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New biomarkers in epithelial ovarian cancer: needed or redundant?

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Summary

Objective: For many years, intensive research has been dedicated to the development of sensitive biomarkers to detect various malignant diseases, including for the differentiation between a benign or malignant ovarian mass. One of these biomarkers is human epididymal protein 4 (HE4), which has been shown to have a higher specificity than, and comparable sensitivity to CA125. HE4 is included in some predictive models. These new models have not yet been widely implemented in standard clinical care. The authors investigated the perceived need for new biomarkers and prediction models among Dutch gynecologists. *Materials and Methods:* A web-based survey containing 38 questions was sent to all gynecologists (in training) registered by the Dutch Society of Obstetrics and Gynecology. *Results:* 313 respondents completed the survey (23% response rate), of which 29% were specialized in or devoted at least part of their practice to oncology. Approximately two-thirds of the respondents indicated that there is a need for a new biomarker. Respondents indicated that they would use HE4 primarily as a diagnostic tool in the case of a pelvic mass (57%), followed by screening in case of risk factors (30%), detection of recurrent disease (23%), monitoring therapy response (22%), and as a prognostic factor (10%). Only 11% would not use HE4 at all. *Conclusion:* Evaluating the need for new technologies and diagnostics, including biomarkers, is important to avoid expensive research with minimal clinical implications. In general, there is a perceived need for a new biomarker, if it can be used to improve the accuracy of diagnosis in patients with a pelvic mass.

Key words: Biomarkers; Ovarian cancer; HE4; Gynecologists; Survey.

Introduction

For many years, intensive research has been done on biomarkers and the development of new prediction models to improve detection of various malignant diseases.

The Risk of Malignancy Index (RMI), first developed by Jacobs *et al.* in 1990 [1], and later revised by Tingulstad *et al.* in 1996 [2], is a widely used prediction model based on serum CA125 level, specific ultrasound features, and menopausal status. The RMI can be used to differentiate preoperatively between a benign and malignant ovarian mass. In the Netherlands, the selection of patients with a pelvic mass who need to be referred to a gynecologic oncology unit, is based on the RMI score, for which a cut-off level of ≥ 200 is used. Using the RMI score to triage between treatment by a general gynecologist or a gynecologic oncologist has proven to be cost-effective [3].

After development of the RMI score, several other diagnostic models for the assessment of an adnexal mass have been described in the literature, and some are preferred over the RMI score [4]. For example, the International Ovarian Tumor Analysis (IOTA) group developed the Logistic Regression model 2 (LR2) and Simple Rules; two models that rely on the presence or absence of malignant features on ultrasound only [5, 6].

New serum biomarkers to detect epithelial ovarian cancer (EOC) have been investigated as well. Biomarkers can play a role in various stages of a disease: 1) before the diagnosis in risk assessment and screening; 2) at diagnosis to enable monitoring of treatment; and 3) during follow-up to detect recurrent disease.

Studies evaluating gene expression profiles in EOC have found that the WFDC2 gene located on chromosome 20, is amplified in EOC and, to a lesser extent, in healthy tissue [7, 8]. This gene encodes the glycoprotein human epididymal protein 4 (HE4). HE4 has been studied extensively as a serum biomarker, and has been found to have a comparable sensitivity to and higher specificity than CA125 in differentiating between benign and malignant ovarian masses [9, 10]. Alternatively to the LR2 and Simple Rules that do not include biomarkers, the RMI divides patients into low- and high-risk of having ovarian cancer using serum levels of CA125 and HE4, and menopausal state [11].

The shared purpose of developing these new biomarkers and prediction models is to improve the preoperative selection and diagnosis of patients with suspected ovarian cancer, as both the disease-specific and progression-free survival of patients with high-stage EOC is improved when surgery is performed by a gynecologic oncologist [12, 13].

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Table 1. — *Demographic features and specialization/focus of gynecologists and gynecologists in training.*

	Setting				Specialization / focus area*				
	Academical center (%)	Community hospital (%)	Specialized oncologic center (%)	Other ** (%)	General gynecology (%)	Oncology (%)	Perinatology (%)	Uro-gynecology (%)	Fertility (%)
Gynecologist (n = 229)	38 (17)	172 (75)	5 (2)	14 (6)	99 (43)	77 (34)	40 (18)	50 (22)	32 (14)
Gynecologist in training*** (n = 84)	39 (46)	44 (52)	1 (1)	0	16 (19)	15 (18)	19 (23)	5 (6)	7 (8)
Gynecologic oncologist (n=92)	24 (26)	58 (63)	6 (7)	4 (4)	-	92 (100)	-	-	-

*More than one answer possible. **Private practice or not otherwise specified. ***62 out of 84 gynecologists in training answered the question about their focus area.

