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# Oncology biomarkers for gynecologic malignancies

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## 1. ABSTRACT

Current therapies efficiently treat most patients with gynecologic malignancies detected at an early stage. Thus, the identification of oncology biomarkers for screening and monitoring of occult tumors has been highly prioritized. Hyperglycosylated human chorionic gonadotropin (hCG) epitomizes oncologic biomarker, as the serum level of this hormone is elevated in virtually all cases of gestational trophoblastic diseases. On the other hand, despite the availability of various markers such as CA125, CA19.9, CA15.3, CA72-4, Inhibin, beta-hCG, AFP, CEA and many more biomarkers under investigation, fewer than 25% of all ovarian cancers are currently detected in stage I. Large efforts have been undertaken to further identify composite markers for gynecologic malignancies that may exhibit greater specificity when studied over time, as well as to develop risk models and screening algorithms aimed at improving the specificity and sensitivity of diagnostic tests. In this review, we provide a comprehensive analysis of the biomarkers currently used in clinics for gynecologic malignancies, as well as an outlook of the most promising oncologic biomarkers currently under study.

## 2. INTRODUCTION

Oncology biomarkers are defined as easily accessible and measurable biologic substances for screening and monitoring of occult tumors (1). Biomarkers are applied to the management of gynecologic cancers, including for the differential diagnosis between malignant and benign masses, to monitor and predict responses to treatment, and to detect early stage or occult recurrent diseases. While CA125, CA19-9 and CEA are well established biomarkers in patients with gynecologic malignancies (2), the most commonly used serum biomarkers for monitoring disease progression are CA125 and hCG. Following earlier studies that evaluated the predictive values of single tumor markers, multiple groups have been investigating the application of combined biomarkers ("composite markers") to predict tumor progression. Statistical and mathematical methods are being developed to assess composite markers sensitivity and specificity.

For optimal use in clinics, disease biomarkers must also meet criteria such as low invasiveness, allowing patient tolerance and adherence to long-term follow up; high benefit/risk ratio, only possible when therapeutic interventions able to improve disease outcome exist; and adequate accuracy (3). The annual incidence rate determines the level of accuracy required to achieve a positive predictive value of 10%. Thus, the less frequent the disease, the closest to perfection the biomarker sensitivity and specificity must be (4).

## 3. BIOMARKERS OF GYNECOLOGIC MALIGNANCIES CURRENTLY USED IN CLINICS

Gynecologic malignancies encompass endometrial cancers, the most common gynecologic malignancy in the United States, and ovarian, cervical and vulvar carcinomas. Primary peritoneal cancers, tubal carcinomas, gestational trophoblastic diseases and various uterine sarcomas and vulvar melanomas are rarely seen in everyday practice.

### 3.1. Ovarian cancer

Each year, approximately 24,000 women are diagnosed with ovarian cancer in the United States. Tragically, most of these women are diagnosed at a late stage. Thus, despite cytoreductive surgery and chemotherapy, 70% to 80% of the patients succumb to the disease within 5 years of diagnosis. Most ovarian cancers are of epithelial origin, and more specifically of serous histology, the most aggressive subtype. Large efforts have been undertaken to identify biomarkers able to detect ovarian cancer at an early stage, when the case/fatality ratio is low, and to monitor disease progression and chemosensitivity. The expected positive outcome of screening with tumor markers is based on the hypothesis that advanced disease arises from curable early stage disease. However, the classification of epithelial ovarian cancer (EOC) in two groups challenges this assumption (5). Type I cancers progress slowly in a step-wise manner from adenoma to borderline tumor to cancer, while type II cancers (high-grade serous carcinomas) progress rapidly from an undefined precursor lesions to advanced cancer. In addition, efficient screening requires an interval between early and advanced stages, yet it is still not completely clear whether the duration of preclinical ovarian cancer is compatible with a positive screening outcome. Using serial longitudinal screening trial with CA125 on 220,000 women, Skates and Singer estimated the mean duration of preclinical ovarian cancer at 1.9+0.4 year and the duration of stage I at 9 months at least when the interval for clinical detection is 1.3 year (6), This work suggests that early detection could save 3.4+ 0.1 year of life per patient. It is also important to keep in mind that because of the high genetic instability of ovarian cancer, one can reasonably expect different sets of tumor markers to be expressed during early versus late stage disease. Finally, the low incidence of ovarian cancer creates extraordinary challenges for the identification of biomarkers that can approach a 10% positive predictive value. Altogether, the unique characteristics of ovarian cancer translate into major hurdles for screening strategies, and to date no diagnostic marker for the early detection of ovarian cancer has been approved for clinical use.

