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Ovarian Cancer Screening – insights from UK trials

Advancing Progress in the Development and Implementation of Effective, High-Quality Cancer Screening: A Workshop
National Cancer Policy Forum, USA

Professor Usha Menon
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
University College London, UK

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Disclosures

Stocks awarded by UCL in Abcodia Pvt Ltd, a UCL spin-out

Abcodia

(1) has an exclusive commercial license to access UKCTOCS Biobank samples for discovery and validation of cancer biomarkers for early detection

(2) has the license from Massachusetts General Hospital for commercial use of the ‘Risk of Ovarian Cancer Algorithm’ (ROCA) which is part of the multimodal ovarian cancer screening strategy

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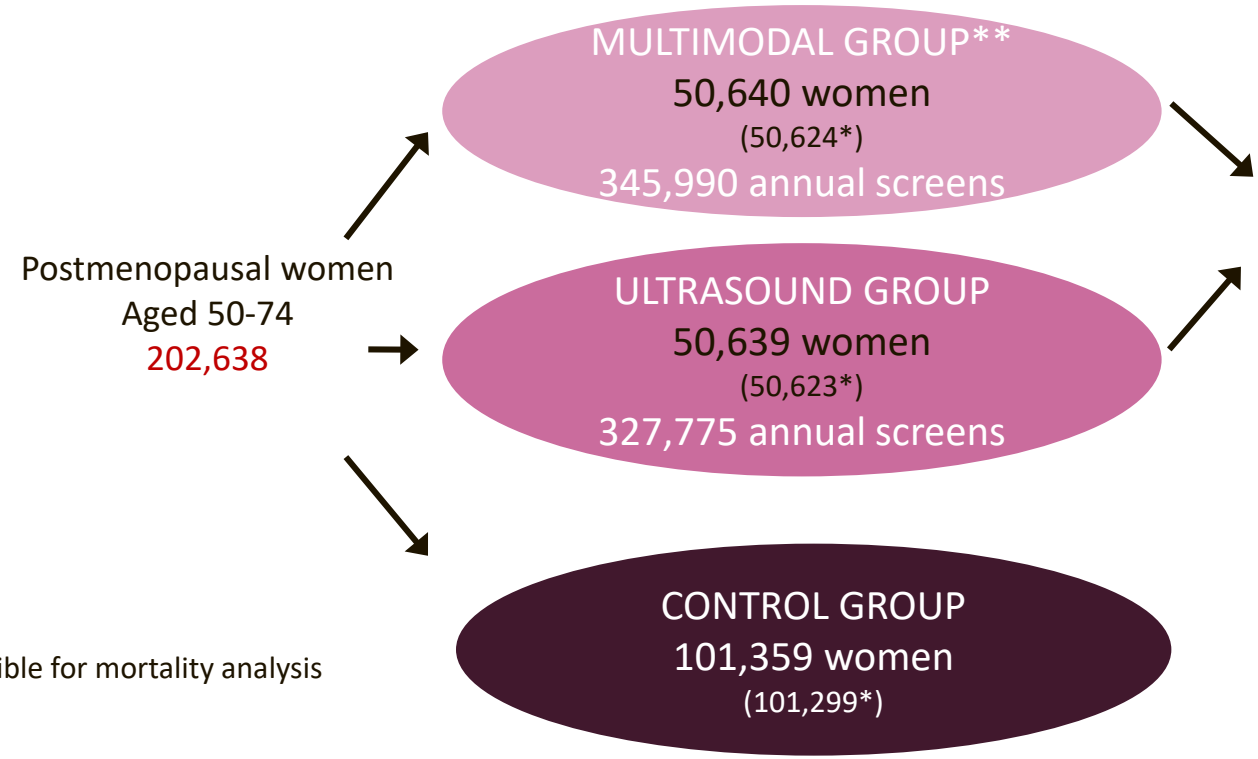
United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)



*eligible for mortality analysis

Annual screens
until 31st Dec 2011
Median 8 (range 7-11)

Primary end point
Ovarian cancer mortality
31st Dec 2014

Follow-up

Linkage to electronic health records –cancer, death and hospital episodes registers
Postal questionnaires

Complete follow-up for primary outcome
98.9% of participants
2.19 million women years

Menon et al, BMJ, 2008
Jacob Menon et al Lancet 2015

Using a longitudinal Risk of Ovarian Cancer (ROCA) CA125 algorithm with repeat testing and ultrasound as 2nd line

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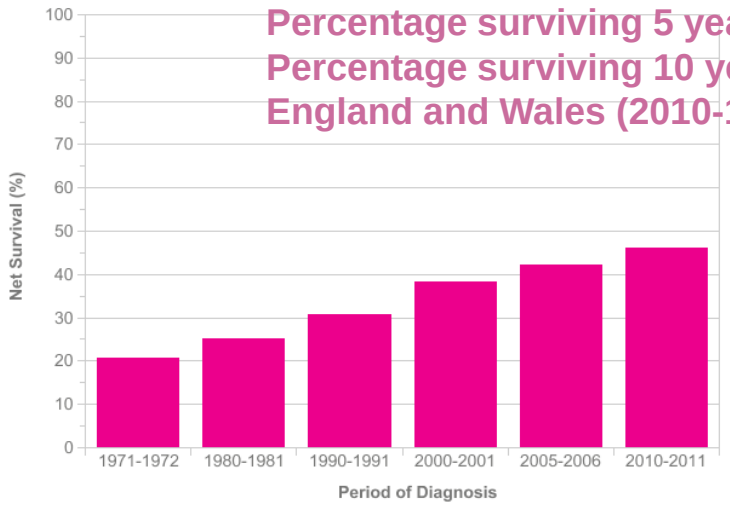
Is there a continuing need for Ovarian Cancer Screening ?

