ovarian cancer is the most common type of ovarian cancer (OC), classified by several histological subtypes based on tumour cell morphology. The main histological subtypes of OC are serous, mucous, clear cell, and endometrioid. The most common is the epithelial serous type [1]. In cancer statistics the estimated number of new OC cases in the USA in 2020 was reported at 21,750. In addition, they accounted for 13,940 estimated deaths for all types of OC in 2020 in the USA alone [2]. In the latest available statistics for Poland, 5,077 new cases of OC were diagnosed in 2018, and 3,204 women died from this disease [3]. Preoperative diagnostic tools detecting OC include: tumour imaging, measurement of serous antigens serum: CA-125 and HE4. OC is diagnosed by pathomorphological examination of tumour samples obtained from the primary surgery. New studies in recent years report some new promising developments regarding plasma levels of new biomarkers for ovarian serous cancer.

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OBJECTIVE

The aim of this review is to present the current knowledge of Nidogen-1 and Nidogen-2 and the possibility of using these proteins as screening tools for ovarian cancer. A literature review was conducted in the PubMed database, the terms: 'ovarian cancer', 'CA-125', 'IOTA', 'RMI', 'ROMA', 'Nidogen-1', 'Nidogen-2' were searched.

Ovarian cancer preoperative detection – Carcinoma Antigen 125. Carcinoma Antigen 125 (CA-125) is routinely measured during the diagnosis and monitoring process of OC. CA-125 is produced physiologically by various cells in the body, including the endometrium, walls of the fallopian tubes and cervical mucosa. The upper limit for the serum CA-125 antigen is 35 U/ml; however, greater specificity for proliferative changes is determined for values above 70 U/ml [4]. This protein is characterized by a very high specificity and sensitivity in the detection of OC. In the case of OC, the values may reach several thousand, especially in the case of serous, endometrial and clear cell carcinomas. CA-125 levels are increased in over 80% of women with OC, and only in less than 1% of healthy women [5]. CA-125 is elevated in approximately 50% of women with FIGO stage I OC. True positive results for FIGO stages II, III and IV are obtained in approximately 80% of women. Unfortunately, using only the CA-125 marker, the remaining percentage of OC would remain undetected. It is worth mentioning that the determination of CA-125 in patients with OC is

more useful in post-surgical control, monitoring of adjuvant treatment (chemotherapy), prognosis and diagnosis of cancer recurrence [6] (Tab. 1).

International Ovarian Tumour Analysis (IOTA) – Simple Rules. In 2008, the International Ovarian Tumour Analysis (IOTA) proposed a new diagnostic method called 'Simple Rules' to distinguish benign from malignant ovarian masses [14]. In the available literature, the reports from the IOTA group are the largest reported study on ultrasound diagnosis of ovarian pathology [15]. The IOTA Simple Rules are intended to help distinguish the clinical features of malignancy from benignity during ultrasound examination [16]. These principles can be successfully applied by novice sonographers. The IOTA Simple Rules have created coherence in the definition of morphological features of ovarian tumours using a standardized examination technique (ultrasound features suggesting malignancy (M-features) or benignity (B-features)) [16,17] (Tab. 2, Tab. 3).

Risk of Malignancy Index. In 1990, Jacobs et al. suggested for the first time distinguishing a benign from a malignant pelvic mass [17]. The Risk of Malignancy Index (RMI) model includes clinical data, biochemical results and sonographic findings of women with suspected malignant changes of the ovary. The RMI is calculated by the formula – RMI=U×M×Ca-125 where: U=ultrasound score, M=menopause status (M=1 for pre-menopausal women, M=3 for post-menopausal women). The cut-off value was 200, which correlated with a high probability of malignancy [23]. Over the years, the RMI model has evolved and three modifications have been developed depending on the values assigned to the U and M features [24]. This model allows separation of patients with benign lesions. Unfortunately, this algorithm does not qualify patients according to the FIGO clinical stage [25,26,27,28].