The diversity and multiplicity of models and biomarkers raises questions about what clinicians really need, what can be easily incorporated into their clinical practice, and what is likely to lead to significant changes in daily practice. This knowledge is indispensable for the implementation of innovative models.

The aim of this survey was to investigate the perceived need for new biomarkers and prediction models among gynecologists and gynecologists in training.

Materials and Methods

All gynecologists and gynecologist in training registered by the Dutch Society of Obstetrics and Gynecology were invited to participate in a web-based survey. The questionnaire contained 38 questions, and the maximum time to complete was estimated at 10-15 minutes. A link to the questionnaire was sent by email in March, 2014 and two reminders were sent in a period of six weeks to those who had not yet responded. The questionnaire was developed for gynecologists treating patients with ovarian masses, but was sent to all gynecologists, including obstetricians, fertility-specialists, and uro-gynecologists to avoid missing colleagues interested in the subject. The survey was closed at the end of May, 2014.

The questionnaire included both closed- and open-ended questions, as well as room for comments. Topics addressed in the questionnaire included: 1) background characteristics; 2) current diagnostic work up in case of a pelvic mass; 3) awareness and use of new biomarkers and prediction models; and 4) perceived need for new biomarkers. The survey was piloted tested on six gynecologic oncologists, resulting in some minor revision of question wording. Results were analyzed for all respondents together, but also for the subgroup of gynecologists in training, gynecologists, gynecologic oncologists or gynecologists devoting at least part of their practice to gynecologic oncology, and gynecologists with another subspecialty than oncology. In case of substantial differences between subgroups, the results are explicitly mentioned. Statistical analyses were performed using SPSS version 22.0. Descriptive statistics and frequency distributions are reported.

Results

The questionnaire was sent to 1,380 gynecologists and gynecologists in training, of whom 313 returned a completed questionnaire (an overall response rate of 23%). The response rate for gynecologists was slightly higher (24%) than for gynecologists in training (21%). The background characteristics of the respondents are shown in Table 1. Of these 313 respondents, 229 (73%) were gynecologists, and 84 (27%) gynecologists in training. Of all respondents, 92 (29%) were specialized in gynecologic oncology or devoted at least a part of their practice to gynecologic oncology. The majority of all respondents worked in a community hospital (69%) or a tertiary referral center (25%). Only a very small percentage worked in a specialized oncology center (2%) or a private clinic (1.6%), and the remaining did not specify their work location.

The large majority of respondents indicated that they perform a gynecological examination (94%) and transvaginal ultrasound (96%) as part of the diagnostic work up of patients with a pelvic mass. Of all available and well-known biomarkers, serum CA125 was used most frequently (93%), followed by CEA (68%), CA19.9 (20%), and CA15.3 (17%). A computerized tomography scan as diagnostic imaging modality for further classification of a pelvic mass was preferred over a magnetic resonance imaging scan (69% *vs*. 7%).

Figure 1 shows how often all respondents determine serum CA125 values for different clinical purposes. Serum CA125 is most frequently used for the diagnosis of patients with a pelvic mass, but also for monitoring response to treatment and detection of recurrent disease of EOC. Subgroup analysis of gynecologic oncologists *vs*. gynecologist with other expertise, revealed that the former more often use CA125 for monitoring of treatment response (72% always or often) compared to the latter (42% always or often). The remaining results were not substantially different when different subgroups were analyzed.

Of all respondents, 85% reported using the RMI score during the diagnostic work up of a patient with a pelvic mass. Only 4% indicated not using the RMI score at all. These results were similar when analyzed for the subgroup of gynecologic oncologist and gynecologists in training separately. The percentage of patients referred unnecessarily to a tertiary center based on a RMI score ≥ 200 was estimated by all respondents at 20% (false positive). In contrast, the percentage of patients not referred to a tertiary center based on a RMI score < 200 that should have been referred was estimated to be only 10% (false negative).