#### 3.1.1. Markers of epithelial ovarian cancers (EOC)

In 2011, the only marker approved for monitoring ovarian cancer progression and treatment response is still CA125.

##### 3.1.1.1. CA125/MUC 16

Cancer antigen 125 (CA125 or MUC16) is a high molecular weight glycoprotein member of the mucin family (7-10). Due to the highly repetitive structure of CA125 detection of the antigen was first performed by radioimmunoassay using only one monoclonal antibody (11). However, the unique structure of the protein proved to be challenging and it took twenty years to identify MUC16, the gene encoding CA125 (12, 13).

CA125 can be detected in the serum of 90% of patients with advanced ovarian cancer at higher levels that those found in 99% of healthy women (35 U/mL). However, there is an on-going debate regarding the use of CA-125 measurements in the follow-up of patients after primary treatment. At the time of surgery, CA125 is elevated in the sera of only 50% to 60 % of patients with early stage ovarian cancer (14). In addition, serum CA125 may also be elevated in premenopausal women with adenomyosis, endometriosis and other benign diseases, which act as confounding factors (6, 15). Furthermore, at the tissue level CA125 expression depends on tumor histology (16). Finally, while the overall expression of CA125 is increased in 80% of ovarian cancers, the breakdown of expression by cancer types reveals that only 12% of mucinous cancers express CA125, compare with 85% of serous, 68% of papillary, 65% of endometrioid, 40% of clear cell and 36% of undifferentiated adenocarcinomas.(17) Yet, response to treatment as well as disease progression can be followed up by CA125 serum levels in more than 90 % of ovarian cancer patients with elevated preoperative level of CA125 (18). Consequently, despite an overall accuracy limited to 66 % to 88 %, the

application of sequential CA125 measurements for monitoring clinical course and response to therapy has been recommended. It is important to note that CA125 values under 35 U/mL do not exclude active disease (19).

The specificity of CA125 can be increased by combining it with ultrasound or by performing repeat measurements over a period of time (4, 20, 21). Serial CA125 measurements are more useful in the clinic than the absolute value of a single measurement. In addition, the serum half-life of CA125 correlates with the odds of reaching complete remission in advanced stage EOC during first-line chemotherapy. For example, the chances of remission (15% vs. 67%, respectively) can be predicted by the half-life duration of CA-125 (more or less than 20 days) (22). Furthermore, the steady decrease of CA125 serum levels during treatment demonstrates chemo sensitivity. Both the North Thames Ovary Trial 4 and the GOG 97 protocol defines second-line responses to chemotherapy by a 50% decrease in CA125 levels in two consecutive samples followed by another confirmatory sample (50% response), or by a serial decrease greater than 75% over three samples (75% response) (23, 24).

CA-125 specificity appears inadequate as a tumor marker for screening due to the high rate of false positive values and the low sensitivity (50–62%) for patients with early stage disease. The causes of false-positive CA125 elevations in the premenopausal population include endometriosis, adenomyosis, and retrograde menstruation (25). Yet, the results of the Prostate, Lung Colorectal and Ovarian Cancer Screening Trial Project Team (26-28) showed that CA125 performed better than transvaginal sonography alone (29). In addition, in one of the first studies evaluating novel ovarian cancer markers in a large well-annotated repository from a prevention study, preclinical elevations of CA125, HE4, and mesothelin provided evidence of ovarian cancer as early as 3 years before clinical diagnosis, while the lead time associated with these markers is likely less than 1 year (30). Taken together, CA-125 remains the most useful marker for ovarian cancer.

**3.1.1.2. Composite markers for EOC**

Currently, no available biomarker can offer a positive predictive value of 10% for EOC. Investigators have hypothesized that greater performances might be achieved with multiple markers. Over the years, tens of markers have been tested in combination with CA125 in an attempt to create a composite marker with improved sensitivity and specificity (4, 14, 15, 31-33).

Cancer Antigen 15-3 (CA15-3) is a tumor-associated antigen used mostly for the diagnosis of breast malignancies. Despite its low specificity for ovarian cancer, it is elevated in 57-71% of ovarian malignancies compared to only 2-6% of benign adnexal masses. Therefore, CA15-3 used in combination with CA125 can be of help for differential diagnosis between malignant and benign masses (31, 34-36).