Calculation of specificity, sensitivity, positive and negative predictive values is not based on the value of the result, but on its value below or above this threshold (200) [4,17]. (Table 4)

Risk of Ovarian Malignancy Algorithm. The Risk of Ovarian Malignancy (ROMA) algorithm uses a combination of cancer antigen 125 (CA-125), human epididymal protein 4 (HE4) and women's menopausal status. ROMA allows assessment of the degree of risk and assignment of women with adnexal/small pelvis masses to groups with low or high risk of an ovarian malignancy. The cut-off points are, respectively: for premenopausal women >13.15 and for postmenopausal women ≥27.7 [30,31,32]. The ROMA algorithm has not been validated for women with previous oncological history,

Table 1. Diagnostic performance of CA 125 in the subset of studies to date

		CA 125				
Author	Systematic review or meta-analysis	SN % (95% IC)	SP % (95% IC)	PPV %	NPV %	AUC (95% IC)
Huy et al.* [5]		92.3	77.0	19.05	99.40	0.872
Huy et al.° [5]		76.5	90.0	81.25	87.10	0.872
Lee et al.* [6]		58.4	55.6	17.5	89.3	0.56
Lee et al.° [6]		57.8	88.3	62.7	86	0.806
Yanaranop et al.* [7]		89.3	43.3	26.9	94.6	
Yanaranop et al.° [7]		80.4	69.7	64.9	83.6	
Goff et al.ᵉ [8]		79 (67–88)	76 (68–83)	63	87	
Shin et al.* [9]		52.6	70.1			0.569
Shin et al.° [9]		90.0	85.7			0.917
Lycke et al.* [10]		95.7	59.6	19.1	99.3	0.776 (0.723–0.829)
Lycke et al.° [10]		92.0	79.5	70.1	95.0	0.857 (0.820–0.895)
Kim et al.* [11]		71.4	69.5	5.5	99	
Kim et al.° [11]		71.4	90.3	67.8	91	
Choi et al.* [12]		74.7	78.7		91	0.777
Choi et al.° [12]		82.1	94.9		62.2	0.852
Torky et al.ᵉ [13]		92.8	68.9	41.9	97.2	0.736

* premenopausal subgroup; ° postmenopausal subgroup; ᵉ - combined (premenopausal and postmenopausal) subgroup;
SN – Sensitivity; SP – Specificity; PPV – Positive Predictive Value; NPV - Negative Predictive value; AUC - Area Under ROC Curve;

Table 2. IOTA Simple Rules for predicting benign or malignant ovarian tumour [14, 16]

Rules for predicting a malignant tumour (M-rules)	Rules for predicting a benign tumour (B-rules)
M1 Irregular solid tumour	B1 Unilocular cyst
M2 Presence of ascites	B2 Presence of solid components where the largest solid component is <7 mm in largest diameter;
M3 At least four papillary structures	B3 Presence of acoustic shadows
M4 Irregular multilocular solid tumour with largest diameter ≥100 mm	B4 Smooth multilocular tumour with largest diameter <100 mm
M5 Very strong blood flow (color score 4)	B5 No blood flow (colour score 1)

women currently undergoing chemotherapy, pregnant women or young women (under 18 years of age) [31,32]. The test is not intended as a screening test or a standalone diagnostic test for ovarian cancer [10,31]. (Table 5)

What are Nidogen-1 and Nidogen-2? Human body cells are divided into specialized groups by a thin membranous layer of connective tissue called the basement membrane, and links body cells to their interstitial matrix [34]. The most important parts of the basement membrane are laminins, collagen IV, nidogens and perlecan. Nidogens connect proteins from laminin networks and collagen IV. This process supports stabilization of the structure created by the basement membrane [35,36]. Nidogen-1 (NID-1) and Nidogen-2 (NID-2) are in a group of nidogens that are observed in human organisms [34].

Both nidogens are made up of three globular domains which are divided by a region resembling a link or a rod [37]. Mesenchymal cells indicate the presence of nidogens which are collected in the endothelial and epithelial basement membranes within the phase of development [38].

Further, fibroblasts are classified as an origin of nidogens in skin tissue [38,39]. Moreover, the nidogens described above have been observed in human perlecan [40,41].

Both NID-1 and NID-2 have the ability to combine with various receptors in human cells. NID-1 concentrates in cartilage tissue and neuromuscular junction, whereas NID-2 is manifested in muscle tissue [42]. Additionally, damage to NID-1 in mouse cells resulted in anionic modification in the glomerular basement membrane and neurological failures, such as structural changes in capillaries in the brain and the capsule of the lens. Moreover, disturbance to wound healing was also observed [43]. Both nidogens are evidently likely to cleave by proteolysis; nevertheless, laminin c1-binding may reduce that tendency for NID-1 [38]. What is more, that effect was also observed between nidogens, thus extraction of both NID-1 and NID-2 may results in destruction of the basement membrane [39,44,45]. NID-2 might also be useful as a biomarker to predict non-small cell lung cancer (NSCLC) or to screen the high-risk population for NSCLC, and additionally for screening for esophageal squamous cell carcinoma [46, 47,48].