The majority (63%) of all respondents believe that there is a need for a new biomarker that can be used in the diagnostic process of in patients with a pelvic mass, and 59% expressed specific interest in biomarker HE4. These per-

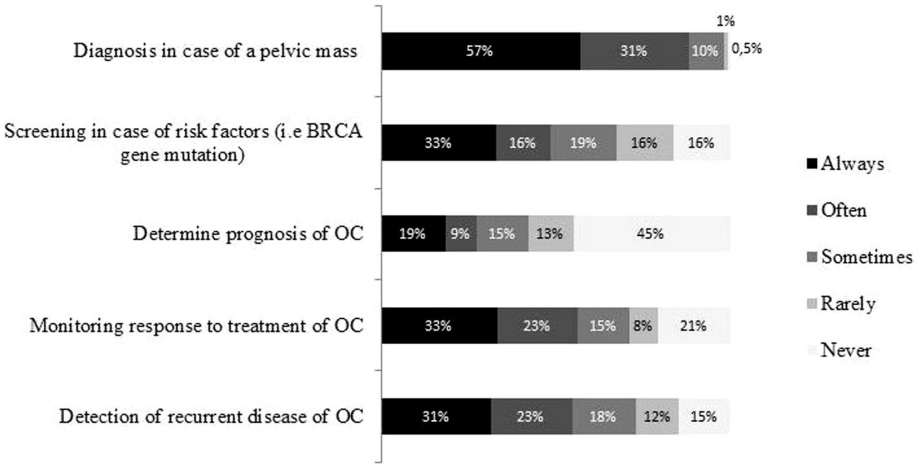

Figure 1. — Histogram showing the distribution of the use of serum CA125 for different clinical purposes in patients with ovarian cancer (OC).

Table 2. — *Overview of purposes and groups of patients for serum HE4 use answered by all respondents and subgroup of gynecologic oncologists and gynecologists in training.*

Question *	All respondents (%) ** n=313	Gynecologic oncologist (%) ** n=92	Gynecologist in training (%) ** n=84
For what purpose would you want to use serum HE4?			
Screening for ovarian cancer in case of risk factors	30	33	21
Diagnostic process in case of a pelvic mass	57	65	51
Monitoring therapy in patients with ovarian cancer	22	16	18
As prognostic factor for ovarian cancer	10	10	12
Detection of recurrent disease of ovarian cancer	23	20	25
I would only use it in combination with CA125	29	39	21
I would only use it if CA125 value is normal	3	4	4
I would not use it at all	11	12	11
For which group of patients do you think determination of HE4 can be of additive value?			
Low stage ovarian cancer	46	54	38
Endometriosis	11	14	7
Pregnant women with an ovarian mass	9	12	5
Every patient with a pelvic mass	44	44	38
No patients	8	12	8

* More than one answer possible. ** Percentages are given with missing values included.

centages were higher among those specialized in oncology (70% and 67%, respectively), but lower for the subgroup of gynecologists in training (61% and 54%, respectively). However, of all respondents, 37% considered the current CA125 and RMI score satisfactory for differentiating between a benign and malignant pelvic mass.

The primary purposes for which HE4 would be used are for diagnostics in case of a pelvic mass (57%) and for screening for ovarian cancer in the presence of risk factors (30%) (Table 2). About 30% of respondents also indicated that they would use serum HE4 in combination with CA125. They would use serum HE4 primarily among patients with a pelvic mass (44%) or with low stage (International Federation of Gynecology and Obstetrics (FIGO) I-II) EOC (46%) (Table 2), but also for patients with endometriosis (11%) and pregnant women with an adnexal cyst (9%). For the subgroup of gynecologic oncologist, the primary purpose for which they would use HE4 was also for diagnostics in case of a pelvic mass (65%) or screening in case of risk factors (33%), and 39% would only use it in combination with CA125.

The present authors asked respondents to indicate the requisite gain in sensitivity and specificity of a new biomarker. Given a sensitivity and specificity of CA125 of 80-85% and a specificity of 75% in FIGO Stage III-IV EOC, respondents indicated that, on average, they would want HE4 to have a sensitivity of 90% (range 65% to 100%) and a specificity of 89% (range 75% to 100%).

In the case of low-stage EOC (FIGO I-II), given a sensitivity of CA125 of 70% and specificity of 75%, these figures were 88% (range 70% to 100%) for sensitivity and 89% (range 75% to 100%) for specificity. Two-thirds of the

respondents believed that costs should be carefully evaluated before implementation of a new tumor marker in clinical practice; 76% expected the costs for HE4 to be acceptable.

Nineteen percent of the respondents were familiar with the RMI compared to 39% of those with an interest in oncology, but only 0.9% reported actually using it. RMI was known by 21% of the gynecologists in training and 2% reported using it. The majority of all respondents (54%) and subgroup of gynecologic oncologist (65%) indicated being familiar with the Simple Rules, and 31% reported using them regularly. Twenty-seven percent of the total sample was familiar with IOTA LR1 and LR2; this was 48% of the 92 gynecologists with a specialization in oncology. Of the gynecologists in training, 52% was familiar with the Simple Rules, but only 18% reported using them regularly, while the IOTA LR1 and LR2 were only known by 26%. The Simple Rules and the IOTA LR1 or LR2 were considered applicable in daily clinical practice by 76% and 62% of all respondents, respectively.

