

ARCHITECT HE4 in Monitoring Patients with Ovarian Cancer and Estimating Risk of Ovarian Cancer with an Adnexal Mass

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Abstract

Aims: Studies were designed to evaluate the clinical performance of the ARCHITECT HE4 assay in monitoring patients with epithelial ovarian cancer (EOC) and in estimating the risk of EOC in women with an adnexal mass. **Methods:** Longitudinal sera (N = 506) from EOC-diagnosed patients (N = 76) during or following the completion of therapy were tested with an investigational ARCHITECT HE4 assay. Single-point sera (N = 494) from women presenting with an adnexal mass were tested with ARCHITECT CA 125 II and investigational ARCHITECT HE4. For the women presenting with an adnexal mass, ROMA (Risk of Ovarian Malignancy Algorithm) values (%) were calculated as $\exp(\text{PI}) / (1 + \exp(\text{PI})) \times 100$, where $\text{PI} = -12.0 + 2.38 \cdot \text{LN}[\text{HE4}] + 0.0626 \cdot \text{LN}[\text{CA125}]$ for premenopausal women and $\text{PI} = -8.09 + 1.04 \cdot \text{LN}[\text{HE4}] + 0.732 \cdot \text{LN}[\text{CA125}]$ for postmenopausal women. **Results:** For monitoring patients with EOC, 98% (209/213) of the subject draws with no evidence of disease (NED) had HE4 levels below 140 pmol/L as opposed to 51% (150/293) of subject draws with clinical manifestations of EOC. A 25% or more increase in the HE4 assay value was established to categorize the successive readings. The sensitivity, specificity, positive predictive value and negative predictive value were 40.3%, 87.2%, 48.8% and 82.9%, respectively. For estimating the risk of EOC in women with an adnexal mass, ROMA cut-points of 7.4% (premenopausal women) and 25.3% (postmenopausal women) were established. The sensitivity for stratifying subjects with EOC into the high-risk group was 93% at a specificity of 75%. **Conclusions:** The ARCHITECT HE4 assay appeared to be effective in recognizing EOC disease progression and provides a powerful indication of whether the disease is still present. A combination of ARCHITECT HE4 and ARCHITECT CA 125 II appeared to be of significance in the risk stratification of women with an adnexal mass.

Introduction

Ovarian Cancer [1-3]
 • 4th most common cause of cancer-related death in women
 • 21,550 new cases and 14,600 deaths in US in 2009
 • CA 125 is the "Gold Reference" biomarker with limitations

HE4 (WFDC2) [4-9]
 • A promising serum biomarker for EOC
 • HE4 EIA assay has been used for monitoring of EOC
 • ROMA has been developed for HE4 EIA - ARCHITECT CA 125 II and HE4 EIA - CA 125 EIA combinations
 • ARCHITECT HE4 assay has been developed as an automated test

STUDY PURPOSE
 Role of the ARCHITECT HE4 assay in monitoring recurrence or progression in patients with EOC and in estimating the risk of EOC in women with an adnexal mass.

Methods

Longitudinal serum samples for EOC monitoring:
 506 samples from 76 subjects with EOC
 Drawn during therapy or following the completion of therapy.
 Average follow-up visits = 5.7 per subject

Single point serum samples for EOC risk estimation:
 From 229 premenopausal women with an adnexal mass
 From 265 postmenopausal women with an adnexal mass

Reagent: Investigational ARCHITECT HE4 reagent
 ARCHITECT CA 125 II reagent

Instrument: ARCHITECT i System

ROMA Calculation:

$$\text{ROMA (\%)} = \exp(\text{PI}) / (1 + \exp(\text{PI})) \times 100,$$

where $\text{PI} = -12.0 + 2.38 \cdot \text{LN}[\text{HE4}] + 0.0626 \cdot \text{LN}[\text{CA125}]$ for premenopausal women and
 $\text{PI} = -8.09 + 1.04 \cdot \text{LN}[\text{HE4}] + 0.732 \cdot \text{LN}[\text{CA125}]$ for postmenopausal women.

Monitoring of EOC Recurrence

HE4 Cutoff	NED (No Recurrence)	NED-negative (With Recurrence)	PPV	NPV
< 140 pmol/L	209	150	58.2%	
≥ 140 pmol/L	4	143		97.3%
Sensitivity	98.1%		Concordance: 70.0%	
Specificity		48.8%		

The sensitivity correctly identifies patients as NED.

The specificity correctly identifies patients with recurrence of EOC.

Monitoring of EOC Progression

	Disease Progression		
	No Progression	Progression	Total
No HE4 Elevation	289	59	348
With HE4 Elevation	42	40	82
Total	331	99	430
	Percent (%)	95% Confidence Interval	
Sensitivity	40.3	31.6 – 49.9	
Specificity	87.2	83.2 – 90.4	
Concordance	76.5	71.1 – 81.1	
PPV	48.8	37.4 – 60.4	
NPV	82.9	76.1 – 88.1	

EOC Risk Estimation

	Premenopausal Patients			Postmenopausal Patients			
	ROMA Value		N	ROMA Value		N	
	< 7.4%	≥ 7.4%		< 25.3%	≥ 25.3%		
LMP	31%	69%	16	50%	50%	6	
EOC	Stage I - II	14%	86%	7	25%	75%	28
	Stage I - III	12%	88%	8	18%	82%	39
	Stage I - IV	6%	94%	16	7%	93%	108
	Stage III - IV	0%	100%	9	1%	99%	80
Unstaged	50%	50%	2	50%	50%	2	
EOC and LMP combined	21%	79%	34	10%	90%	116	
Benign	75%	25%	195	75%	25%	149	

LMP = Low Malignant Potential

Test combination for ROMA calculation:
 ARCHITECT HE4 + ARCHITECT CA 125 II

Comparison of 3 ROMA Test Combination

		ARCHITECT HE4 + ARCHITECT CA 125 II	HE4 EIA + ARCHITECT CA 125 II	HE4 EIA + CanAg CA 125 EIA
ROMA Cutpoint Values for Estimation of Risk for EOC				
Premenopausal Women	High risk	≥ 7.4%	≥ 13.1%	≥ 12.5%
	Low risk	< 7.4%	< 13.1%	< 12.5%
Postmenopausal Women	High risk	≥ 25.3%	≥ 27.7%	≥ 14.4%
	Low risk	< 25.3%	< 27.7%	< 14.4%
Estimation of High Risk for EOC (Stage I - IV)				
Sensitivity	Premenopausal Women	94%	89%	93%
	Postmenopausal Women	93%	95%	
Specificity	Premenopausal and postmenopausal Women	75%		
ROMA (%) Calculation		Same algorithm		

Conclusions

- The ARCHITECT HE4 assay showed indications for use as an aid in monitoring recurrence or progressive disease in patients with EOC.
- In conjunction with ARCHITECT CA 125 II, ARCHITECT HE4 assay showed indications for use as an aid in estimating the risk of EOC in premenopausal and postmenopausal women presenting with an adnexal mass.
- The ARCHITECT HE4 – ARCHITECT CA 125 II combination performed as well as the HE4 EIA – ARCHITECT CA 125 II and HE4 EIA – CanAg CA 125 EIA combinations in estimating the risk of EOC in women with an adnexal mass.

References

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PP-089 • 38th ISOBM Meeting 2010 • Sept. 3 - 8 • Munich, Germany

FDI-291 08/2010

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