Table 3. Diagnostic performance of IOTA Simple Rules algorithm in the subset of studies to date

		IOTA Simple Rules				
Author	Systematic review or meta-analysis	SN % (95% IC)	SP % (95% IC)	PPV %	NPV %	AUC (95% IC)
Auekitrungrueng et al.ε [15]		83.8 (77.1–90.4)	92 (88.8–95.2)	81.7 (74.7–88.6)	93 (88.5–97.6)	
Garg S et al.ε [16]		91.66	84.84	68.75	96.55	0.889
Tongsong et al.ε [18]		82.9	94			
Ning et al.ε [19]		98.4	73.9	70.9	98.6	0.85
Ning et al.ε [19]		96.2	96.3	92.7	98.1	0.96
Ning et al.ε [19]		72.4	88.8	77.8	85.6	0.86
Ning et al.ε [19]		100	94	90.5	100	0.97
Ning et al.ε [19]		96.7	87.3	81.7	97.8	0.92
Knafel et al.ε [20]		96.3	81.9	87.2	75.2	
Knafel et al.ε [20]		96.3	95.1	91.9	97.9	
Knafel et al.ε [20]		95.1	89.6	83.9	97	
Knafel et al.ε [20]		95.1	93.8	89.7	97.1	
Shetty et al.ε [21]		92.8 (77-99)	92.9 (88-96.4)	70.2 (53-84)	98.6 (95-99)	
Hidalgo et al.ε [22]		95.6	97.8			
Hidalgo et al.ε [22]		94.1	97.6			

* premenopausal subgroup; ° postmenopausal subgroup; ε- combined (premenopausal and postmenopausal) subgroup;
SN - Sensitivity; SP - Specificity; PPV - Positive Predictive Value; NPV - Negative Predictive Value; AUC - Area Under ROC Curve;

Table 4. Diagnostic performance of RMI algorithm in the subset of studies to-date

			RMI			
Author	Systematic review or meta-analysis	SN % (95% IC)	SP % (95% IC)	PPV %	NPV %	AUC (95% IC)
Yanaranop et al.* [7]		75	80.8	47.7	93.3	
Yanaranop et al.° [7]		80.4	77.3	71.2	85.0	
Lycke et al.* [10]		87.0	89.6	45.5	98.6	0.883 (0.810–0.956)
Lycke et al.° [10]		89.3	80.5	70.4	93.5	0.849 (0.810–0.888)
Auekitrungrueng et al.ε [15]		77.2 (70.4–84.1)	86.8 (83.2–90.5)	71.8 (64.7–78.9)	89.8 (85.0–94.5)	
Auekitrungrueng et al.ε [15]		82.1 (75.8–88.3)	82.6 (78.6–86.7)	67.2 (60.3–74.1)	91.4 (87.3–95.5)	
Meys et al.ε [29]	X	75 (72–79)	92 (88–94)			
Chacón et al.ε [30]	X	87	75			

* premenopausal subgroup; ° postmenopausal subgroup; ε – combined (premenopausal and postmenopausal) subgroup
SN – Sensitivity; SP – Specificity; PPV – Positive Predictive Value; NPV – Negative Predictive Value; AUC – Area Under ROC Curve

Table 5. Diagnostic performance of ROMA algorithm in the subset of studies to date

		ROMA				
Author	Systematic review or meta-analysis	SN % (95% IC)	SP % (95% IC)	PPV %	NPV %	AUC (95% IC)
Huy et al.* [5]		76.9	82.9	21.28	98.36	0.912
Huy et al.° [5]		82.4	96.7	93.33	90.62	0.912
Lee et al.* [6]		45.5	81.8	28.8	90.3	0.768
Lee et al.° [6]		50	88.8	60.4	83.9	0.79
Yanaranop et al.* [7]		85.7	70.8	40.7	95.5	
Yanaranop et al.° [7]		82.6	65.2	62.3	84.3	
Shin et al.* [9]		52.6	87.9			0.792
Shin et al.° [9]		95.0	87.1			0.980
Lycke et al.* [10]		87.0	80.9	31.3	98.4	0.839 (0.764)
Lycke et al.° [10]		91.1	77.2	67.5	94.3	0.841 (0.803–0.880)
Kim B et al.* [11]		71.4	87.5	12.3	99.2	
Kim B et al.° [11]		69.6	91.3	69.6	91.3	
Choi et al.*[12] [12]		70.7	92.6		91.1	0.875
Choi et al.° [12]		82.9	97.4		63.9	0.864
Chacón et al.ε [30]	X	77	85			
Cui et al.ε [32]	X	90 (88–93)	91 (89–94)	90 (88–95)	93 (91–95)	0.96
Abdalla et al.* [33]		70 (41.6–98.4)	82 (76.4–87.7)	17.9 (5.9–30)	98 (95.7–100)	0.814 (0.758–0.869)
Abdalla N et al.° [33]		82.5 (70.7–94.3)	83.8 (75.4–92.2)	73.3 (60.4–86.3)	89.9 (82.7–97)	0.833 (0.765–902)

