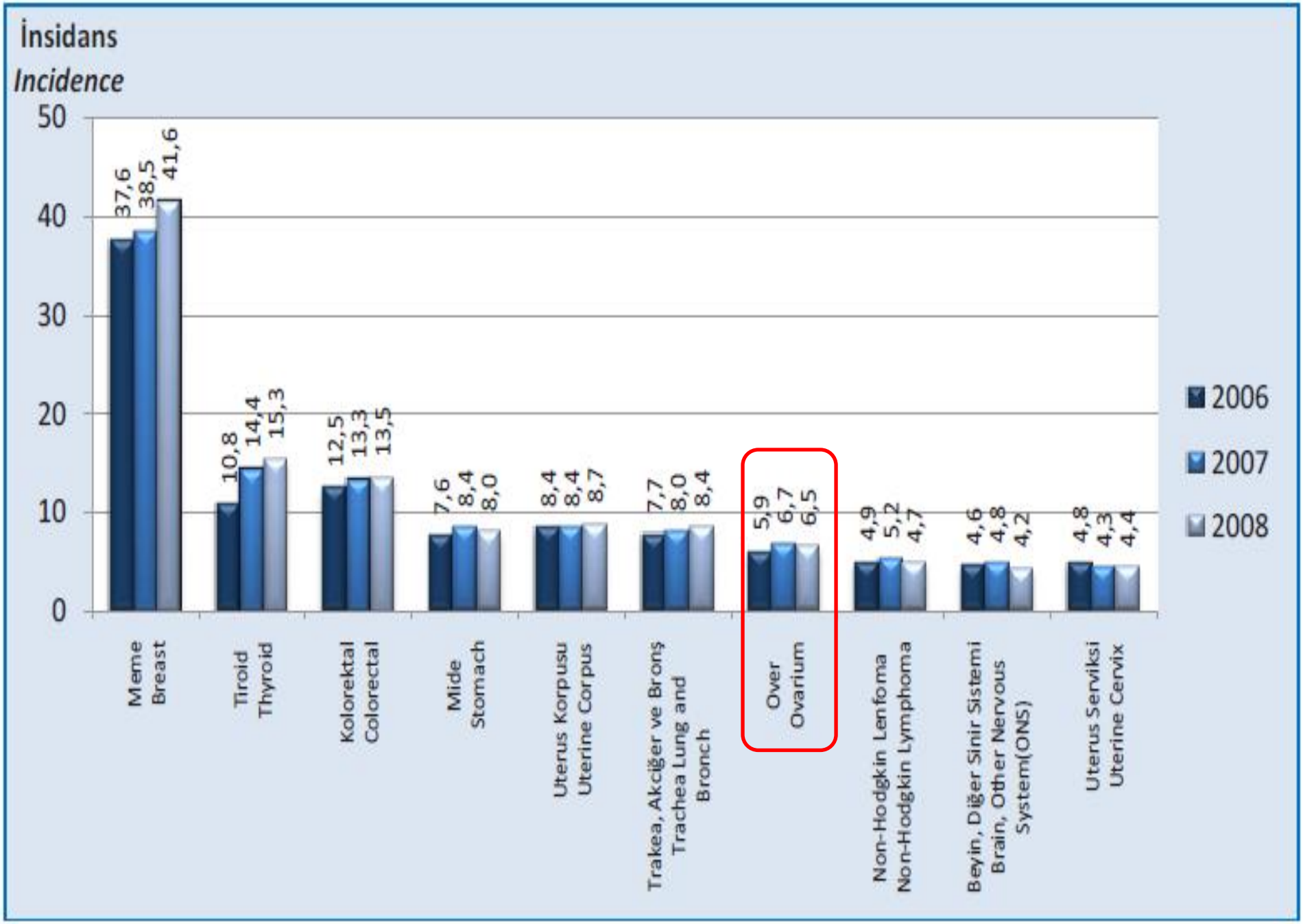
Evaluation of serum level of CA-125 and HE4 in patients with an adnexal mass for the discrimination of benign from malignant cases

Ahmet Göçmen, Fatih Şanlıkan, Yüksel Sayın, Fatma Seda Öztürk, Abdülhamid Güler

Ümraniye Eğitim ve Araştırma Hastanesi

Epidemiology

- 225000 new incidence annually worldwide. Incidence stable since 1970s
- Median age at diagnosis 63
- Fifth most common cause of cancer death in women worldwide
- >60% of women diagnosed with Stage III/IV
- To date, no mortality benefit demonstrated with CA125 and TVUS screening.



