Ovarian Cancer Screening

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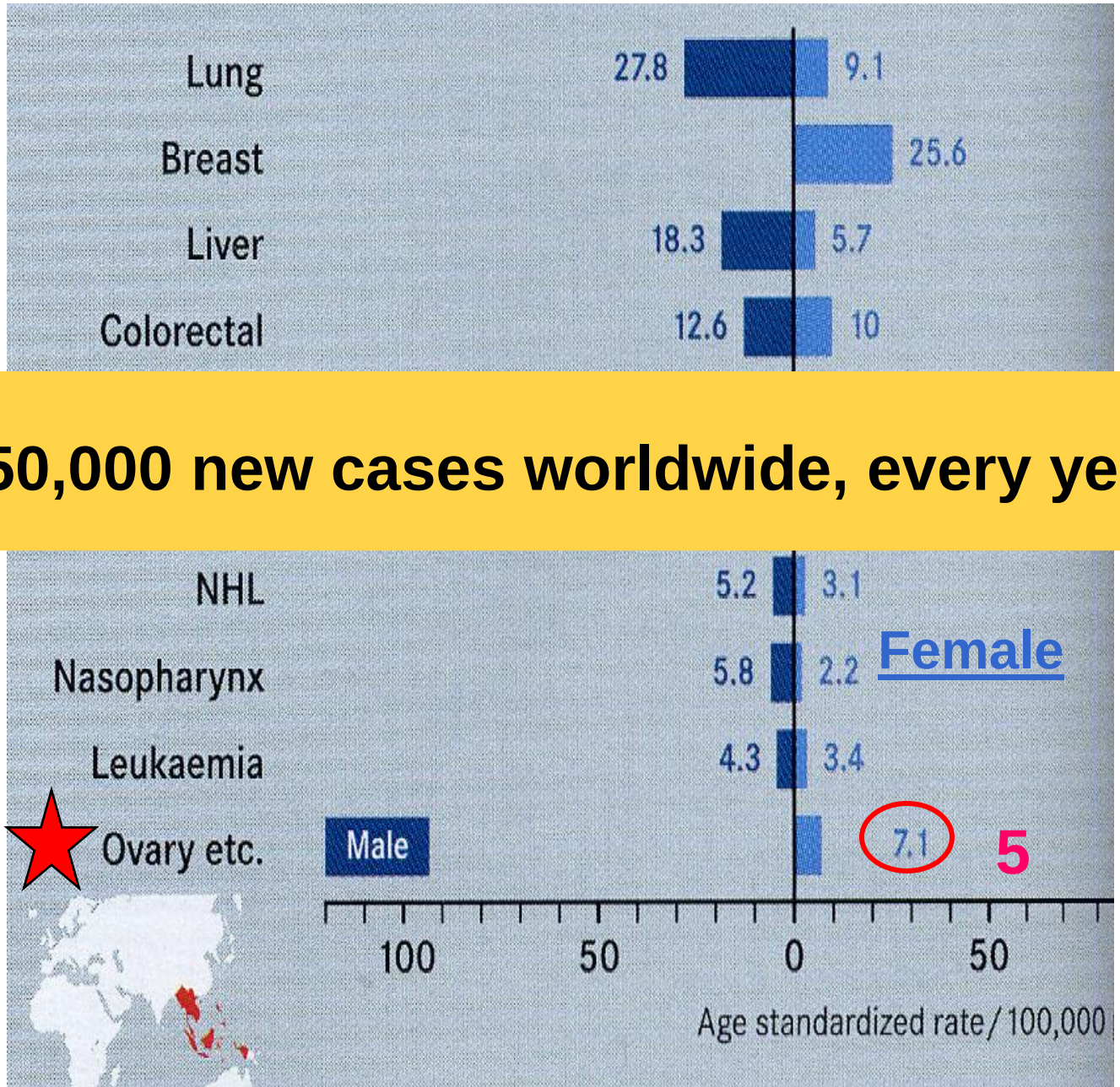
Disclosure

- I am one of the investigators of the A-P HE4 trial which was partially supported by Abbot Co.

Content

- Ovarian cancer statistics
- Ovarian cancer screening
  - to detect early-stage disease
    - * in general population
    - * in high-risk population
  - to differentiate between benign and malignant pelvic mass
- Conclusion

Cancer ‘incidence worldwide



> 250,000 new cases worldwide, every year

Cancer in Thailand

Volume VII, 2007-2009

MINISTRY OF PUBLIC HEALTH
National Cancer Institute
Lampang Cancer Center
Ubon Ratchathani Cancer Center
Udon Thani Cancer Center
Lop Buri Cancer Center
Chon Buri Cancer Center
Surat Thani Cancer Center
Maha Vajiralongkorn Cancer Center

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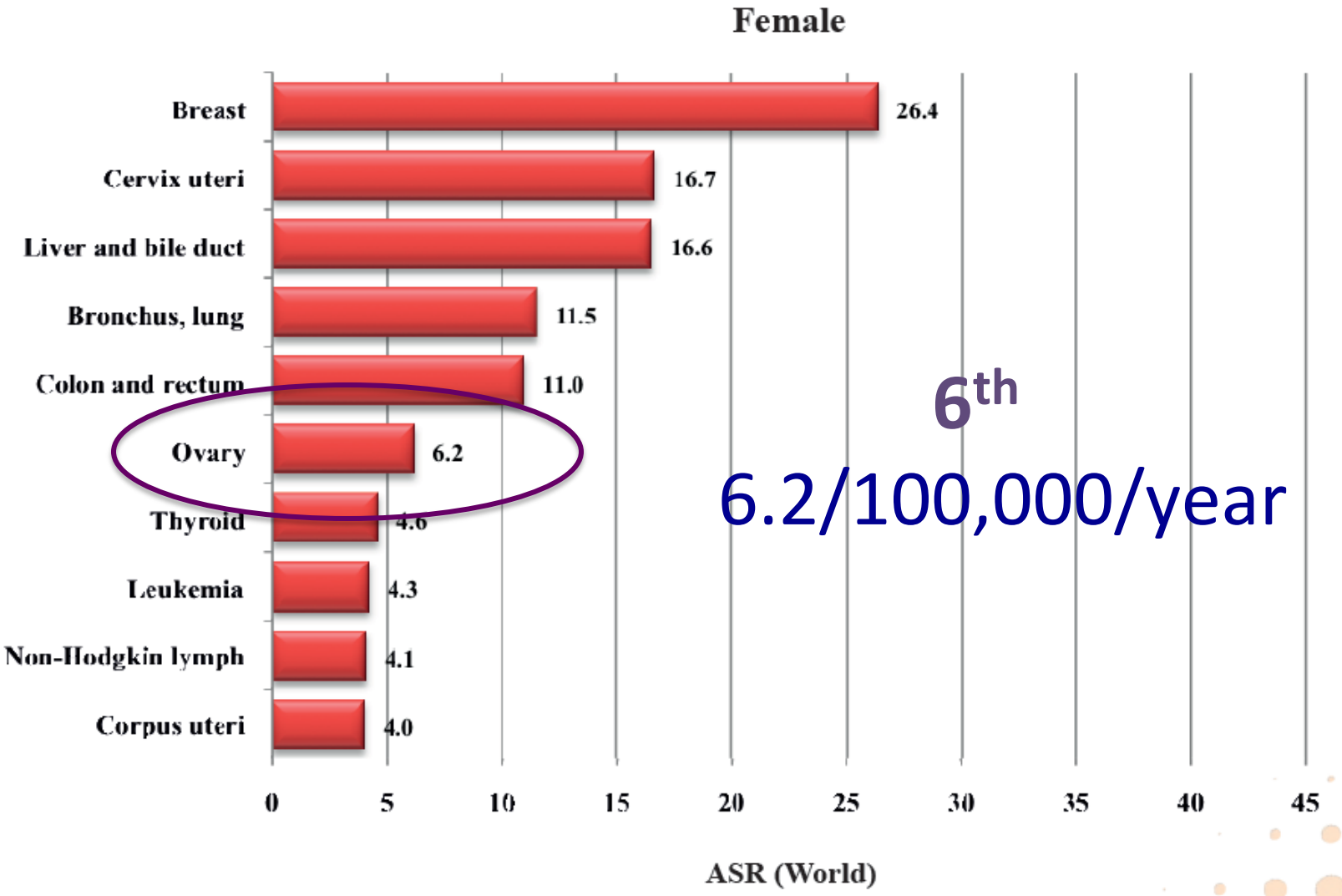
S. Sangrajrang