The tumor-associated glycoprotein 72 (TAG-72 or CA72-4) is a mucin-like, high molecular weight glycoprotein that is expressed by a variety of gastric, intestinal, colorectal and pancreatic tumors, as well as by mucinous ovarian carcinomas (37). Lenhardt *et al.* assessed the prognostic values of CA125 and CA72-4 in patients with borderline ovarian tumor (BOT) and found that both serum concentrations were altered in BOT patients compared with healthy controls; however, only CA125 correlated with tumor stage at primary diagnosis and increased with the presence of ascites, endometriosis or peritoneal implants (38). Used in combination with CA125 and ultrasound, CA72-4 can also efficiently contribute to the differential diagnosis between benign and malignant adnexal masses (39). Finally, the combination of CA125 (>65 U/ml) with increased levels of CA15-3 and/or CA72-4 can help distinguish EOC from benign adnexal masses with a sensitivity of 73% and a specificity of 98% in the general patient population, while sensitivity and specificity reach 81% and 100 %, respectively, in patients older than 50 (31).

Carbohydrate antigen 19-9 or sialylated Lewis (a) antigen (CA19.9) is a member of the Lewis blood group antigens (34). Its serum levels are elevated in 76% of mucinous ovarian tumors and in 27% of serous ovarian tumors (40). In combination with CA125, CA19.9 exhibits a significantly higher sensitivity (93.2% vs. 81.1%) but lower specificity (78.9% vs. 86.0%) than CA125 alone for differentiating between benign and malignant masses (41). CA19-9 used together with CA125 proved to be a useful marker for BOT (42).

The carcinoembryonic antigen (CEA) is a complex glycoprotein expressed by over 90% of colorectal carcinomas. Interestingly, in contrast with CA125, its level remains normal in benign and inflammatory diseases of the adnexa, while it is elevated in 25% to 50% of women with epithelial ovarian carcinomas (43, 44). Tissue expression of CEA by immunohistochemistry was found to be specific for Brenner tumors, endometrioid carcinomas and areas of intestinal differentiation in mucinous tumors (44).

Finally, tumor-associated trypsin inhibitor (TATI), CA19-9, CA72-4 and CEA may be useful for follow up when combined with CA125 in mucinous ovarian tumors (33).

**3.1.1.3. The human epididymis protein 4 (HE4)**

HE4, also known as WAP four-disulphide core domain protein 2 (WFDC2), is an 11 KDa protein encoded by *WFDC2* gene located on chromosome 20q12-13.1. HE4 protein is overexpressed by ovarian tumors, especially serious and endometrioid carcinomas, as well as lung adenocarcinomas (45). While HE4 sensitivity and specificity are equivalent to CA-125 for late-stage disease, HE4 serum levels are less frequently elevated in patients with non-malignant adnexal diseases. Thus, HE4 has the greater specificity in distinguishing ovarian cancer from women with benign adnexal disease (46). In addition, the diagnostic performance of HE4 is superior to the one of Mesothelin in differentiating ovarian cancers from benign tumors. The antibodies developed for an HE4 ELISA assay by Hellström and colleagues (47) were exclusively licensed

to Fujirebio Diagnostics, Inc and used to develop an HE4 enzyme immunometric assay that received FDA clearance in 2009 for the monitoring of patients with ovarian cancer.

### 3.1.2. Markers of non-epithelial ovarian cancers (non-EOC)

Non-EOC account for only 10% of all ovarian cancers and consist of malignancies of various origins, including germ cell, sex cord stromal cell, metastatic carcinomas to the ovary, as well as the extremely rare sarcomas and lipoid cell tumors. Contrary to EOC, non-EOC are usually found in young patients (34). HCG and AFP are the main tumor markers used to monitor germ cell tumors and their values can have significant effects on the treatment plan.

#### 3.1.2.1. Human chorionic gonadotropin (hCG)

The Human Chorionic Gonadotropin (hCG) is an hormone normally synthesized in pregnancy by the syncytiotrophoblast, and it contains two non-covalently linked, alpha and beta subunits. HCG is glycoprotein of 36.7 kDa composed of 244 amino acids and forming heterodimers, including the α (alpha) subunit that is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH), and a unique β (beta) subunit. HCG β-subunit contains 145 amino acids and is encoded by six highly homologous genes located on chromosome 19q (48).