* premenopausal subgroup; ° postmenopausal subgroup; ε - combined (premenopausal and postmenopausal) subgroup
SN - Sensitivity; SP - Specificity; PPV- Positive Predictive Value; NPV- Negative Predictive Value; AUC - Area Under ROC Curve

Despite the protective function of nidogens for the basement membrane, they have potential to be a target for destruction of tissues during carcinogenesis, metastasis formatting and angiogenesis stimulation, which might explain the promoting impact for carcinogenesis of the stomach or colon triggered by nidogens loss [46].

DISCUSSION

Nidogen-1 in ovarian cancer. Several authors from Beijing checked the level of NID-1 and CA-125 in ovarian tissues from 265 patients with serous carcinoma (OSC). The results of the study indicated a high level of NID-1 in advanced stage cells (stage III and IV), compared to the early stages (stage I and II) [49]. In their analyses, they also took into consideration the plasma concentration of the protein in cell samples obtained from OSC patients. They found that the levels of NID-1 were noticeably increased in the examined tissues in opposition to normal cells. It was observed, however, that CA-125 rather than NID-1 may be more useful in OC patients in the early stages of the disease (CA-125: 0.88, 95% Cl, 0.80–0.96, NID-1: 0.53, 95% Cl, 0.41–0.64) [49].

Statistical analysis shows that NID-1 has a potential value to predict certain aspects of responses to treatment. The levels of NID-1 were compared in two groups of women: 138 patients with primary inoperable cancerous tumour after chemotherapy, and 127 patients who underwent surgical macroscopic cytoreduction of the neoplasm. Interestingly, in patients after chemotherapy, the levels of NID-1 and CA-125 were higher than in those who underwent surgery alone. These results indicate that the level of NID-1 may predict the volume of tumour burden and the most appropriate and individually tailored therapeutic path.

Moreover, it was observed that the levels of both NID-1 and CA-125 correlated with grading of OC and its sensitivity to chemotherapy. On the other hand, no correlation was found between nidogen-1 and metastases in lymph nodes, in opposition to CA-125 [49].

Additionally, a study by Li-Zhang et al. examined the expression of NID-1 in the tissues from 44 patients with ovarian serous carcinoma (OSC). The protein was detected in intracellular substance and cytoplasm. It is worth noting that in the group of patients with OSC, the expression of NID-1 in the analyzed tissues was not related to progression of the tumour [49]. Interestingly, some authors concluded that there was a significant relationship between the level of NID-1 and poor clinical prognosis in patients with OSC. A study by Zhou et al. revealed that NID-1 propagates the epithelial-to-mesenchymal transition (EMT) of ovarian tissue in serous cancer. Additionally, under the influence of NID-1 the tissue may change its epithelial features into mesenchymal attributes. NID-1 supports migration, penetration, and decreases the sensitivity of ovarian tissue to OC. The regulation uses the mechanism of initiation of the ERK/MAPK pathway [50].

On the basis of the study by Yuan et al., it was concluded that NID-1 became a direct target of miR-204–3p. LncRNA-ATB controls miR-204–3p in a negative way. Through NID-1 over-expression, LncRNA-ATB, which promotes apoptosis and inhibits proliferation of ovarian cancer cells, may be inhibited and will stimulate the growth of OC cells [51]. Furthermore, Zhou et al. reported the impact of NID-1 on the loss of sensitivity to chemotherapy based on cisplatin in ovarian cancer. Among the examined neoplastic tissues, the levels of NID-1 correlated with higher resistance to cisplatin-based chemotherapy [50]; therefore, NID-1 may represent a candidate prognostic indicator and a potential therapeutic target in OC.