Bangkok, 2013

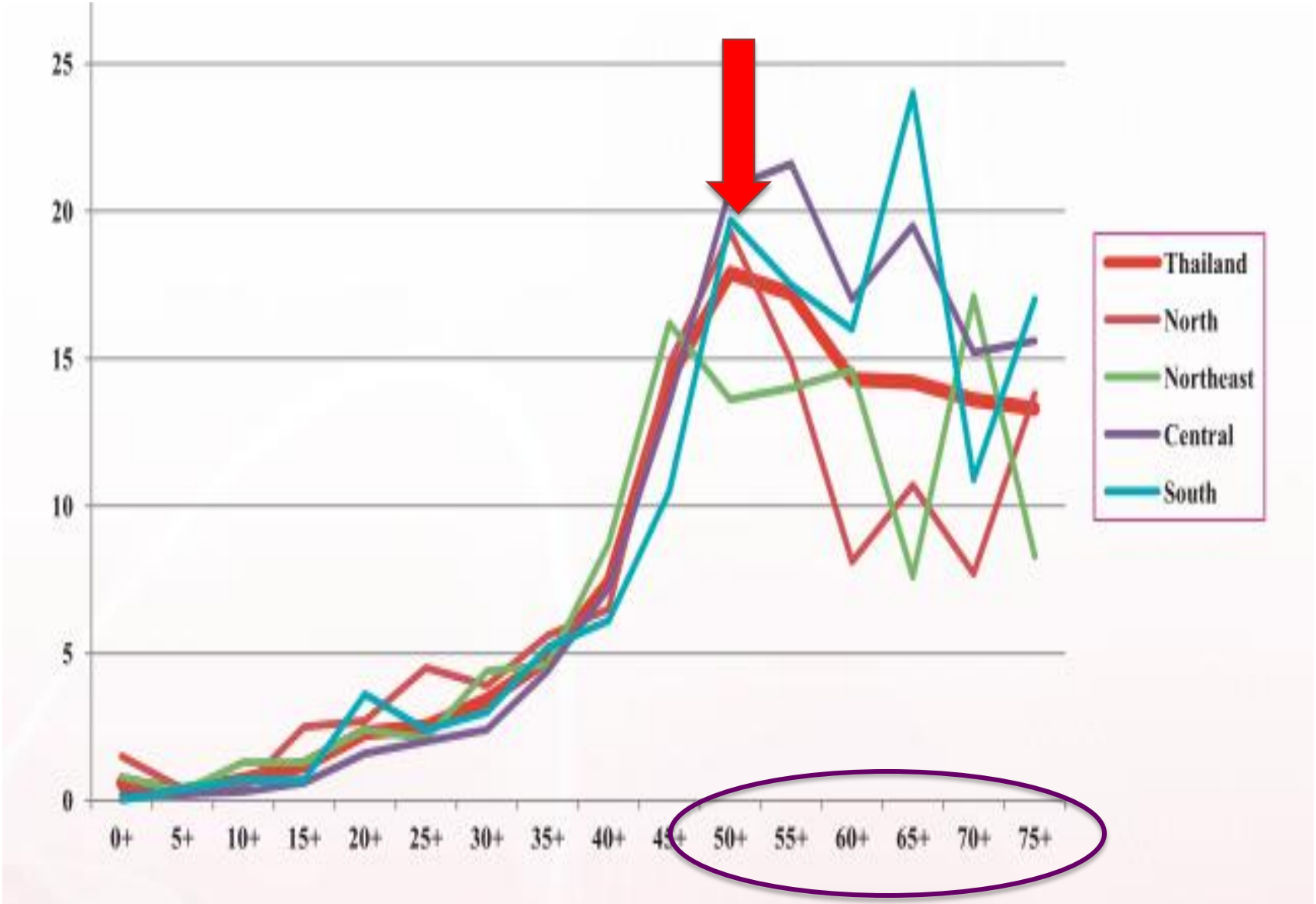
Leading cancer in Thailand (estimated), 2008



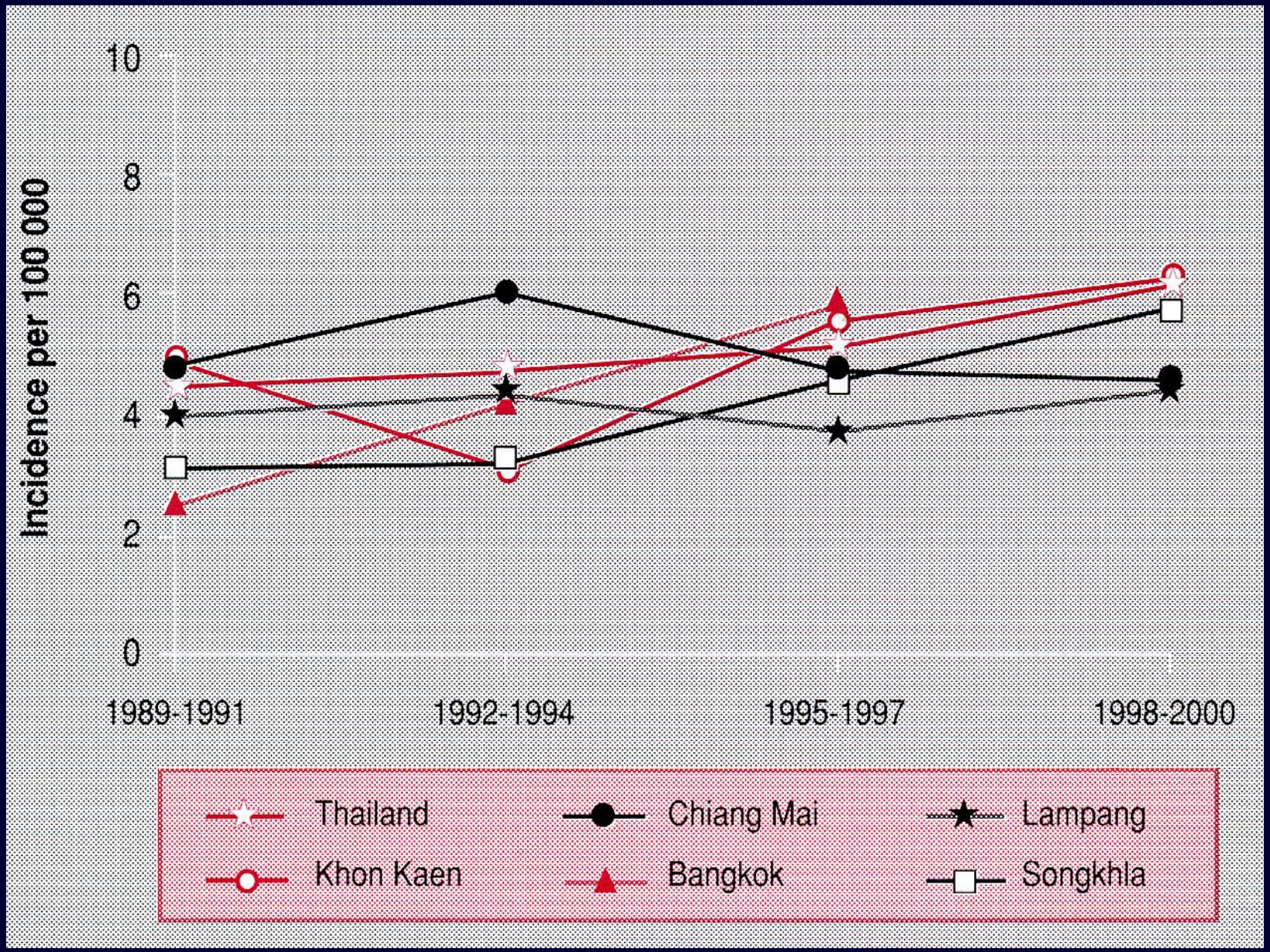
6th

6.2/100,000/year

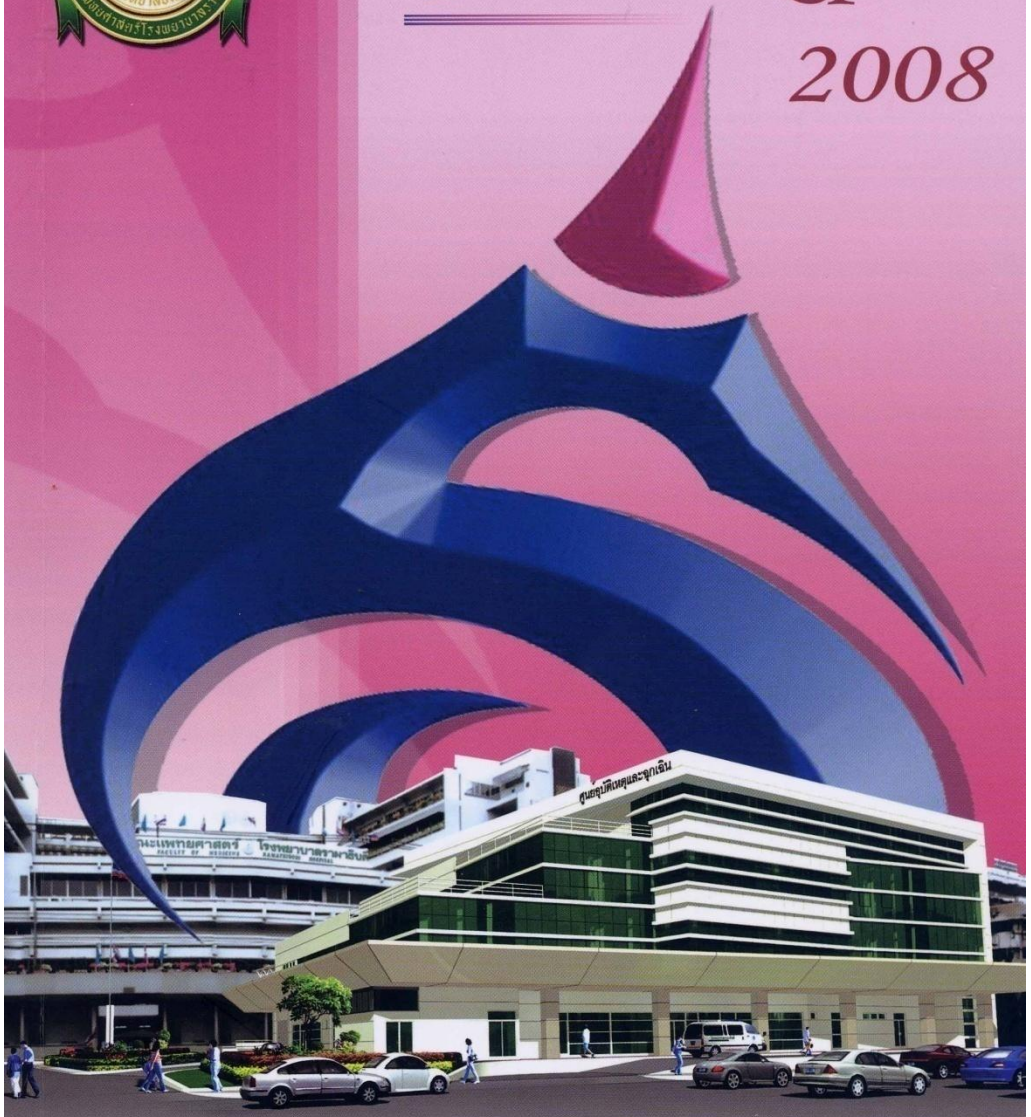
Age-specific incidence rate of ovarian cancer ; 2004-2006