UK Office of National Statistics

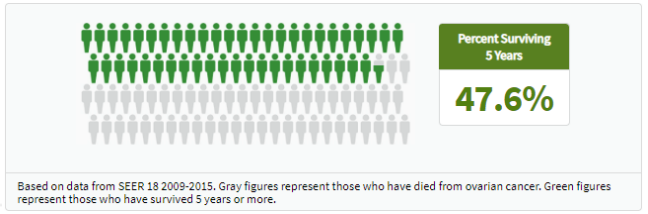


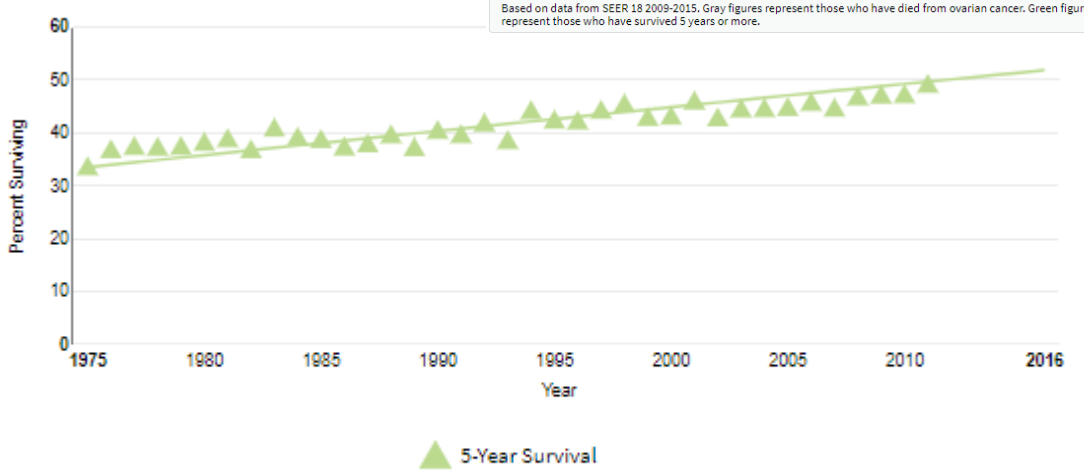
Women (Aged 15-99) England and Wales, 1971-2011

http://www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/survival/

CANCER RESEARCH UK

SEER





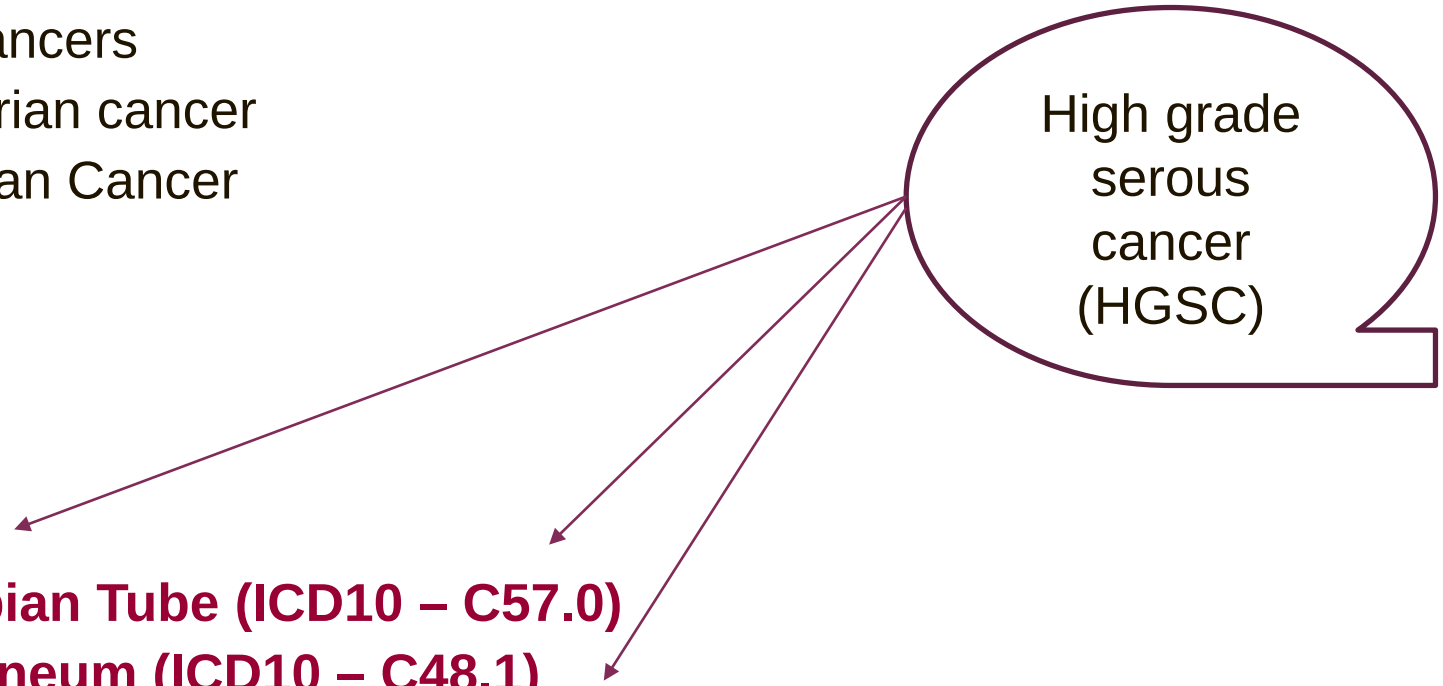
SEER 9 5-Year Relative Survival Percent from 1975-2011, All Races, Females.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Survival Model Software.

https://seer.cancer.gov/statfacts/html/ovary.html

What do we mean by ‘ovarian cancer’ ?

International classification of disease (ICD)

- Malignant neoplasm of ovary (ICD10-C56)
    - Non epithelial ovarian cancers
    - Borderline epithelial ovarian cancer
    - Invasive Epithelial Ovarian Cancer
        - Mucinous
        - Clear cell
        - Endometriod
        - Low grade serous
        - **High grade serous**
- **Malignant neoplasm of Fallopian Tube (ICD10 – C57.0)**
- **Malignant neoplasm of peritoneum (ICD10 – C48.1)**



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- **Malignant neoplasm of peritoneum (ICD10 – C48.1)**

SEER – Ovarian cancer (invasive)
Ovary (C569) **but excludes borderline cases**

Since 2007 includes Fallopian tube (C570), Broad ligament (C571), Round ligament (C572), parametrium (C573), Uterine adnexa (C574)

What do we mean by 'ovarian cancer' ?