Nidogen-2 in ovarian cancer. In the research by Kuk et al., the levels of NID-2 and CA-125 were compared in three groups of women. The groups included a control group, a group with benign ovarian pathologies, and a group with ovarian cancer (FIGO stage I/II and III/IV). Each group comprised 100 patients. The study revealed that the level of NID-2 in the serum of patients with OC was elevated (median 18.6 μg/L), compared to patients with benign ovarian pathologies and the control group (median 12.1 and 13.2 μg/L, respectively) [52].

Analysis showed that NID-2 has a potential statistical value. The results revealed that NID-2 strongly correlates with the values of CA-125. Both CA-125 and NID-2 are more often elevated in the serous type compared to the mucinous, endometrioid or clear cell type of ovarian cancer. Serum NID-2 is also more frequently elevated at the late-stage disease (FIGO stage III/IV), similar to CA-125 [52]. Several other potential biomarkers were also determined; however, most of them are not clinically relevant in the prediction of ovarian cancer [53,54]. It was the first study measuring the level of NID-2 and showing its correlations with CA-125. It demonstrated possible clinical benefits in OC prophylaxis, after prior extensive proteomic analysis of OC ascites, identifying over 450 proteins [55].

Torky et al., assessed in their study the levels of NID-2 and CA-125 in the serum of OC patients, and the value of transvaginal ultrasonography in the prediction of the disease. The study group comprised 144 women with an adnexal mass detected, including 116 benign and 28 malignant cases. In histopathological examination of the benign and malignant cases, CA-125 and NID-2 serum concentrations were similarly distributed. In this study, the cut-off value for NID-2 was 28.35 ng/ml, which showed 91.6% sensitivity, 62% specificity, PPV 37.1%, NPV 97.9% and 68% accuracy [13]. The study showed that the combination of more than one marker is much more beneficial in OC prediction. Low sensitivity of transvaginal ultrasonography is augmented by a much higher sensitivity of tumour markers, while in the opposite situation, Doppler ultrasonography (U/S) corrects low results of tumour markers [13].

The study by Chen et al. concerned an increase in NID-2 and CA-125 levels in patients with serous OC. The levels of NID-2 and CA-125 were examined by the ELISA method and immunoassay in 15 patients in the control group, 22 patients with benign ovarian pathologies and 40 patients with serous OC [56]. Comparing the obtained results, it was found that the level of NID-2 in the control group and in patients with benign ovarian pathologies was significantly lower compared to patients with serous OC. The results correlated with the conclusions of Kuk and Torky in their studies. The differences in NID-2 levels between the control group and patients with benign ovarian pathologies were not significant. In the serous type of OC the level of serum NID-2 was higher in patients at stages III–IV than in patients at stages I–II. Diagnostic specificity and sensitivity were improved due to the combined detection of serum NID-2 and CA-125. The study showed that NID-2 could not only be used as a new biomarker, but also as a prognostic marker to assess progression of ovarian cancer [56].

Several diagnostic biomarkers can be combined in order to increase sensitivity and specificity of tests in the detection of ovarian cancer. Such studies have already been conducted. Comparing NID-2 values with CA-125 values, transvaginal ultrasonography and currently used preoperative methods in ovarian cancer, it can be seen that NID-2 is more sensitive than Doppler U/S, CA-125, RMI and ROMA, and slightly less sensitive than the IOTA Simple Rules. NID-2 specificity, PPV and accuracy are lower than all the above- mentioned methods, but NPV is the highest compared to CA-125, Doppler U/S, RMI, ROMA and the IOTA Simple Rules.

CONCLUSIONS

To-date, no effective screening methods have been developed for decreasing the incidence of ovarian cancer and its its high mortality. Effective biomarkers for early detection of this malignancy are needed. Diagnostic markers and indicators are desirable – sensitive and very specific for a given histological type of ovarian cancer. In the future, NID-1 and NID-2 may be useful in early diagnostics of ovarian cancer, especially its serous type. Their increased concentration suggests adenocarcinoma of the ovary, both at the early and late stages. A decrease in their concentration may suggest growth of the stomach and colon tumours. There is still a need for prospective studies combining the diagnostic value of NID-1, NID-2 and current ovarian cancer diagnostic algorithms in order to check their diagnostic and predictive value. Close correlation between CA-125 and NID-2 prevents their combination in one diagnostic panel which would perform better than CA-125 alone. However, NID-2 seems to be a promising biomarker that correlates closely with ultrasound and CA-125. Although it has improved the accuracy of diagnosis, further studies are still needed to validate the described biomarkers.

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