SC07
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9:10am

Rudolf Kaaks, PhD., Division of Cancer Epidemiology, German Cancer Research Center

Evaluation and Discovery of Early Detection Markers in Large-scale Prospective Population Cohorts

Rudolf Kaaks
Division of Cancer Epidemiology
German Cancer Research Center

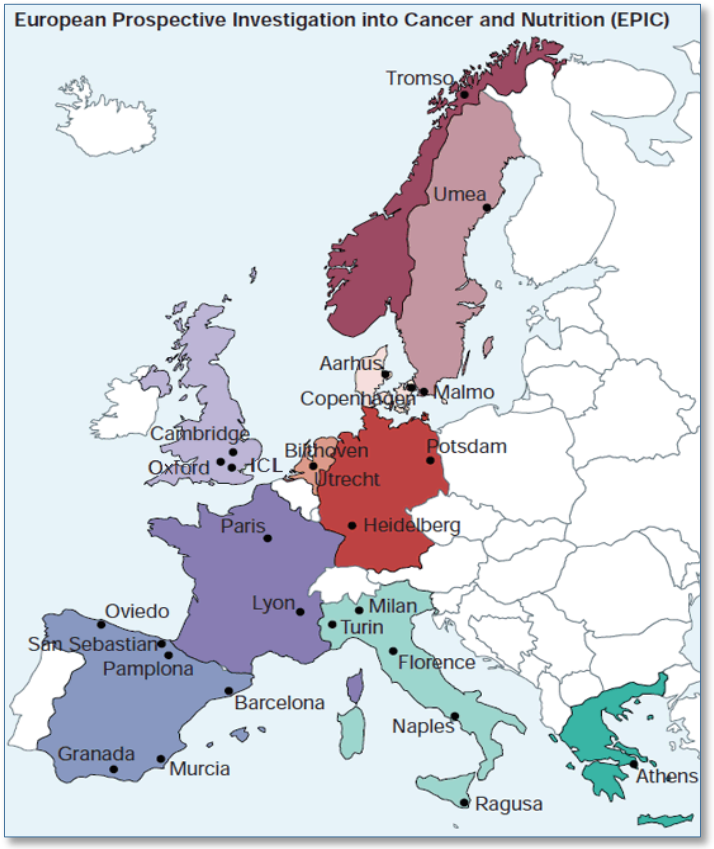
dkfz.
GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

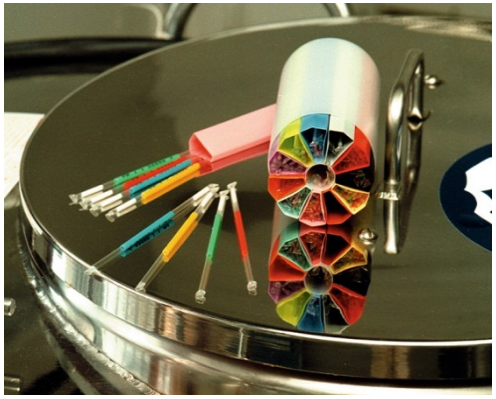
EPIC

Age range: 27-70 years

Population-based: General population

Large study size Total of over 500,000 women & men





Prospective validation in PLCO of selected candidate markers for ovarian cancer from Phase 2 (clinical case-control) studies (EDRN)

AFP, Apolipoprotein A1, B7-H4, B2M, **CA125, CA15.3, CA19.9, CA72.4, CEA**, Chitinase, CTAP-III, Cytokeratin 19, DcR3, EGFR, Eotaxin, ErbB2, **FSH, GH,** HE4, Hepcidin, **IGF2, IGFBP1, IGFBP2, Interleukin 10, Interleukin 2 receptor, Interleukin 6, Interleukin 6 receptor, Interleukin 8,** ITIH4, KLK6, KLK8, **Luteinizing hormone**, MIF, MIC1, Mesothelin, MMP2, MMP3, MMP9, MPO, **Prolactin**, Soluble intracellular adhesion molecule 1, sV-CAM, Spondin-2, **TNFα, TNFr2,** Total plasminogen activator inhibitor, Transthyretin, Transferrin, **TSH**

Marker Name	<6 Months		>6 Months	
	Sens.	Rank	Sens.	Rank
CA 125	**0.86**	1	**0.14**	2
HE4	**0.73**	2	**0.16**	1
CA 15.3	**0.45**	3	**0.08**	7
CA 72.4	**0.44**	4	**0.11**	4
Mesothelin	0.40	5	0.01	23
B7-H4	0.36	6	0.05	17
KLK6 (HK6)	0.32	7	0.06	16
MMP7	0.20	8	0.14	3
SLPI	0.16	9	0.05	18
CA 19.9	0.14	10	0.08	8
Spondin-2	0.11	12	0.11	5
B2M	0.09	13	0.08	9
CTAPIII	0.09	14	0.08	10
SV-CAM	0.04	19	0.10	6

Cramer et al., Cancer Prev Res 2011

Frequent discrepancies between phase-2 (clinical case-control) and phase 3 (prospective biobank) studies

- **Methodologic biases** [lack of “internal” validity]:

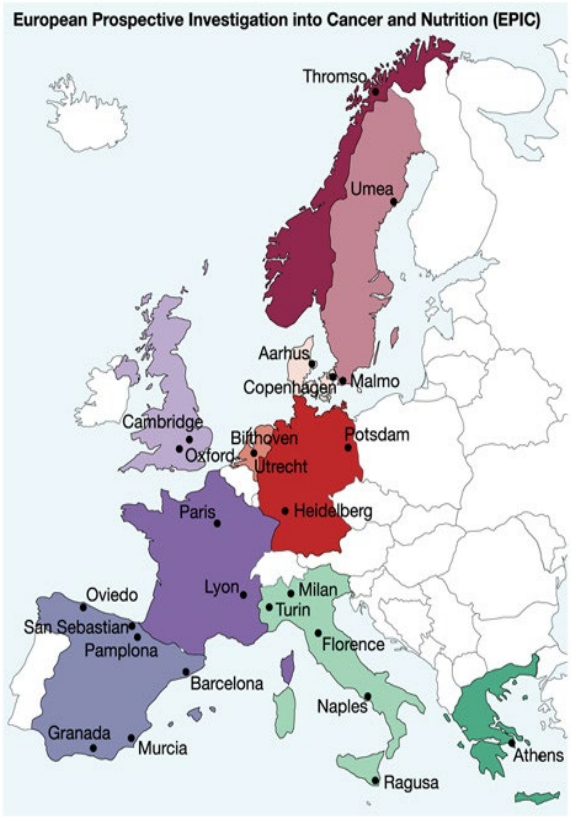
  e.g. case-control differences in sample collection & processing; selection bias

- **Lack of specificity for [early stage] tumors**

  Discrimination markers may be related to late-stage epi-phenomena of tumor development – e.g., acute-phase plasma proteins related to inflammatory response ➔ lack of tumor specificity

- **Lack of sensitivity for early-stage tumors**

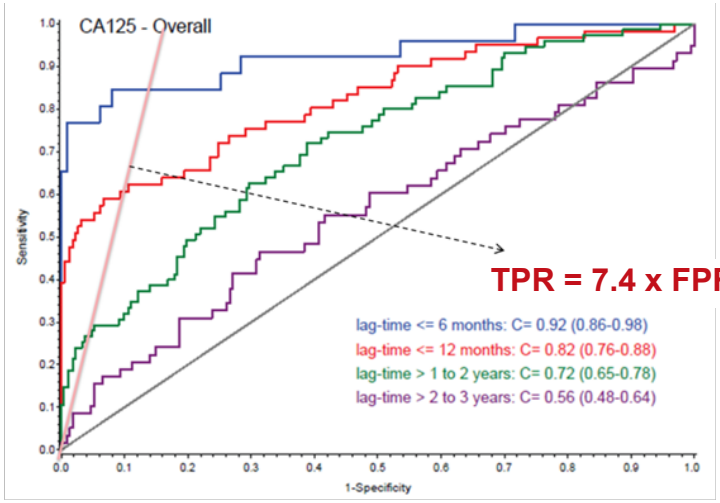
European Prospective Investigation into Cancer (EPIC) cohort

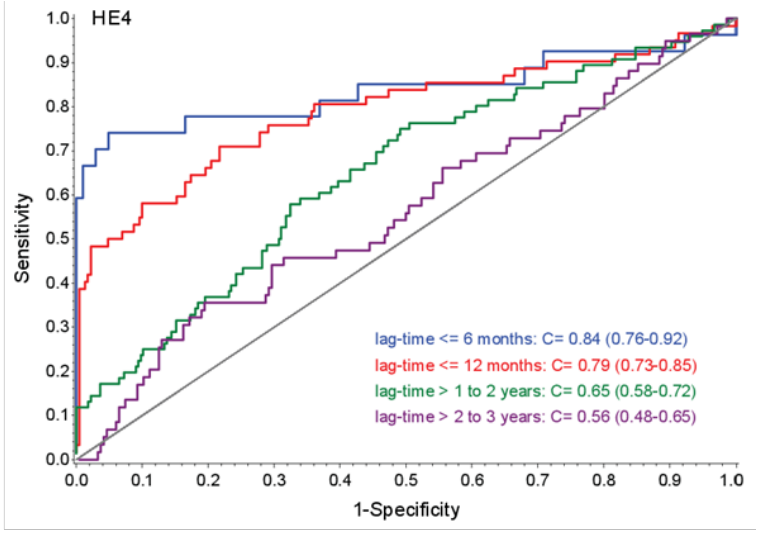


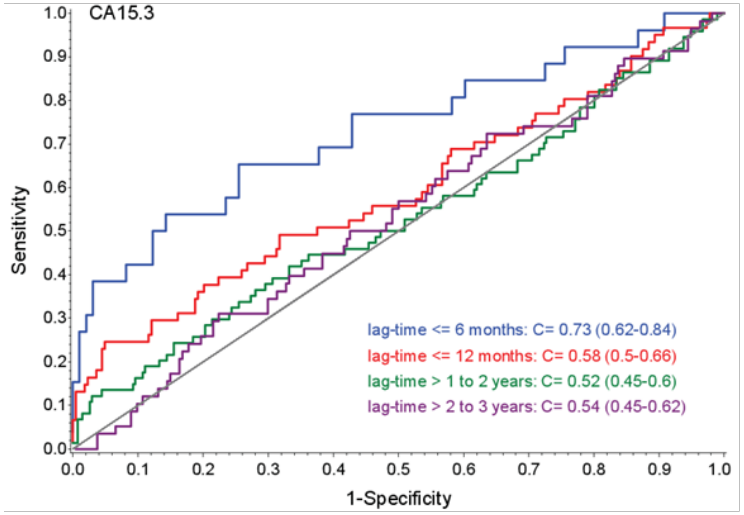
- 226,673 women with baseline blood sample (1992-2000) from 10 European countries
- 810 incident invasive cases of ovarian carcinoma
- Cases by time between blood collection and diagnosis:

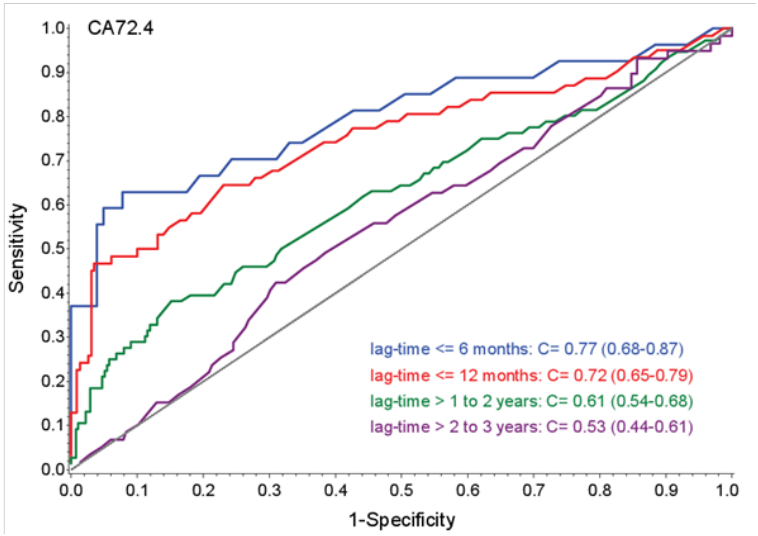
Overall	807
≤ 6 months	26
≤ 12 months	61
> 1 to 2 years	75
> 2 to 3 years	58