Kanserle Savaş Dairesi Başkanlığı

Ovarian Cancer

- 1/71 lifetime risk[1]
- 5-year survival rates (by year of diagnosis)[2]
  - 1990-1992 42.5%
  - 1993-1995 43.5%
  - 1996-2003 45%
- Mortality relatively unchanged but statistically significant improvement in 5-year survival rates

1. SEER (Surveillance, Epidemiology, and End Results) Program Web site. http://seer.cancer.gov/statfacts/html/ovary.html. Accessed April 22, 2007.

2. http://seer.cancer.gov/csr/1975_2004/results_merged/sect_21_ovary.pdf. Accessed April 22, 2007.

Ca 125 limitations

- An insufficient sensitivity in early stage OC

  (only 23-50%→ surgical stage I cases)

- It increases in cases of different physiological and pathological conditions (menses, pregnancy, endometriosis, pleura or peritoneal inflammatory diseases etc)

HE4

- Human Epididymis-specific protein (HE4- WFDC2)
- It is expressed in normal ovarian tissue but over expressed in ovarian cancer, especially serous and endometrioid histotype.
- It is also expressed in some pulmonary, endometrial and breast adenocarcinomas, mesotheliomas and less often gastrointestinal, renal and transitional cell carcinomas.

Material and Methods

- n=63 patients who had adnexal mass on imaging studies and underwent surgical intervention.

- The exclusion criterias→history of adnexal surgery for benign disease, the diagnosis of pelvic mass during pregnancy, ovarian malignancy.

- Serum Ca-125 and HE4 levels were measured on preoperative samples with the upper limit of normal defines as 150 pmol/L and 35 U/mL respectively for HE4 and CA-125

- Serum Ca-125, HE4 and ROMA (Risk of Ovarian Malignancy Algorithm) were evaluated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). ROC curves were constructed to determine the sensitivity and specificity of tumor markers at several cut-off points for clinical parameters.

	Benign n=54		Malign n=9		p
	Med (Min-Max)	Mean±SD	Med (Min-Max)	Mean±SD	
Age	41 (18-77)	42.8±13.1	51 (40-60)	50.8±5.7	0.077
Parity	3 (0-8)	2.5±2.6	4 (1-7)	3.7±1.9	0.198
Body mass index	27 (19-38)	27.5±4.9	30 (23-33)	28.9±3.6	0.402

Histopathology	n (%)
Endometriosis	18 (33,3)
Serous cystadenoma	9 (16,6)
Mucinous cystadenoma	7 (12,9)
Fibrotecoma	7 (12,9)
Hemorrhagic cyst	3 (5,5)
Struma ovari	2 (3,7)
Mature teratoma	2 (3,7)
Abscess	2 3,7)
Others	1 (1,8)

Histopathology	n (%)
Serous Papillary carcinoma	6 (66,6)
Mixed type adenocarcinoma	1 (11,1)
Mucinous adenocarcinoma	1 (11,1)
Granulosa cell carcinoma	1 (11,1)

	CA-125				p
	Minimum	Maximum	Mean	SD	
Bening	9,3	568	99,96	137,26	0,010*
Malign	14,9	2049	568,28	653,47	
Endometriozis	14,7	479	142,71	143,77	