Trend in incidence of ovarian cancer in Thailand

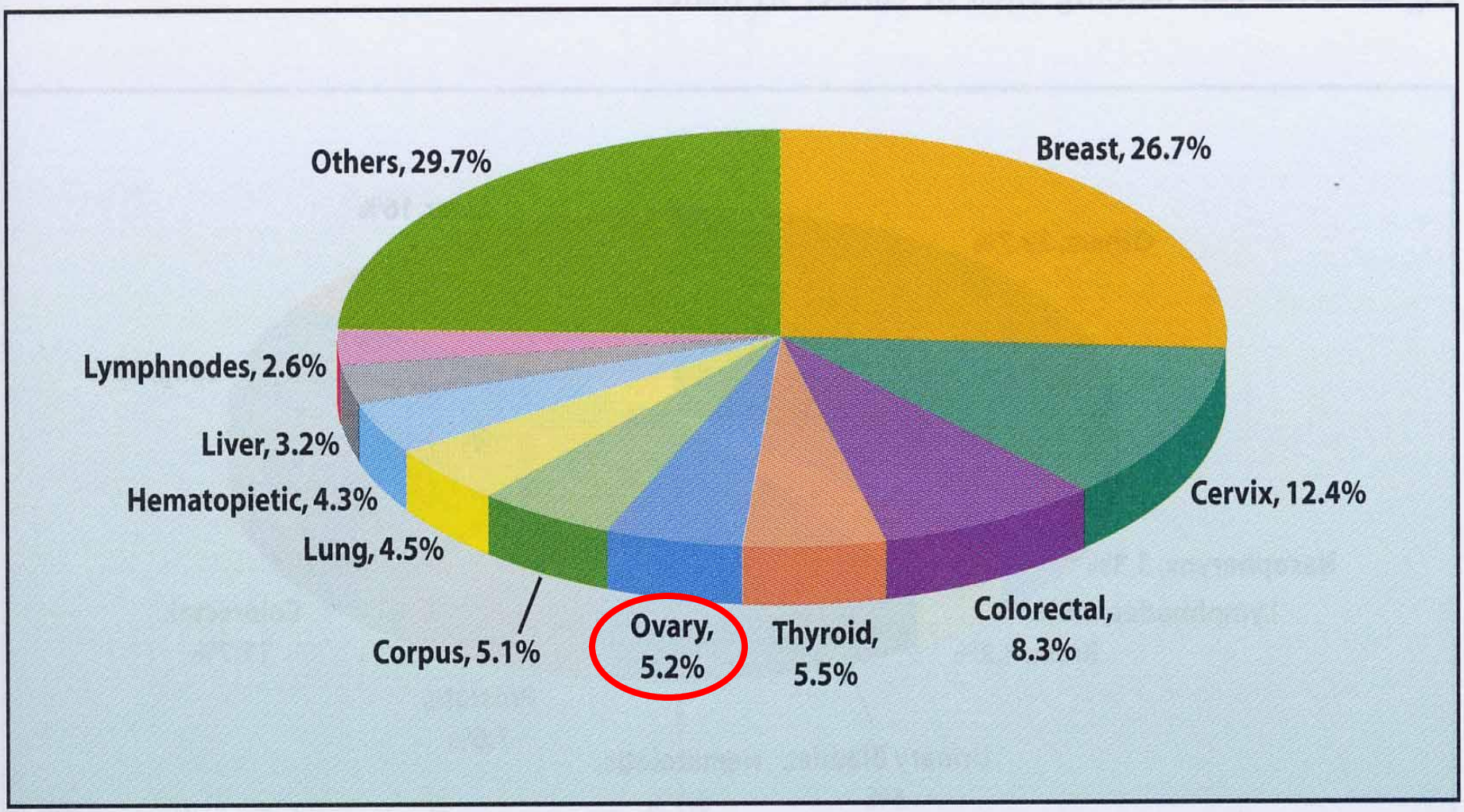


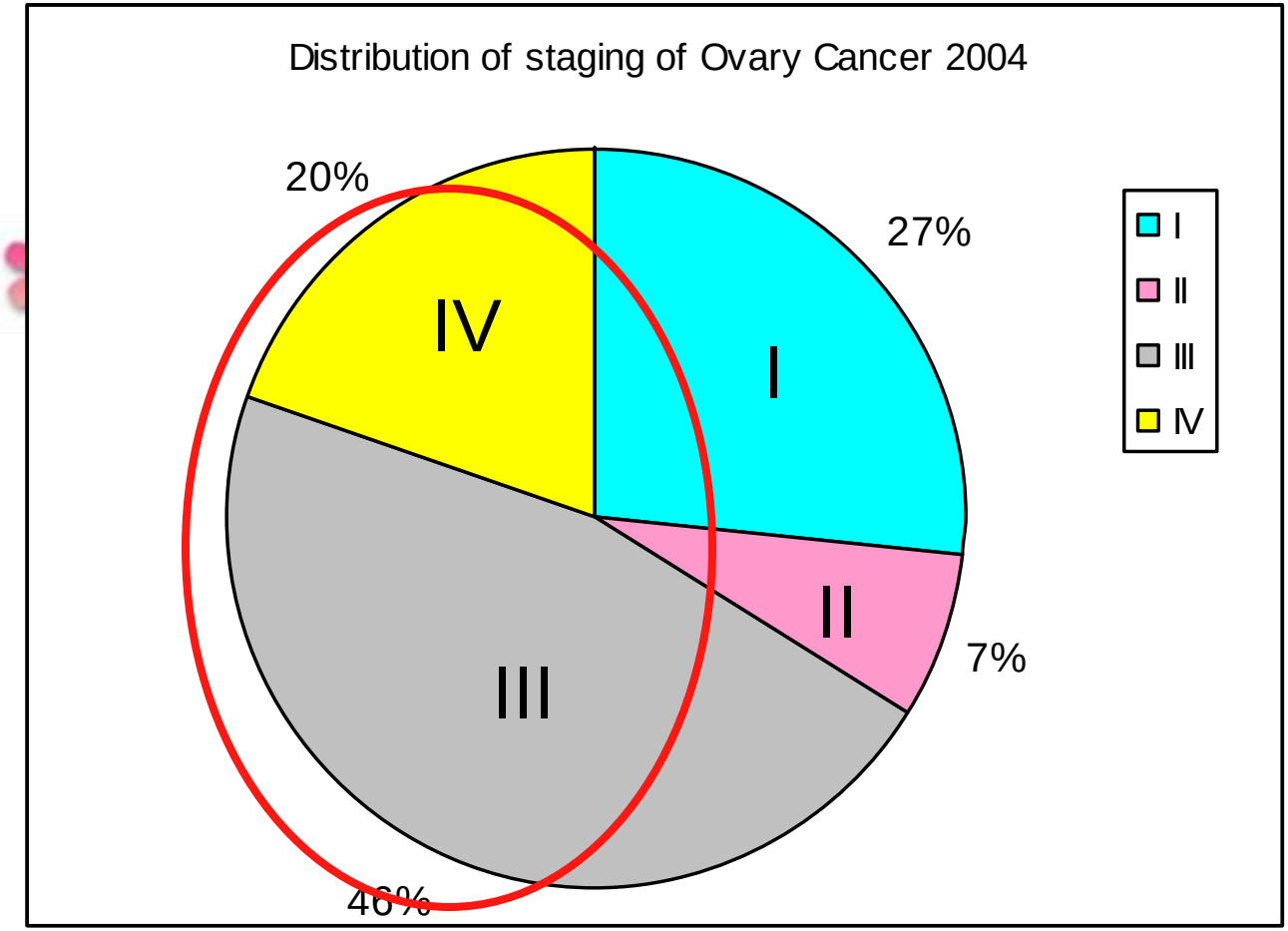
Cancer Report 2008



RAMATHIBODI CANCER REGISTRY
Faculty of Medicine, Ramathibodi Hospital,
Mahidol University, Bangkok, Thailand.
ISBN: 978-974-11-1291-3

Figure 3.1.3 Ten leading sites of cancer in female




Distribution of staging of Ovary Cancer 2004
20%
27%
IV
I
II
III
7%
46%
I
II
III
IV

* Ovarian Cancer:'National database * Stage Distribution & 5-yr Survival

Stage	%	5-yr Survival
I	25	90%
II	15	80%
III	45	25%
IV	15	15%;

Source : Cancer in Thailand. Vol III

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    - * in general population
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  - to differentiate between benign and malignant pelvic mass
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Aim of ovarian cancer screening

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Is limited to

- An attempt to detect early-stage disease

-’No precancer; better survival

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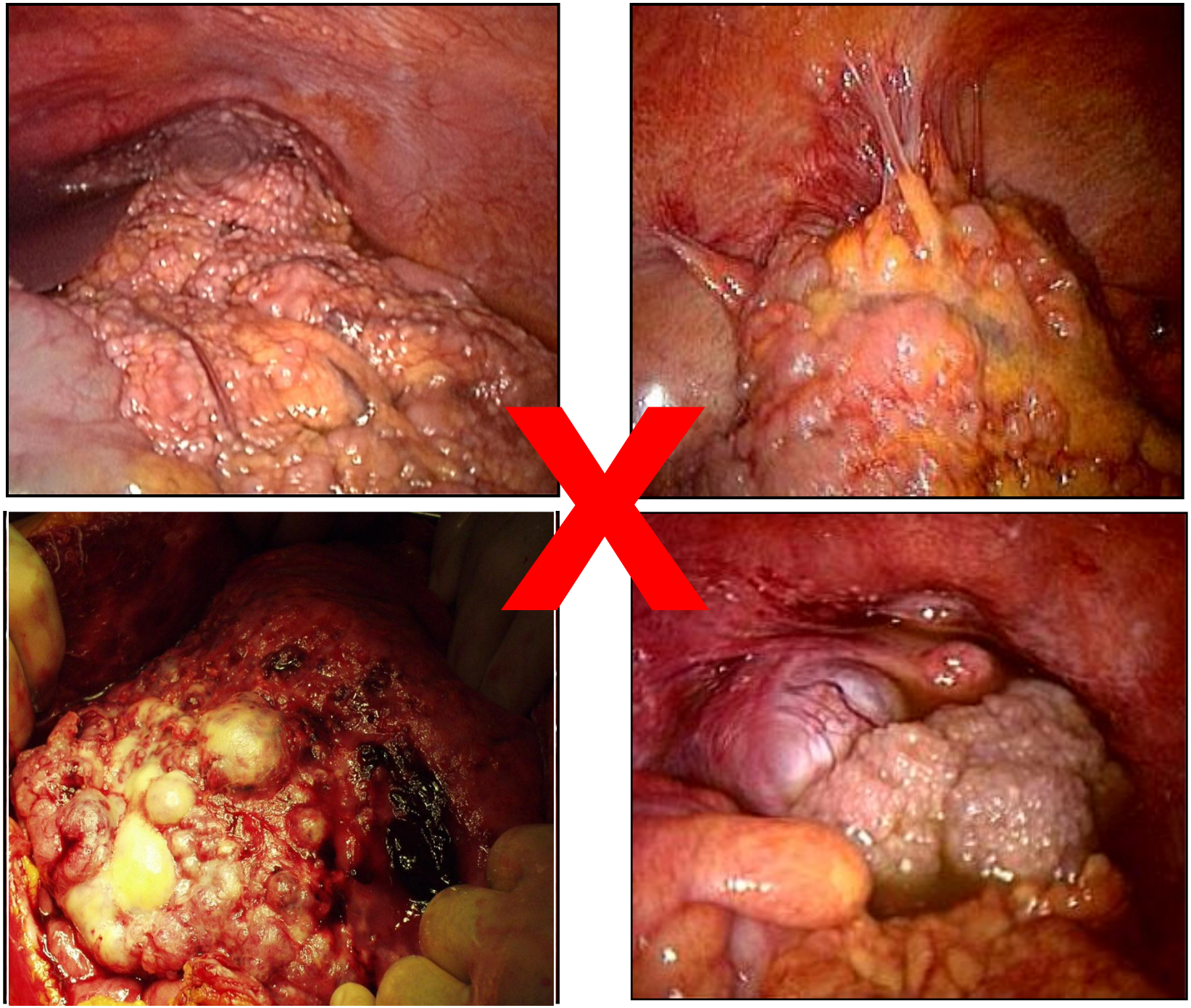
  -'No precancer; better survival