The free beta-subunit of hCG is produced in most gynecologic malignancies and it enhances tumor growth and invasion, leading to poor prognosis. However, although free beta-subunit and degradation products of the beta-core fragment can be found in serum or urine of patients with ovarian, endometrial or cervical cancers (56% to 84%, 51%, and 46%, respectively) (49-51), they fail to detect ovarian cancer at early stages (52). Amongst all ovarian cancers, the germ-cell tumors with chorionic component are the only one to produce high levels of hCG (53). The structure of the hyperglycosylated hCG varies significantly from hCG and is produced by cytotrophoblast cells. It is an absolute marker of invasive mole and invasive choriocarcinoma, with serum levels closely correlated to the tumor burden (51).

#### 3.1.2.2. Serum alpha-fetoprotein (sAFP)

AFP is a glycoprotein normally produced by the fetal yolk sac, the fetal gastrointestinal tract, and the fetal liver. AFP serum levels (sAFP) are elevated in pregnancy and in benign liver diseases. sAFP is also elevated in germ cell tumors, including in endodermal sinus tumors (100%), immature teratomas (62%) and dysgerminomas (12%) (54). sAFP is a reliable marker for monitoring therapeutic responses, detecting recurrences in endodermal sinus tumor and embryonal carcinomas, as well as predicting the presence of yolk sac elements in mixed germ-cell tumors (55-57).

#### 3.1.2.3. Inhibin and activin

Inhibin and Activin are dimeric glycoproteins, both closely related to transforming growth factor-β (TGF-β) but with opposing biological effects. Like Activin, Inhibin protein complexes are made of two monomers linked by a single disulfide bond. However, while Inhibin down regulates pituitary follicle-stimulating hormone (FSH) synthesis and secretion, activin enhances it. (34) The original report by Lappohn *et al.* in 1989 demonstrated elevated serum levels of Inhibin in women with ovarian granulosa-cell tumors (58); higher levels were also described later in women with ovarian sex cord-stromal tumors. Inhibins are useful to determine therapeutic responses and predict recurrence of ovarian granulosa cell tumors (59), but not in the case of EOC where serum levels are elevated in only 5 % to 31 % of these patients (60, 61). Although a serum immunoreactive form of the alpha-subunits (pro-αC) has been found to be preferentially secreted by EOC, its use as a composite marker with CA125 is not well established (61, 62). Finally, amongst all the members of the TGFβ superfamily, Activin is the only one to be significantly elevated in undifferentiated EOC. Yet, Activin does not correlate with the clinical course of the disease (62).

### 3.2. Cervical cancer

Exfoliative cytology remains the major tool for diagnosis and detection of cervical cancer recurrences (34). However, despite its undisputable merit for the screening of premalignant conditions, exfoliative cytology is not a useful tool for monitoring therapeutic responses, which creates an impetus to identify novel biomarkers for cervical carcinoma. Several biomarkers have been investigated, but as yet none of them has gained a dominant role in clinical applications.

#### 3.2.1. Squamous-cell carcinoma antigen (SCC-Ag)

SCC-Ag is a marker of cellular differentiation for squamous cells that was first isolated as one of the 14 sub-fractions of the tumor antigen TA-4 (63). Serum levels of SCC-Ag are elevated in 67% to 78 % of moderately and well-differentiated carcinomas but only in 38% of poorly differentiated carcinomas (64). Postoperative elevated serum levels of SCC-Ag correlate with tumor volume, stage and lymph node status (65, 66), and serial determination of post-treatment levels of SCC-Ag correlates with clinical responses in 72% of patients. While the normalization of SCC-Ag levels is associated with complete response (67, 68), elevated post-treatment values predict treatment failure and recurrence in 50% to 71% of the patients (69). SCC-Ag is also found elevated in sera of patients with other squamous-cell diseases, including cancers of the esophagus, lung and head and neck, as well as benign skin diseases such as eczema (70), and this lack of specificity limits the general use of SCC-Ag for cervical cancer.

#### 3.2.2. CA125

Serum levels of CA125 were extensively evaluated in cervical carcinoma. While only 13% to 21% of women with squamous cell carcinoma of the cervix have elevated levels of CA125 (67), CA125 appears more sensitive than SCC-Ag for cervical adenocarcinomas. It also serves as an important prognostic factor and an implicit indicator of tumor virulence (71). CA125 used in combination with CA19-9 can increase the sensitivity to

60%, and up to 70% when combined with both CEA and SCC-Ag (72). Finally, steady decrease of CA125 levels during treatment for cervical carcinoma correlates with chemosensitivity in 83% of patients (73).