Discussion

The results of our survey indicate that there is a perceived need for a new biomarker that can be used in the diagnostic process of a patient with a pelvic mass. The main reason given for this was that the specificity of CA125 is considered too low for this purpose. However, 37% of the clinicians considered the current CA125 and RMI score satisfactory for differentiating between a benign and malignant pelvic mass.

Previous studies have shown that the prognosis of patients with high-stage EOC is improved when their surgery is performed by a gynecologic oncologist [12]. For this reason, a good deal of research has focused on improving the selection of patients with suspected ovarian cancer. Currently, in the Netherlands, the RMI score is used to identify patients with a high risk of having ovarian cancer for whom referral to a specialized center for further treatment is indicated. The present sample of gynecologists (in training) estimated that about one in five patients with a pelvic mass are misclassified as being at 'high risk' for ovarian cancer (RMI $\geq$ 200), and 10% are misclassified as being at 'low risk'. Neither of these estimates reflects the expected specificity and sensitivity of the RMI score of 87-91% and 70-75%, respectively, based on a recent review and meta-analysis [4]. This suggests that in spite of their clinical experience, gynecologists may underestimate the screening properties of the RMI score as described in literature.

The present results indicate that the majority of respondents is interested in HE4 as a possible new biomarker. In line with the results of Macedo *et al.* [9], other studies have shown that it is primarily the specificity that is improved when HE4 is used instead of CA125 for the differentiation between benign and malignant pelvic masses [10, 14].

The mean sensitivity and specificity of HE4 in postmenopausal women indicated as desirable by the present sample for differentiating between a benign and malignant ovarian mass was 90% and 89%, respectively. This is substantially higher than the sensitivity and specificity of CA125, which is estimated by the respondents to be 74% and 72%, respectively, in their own patient population. A recent meta-analysis on HE4 as a tumor marker reported a pooled sensitivity of 74% and specificity of 87% in postmenopausal women; thus HE4 does not appear to yet meet these high expectations [9].

CA125 is known to be elevated in only 50% of patients with low-stage ovarian cancer. With this background information, approximately half of the present sample indicated that the use of HE4 could be a useful addition to CA125 for diagnosing patients with low-stage ovarian cancer. For high-stage EOC (FIGO III-IV), a biomarker is thought to be of less diagnostic value given that, in most cases, the diagnosis can be made based on clinical and ultrasound examination.

While 57% of respondents would use serum HE4 for the diagnosis of patients with a pelvic mass, there is less interest in the use of HE4 as a prognostic factor, for detecting recurrent disease or for monitoring of treatment. This may change, as the results of future studies become available and HE4 is used more widely in clinical practice.

There have also been developments concerning new predictive models that do not use biomarkers [4, 15]. Kaijser *et al.* [4] concluded in their systematic review and meta-analysis that an evidenced-based approach to the preoperative characterization of a pelvic mass should include the use of IOTA Simple Rules or the LR2 model, particularly for premenopausal women. Both models are based on the presence or absence of factors suspicious for malignancy on ultrasound. The fact that these prediction scores are not used more regularly might be explained by the fact that they are both relatively new and may require specific training.

There are several limitations of the present study that should be noted. First, although the authors attempted to survey the entire population of gynecologists (in training) in the Netherlands, the response rate was low (23%). Thus, the results of this survey cannot necessarily be generalized to the large population of gynecologists of interest. Second, these results are based on an ad hoc questionnaire, albeit one developed by professionals experienced in clinical gynecology and survey research. Although the authors are confident of the content validity of their questionnaire, there are no other published data with which to compare these results. Finally, they realize that the field of biomarker research is developing quickly. Thus this survey represents a snapshot of the views and perceptions of gynecologists given current levels of knowledge and understanding. This picture may change as new studies emerge, and the use of new biomarkers in clinical practice increases.

The present study also has several noteworthy strengths. To the authors' knowledge, it is the first survey conducted among gynecologists (in training) to evaluate the perceived need for and opinions about the use of biomarkers in patients suspected of having ovarian cancer. Although the overall response rate was low, the authors nevertheless were able to recruit a relatively large number of gynecologists (> 300) into the study.

In summary, this survey results suggest that there is interest in the use of new biomarkers that can be used in the diagnosis of patients with a pelvic mass and possibly for other purposes as well. The sine qua non for using these new markers is that they perform significantly better than those currently available.

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