- Differential diagnosis between benign and malignant pelvic mass;

Aim of ovarian cancer screening

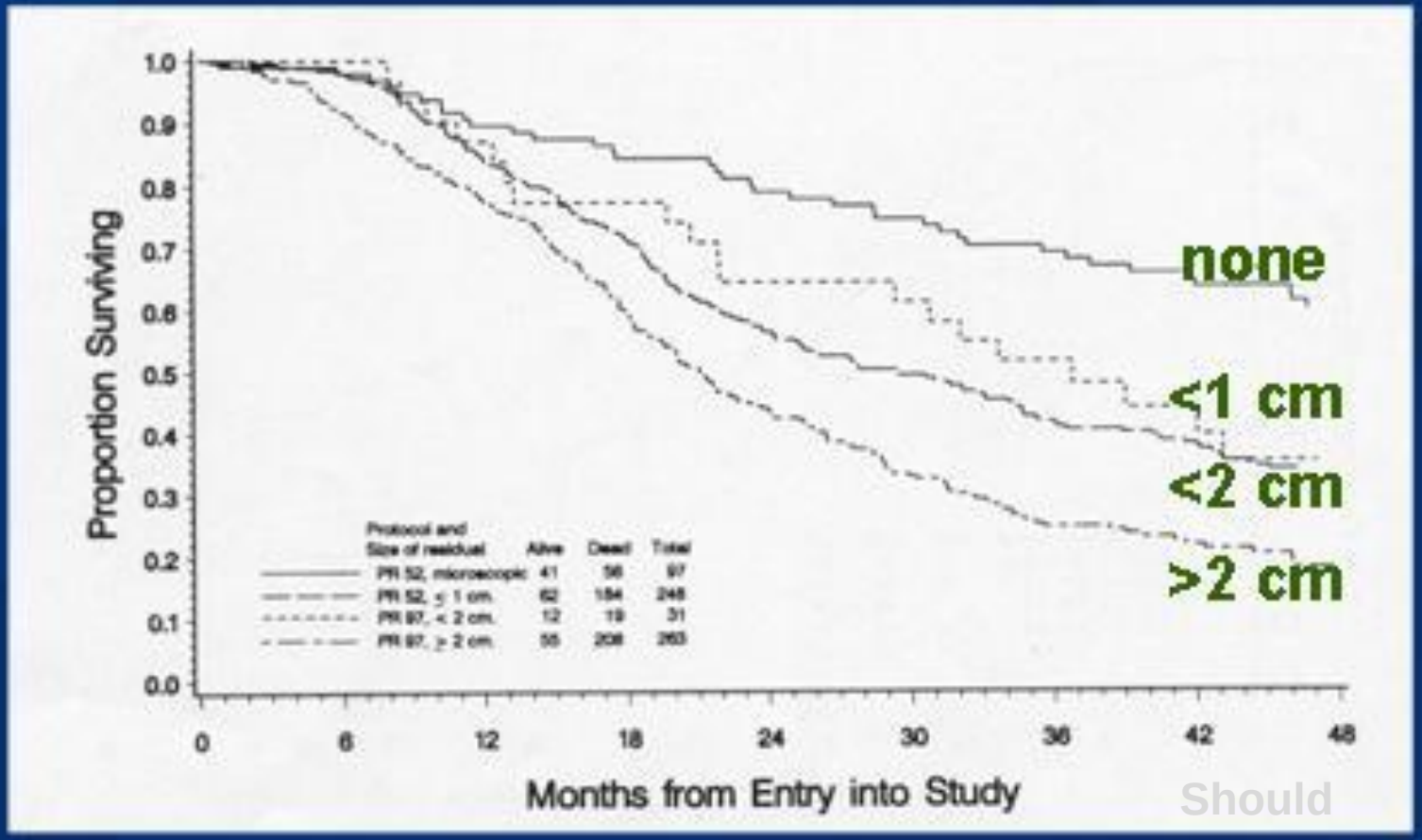
Is limited to

- An attempt to detect early-stage disease
- Differential diagnosis between benign and malignant pelvic masses



AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Residual Disease vs. Survival (GOG 52/97)



Should

Screening target population

General population

Increased-risk population

- **Menopause**
- **Positive family history**
- **Having adnexal mass**

Screening target population

Increased-risk population

- **Menopause**
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Screening target population

Increased-risk population

- **Menopause**
- **Positive family history**
- **Having adnexal mass**

°	University of Kentucky (≥ 50 yr)	Japanese Shizuoka Cohort Study of Ovarian Cancer Screening (post-menopause, PM)	Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial(55-74yr)	United Kingdom Collaborative Trial of Ovarian Cancer Screening(UKCTOCS)PM
Study design	Single arm prospective study	RCT with 1 screening strategy	RCT with 1 screening strategy	RCT with 2 screening strategies
Cohort	25,327	41,688	30,630	98,305
Screening strategy	USG	PE, USG, CA125	USG, CA125	• USG • CA125, USG (MMS)
Interpretation of CA125		35 kU/l cut-off	35 kU/l cut-off	ROCA
Key Findings	Encouraging sensitivity • 81% for OC, FT cancer • 76.3% for invasive cancer	Encouraging sensitivity (77.1%)	Low sensitivity • 69.5% for OC, FT cancer • 68.2% for invasive cancer Only 28% stage I/II	Encouraging sensitivity • 89.4% MMS • 84.9% USG Superior sensitivity (88.6% vs 65.8%) and PPV (21.7% vs 5.8%) of MMS
Key mortality	Longer 5-year survival in the screened pop (74.8% vs 53.7%)	Stage shift: more stage I (63% vs 38%)	No mortality benefit	Data awaited in 2015

U Menon et al. Gynecol Oncol 2014; 132: 490-5.

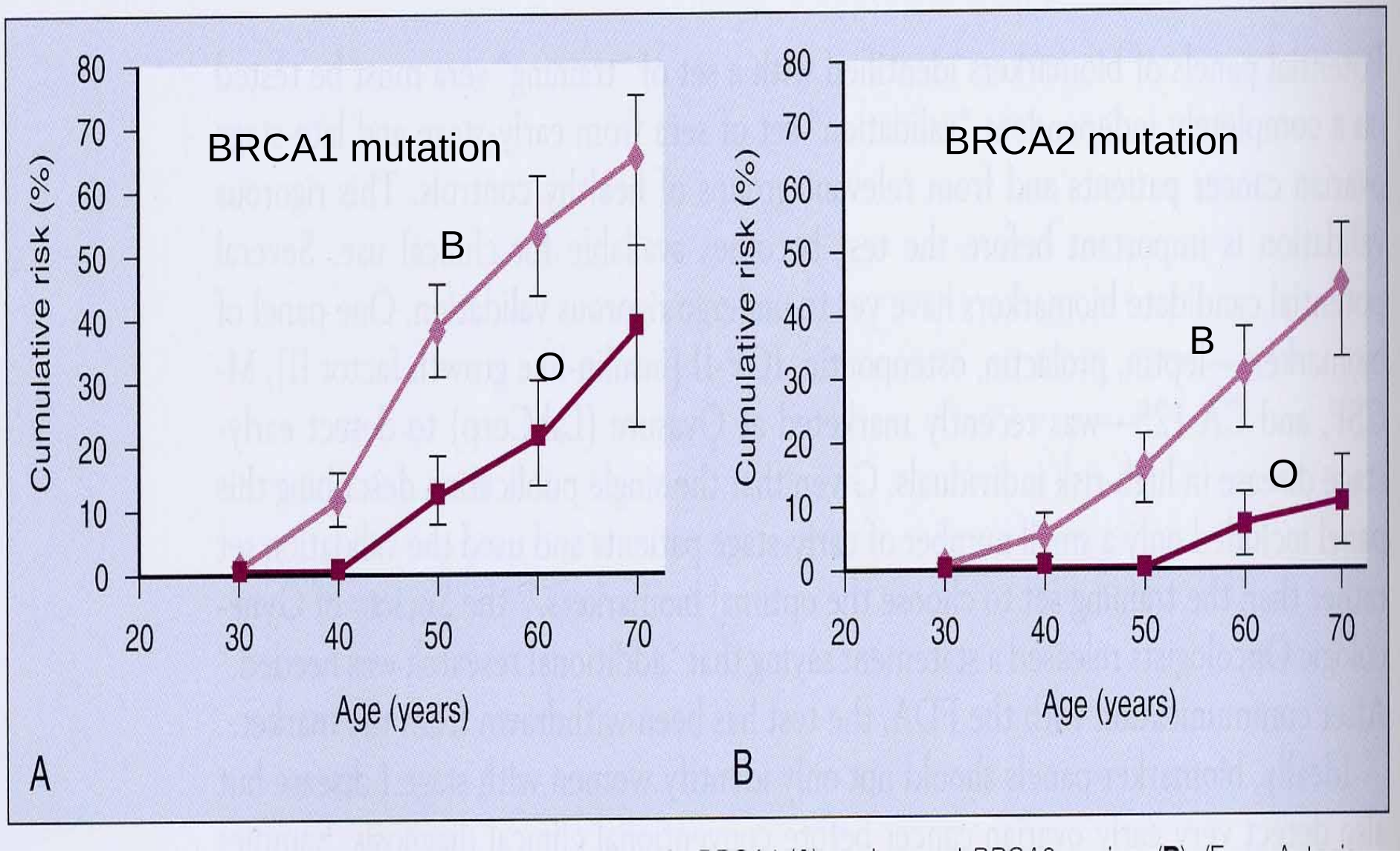
Screening target population

Increased-risk population

- **Menopause**
- **Positive family history**
- **Having adnexal mass**

Risk of ovarian cancer

- Women in the general population have a 1.4% lifetime risk of developing ovarian cancer
- Women with a BRCA1 mutation have a 39-46% life time risk of ovarian cancer
- Women with a BRCA2 mutation have a 12-20% life time risk of ovarian cancer:



Cumulative risk of breast and ovarian cancer in BRCA1 (A) carriers and BRCA2 carriers (B). (Form Antoniou A, Pharoah PD, Narod S, et al: Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117-1130,2003:Figs. 3 and 4).

Hereditary ovarian cancer

- HBOC (Hereditary breast-ovarian cancer) is associated with BRCA1 and BRCA 2 mutations
- HNPCC (Hereditary nonpolyposis colorectal cancer) Lynch II is associated with mismatched repair gene mutations:in (hMSH2, hMLH1, hPMS2, hMSH3 and hMSH6)

UKFOCSS (the United Kingdom Familial Ovarian Cancer Screening Study)

- 3,563 women with ovarian cancer syndrome, declined/deffered RRSO (risk reducing salpingo-oophorectomy)
- Screened annually with TVS+CA125
- Sensitivity to detect OVCA/FTCA was 81.0-87.5 %, PPV was 25.5 % (exceeds the threshold of 10 % considered necessary for OVCA screening);

Rosenthal AN, et al. J Clin Oncol 2013;31:49

- The mean age of diagnosis of ovarian cancer in BRCA mutation is 10-15 years earlier than 61 years – the mean age of diagnosis in women with sporadic ovarian cancer
- NCCN recommends CA125 and TVS every 6 mo. in women with known BRCA mutation starting at age 35 or 5-10 years than the age of first diagnosis of ovarian cancer in the family

Box 6-3. Reasons Why Young High-Risk Women Might Choose Ovarian Cancer Screening Rather Than Prophylactic Surgery

Young age

Concerns about iatrogenic premature menopause

Concerns about use of hormone replacement therapy

Wish to retain fertility

Unwillingness to undergo surgery

Psychological impact of oophorectomy

Poor operative risk (e.g., medical comorbidity/multiple adhesions)

From Rosenthal A, Jacobs I: Familial ovarian cancer screening. Best Pract Res clin Obstet Gynaecol 20(2):321-338, 2006.Box 2.

Screening of ovarian cancer: ‘Recommendation from professional groups

Professional group	Recommendation
US preventive services task force (2012), SGO, US NCI, Canadian Task Force on the Periodic Health Examination, A NZ professional Soc	Does not recommend routine screening in asymptomatic women
National Comprehensive Cancer Network NCCN (2014), ACOG	Does not recommend routine screening , recommends screening of high-risk women (either a family history of ovarian or breast cancer or BRCA mutation) with TVS and CA125 measurement every 6 months beginning between 30-35 yr or 5-10 yr earlier than the earliest age of first diagnosis of OVCA in the family

Screening target population

Increased-risk population

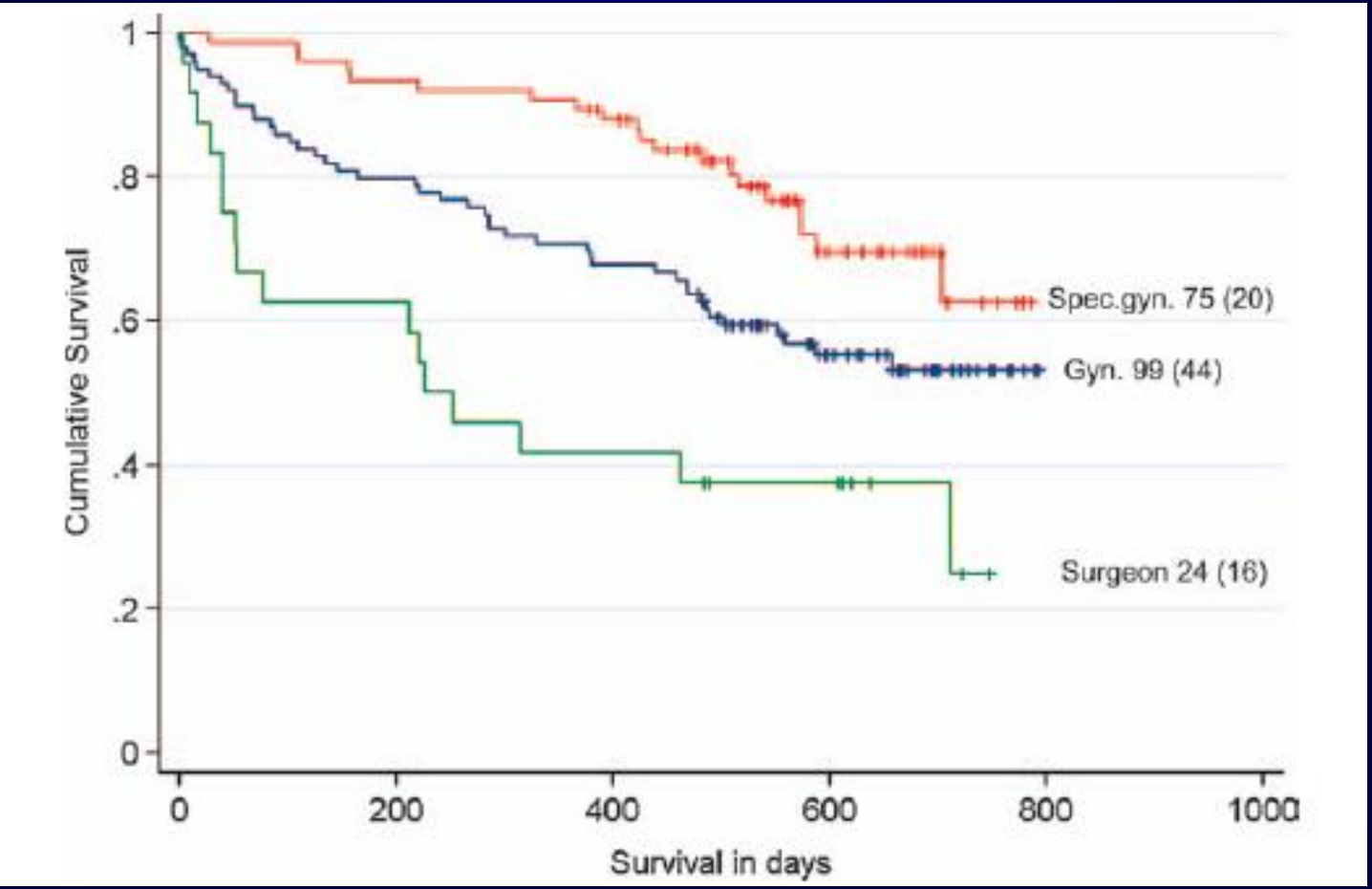
- **Menopause**
- **Positive family history**
- **Having adnexal mass**

Aim of ovarian cancer screening

Is limited to

- an attemp to detect early-stage disease
- Differential diagnosis between benign and malignant pelvic mass

Survival Rates Improve with Specialist



'Paulsen T. et al. Int J Gynecol Cancer. 2006;16(Suppl 1):11-17

Other Studies also Show Survival Benefit

Study	Gynecologic Oncologists	Gynecologists/General Surgeons	*p value*
Eisenkop 1992	35 months	17 months	<0.001
Junor 1999	18 months	13 months	<0.005
Carney 2002	26 months	15 months	<0.01
Tingulstad 2003	21 months	12 months	0.01

Eisenkop SM et al. *Gynecol Oncol*. 1992;47(2):203-209.

Junor EJ et al. *Br J Obstet Gynaecol*. 1999;106(11):1130-1136.

Carney ME et al. *Gynecol Oncol*. 2002;84:36-42.

Tingulstad S et al. *Obstet Gynecol*. 2003:102(3):499-505.