	Benign		Malign		Endometriozis		[a]p
	Min Max	Mean ±SD	MinMax	Mean ±SD	Min Max	Mean ±SD	
HE4	1 368	54,54± 58,97	64 1317	418,62± 457,32	2-92	39,62± 24,91	0,001**
ROMA	0 77	11,82± 15,96	14 100	62,30± 37,18	0-38	8,66± 10,27	0,001**

		n	%	n	%	n	%	[b]p
Risk	**Benign**	26	70,3	1	11,1	13	76,5	***0,002***
	Malign	11	29,7	8	88,9	4	23,5	

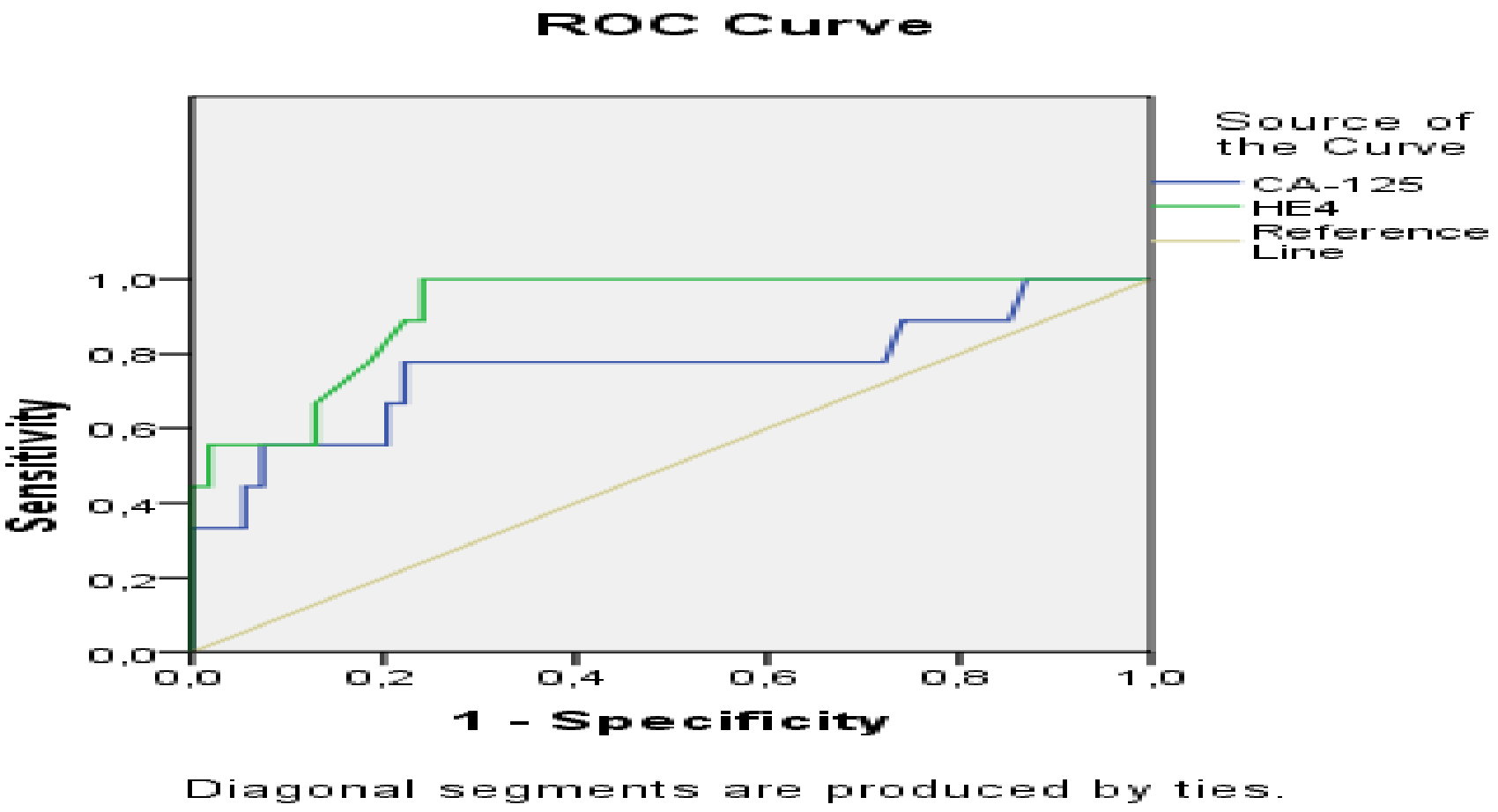
[a]*Kruskall Wallis* [b]*Fsiher Freeman Halton* ***p<0,01*