### 3.3. Endometrial cancer

Over 40,000 new cases of uterine cancer are diagnosed in the United States annually, resulting in over 7,000 deaths per year (74). As the prevalence of cervical carcinoma declines and the average life span gets longer, an increase of the prevalence of endometrial carcinoma is being seen. Although endometrial carcinoma is primarily a disease of the postmenopausal woman, about 25 % of the patients are premenopausal. Among patients aged 40 years and younger, many women have a mismatch repair deficiency (75, 76). Compared to ovarian cancer, endometrial cancer is not a silent killer. The single most common cause leading to the diagnosis of endometrial cancer is postmenopausal bleeding (77). Patients with endometrial cancer have symptoms at early stage of the disease, which facilitates prompt diagnosis. However, high risk groups such as women with Lynch syndrome, PTEN gene defect, breast cancer patients on Tamoxifen and women with severe obesity and diabetes are at high risk for endometrial cancer and thus may benefit from screening for early detection. Various tumor markers such as CA125, CA72-4, CA19-9, CA15-3, OVXI and CEA have been evaluated for endometrial cancer (77-79) but CA125 is the only one that has been approved for clinical use. CA125 detects less than 20 % of patients with early stage disease (77) and only about 25% of patients with asymptomatic recurrent disease (80, 81). However, CA125 serum levels above 35 U/ml correlate with advanced endometrial cancer and the presence of extra-uterine disease such as peritoneal seeding and lymphovascular space involvement (82-84). In addition, CA125 levels in preoperative sera correlate with endometrial carcinoma stage, histological grade, cervical invasion, peritoneal cytology, lymph node status and clinical outcome (85). Finally, serial measurements of CA125 can indicate disease activity and provide a useful biochemical tool for post-treatment surveillance of patients with endometrial carcinoma (85).

## 4. BIOMARKERS OF GYNECOLOGIC MALIGNANCIES UNDER STUDY.

### 4.1. Ovarian cancer

Recent studies have identified several new candidates for early detection of ovarian cancer. Murine monoclonal antibodies have been developed against mesothelin (86, 87) and M-CSF (88) and used as markers to identify ovarian carcinomas. Lysophosphatidate, the simplest natural phospholipid, is a highly mitogenic agent that was found elevated in serum and ascites fluid of ovarian cancer patients (89). Expression array analysis has identified upregulation of HE4 (47, 90), prostasin (91), osteopontin (92), kallikreins (93), VEGF (94), and IL8 (95).

#### 4.1.1. Mesothelin

Mesothelin is a 40 kDa GPI-anchored glycoprotein and a differentiation antigen whose normal expression is limited to the mesothelial linings of the peritoneum, pleura and pericardium.(86) Mesothelin physiological function is not known but the absence of phenotype in mesothelin-knockout mice suggests that mesothelin is a non-essential protein (96). Mesothelin is an epithelial marker highly expressed by ovarian adenocarcinomas, pancreatic adenocarcinomas and mesotheliomas (97-99), as well as a soluble marker for ovarian and lung cancers.(87, 100-103) Fujirebio Diagnostics, Inc exclusively licensed the antibodies originally developed by Scholler *et al.* for the first mesothelin ELISA assay (87) and released on the market the Mesomark® kit (104) that was approved by the FDA in 2007 for the management of mesothelioma patients. Recent studies revealed that mesothelin tissue expression is linked to poor survival and chemoresistance of ovarian cancer patients (105).

#### 4.1.2. Lysophosphatidic acid (LPA)

Lysophosphatidic acid (LPA, 1-acyl-2-lyso-sn-glycero-3-phosphate) is present in elevated levels (up to 80μM) in the ascites and plasma of ovarian cancer patients, even at an early stage of the disease (89, 106). At high concentrations, such as those found in ovarian cancer ascites, LPA can induce tumor growth, anchorage-independent growth, and increase the production of growth and neovascularization factors including IL8 (107), VEGF and LPA itself, while simultaneously preventing apoptosis and anoikis (89, 108). LPA also increases the production and action of proteases and the invasiveness of ovarian cancer cells. The mechanisms leading to the elevated levels of LPA in ovarian cancer ascites are not completely understood. Although ovarian cancer cells can release LPA into cell supernatants (109), the primary source of LPA is not known. Furthermore, increased levels of LPA could be due to both increased rates of production and decreased rates of degradation. Indeed, the major mechanism of LPA degradation by ovarian cancer cells occurs mainly through lipid phosphate phosphatase (LPP)-like activity and a decreased expression of LPPs was found in ovarian cancer (110, 111). Altogether, these results suggest that LPA is likely to contribute to ovarian cancer spread and may be a promising candidate marker for early detection of ovarian cancer (108).

