



HE4 in benign and malignant diseases

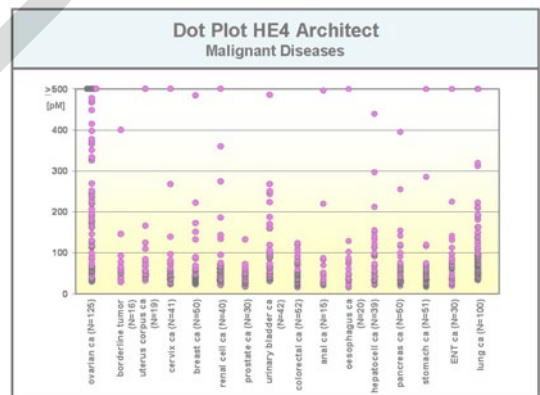
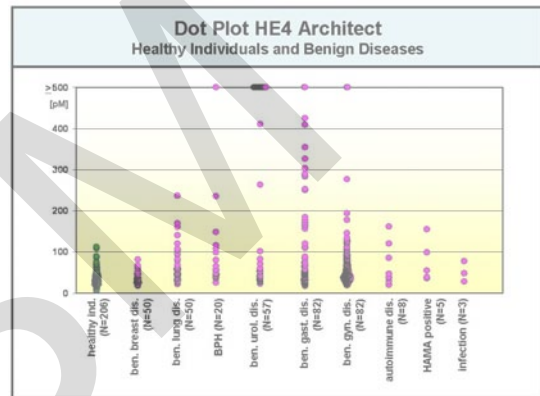
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Aims: Human epididymis protein 4 (HE4) is a novel biomarker for ovarian cancer. However HE4 as non tumor specific and non organspecific protein might be released in an increased amount in patients with benign diseases and other cancers besides ovarian cancer.

Methods: We investigated retrospectively the sera (stored at -80°C) of 206 healthy individuals, 655 patients with various benign disorders (gynaecological:396, gastrointestinal (GI):82, urological:57, lung:50, breast:50 and benign prostate hyperplasia:20), and 720 patients suffering from cancer at time of diagnosis before first treatment measuring HE4 on the Architect system (Abbott Diagnostics, US).

Patients			
Diagnosis	Number	Diagnosis	Number
healthy individuals	206	ovarian ca	125
ben. breast dis.	50	borderline tumor	16
ben. lung dis.	50	uterus corpus ca	19
BPH	20	cervix ca	41
ben. urolog. dis.	57	breast ca	50
ben. gastroint. dis.	82	renal cell ca	40
ben. gyn. dis.	396	prostate ca	30
autoimmune dis.	8	urinary bladder ca	42
HAMA positive	5	colorectal ca	52
infections	3	anal ca	15
		oesophagus ca	20
		hepatocellular ca	39
		pancreas ca	50
		stomach ca	51
		ENT ca	30
		lung ca	100



Results: Lowest concentrations of HE4 were observed in healthy men (Median: 26.2 pM, max 87), followed by healthy women (Median: 40.4 pM, max 110) and benign breast disorders (Median: 31.7 pM). The medians (95th perc) of other benign diseases were: lung 48 pM (160), GI 47 pM (401), gynec. 41 pM (95), urol. 660 pM (3600), the highest benign values were reached in urological diseases with 7050 pM.

In cancer patients the highest concentrations were observed in ovarian cancer (Median: 242 pM, 95th perc. 3000, max 7000), followed by lung cancer (Median: 85.7 pM, 95th perc. 691), ENT cancer, stomach and urinary bladder cancer. Prostate cancer has no increased release, all other cancers show at least a slightly increased release.

The AUC of HE4 was highest in ovarian cancer and borderline tumour (88.9). Sensitivities at 95% specificity in ovarian cancer and borderline tumour were 68.0, followed by uterus corpus cancer with 21.0, lung and breast cancer with 18%.

Distribution of HE4 Architect [pM]					
Diagnosis	N	Median	Range	5 th Pctl	95 th Pctl
healthy men	97	26.2	13.6 – 87.2	16.4	47.1
healthy women	109	40.4	4.5 – 111	12.8	74.0
ben. breast dis.	50	31.7	16.4 – 81.1	18.8	65.1
ben. lung dis.	50	47.9	20.3 – 237	25.8	165
BPH	20	51.5	24.2 – 710	24.8	686
ben. urolog. dis.	57	661	22.8 – 7043	28.2	3579
ben. gastroint. dis.	82	46.7	16.4 – 2366	21.4	401
ben. gyn. dis.	396	40.7	18.3 – 1178	26.0	94.6
autoimmune dis.	8	42.1	19.8 – 161	19.8	161
HAMA positive	5	53.7	35.7 – 154	35.7	154
infections	3	46.9	26.8 – 76.8	26.8	76.8
ovarian ca	125	242	13.6 – 7000	36.1	3073
borderline tumor	16	52.1	28.2 – 399	28.2	399
uterus corpus ca	19	53.7	31.1 – 523	31.1	523
cervix ca	41	43.3	22.1 – 2412	24.8	254
breast ca	50	37.2	22.5 – 483	24.4	194
renal cell ca	40	52.4	21.7 – 585	22.4	355
prostate ca	30	39.8	17.1 – 132	19.7	95.1
urinary bladder ca	42	73.5	26.7 – 484	30.9	264
colorectal ca	52	52.3	22.8 – 129	25.9	116
anal ca	15	48.5	27.7 – 496	27.7	496
oesophagus ca	20	54.3	22.8 – 1487	22.8	1419
hepatocellular ca	39	62.0	28.6 – 439	28.0	298
pancreas ca	50	47.5	25.0 – 396	28.4	204
stomach ca	51	47.0	23.9 – 2482	26.5	382
ENT ca	30	68.4	25.4 – 1781	28.2	927
lung ca	100	85.7	25.4 – 691	42.2	691

Sensitivity of HE4 Architect at 95% Specificity					
Diagnosis	N	Comparison Group	N	HE4 Architect	
				Sensitivity	AUC
ovarian ca + LMP	141	ben. gyn. dis.	396	68%	
uterus corpus ca	19	ben. gyn. dis.	396	21%	
cervix ca	41	ben. gyn. dis.	396	12%	55.3%
breast ca	50	ben. breast dis.	50	18%	65.4%
prostate ca	30	BPH	20	0%	25.7%
renal cell ca	40	ben. urolog. dis.	57	0%	28.3%
urinary bladder ca	42	ben. urolog. dis.	57	0%	35.0%
colorectal ca	52	ben. gastr. dis.	82	0%	48.8%
anal ca	15	ben. gastr. dis.	82	6%	50.3%
oesophagus ca	20	ben. gastr. dis.	82	5%	53.8%
hepatocellular ca	39	ben. gastr. dis.	82	2%	60.5%
pancreas ca	50	ben. gastr. dis.	82	2%	51.2%
stomach ca	51	ben. gastr. dis.	82	3%	48.4%
lung ca	100	ben. lung dis.	50	18%	75.2%

Conclusions: HE4 has the highest relevance in ovarian cancer but might be released in a broad variety of benign and malignant lesions as well. This knowledge must be respected especially in asymptomatic patients. If HE4 might be additive in other cancers in combination with other biomarkers has to be evaluated.