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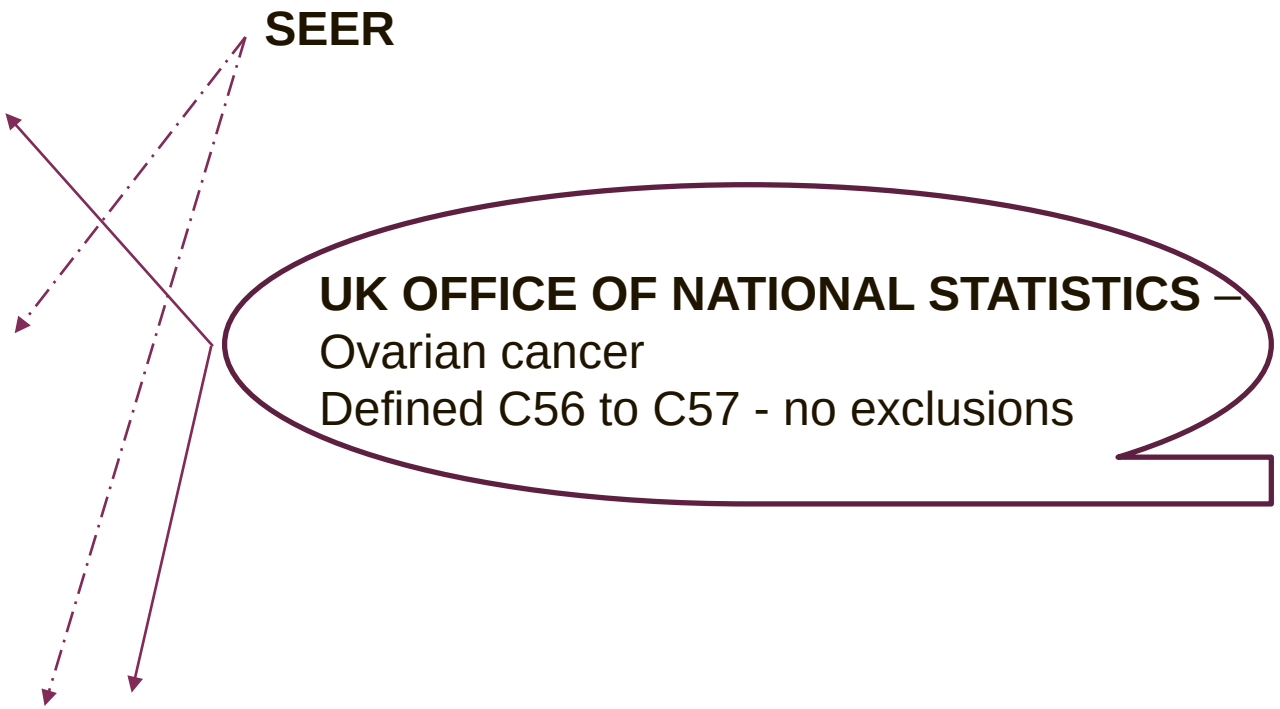

In 2014 WHO revised its classification – as a result most peritoneal cancers will be now classified as tubal or ovarian and therefore will appear in the national statistics.

However site assignment has been left to the ‘experience and professional judgement’ of the reporting pathologist.

WHO Classification of Tumors of the Female Reproductive Organs, Fourth ed., 2014 (Lyon)

Uniform approach to site assignment in high grade serous cancer recommended by the International Collaboration on Cancer Reporting (ICCR)

Singh N et al Gynaecological Oncology 2016

All cases in UKCTOCS have had site assignment reviewed using above rules

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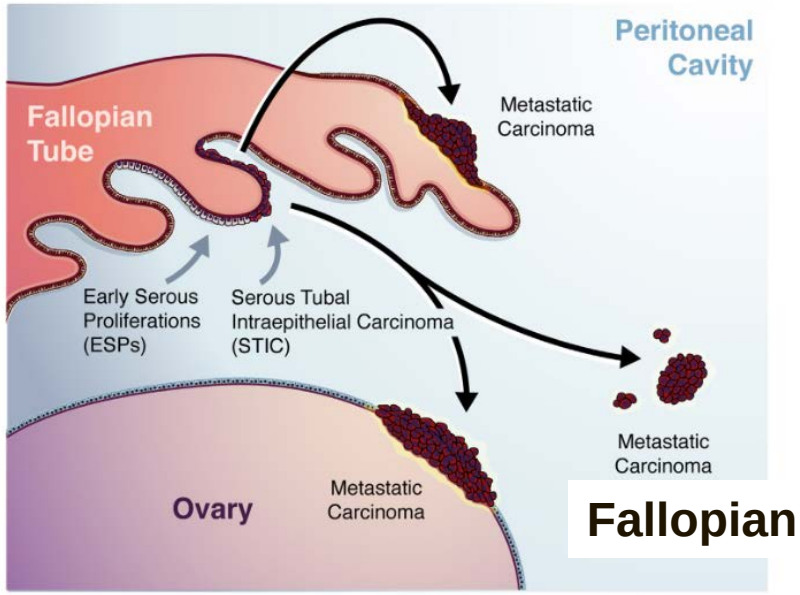
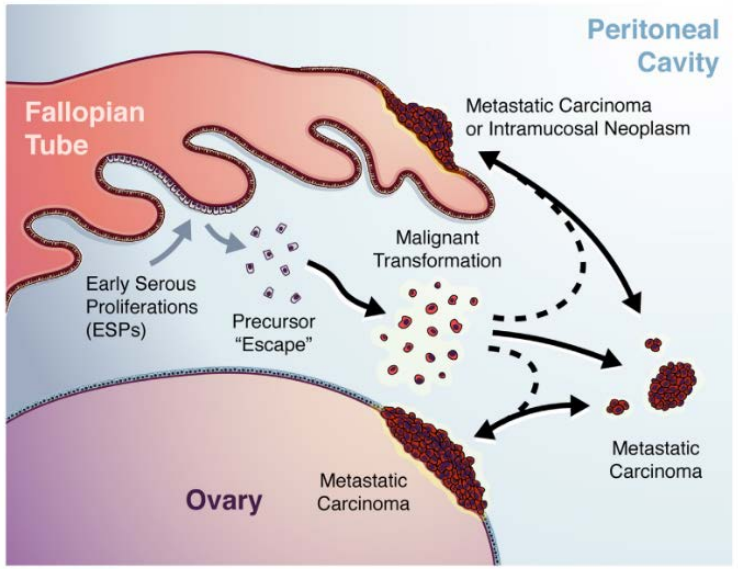
What are precursor lesions of high grade serous cancer ? Are they amenable to early detection?