Tools for ovarian cancer screening

- Tumor markers
- Ultrasonography

Tools for ovarian cancer screening

- Tumor markers
- Ultrasonography

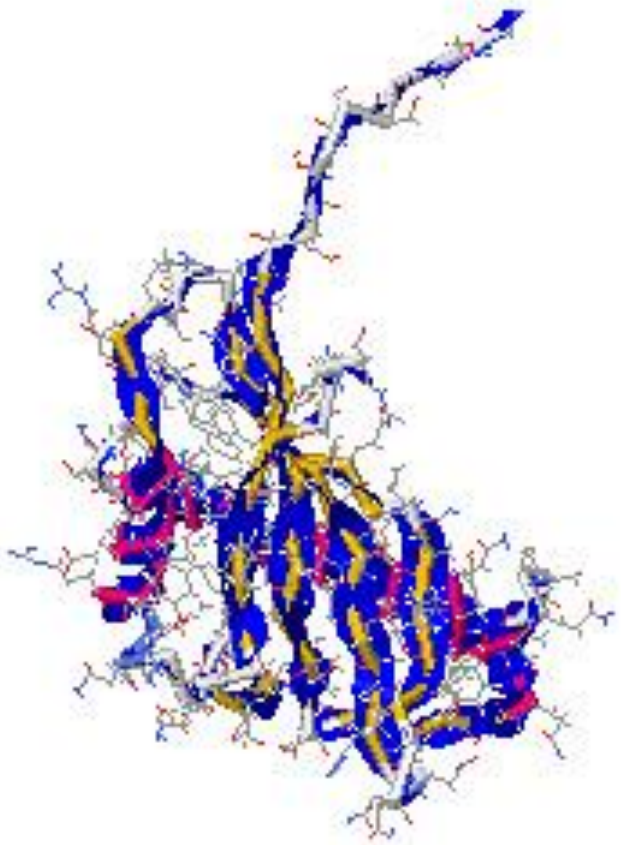
Technologies for biomarker discovery

- Monoclonal antibodies
- Lipid analysis
- Gene expression arrays
- Proteomic analysis;

Box 6-2. Tumor Markers That May Be Useful in Screening for Ovarian Carcinoma

Alpha-I-antitrypsin	Galactosyltransferase	M-CSF
BHCG	HE4	Mesothelin
CA15-3	HER-2/neu	Mucin-like carcinoma antigen
CA19-9	Human milk fat globule protein	Osteopontin
CA50	Human milk globule 2	Ovarian serum antigen
CA54-61	IL-2 receptor	OVXI
CA72-4	IL-6	p110 epidermal growth factor receptor
CA-125	IL-8	Placental alkaline phosphatase
CA-195	IL-10	Prostasin
Cathepsin L	Inhibin	Sialyl TN
Carcinoembryonic antigen	Kallekrein-6	Soluble Fas ligand
Ceruloplasmin	Kallekrein-10	Tetranectin
CRP	Lipid-associated sialic acid	Tumor-associated trypsin inhibitor
CYFRA21-1	Lysophosphatidic acid	Tumor necrosis factor receptor
Dianon marker 70/K	Matrix metaloproteinase 2	Urinary gonadotropin peptide

From Chu CS, Rubin SC: Screening for ovarian cancer in the general population Best Pract Res Clin Obstet Gynaecol 20:307-320,2006, page 312.



CA-125

Conventional tumor marker

CA125 is a Sensitive Marker for Ovarian Cancer

CA125

Elevated in 80 % of women with ovarian cancer

CA125 in ovarian cancer

Elevated in > 90 % of women with advanced disease

Sturgeon C et al. Clin Chem. 2008;54:e11-e79

CA125 has Some Limitations

CA125 in diagnosis of Ovarian cancer

Elevated in only 50 % of early stage cancers

In premenopausal women, CA125 can be elevated due to:

Several benign conditions, Endometriosis

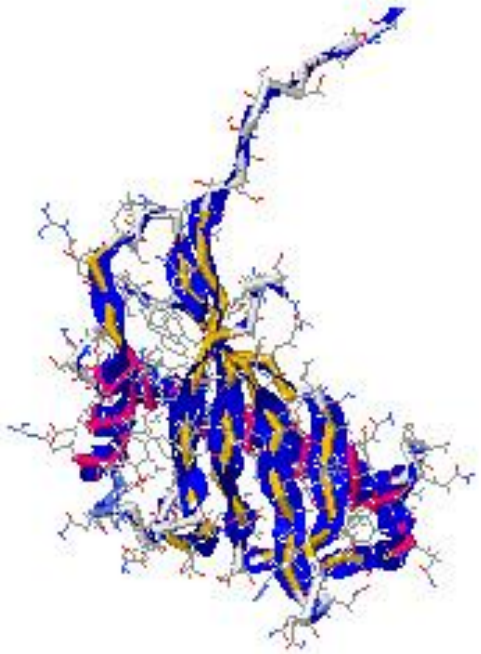
Pregnancy

Hemorrhagic cyst, Pelvic Inflammatory disease

Pancreatitis, pnuemonia

CA125 can also be elevated in breast, pancreatic, colon, lung and endometrial cancer.

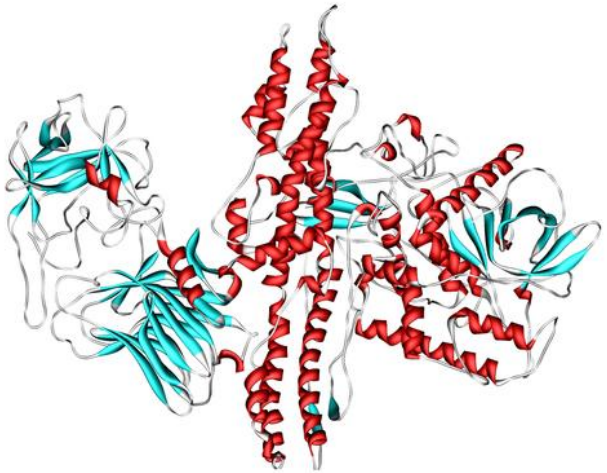
Clarke-Pearson DL NEJM 2009;361:170-177



Conventional tumor marker

CA-125

HE4



Novel tumor marker

HE4 (Human epididymal protein4)

- HE4 is a glycoprotein and is present in high concentration in the epididymis.
- HE4 is regulated by the WFDC2 gene.which is one of the most frequently upregulated genes in epithelial ovarian carcinoma based on gene expression profiles.

- Its function is still unknown.

- HE4 was found to be elevated in more than half of the ovarian cancers that do not express CA125

Li J, et al. Expert Rev Mol Diagn. 2009;9:555
Galgano MT, et al. Modern Pathol. 2006;19:847
Moore RG, et al. Gynecol Oncol 2008;108:402-8.

HE4 in detection of ovarian cancer in patients with pelvic mass

“20% of women will be diagnosed with a pelvic mass in their lifetime”

Curtin JP. Gynecol Oncol. 1994;55:S42-S46.

Hoffmann MS, UpToDate, update as of August 30, 2007, printed from www.uptodate.com on 2/18/2009.

Pelvic (or Adnexal) Mass

- Of those, ‘13 - 21% of women will have a malignant pelvic mass

Is there a way to determine if a pelvic mass is malignant before surgery?;

NIH Consensus Development Conference Statement. Gynecol Oncol. 1994;55:S4-S14.

Are there Complementary Markers to CA125?

Moore 2008: Multiple Novel Tumor Markers

Patient Distribution

- 166 patients with benign disease, 67 patients with invasive ovarian cancer

		Sensitivity (%) at	
Marker	ROC-AUC (%)	95% Specificity	98% Specificity
CA125	83.6	43.3	23.9
HE4	90.8	72.9	64.2
SMRP	82.4	53.7	43.3
CA72-4	77.5	35.0	22.0
Osteopontin	64.8	7.6	4.9
Urine SMRP	71.0	37.5	24.6
Urine CA125	73.4	17.4	3.3
Activin	69.1	23.9	13.4
Inhibin	65.4	0.0	0.0

‘Moore RG et al. Gynecol Oncol 2008;108:402-408

Combined Tumor Marker Sensitivities for 'All Stages of ovarian cancer

		Sensitivity (%) at	
Marker	ROC-AUC (%)	95% Specificity	98% Specificity
CA125	83.6	43.3	23.9
HE4	90.8	72.9	64.2
CA125+HE4	91.4	76.4	71.6
CA125+SMRP	86.3	56.8	50.7
CA125+CA72-4	86.2	45.1	31.4
HE4+SMRP	91.4	71.6	65.7
HE4+CA72-4	90.9	70.2	67.2
CA125+HE4+SMRP	91.1	74.7	71.7
CA125+HE4+CA72-4	91.4	78.7	71.5

The combination of CA125 and HE4 has the best sensitivity for ovarian cancer

Moore RG et al. Gynecol Oncol 2008;108:402-408

ROMA – Risk of Ovarian Malignancy Algorithm;

‘ROMA Validation Study

Prospective double blinded multicenter trial

14 geographically dispersed sites

Eligibility criteria:

- ≥18 years of age
- Have an ovarian cyst or a pelvic mass
- Planned surgical intervention

All blood samples were obtained preoperatively

Central pathology review

Biomarker analyzed after the study completion:

Moore RM et al. Gynecol Oncol. 2009;112:40

Most Ovarian Cancers Correctly Classified

Disease	Low Risk (N)	High Risk (N)	All (N)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Benign	263	89	352				
EOC + LMP	17	134	151	88.7	74.7	60.1	93.9
Total	280	223	503				

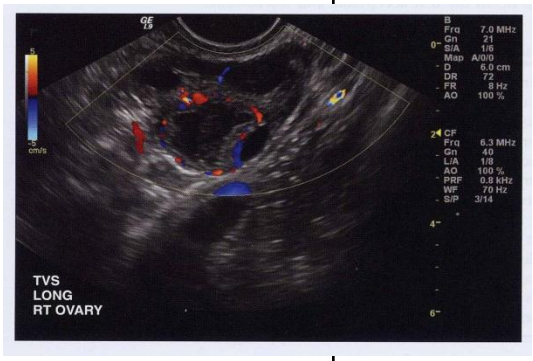
> 90% of the women that are classified as low risk by the ROMA algorithm don't have ovarian cancer:

ROMA Validation Study

Moore RM et al. Gynecol Oncol. 2009;112:40

ROMA vs RMI

Risk of Malignancy Index (RMI);

Criteria	Scoring System
Menopausal Status (A) Premenopausal Postmenopausal	 1 3
Ultrasound Features (B) Multiloculated Solid Nodule Bilateral Ascites Metastases	 No feature = 0 1 feature = 1 > 1 feature = 3
Serum CA125 (C)	Absolute level
'Risk of Malignancy Index (RMI) = A x B x C	

Jacobs I et al. Br J Cancer. 1990;97:922-929

Risk of Malignancy Index

If RMI is > 200, greater risk of ovarian cancer

Sensitivity = 85%

Specificity = 97%:

- RMI has been widely used in the UK and Europe for many years and is considered the standard way to discriminate between a benign and malignant mass prior to surgery.