Prospective evaluation of diagnostic biomarkers – EPIC cohort



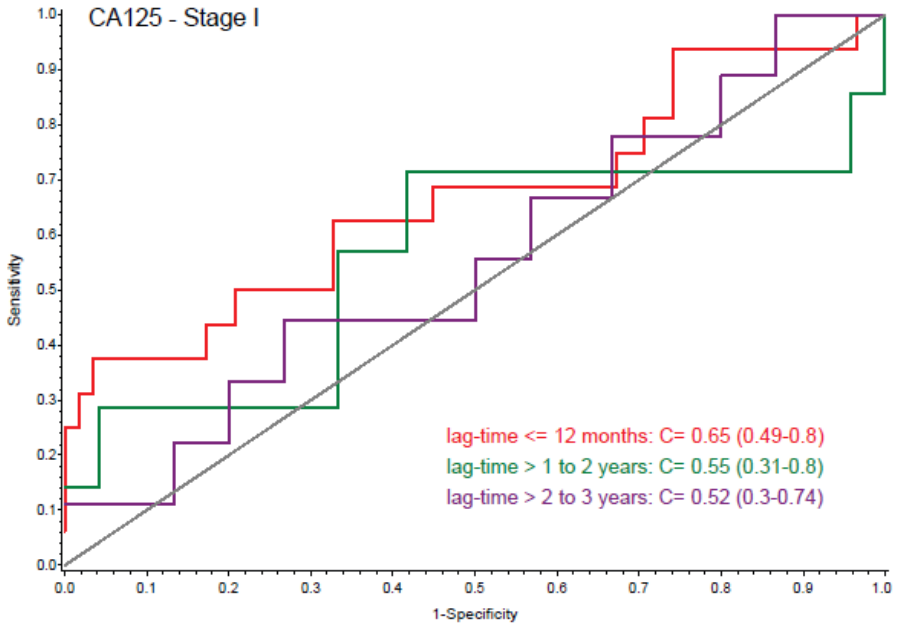


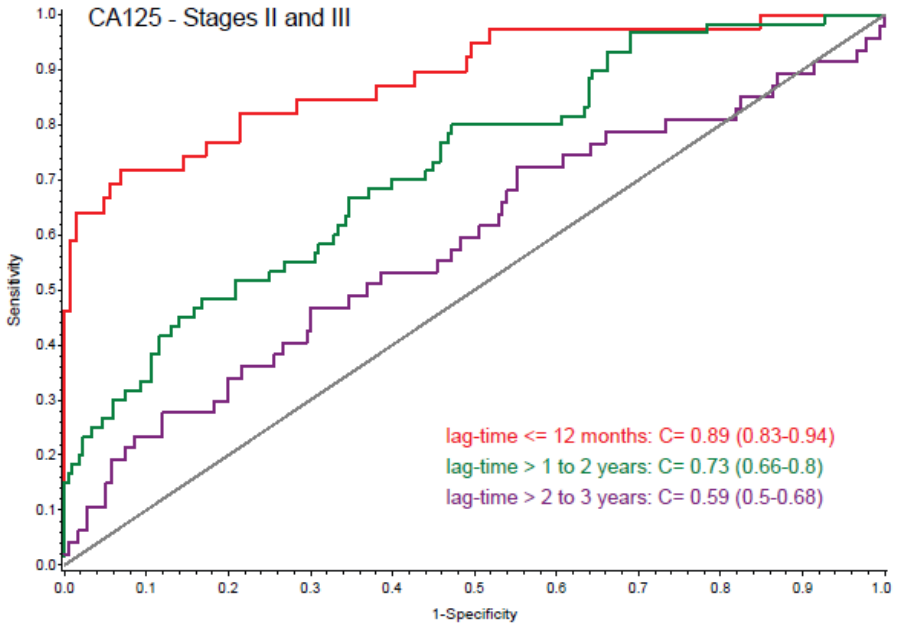




Terry, … Kaaks, Clin Cancer Res, 2016

Serum CA125 as diagnostic marker for ovarian cancer – ROC curves, by lag-time and tumor stage at diagnosis - EPIC cohort



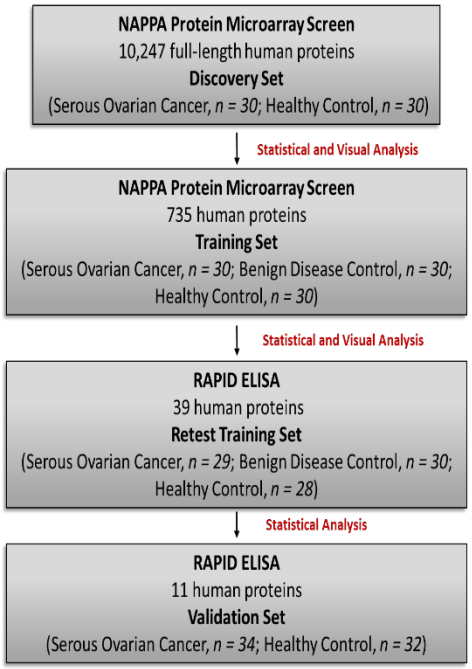


By histology: Sensitivity at 98% specificity

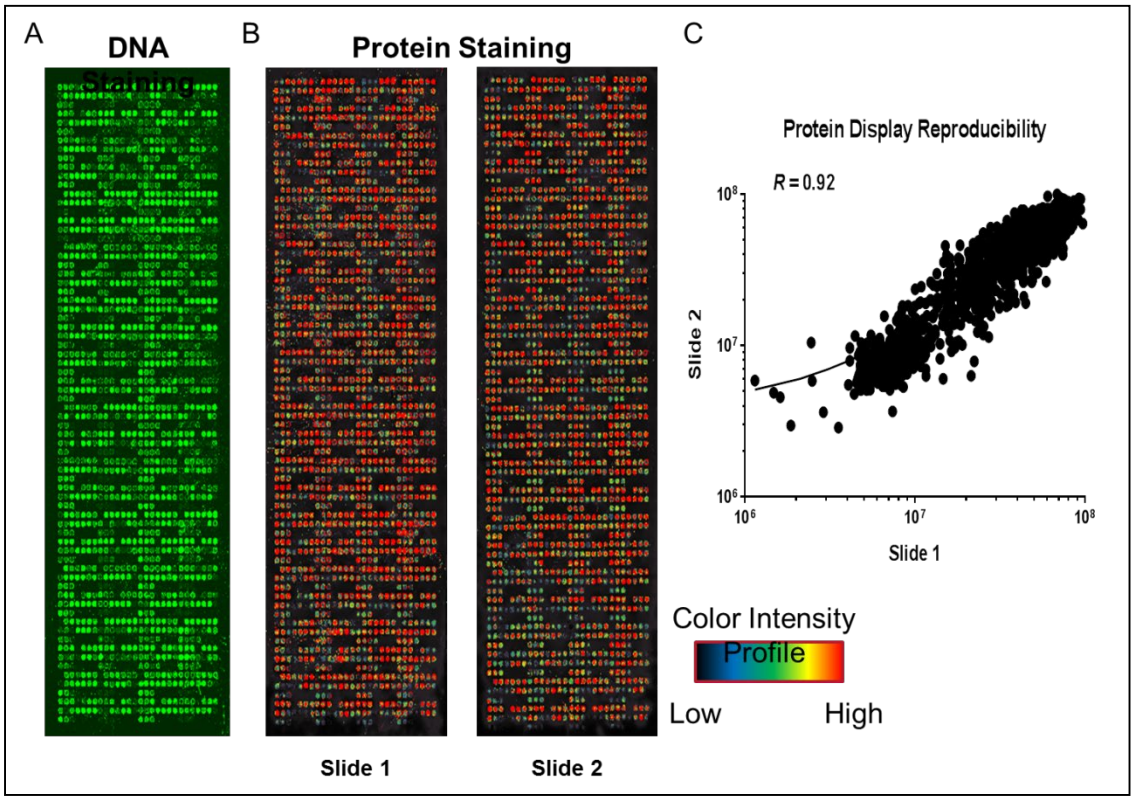
	All Ovarian Cancer (N=194)		High-Grade Serous Cancer (N= 75)	
Lead time (months)	**# Cases**	**SE98 (95% CI)**	**# Cases**	**SE98 (95% CI)**
≤ 6	26	0.77 (0.56-0.90)	9	0.89 (0.49-0.99)
>6-12	35	0.34 (0.19-0.53)	12	0.33 (0.13-0.64)
>12-24	75	0.20 (0.11-0.33)	31	0.13 (0.05-0.31)
>24-36	58	0.03 (0.01-0.14)	23	0.04 (0.01-0.26)