Multiple complementary pathways to development of HCSC



Fallopian tubal theory

‘Precursor escape’ theory



Soong TR et al Gynaecol Oncol 2019

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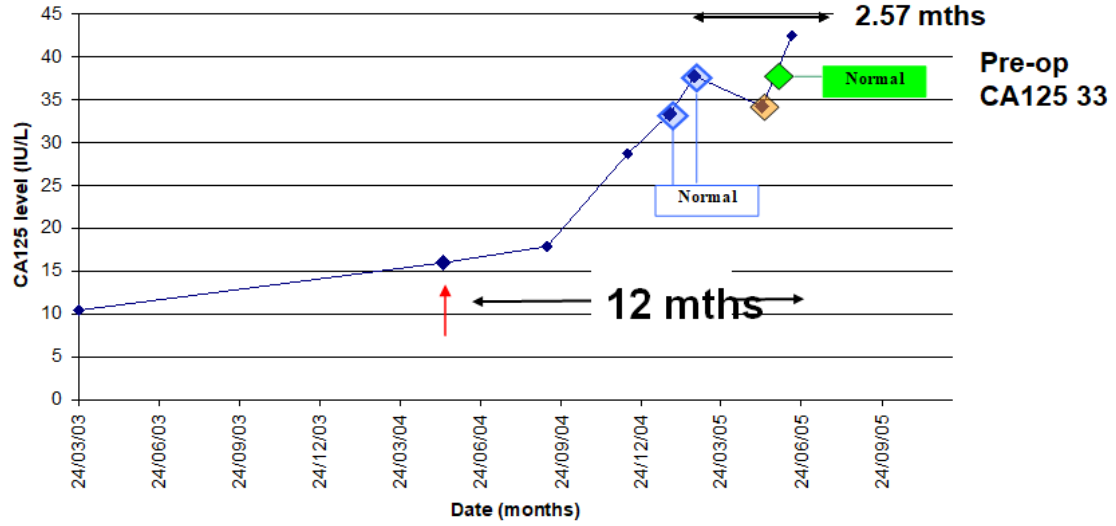
High Grade Serous Ovarian Cancer - defining the target for early detection

High grade serous ovarian cancer: **IIIB**
Pathology: Right ovary 3x1.5x1.5 cm with tumour breaching the capsule and extending into the paratubal connective tissue. Left ovary 4x3x1 cm with deposits within the stroma and surface.. 3 small <0.5 cm white nodules in deep pelvis. Previous hysterectomy.



UKCTOCS

Rising but low biomarker levels, normal imaging

Screening needs to focus on low volume surgically resectable metastatic disease rather than Stage I / II disease

UKCTOCS – unpublished data

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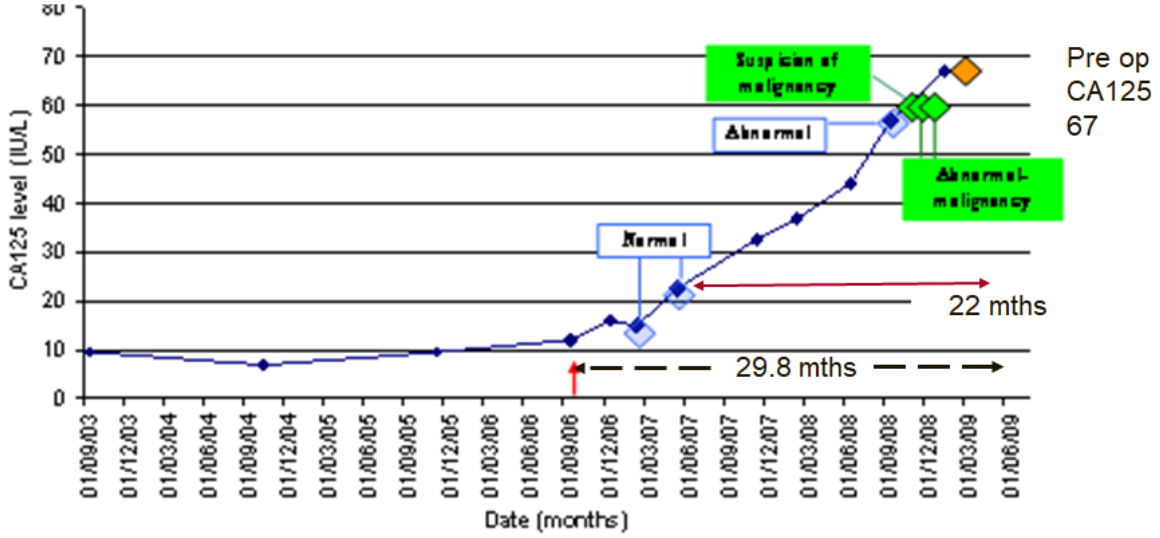
UKCTOCS – rising biomarker levels, normal imaging

Final diagnosis: **Fallopian tube adenocarcinoma; IIIB**
Histology: Left tube 35x20x20 Poorly differentiated papillary carcinoma - lumen, mucosa, wall. Right ovary normal with adjacent 10x10x20 mm friable tumour tissue. Nodules of poorly differentiated adenocarcinoma - omentum