Jacobs I et al. Br J Cancer. 1990;97:922-929

ROMA versus RMI

TABLE 3

Risk stratification of premenopausal and postmenopausal women with pelvic masses based upon Risk of Ovarian Malignancy Algorithm and Risk of Malignancy Index at a set specificity of 75%

	n		Sensitivity			Positive predictive value		Negative predictive value		Overall agreement	
Group	Benign	Cancer	ROMA	RMI	Pretest *P* value	ROMA	RMI	ROMA	RMI	ROMA	RMI
Benign vs EOC and LMP	312 (68%)	145 (32%)	89.0%	80.7%	.0113	62.3%	59.7%	93.6%	89.3%	79.4%	76.6%
Benign vs stage I-IV EOC	312 (72%)	123 (28%)	94.3%	84.6%	.0029	59.8%	56.8%	97.1%	92.5%	80.5%	77.5%
Benign vs stage I-II EOC	312 (90%)	34 (10%)	85.3%	64.7%	.0000	27.1%	21.8%	97.9%	95.1%	76.0%	73.7%
Benign vs stage III-IV EOC	312 (78%)	86 (22%)	98.8%	93.0%	.0350	52.1%	50.3%	99.6%	97.5%	80.2%	78.6%
Benign vs stages I-IIIB and IIIC (omentum– and LN+)	312 (88%)	44 (12%)	88.6%	68.2%	.0037	33.3%	27.5%	97.9%	94.3%	76.7%	73.9%

EOC, epithelial ovarian cancer; *LMP*, low malignant potential; *RMI*, Risk of Malignancy Index; *ROMA*, Risk of Ovarian Malignancy Algorithm.

Moore. Comparison of a novel multiple marker assay vs the RMI. Am J Obstet Gynecol 2010.

ROMA achieved significantly higher sensitivity for identifying women with ovarian cancer than RMI

Moore R et al. Am J Obstet Gynecol. 2010;202:

Asia-Pac HE4 ROMA Multicenter Study

Gynecologic Oncology 128 (2013) 239–244

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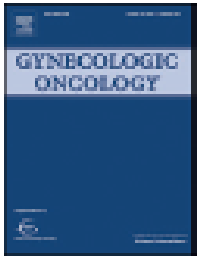
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



The use of HE4 in the prediction of ovarian cancer in Asian women with a pelvic mass

Karen K.L. Chan [a,*], Chi-An Chen [b], Joo-Hyun Nam [c], Kazunori Ochiai [d], Sarikapan Wilailak [e], Aw-Tar Choon [f], Subathra Sabaratnam [g], Sudarshan Hebbar [h,1], Jaganathan Sickan [h], Beth A. Schodin [h], Walfrido W. Sumpaico [i]

ROMA cutoffs

	Sensitivity	Specificity
Premenopausal Published (cutoff = 7.4)	41.7%	91.6%
Premenopausal Optimal (cutoff = 6.4)	54.2%	89.6%
Postmenopausal Published (cutoff = 25.3)	90.9%	93.2%
Postmenopausal Optimal (cutoff = 24.6)	93.9%	93.2%

The 'optimal cutoffs for A-P ROMA are very close to Dr. Moore's recommended cutoffs.

A-P HE4 ROMA

Sensitivity/Specificity for CA125, HE4, ROMA, RMI

	Sensitivity	Specificity	Sensitivity at 75% Specificity
CA 125 at cutoff = 35 U/mL	77.2%	68.3%	68.4%
HE4 at cutoff = 70 pmol/L	63.2%	97.0%	80.7%
ROMA at 7.4 for premeno, 25.3 for postmeno	70.2%	91.2%	80.7%
RMI 1 at 200	66.7%	90.4%	78.9%

Conclusion: HE4 demonstrated the best specificity of the markers tested for distinguishing between benign and malignant pelvic mass. 'HE4, ROMA, and RMI demonstrated better sensitivity at 75% specificity than CA125.

A-P HE4 ROMA

Performance in early stage ovarian cancer

- ‘In early stage cancer (stage I and II), HE4 showed better sensitivity at 90% specificity than CA125 (60.5% versus 47.4%).
- HE4 also showed a better AUC than CA125 in women with early stage cancer (0.82 versus 0.74) for distinguishing benign versus malignant pelvic mass.

A-P HE4 ROMA

Performance in mucinous tumors

- ‘In mucinous tumors, HE4 showed better sensitivity at 90% specificity than CA125 (55.2% versus 27.6%).

Summary (A-P HE4 ROMA)

-**HE4** and **ROMA** have an advantage over CA125 in prediction of ovarian cancer in the presence of a pelvic mass

-HE4 has better prediction of **early** and **mucinous cancers**, which were the areas of weakness for CA125

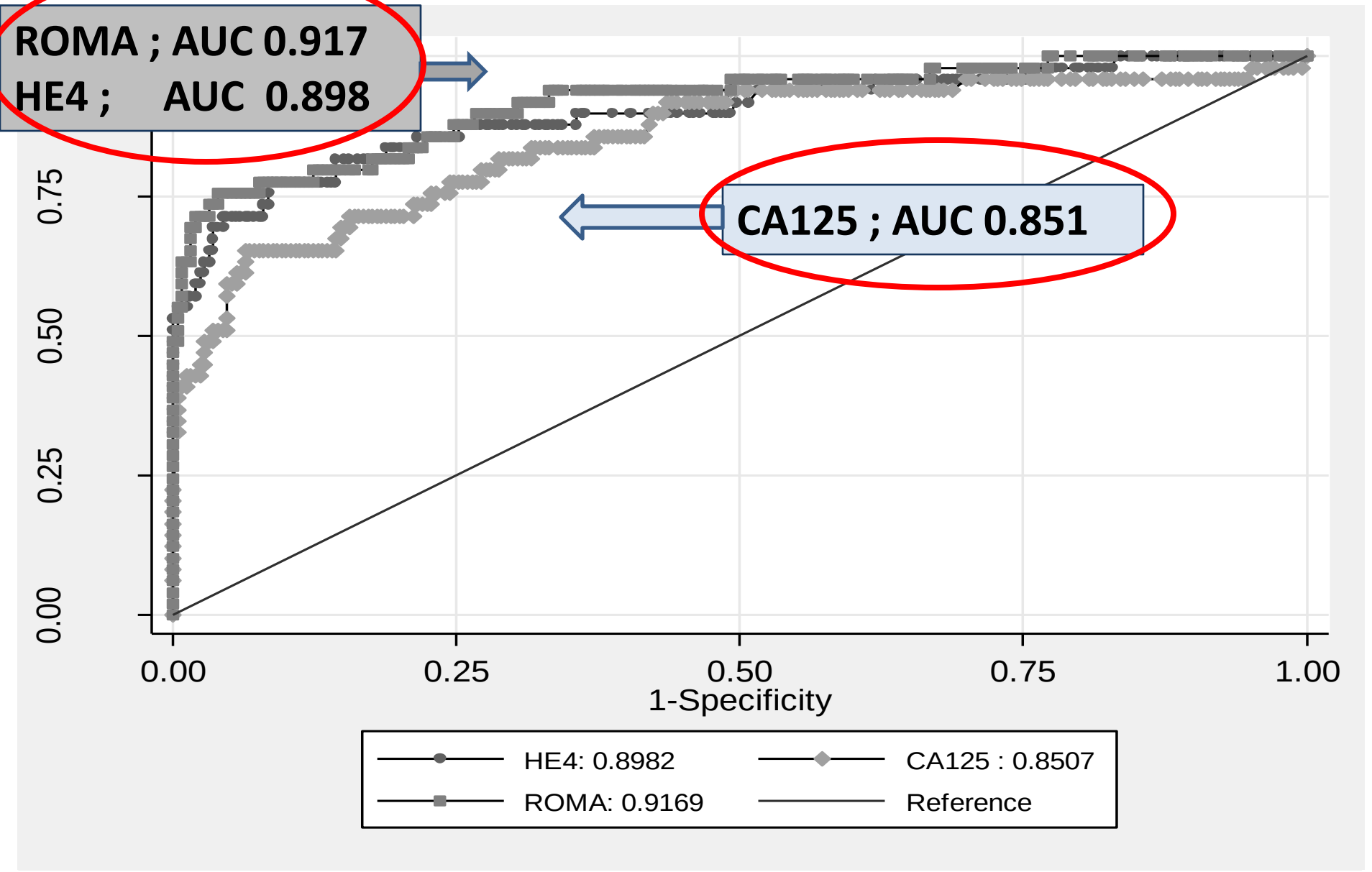
Assessment of HE4, CA125 and Risk of Ovarian Malignant Algorithm(ROMA) as Diagnostic Tools of Ovarian Cancer in Patients with Pelvic Mass Suspected Ovarian Tumor