#### 4.1.3. Osteopontin (OPN)

Osteopontin is an acidic and calcium-binding glycophosphoprotein with a molecular weight ranging from 44 kDa to 66 kDa. It is found in all bodily fluids and also in the extracellular matrix components (92, 112). OPN functions both as a cell adhesion protein and as a cytokine for several integrins and CD44 (113). It is also involved in inflammation, especially in regulation of macrophages (114) and tumorigenesis (115). Although inferior to CA125 for predicting clinical response to therapy, levels of OPN rise earlier than CA125 in 90% of the patients that develop recurrent disease, which suggests that OPN may be a clinically useful adjunct to CA125 in detecting recurrent ovarian cancer (8, 92, 116, 117).

#### 4.1.4. Kallikreins (KLK)

Human kallikreins form a family of 15 highly conserved serine proteases, which are encoded by the

largest uninterrupted cluster of protease genes in the human genome serine protease family (118). These genes and their encoded proteins share a high degree of homology and are expressed in various tissues. Several kallikreins are emerging as cancer biomarkers, including KLK5, 6, 7, 10, 11, and 14 for ovarian cancer, and KLK3 (better known as Prostate-specific antigen (PSA)), KLK2, and KLK11 for prostate cancer (119). A combined panel of KLK6, KLK13 and CA125 was recently found to be more sensitive to detect early stage ovarian cancer than CA125 alone (120).

**4.1.5. Risk models and screening algorithms**

To facilitate the development of composite markers, several mathematical modeling have been tested. A Neural Network Analysis (NNA) was created to distinguish malignant from benign pelvic masses and to detect early-stage epithelial ovarian cancer (15, 32). For example, at a fixed specificity of 98%, such that no more than 2% of women screened would undergo a second procedure such as ultrasound, the NNA using CA125, CA72–4, CA15–3, and M-CSF presented with a sensitivity of 72% for early-stage disease, whereas CA125 alone exhibited a sensitivity of 48% (32). Another approach used a combination of multivariate normal distributions to analyze data at a fixed specificity of 98%. The same combination of CA125, CA72–4, CA15–3, and M-CSF exhibited a sensitivity of 75% for early-stage disease (121), similar to that seen with NNA.

Finally, Horvath and colleagues are developing an original, inexpensive and simple method for early diagnosis of ovarian carcinoma. It is based on canine scent detection of specific odors released by ovarian cancer tissue can serve as a new diagnostic tool for malignancy (122). Using this approach, different histopathological types of ovarian carcinoma could be differentiated with 100 % sensitivity and 97.5 % specificity. The same group used an electronic nose to demonstrate that 84.8 % of cancer tissues (sensitivity 84.8%) and 88.6 % of the control healthy samples (specificity 88.6%) were correctly classified (123).

**4.2. Cervical cancer**

The Papanicolaou (Pap) smear test for the screening of cervical carcinoma has lead to a significant decline in overall incidence and mortality rates of cervical cancer (CC) over the past three decades. However, recent data indicate that these declines have slowed down and that the number of new cervical adenocarcinoma (AD) cases, which carries a poorer prognosis than squamous cell carcinoma (SCC), has started to rise (124). Several reasons can be attributed to this rise, including the facts that cervical AD generates many more false-negative PAP smear results than SCC (125) and that cervical AD histology is similar to this of primary endometrial AD. However, it is important to distinguish between cervical AD and endometrial AD because the clinical treatment for these diseases is different (126).

**4.2.1. Carcinoembryonic antigen (CEA)**

Serum CEA levels are elevated in patients with progressive adenosquamous tumors (127). However, despite a specificity of 90%, in cervical cancer CEA sensitivity as a single marker does not exceed 15% (71, 128). The combination of CA-19-9, CA125 and CEA improves the sensitivity but on multivariate analysis only CA125 appears as an independent marker (72). Finally, the addition of CEA does not significantly increase the sensitivity obtained by using SCC alone (129). Thus to date, SCC remains the tumor marker of choice in squamous tumors.