Pre op CA125 67

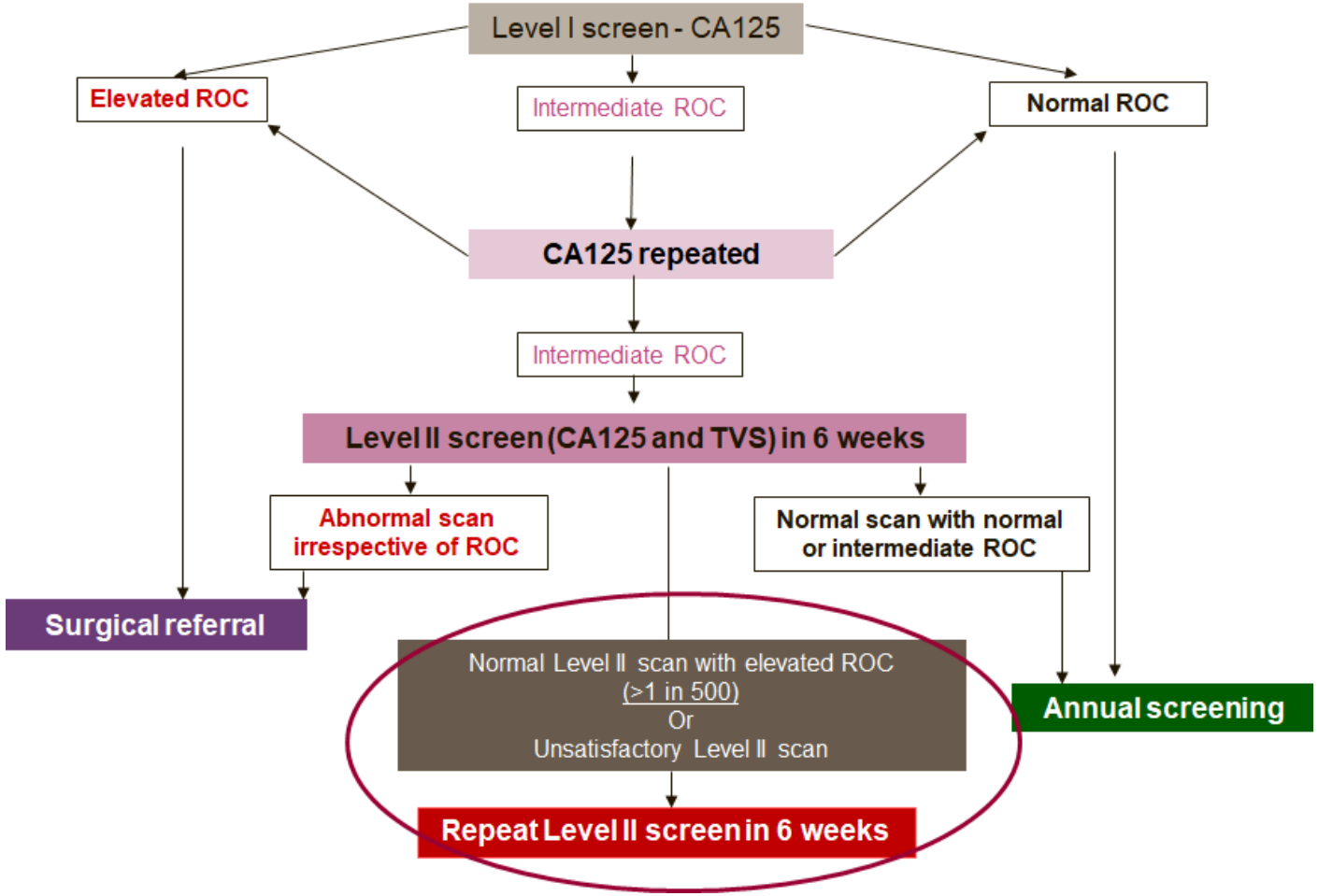
Early detection of high grade serous ovarian cancer requires

- Change in clinical norm- surgery (laparoscopic bilateral salpingo-oophorectomy and peritonea washings) based on rising biomarker levels
- Change in imaging strategies

UKCTOCS – unpublished data

Screening strategy as opposed to a screening test

Multimodal Screening (MMS)



Menon U et al Lancet Oncology 2009

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Longitudinal biomarker algorithms – personalised early detection

VOLUME 33 · NUMBER 18 · JUNE 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening

Usha Menon, Andy Ryan, Jatinderpal Kalsi, Aleksandra Gentry-Maharaj, Anne Dawnay, Mariam Habib, Sophia Apostolidou, Naveena Singh, Elizabeth Benjamin, Matthew Burnell, Susan Davies, Aarti Sharma, Richard Gunu, Keith Godfrey, Alberto Lopes, David Oram, Jonathan Herod, Karin Williamson, Mourad W. Seif, Howard Jenkins, Tim Mould, Robert Woolas, John B. Murdoch, Stephen Dobbs, Nazar N. Amso, Simon Leeson, Derek Cruickshank, Ian Scott, Lesley Fallowfield, Martin Widschwendter, Karina Reynolds, Alistair McGuire, Stuart Campbell, Mahesh Parmar, Steven J. Skates, and Ian Jacobs

Author affiliations appear at the end of this article.