Terry, … Kaaks, Clin Cancer Res, 2016

Autoantibodies against tumor-related antigens as early detection markers



Flow chart for the TAAb Discovery Study by Katchman et al, Gynecol Oncol 2017



➔ Panel of 11 AAbs – CTAG2, ICAM3, KSR1, NUDT11, NXF3, POMC, PVR, STYXL1, TP53, TRIM39, and UHMK1 → combined 45% sensitivity at 98% specificity, for any 2 AAb positive

➔ Two of the AABs – against P53 and CTAG2 – provided a large part of diagnostic discrimination.

(Katchman, …, Anderson; Gynecol Oncol 2017)

Early detection of ovarian cancer by selected Autoantibodies (i) Sensitivity at 98% specificity – European EPIC cohort (226,673 women)

	All Ovarian Cancer (N=194)		High-Grade Serous Cancer (N=75)	
Lead time (months)	# Cases	SE98 (95% CI) [b]	# Cases	SE98 (95% CI) [b]
P53				
≤ 6	26	**0.23 (0.10-0.44)**	9	**0.33 (0.11-0.68)**
>6-12	35	0.11 (0.04-0.28)	12	0.17 (0.04-0.49)
>12-24	75	0.04 (0.01-0.13)	31	0.03 (0.00-0.21)
>24-36	58	0.05 (0.02-0.16)	23	0.09 (0.02-0.30)
CTAG1A				
≤ 6	26	**0.19 (0.08-0.40)**	9	**0.22 (0.05-0.59)**
>6-12	35	0.06 (0.01-0.21)	12	0.00 (0.00-0.26)
>12-24	75	0.11 (0.05-0.22)	31	0.16 (0.06-0.35)
>24-36	58	0.03 (0.01-0.14)	23	0.04 (0.01-0.26)

(Kaaks et al., Int J Cancer 2018)

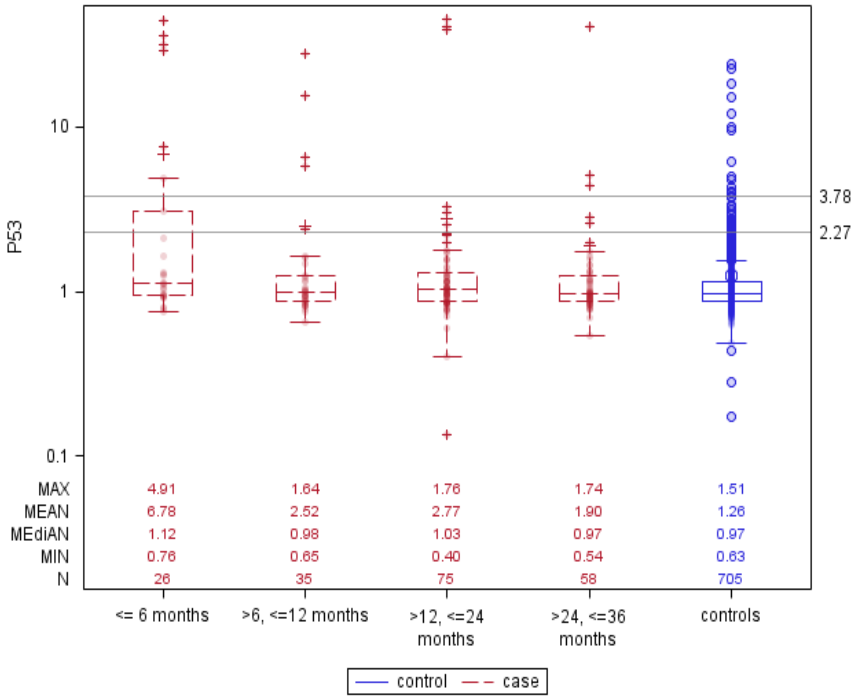
Early detection of ovarian cancer by selected Autoantibodies (ii) Sensitivity at 98% specificity – European EPIC cohort (226,673 women)

	All Ovarian Cancer (N=194)		High-Grade Serous Cancer (N=75)	
Lead time (months)	**# Cases**	**SE98 (95% CI) [b]**	**# Cases**	**SE98 (95% CI) [b]**
CTAG2				
≤ 6	26	**0.19 (0.08-0.40)**	9	**0.22 (0.05-0.59)**
>6-12	35	0.03 (0.00-0.19)	12	0.00 (0.00-0.26)
>12-24	75	0.05 (0.02-0.15)	31	0.10 (0.03-0.27)
>24-36	58	0.02 (0.00-0.12)	23	0.04 (0.01-0.26)
NUDT11				
≤ 6	26	**0.19 (0.08-0.40)**	9	**0.22 (0.05-0.59)**
>6-12	35	0.03 (0.00-0.19)	12	0.00 (0.00-0.26)
>12-24	75	0.01 (0.00-0.09)	31	0.03 (0.00-0.21)
>24-36	58	0.02 (0.00-0.12)	23	0.00 (0.00-0.15)