**4.2.2. CYFRA 21-1**

CYFRA 21-1 is a soluble serum fragment of cytokeratin 19 and is elevated in 35% to 64% of patients with squamous cell carcinoma of the cervix (130). Serum levels of CYFRA 21-1 correlate with tumor size and stage of cervical squamous cancer (131) and can help the discrimination between malignant and benign adnexal masses with a 94% positive predictive value (132). However, as SCC-Ag, CYFRA 21-1 lacks specificity. CYFRA 21-1 is elevated in 63% of cervical adenocarcinomas, 52 % of endometrial adenocarcinomas of the uterus, and in 15 % of healthy controls and when used together with SCC-Ag, CYFRA 21-1 lowered the sensitivity of SCC-Ag (133). CYFRA 21-1 serial pre- and post-treatment measurements could predict chemosensitivity, but fail to provide a prognostic for survival. Finally, the sensitivity of CYFRA 21-1 in EOC was found to be consistently low (41% to 44%) leading to the conclusion that CYFRA 21-1 is not a suitable biomarker for EOC (134, 135). Thus, the clinical relevance of CYFRA 21-1 remains unclear (136).

**4.3. Endometrial cancer**

**4.3.1. HE4**

As a single marker, HE4 showed the highest sensitivity in both early and advanced stage endometrial cancers when compared with any of the other markers (CA125, CA72.4 and SMRP). Furthermore, HE4 has the strongest correlation with endometrial cancer of all markers tested to date, and the combination of CA125 and HE4 compared to HE4 alone shows a statistical significance when evaluating the ROC-AUC curves for stages II to IV cases (137, 138).

**4.3.2. Kallikreins**

Using gene expression profile analysis, *KLK6* and *KLK10* expression levels are significantly higher in uterine serous papillary carcinoma (USPC) patients than in endometrioid endometrial carcinoma, while serum and plasma KLK10 levels in USPC patients are increased compared to control groups (139, 140).

**4.3.3. Serum Amyloid A (SAA)**

*SAA* gene expression levels are significantly higher in USPC compared to normal endometrial cells (141) and a recent study reported that SAA values in the serum of USPC patients had a median significantly higher than those in the normal healthy females or in patients with benign disease. These results suggest that SAA could be a novel biomarker for USPC that could be used to assist in staging patients preoperatively, and to monitor response to therapy (142).

#### 4.3.4. CA72-4 and CA19-9

Serum levels of CA72-4 are increased in 31.9% of the patients with endometrial carcinoma (78), and are positively correlated by multivariate analysis with the depth of myometrial invasion, adnexal metastasis, lymphovascular space involvement, and pelvic and para-aortic lymph node metastasis. Thus, the measurement of serum concentrations of CA72-4 are thought be clinically useful for predicting and monitoring disease progress (78). In contrast, despite the high sensitivity of CA19-9 for mucinous ovarian cancers, its concomitant use with CA125 does not offer any additional benefit for monitoring endometrial carcinomas (85).

## 5. SUMMARY AND PERSPECTIVE

Emphasis on the development of biomarkers for the detection of gynecologic malignancies is based on the fact that treatments administered during early stage disease yield the highest efficiencies. Unfortunately early stage disease is often clinically undetectable, particularly in the case of ovarian cancer. In other gynecologic malignancies where patients do present with early symptoms, like in endometrial cancer, high risk groups can be identified that would benefit from early and frequent screening. These observations have created a strong impetus for the identification of oncology biomarkers. In the case of GTD, the hyperglycosylated hCG behaves as an ideal biomarker as it is elevated in virtually all cases. However, for the majority of gynecologic malignancies, CA125 remains the most commonly used serum biomarker for monitoring disease progression, 30 years after its discovery and despite a limited overall accuracy.

To improve sensibility and specificity, CA125 use in combination with other biomarkers and/or imaging tools has been extensively studied (143). Longitudinal measurements have also been employed to monitor clinical course and response to therapy. Yet, at present the field is divided between negative (29, 144, 145) and mildly positive (4, 146) recommendations that emphasize stable markers in healthy controls over time. Clearly, to become a standard of care, screening modalities must be improved. Numerous biomarkers are currently under study and, at this point of time, HE4 is arguably the most promising serum biomarker for ovarian and endometrial cancers.

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