Published online ahead of print at

Half the cases of invasive epithelial ovarian cancers would not have been detected if CA125 cut-off had been used

Menon et al JCO June 2015

Other longitudinal algorithms

Method of Mean Trends (MMT)
Parametric Empirical Bayes (PEB)
were similar to ROCA **and significantly better than** Single Threshold

Clinical Cancer Research

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Precision Medicine and Imaging

Comparison of Longitudinal CA125 Algorithms as a First-Line Screen for Ovarian Cancer in the General Population

Oleg Blyuss, Matthew Burnell, Andy Ryan, Aleksandra Gentry-Maharaj, Inés P. Mariño, Jatinderpal Kalsi, Ranjit Manchanda, John F. Timms, Mahesh Parmar, Steven J. Skates, Ian Jacobs, Alexey Zaikin, and Usha Menon

DOI: 10.1158/1078-0432.CCR-18-0208 Published October 2018

Blyuss O et al. Clinical Cancer Research, 2018

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Next generation screening tests

PapSEEK (multiplex PCR to detect mutations in 18 genes and assays to detect aneuploidy)

Clinical case control studies

Liquid cytology specimens	Sensitivity 31%
Plus Plasma	Sensitivity 63%
Specificity	~99%

Wang, Y. et al. Sci Transl Med Jan 2018

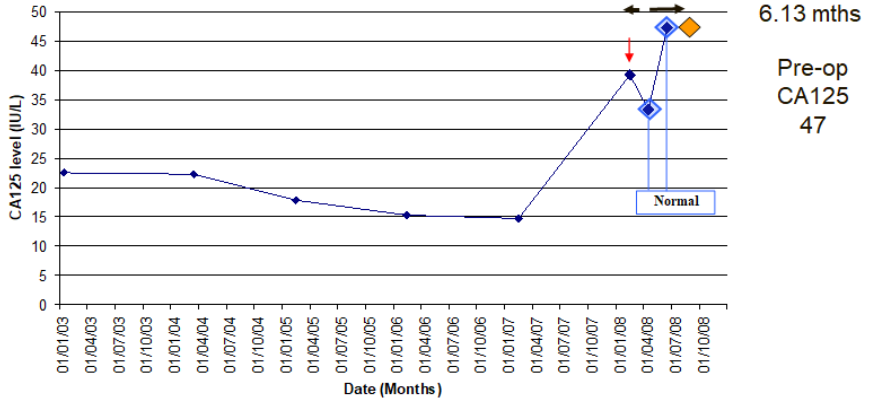
CANSEEK (multiplex PCR to detect mutations in16 genes in ctDNA and **CA-125,** CEA, CA19-9, PRL, HGF, OPN, MPO, TIMP-1 levels in plasma)

Clinical case control studies

Sensitivity	98%
Specificity	>99%

Cohen DJ et al Science 2018

High grade serous ovarian carcinoma; **IIIC**
Right ovarian 50x25x20 mm cyst which contains poorly differentiated serous carcinoma less than 1 mm in size. Normal looking left ovarian (25x15x10 mm) with tumour on the serosa invading the stroma. Both Fallopian tubes with tumour within the lumen. 1-2 mm multiple peritoneal deposits in pelvis and POD. Solitary 1 cm lesion in POD. Multiple deposits on right diaphragm and omentum and the serosa of the appendix



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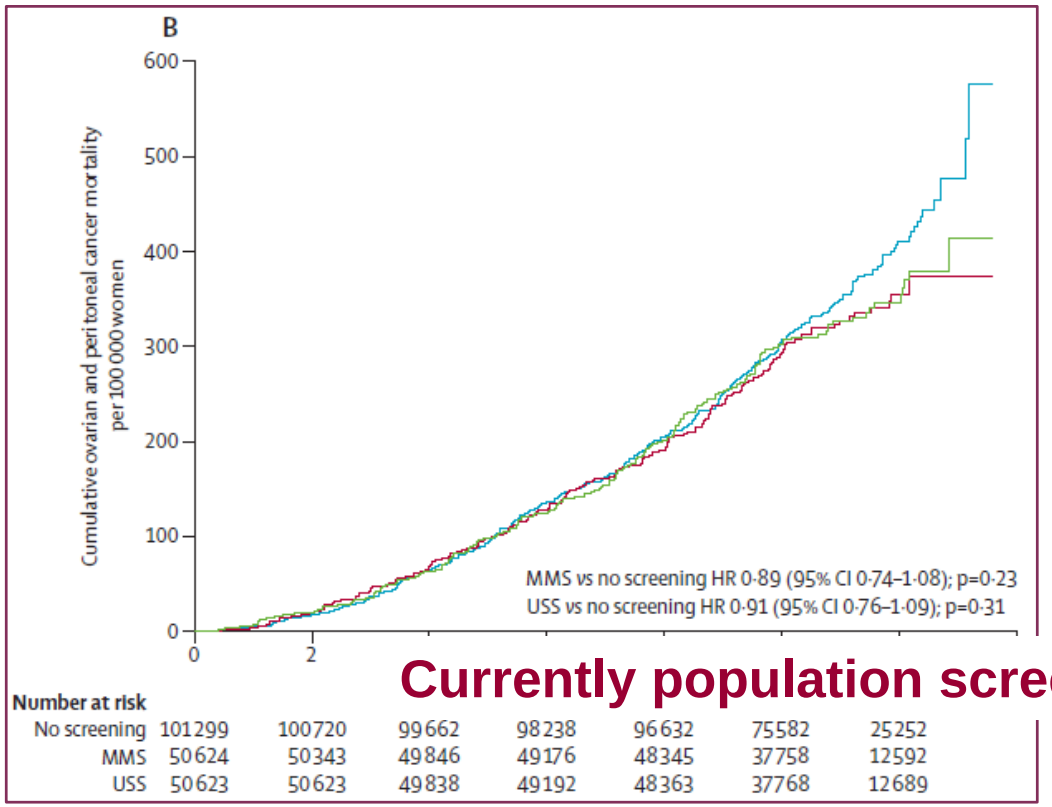
UKCTOCS Multimodal screening - Ovarian and peritoneal cancer mortality



Mortality reduction:
Cox 0-14 years: 11% (-7, 28)
p = 0.23

Royston Parmar model
0 – 7 years: 4% (-25, 27)
7 – 14 years: 18% (-5, 40)

Currently population screening is not recommended

Jacobs IJ*. Menon U* et al Lancet 2015

What is the correct statistical analysis for a screening trial?

Delay in mortality reduction the norm in cancer screening trials reporting a positive impact

European Randomised Study of Screening for Prostate Cancer	- 6 to 7 years after randomisation
Norwegian Colorectal Cancer Prevention Trial	- 5 to ~9 years from randomisation
National Lung Cancer Screening Trial	~1.5 years
UKFSST, UK Age	~3 years
Edinburgh	~6 years

In a RCT of screening, there are three time windows

- several years after screening begins in which there is no sizeable mortality reduction
- one where the reductions become evident
- after end of screening where the mortality rates in the screened arm revert to that of the unscreened group

A one number summary measure underestimates the steady state mortality reductions that would be realised with a sustained screening programme – important to use time specific measures

Hanley JA Epidemiologic Reviews May 2011

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What was found in the ovarian cancer screening trials?