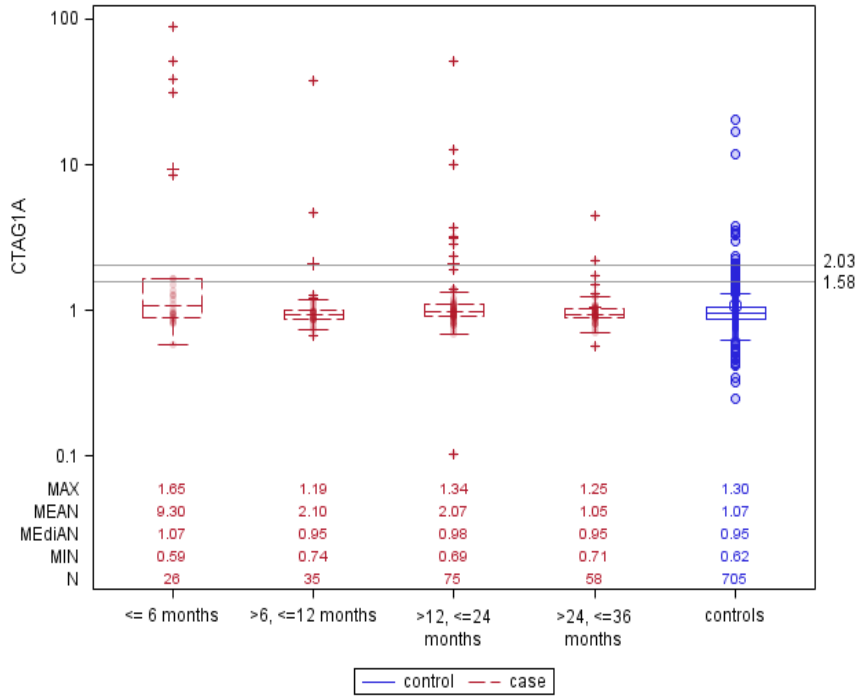
Kaaks et al., Int J Cancer (2018)

AAbs as markers for early ovarian cancer detection – EPIC
Box & whisker plots for cases (by lead-time) and controls

P53



CTAG1a / NY-ESO-1



Cancer specificity of elevated AAb levels appears to be limited

Kaaks, Fortner ... Anderson. *Int J Cancer* 2018

Sensitivity and specificity of ovarian cancer detection using CA125 only or CA125 combined with AAbs, by lead time until diagnosis

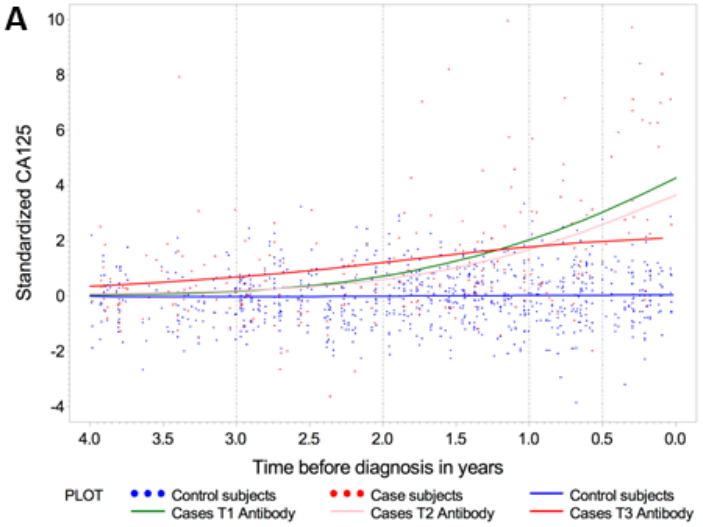
Lead Time (mnth)	Cases					Controls testing marker positive (FPR %)	Sensitivity for CA125 alone, at equivalent FPR cutpoint
	# Cases	CA125-positive; Sensitivity (%; cumulative %) [a] at 98% specificity	CA125 negative		Total testing positive CA125 or AAb; Sensitivity (%; cumulative %)		
			AAb pos.	AAb neg.			
CA125 + any of four AAbs							
≤6	26	20 (77%)	0	6	20 **(77%)**	**59 / 705 (8.4%)**	21 **(81%)**
>6-12	35	12 (34%; 52%)	**2**	21	14 (40%; **56%**)		15 (43%; **59%**)
>12-24	75	15 (20%; 35%)	**6**	55	21 (28%; 40%)		23 (31%; 43.4%)
>24-36	58	5 (9%; 27%)	**2**	51	7 (12%; 32%)		7 (12%; 34%)

Positive for CA125 or any of the four Aabs → FPR=8.4%

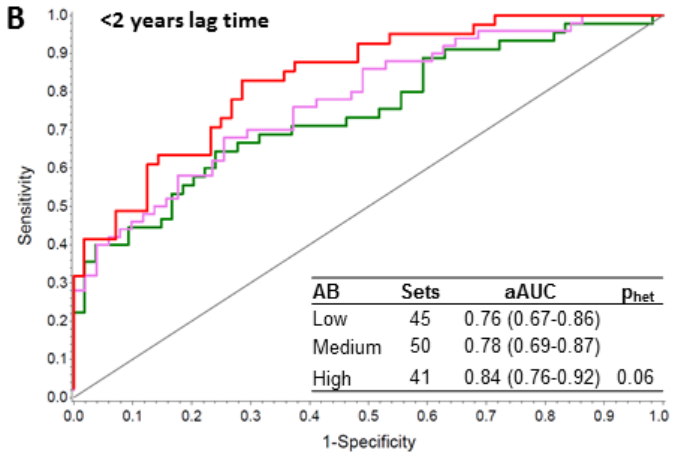
Setting CA125 FPR to 8.4% → equivalent increase in sensitivity for CA125 alone