	Benign		Malign		p	Odds Ratio (95% CI)
Ca125_Grup						
0-35 (Normal)	21	38,9	2	22,2	0.467	2.2 (0.4-11.7)
>35	33	61,1	7	77,8		
He-4_Grup						
1-150 (Normal)	53	98.1	5	55.6	0.001	42.4 (3.9-456.0)
>150	1	1.9	4	44.4		

		Patology						p
		Malign		Benign		Total		
		n	%	n	%	n	%	
CA-125	Malign	7	11,1	33	53,4	40	63,5	0,001**
	Benign	2	3,2	21	33,3	23	36,5	
	Total	9	14,3	54	85,7	63	100,0	
Sensitivity (%)			77,77					
Spesificity (%)			38,89					
Positive predictive value			17,5					
Negative predictive value			91,30					
ODDS			2,22					

		n	%	n	%	n	%	p
HE4	Malign	8	12,7	15	23,8	23	36,5	0,001**
	Benign	1	1,6	39	61,9	40	63,5	
	Toplam	9	14,3	54	85,7			
Sensitivity (%)			88,88					
Spesificity (%)			72,22					
Positive predictive value			34,78					
Negative predictive value			97,50					
ODDS			20,8					

		Pathology						p
		Malign		Benign		Total		
		n	%	n	%	n	%	
CA-125+ HE4	Malign	7	77.8	34	63.0	22	34.9	0,001**
	Benign	2	22.2	20	37.0	41	65.1	
	Total	9	14,3	54	85,7	63	100,0	
Sensitivity (%)			44.44					
Spesificity (%)			99					
ODDS			2,06					



Cut-off values for Ca-125 and HE4 were set at 152 U/mL and 65,5 pmol/L with 76,1% and 91,7% diagnostic accuracy respectively

Baseline data.

	Benign	Borderline ovarian tumor	Epithelial OC [early/late]	Non-epithelial tumors	Non-ovarian cancers
Numbers (pre-/post-menopausal)	809 (530/279)	79 (24/55)	252 [64/188] (49/203)	9 (4/5)	69 (14/55)
Age (median, range)	42 (19–90)	60 (22–88)	64 (16–89)	47 (31–72)	64 (25–87)
HE4 (pmol/l) (median, range)	53.4 (19–1426)	81.8 (29–1109)	436 (16–15,000)	68 (22–250)	110 (28–7389)
CA125 (U/ml) (median, range)	28.7 (3–3586)	87.6 (10–6410)	647 (10–10,000)	26 (11–623)	159 (8–4586)
ROMA (median, range)	10.7 (0.9–99.6)	32.0 (2.2–96.9)	95.7 (0.6–1000.0)	17.0 (1.2–12.0)	61.2 (2.0–99.9)
RMI (median, range)	48 (2–17,154)	360 (13–15,264)	3330 (6–153,432)	135 (12–6156)	747 (13–77,400)

Suggested cut-off values for HE4 and ROMA.

HE4 and ROMA:	Suggested cut-offs	SN	SP
HE4 (pmol/L)[a]	**150**	78.6	96.0
HE4 (pmol/L)[b]	**140**	79.4	94.9
HE4 (pmol/L) premenopausal[b]	**70**	79.6	82.5
HE4 (pmol/L) postmenopausal[b]	**140**	81.8	89.6
ROMA premenopausal[b]	**7.4**	93.9	52.6
ROMA postmenopausal[b]	**25.3**	97.5	57.0

Conclusion. HE4 and ROMA helps differentiating OC from other pelvic masses, even in early stage OC. ROMA performs equally well as the ultrasound depending RMI and might be valuable as a first line biomarker for selecting high risk patients for referral to a tertiary center and further diagnostics. Further improvements of HE4 and ROMA in differentiating pelvic masses are still needed, especially regarding premenopausal women.

n=1218

Karlsen MA,Gynecol Oncol 2012

Comparison of HE4, CA125 and ROMA algorithm in women with a pelvic mass: Correlation with pathological outcome

Comparison of the sensitivities for ovarian malignancy at a set specificity of 75%, 80% and 90%.