Consistent down staging in women with invasive epithelial ovarian/tubal/peritoneal cancer with multimodal screening.

UKCTOCS (intention to screen analysis) Stage I/II/IIIa

USS vs no screening	23.9% vs 26% (p=0.57)
MMS vs No screening	40.1% vs 26% (**p=0.0001**)

UKFOCSS During screening phase vs during follow-up

Jacob IJ*, Menon U* et al. Lancet 2015

Stage I/II	53%(10/19) vs 5.6% (1/18) **(p=0.002)**
Stage IIIb-c/IV	37% (7/19) vs 94% (17/18) (**p=0•0004**)
Neoadjuvant chemotherapy	5% (1/19) vs 44% (8/18) (**p0.008**)

Rosenthal A et al JCO 2017

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Other outcomes with multimodal screening

Low volume disease (I/II/IIIa)

MMS	Control

Type II (high grade serous cancers)

33%	**17%**

p<0·0010

Type I (other invasive cancers)

88%	83%

p=0.65

Compliance with annual screening episode	81%
Sensitivity	86.2%
Specificity	**99.8%**
Operations per ovarian cancer detected	**4**

Harms

Complaints screen tests	0.86 / 10,000 screens
No long term psychosocial harms	
Unnecessary surgery	**14 / 10,000 screens**
Major complication rate in above women	3.1%

Menon U et al ASCO 2016

Jacob IJ*, Menon U* et al. Lancet 2015

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Cost effectiveness

UK

Compared to national willingness to pay thresholds, lifetime cost-effectiveness with MMS is promising

Kearns B et al. BMC Med. 2016 Dec

After accounting for the lead time required to establish full mortality benefits, a national OCS programme based on the MMS strategy quickly approaches the current NICE thresholds for cost-effectiveness

Menon U, Mcguire A et al. BJC. 2017

USA

Potentially cost-effective depending on final significance of mortality reduction and cost of ROCA

Moss HA et al. JAMA Oncol 2018

ROCA can improve detection of early ovarian cancer but is not practical for screening in an average-risk population

Naumann RW, Brown J. Gynecol Oncol. 2018

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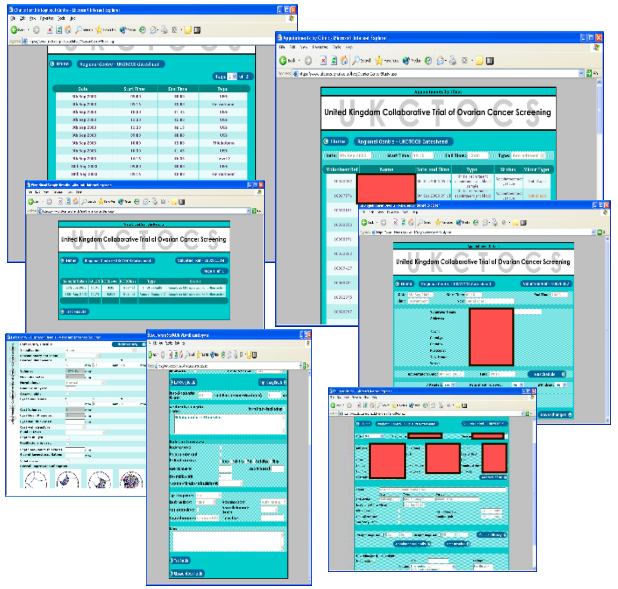
Implementing screening strategies

Annual screens 345, 990
Median number of screens 8

Direct communication with participants and automated implementation algorithms

Minimal manual data entry
Invitation using electronic data transfer from registries
Automated eligibility checks
Automated scheduling of appointments and follow-up
All blood tests tracked using bar codes
Biomarker results directly uploaded from analyser
Automated classification of results, letters to patient and doctor of results and follow-up appointments



Direct communication between coordinating centre and participants

NCI - Population-based Research to Optimize the Screening Process (PROSPR)

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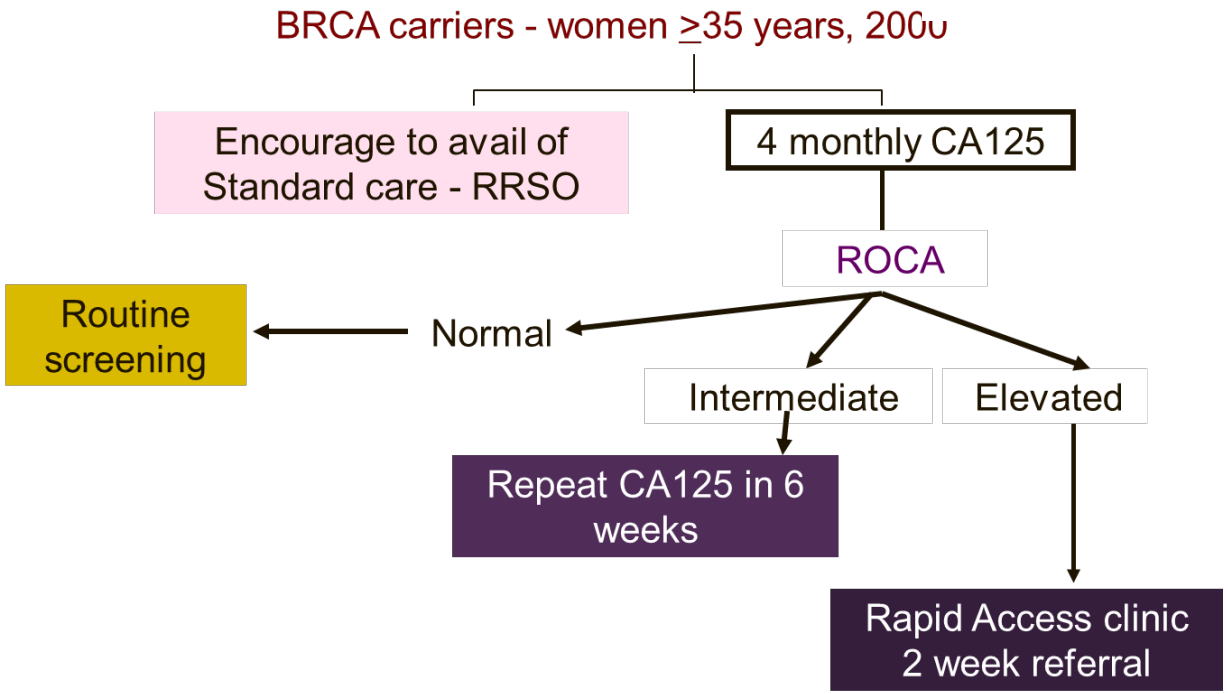
Current status of ovarian cancer screening UK