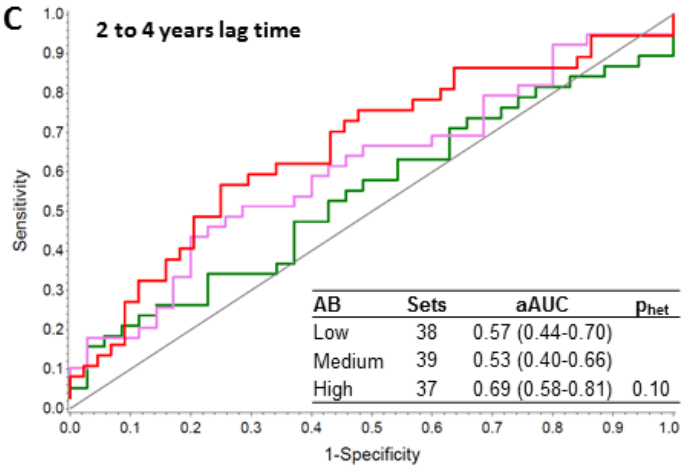
Kaaks, Fortner ... Anderson, *Int J Cancer* 2018

CA125 in the context of anti-CA125 AAbs



- **Proximate to diagnosis: Lower CA125 levels among cases with higher anti-CA125 AAbs**
- **Interaction between CA125 and its antibody**
  - **(Somewhat) better discrimination between cases and controls considering CA125 in the context of anti-CA125**

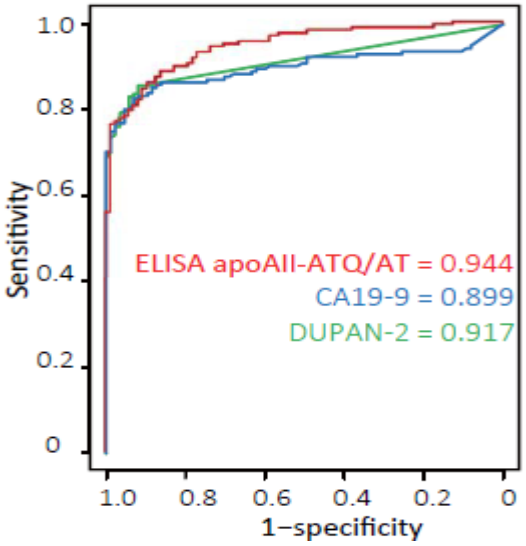


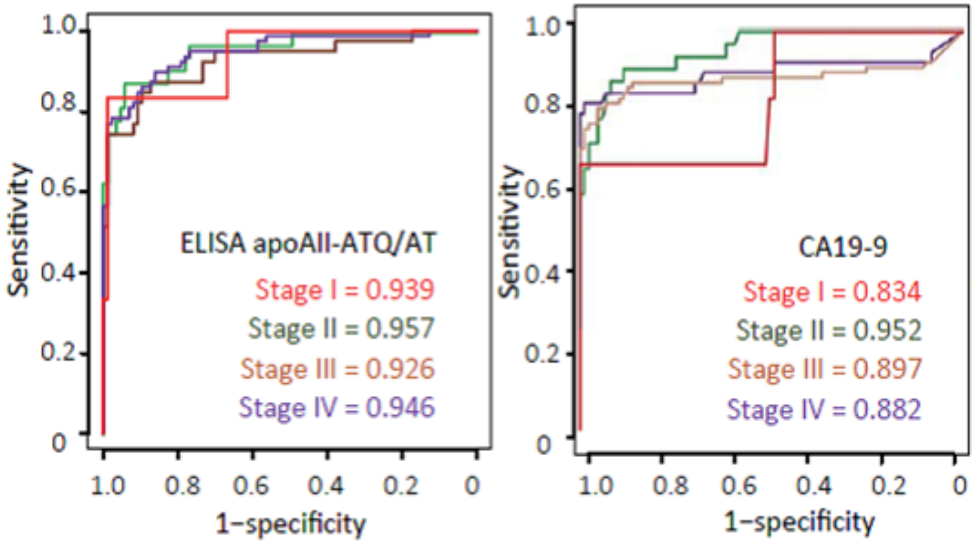


Fortner, Terry …. , Cramer, Kaaks. *Int J Cancer* 2017.