Menopausal status	Test	Specificity (%) (95% CI)		
		75	80	90
Overall	CA125	86.9 (80.6–91.7)	84.4 (77.8–89.6)	73.1 (65.6–79.8)
	HE4	87.5 (81.3–92.2)	86.3 (79.9–91.2)	83.1 (76.4–88.6)
	ROMA	91.2 (85.7–95.1)	91.3 (85.7–95.1)	84.4 (77.8–89.6)
Pre-menopausal	CA125	87.0 (75.1–94.6)	81.5 (68.6–90.7)	74.1 (60.3–85.0)
	HE4	85.2 (72.9–93.4)	85.2 (72.9–93.4)	83.3 (70.7–92.1)
	ROMA	85.2 (72.9–93.3)	85.2 (72.9–93.3)	83.3 (70.7–92.1)
Post-menopausal	CA125	88.7 (81.1–94.0)	86.8 (78.8–92.6)	69.8 (60.1–78.3)
	HE4	85.8 (77.7–91.9)	84.9 (76.6–91.1)	81.1 (72.4–88.1)
	ROMA	91.5 (84.5–96.0)	89.6 (82.1–94.7)	79.2 (70.3–86.5)

Sandri MT[1] Gynecol Oncol. 2013

RESEARCH ARTICLE Open Access

Does risk for ovarian malignancy algorithm excel human epididymis protein 4 and ca125 in predicting epithelial ovarian cancer: A meta-analysis

Fake Li[1†], Ruxiu Tie[1†], Kai Chang[1], Feng Wang[1], Shaoli Deng[1], Weiping Lu[1], Lili Yu[2*] and Ming Chen[1*]

N= 7792 tests (11 studies)

ROMA for EOC → sensitivity 89%, specificity 83% and AUC 93%

Comparison of EOC predictive value → specificity: HE4 (93%) > CA125 (84%)
AUC: CA125 88% > HE4 82%
Comparison of OC predictive value → AUC: CA125 (89%) > HE4 (79%).

Comparison among the three tests for EOC prediction→ sensitivity: ROMA (86%) >HE4 (80%)
specificity: HE4 (95%) > ROMA (84%) > CA125 (78%).

Conclusions: ROMA is helpful for distinguishing epithelial ovarian cancer from benign pelvic mass. HE4 is not better than CA125 either for EOC or OC prediction. ROMA is promising predictors of epithelial ovarian cancer to replace CA125, but its utilization requires further exploration.

Li,2012

OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis

n= 6,269 (31 trials)

- **HE4 →Sensitivity 73% (95% CI 0.71–0.75)**
  Specificity 89% (95% CI 0.88–0.90)
  Positive likelihood ratio 7.30 (95% CI 5.42–9.84)
  Negative likelihood ratio 0.15 (95% CI 0.10–0.23)

Conclusion: Our study demonstrates that the sensitivity and specificity of HE4 was higher than that of cancer antigen 125. The results indicated that HE4 could be a useful tumor marker for ovarian cancer diagnosis. However, the results of this meta-analysis should be interpreted with caution, due to the heterogeneity among study designs. Further study should pay more attention to the possibility that HE4 can be a marker for monitoring recurrence of ovarian cancer.

Yang et al,2013

Conclusion

- The combination of CA-125 and HE4 may improve the diagnostic accuracy for the discrimination of benign adnexal mass from malignant cases.
- Further studies into the molecular basis of tumor biology might contribute the current understanding of the nature of the ovarian cancer and tumor markers.