C.Charakorn, S. wilailak
Ramathibodi Hospital,
Mahidol University

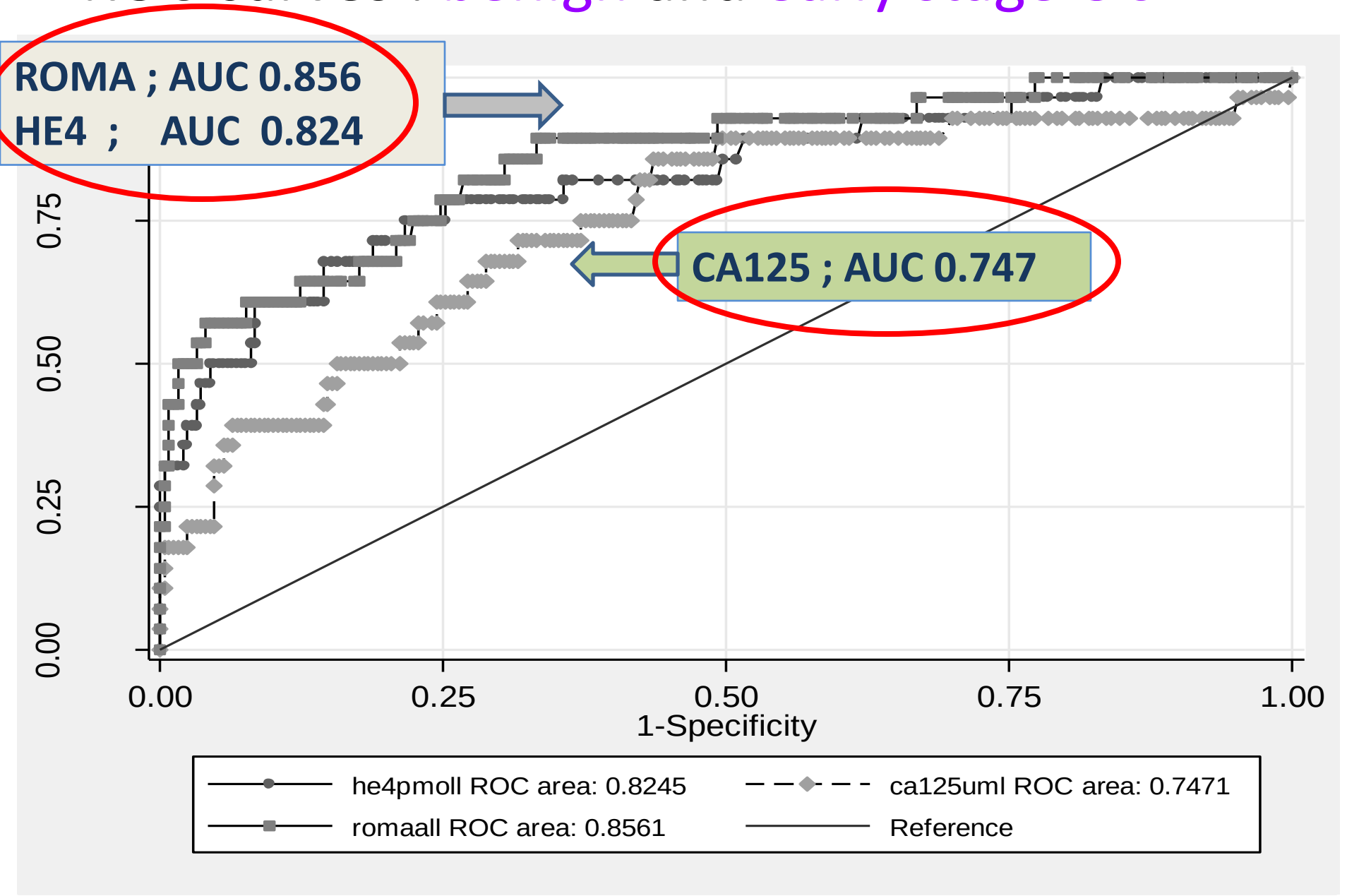
Pathological Results

	n (%)
Benign gynecologic diseases	250 (82.5)
BOT	5 (1.7)
Ovarian cancers	44 (14.5)
Non-ovarian cancer	4 (1.3)
Total	**303 (100)**

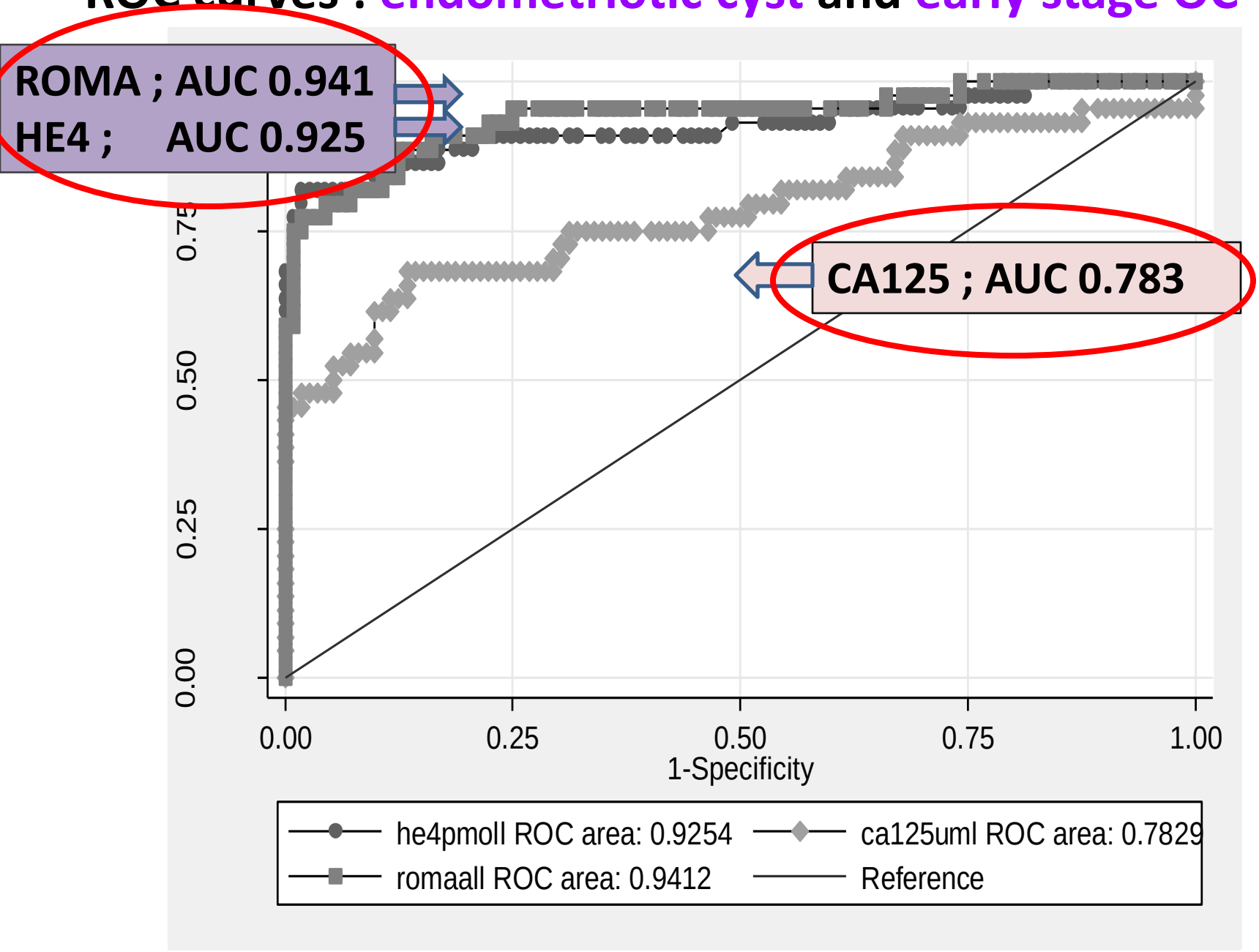
ROC curves : benign and ovarian cancer



ROC curves : benign and early stage OC



ROC curves : endometriotic cyst and early stage OC



Summary (Ramathibodi HE4-Roma)

❖***ROMA and HE4*** were shown to be **better than CA125 alone** to discriminate **benign** and **malignant pelvic mass.**

❖ Apart from that, ROMA and HE4 are better than CA125 alone in discriminating between ***benign*** *and* the ***early stages ovarian cancer*** and especially between ***endometriotic cyst*** *and* ***early stages ovarian cancer***.

The new algorithm
A-P data

Distinguishing Benign from Malignant Pelvic Mass Utilizing an Algorithm with HE4, Menopausal Status, and Ultrasound Findings

Authors: Sarikapan Wilailak MD[1], Karen KL Chan MD[2], Chi-An Chen MD [3], Joo-Hyun Nam MD[4], Kazunori Ochiai MD[5], Tar-Choon Aw MD[6], Subathra Sabaratnam MD[7], Sudarshan Hebbar MD[8*], Jaganathan Sickan MD[8], Beth A Schodin PhD[8], Chuenkamon Charakorn MD[1], Walfrido W Sumpaico MD[9].

Pathology Distribution (Total n = 328)

The A-P ROMA study included 414 women with pelvic mass that underwent surgery. Of those, 328 had complete ultrasound data submitted for analysis to compare ROMA to RMI (Risk of Malignancy Index).

Patients included in the RMI analysis:

Pathology	Premenopausal	Postmenopausal	Total
Benign	227	44	271
EOC	13	24	37
LMP	7	5	12
Metastatic	0	2	2
Non-EOC	3	2	5
Other	1	0	1

Describe characteristic of patients

Characteristics	Mean	SD
Age	41.2	13.0
Menopausal status[a]		
Pre-menopause	251	76.5
Post-menopause	77	23.5
Ultrasound features[a]		
None	125	38.1
One feature	128	39.0
Two features	55	16.8
Three features	13	4.0
Four features	7	2.1:
CA125, U/mL[b]	23.85	2.5, 1000
HE4, pmol/L[b]	35	16.7,1500
FSH, mIU/mL[b]	5.4	0.1, 119.0
CEA, ng/mL[b]	1.4	0.5, 216.4

[a]number and percent age; [b]median and range

Univariate analysis

- Multivariate analysis
  - Created logistic regression equation: HE4, CA125, HE4+CA125, ROMA, RMI
- **Score** = 0.04x**HE4** + 0.82xMS(postmenopause=1) + 0.5x(1feature=1) + 1.68x(2features=1) + 3.47x(3features=1)

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Simplified score and its performance in predicting ovarian cancer

Score	Probability	Derivation		
		Group		LR^+ (95% CI)
		Cancer	Benign	
<1.49	No or very low;	2	79	1.0
1.49-1.94	Low	6	77	1.36 (1.24, 1.49)
1.94-2.95	Low-medium	4	77	2.03 (1.70, 2.41)
2.95-3.33	Medium	1	16	5.63 (4.07, 7.78)
>3.33	High	22	44	9.51 (6.22, 14.50)

model.

Findings: A total of 414 women with a pelvic mass were enrolled in the study, of which 328 had documented ultrasound findings. The risk prediction model that contained HE4, menopausal status, and ultrasound findings exhibited the best performance compared to models with CA125 alone, or a combination of CA125+HE4. This model classified 77·2% of women with ovarian cancer as medium or high risk, and 86% of women with benign disease as very-low, low, or medium-low risk. This model exhibited better sensitivity than ROMA, but ROMA exhibited better specificity. Both models performed better than CA125 alone.

Interpretation: Combining ultrasound with HE4 can improve the sensitivity for detecting ovarian cancer compared to other algorithms.

Summary: **The new equation** of the risk prediction model contained **HE4** marker and **ultrasound features** had the best performance in terms of the sensitivity

Content

- Ovarian cancer statistics
- Ovarian cancer screening
  - to detect early-stage disease
    - * in general population
    - * in high-risk population
  - to differentiate between benign and malignant pelvic mass
- Conclusion

Conclusion

- CA125 or TVS alone is not recommended in OVCA screening either in average or high risk women
- Multimodal screening (MMS) may be beneficial in high risk women and is recommended by professional groups
- Algorithms using HE4 were found to be beneficial in discriminating benign and malignant ovarian mass

Thank you for your attention