Apolipoprotein A2 (ApoA2) isoforms as pancreatic cancer marker

- Identification of a highly promising isoform – **“ ApoA2-ATQ/AT ”** → AUC total = 0.944 vs 0.899 of CA19-9
- Highly predictive also for early stage-cancer, and pancreatic diseases predisposing to cancer





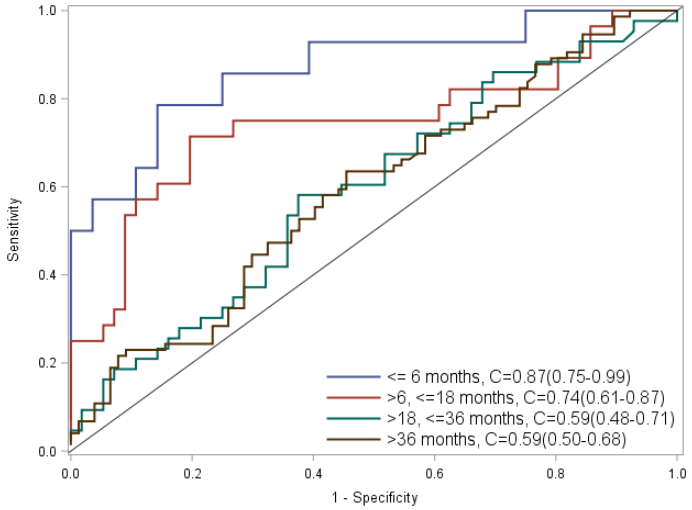
Honda et al *Cancer Res* 2005;

Honda et al. *PLoS One*, 2012;

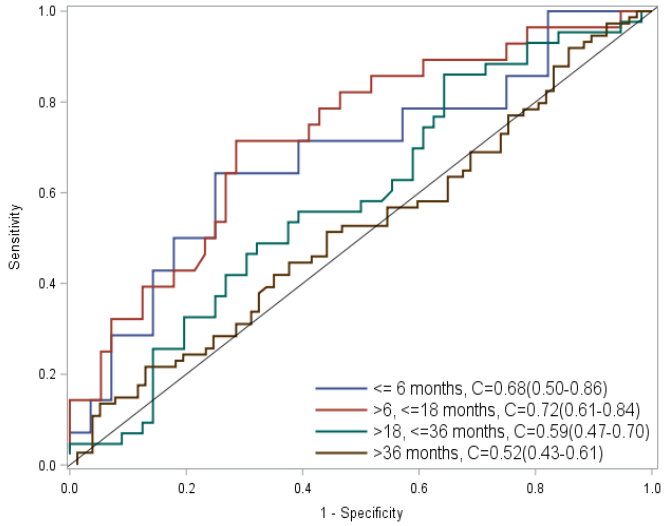
Honda et al *Sci Rep* 2015

Pancreas cancer detection by CA19-9 and ApoA2i – EPIC study

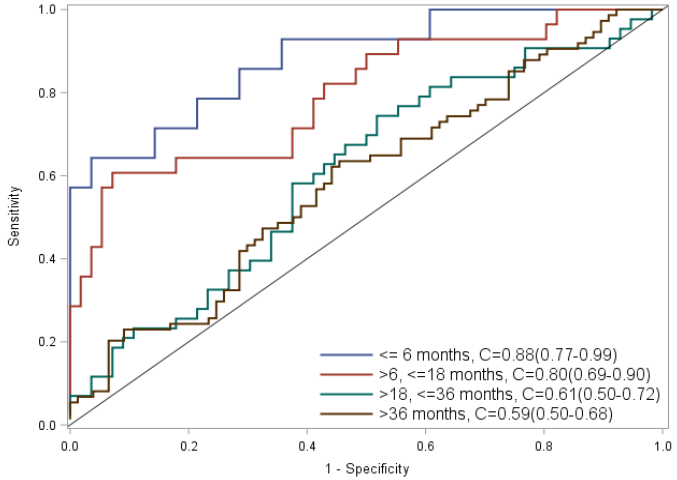
CA19-9



ApoA2_ATQ/AT



CA19-9 + ApoA2_ATQ/AT



Lag-time (months)	CA19-9	CA19-9 plus ApoA2-ATQ/AT
≤6	**0.50** (0.23-0.77)	**0.57** (0.29-0.82)
>6-18	**0.29** (0.12-0.53)	**0.36** (0.19-0.56)
≤18	**0.36** (0.19-0.58)	**0.43** (0.28-0.59)

Honda et al …Kaaks, *Int J cancer* (2019)

Ongoing omics discovery studies in EPIC – Ovarian Cancer (102 cases diagnosed <=18 months after blood collection)

- Anderson, Biodesign Institute, Tempe (Az)
  - **HD-NAPPA** scan with Karen Anderson's lab
  - 768 Aabs
- Hoheisel, DKFZ Heidelberg:
  - **Protein binding array** – 3,000 selected proteins (sustepected tumor antigens)
- **Olink** panels (proximity extension assays)

General points

- **Use prospective studies more for marker discovery, not only validation** (provided small serum/plasma volumes suffice)
- **Useful early detection markers for cancer must have high sensitivity (diagnostic likelihood ratio TPR/FPR)**
  - Diagnostic sensitivity must be for early-stage [and small] tumors (localized cancer)
  - Sensitivity of the laboratory method [detection limits]
- **Consortia needed to reach sufficiently large case numbers**
  - „OMICs“ type discovery → multiple testing: avoidance of chance findings (false-positive marker identification)
  - Multi-marker panels → development of reliable detection algorithms, avoidance of overfitting → re-sampling approaches: training-test, bootstrapping
  - Comparison of detection discrimination between sub-sets of cancer cases, e.g. histologic sub-types
- **[Need for complementary clinical biobanks of early-stage tumors, with in-depth clinical specification (histology, garde, stage) & tumor samples]**

Thank you for your attention

5 minute Q&A

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