High risk



UK Cancer Vanguard Project

Avoiding late diagnosis of ovarian cancer (ALDO)

Pilot trial in the NHS

Current status of UK trials

Average risk

UKCTOCS

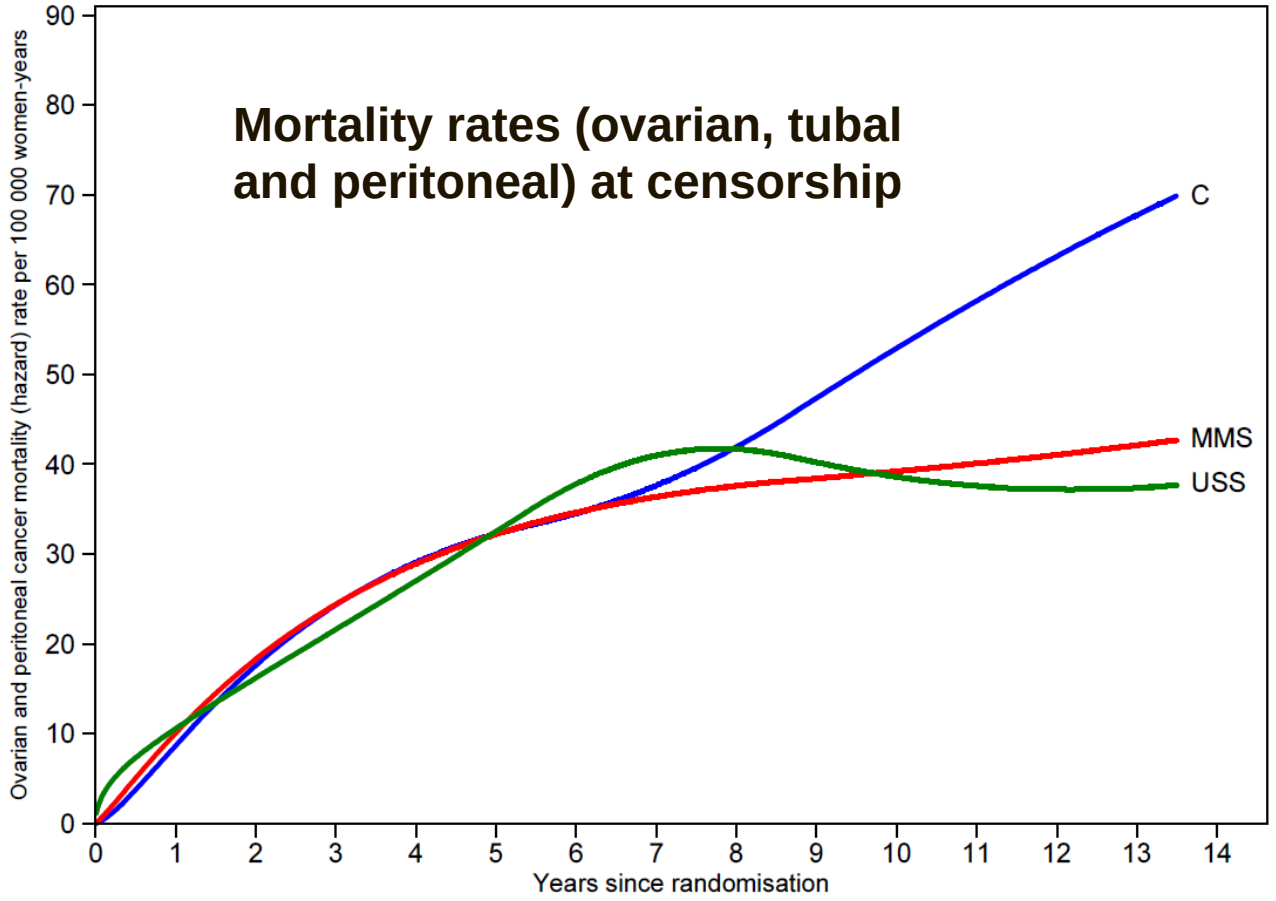
Further follow up is underway

Censorship

591 events in C arm

~June 2020

Web Figure 6: Rates of ovarian and peritoneal cancer by randomization group. (C = no screening)



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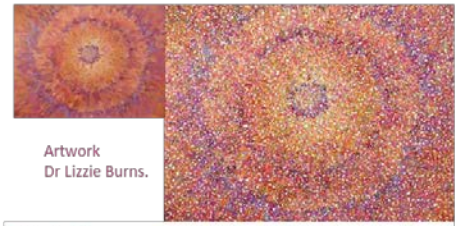
Women who took part



Artwork
Dr Lizzie Burns.

Each dot represents 8 of the 202,638 women who participated in UKCTOCS

The research teams

Funders

UCL
MRC Medical Research Council
NHS National Institute for Health Research
CANCER RESEARCH UK

Oversight committees

The NHS and Universities hosting the trial

Principle Investigators
Ian Jacobs
Usha Menon

Co-investigators
Mahesh Parmar
Steve Skates
Stuart Campbell
Lesley Fallowfield
Ali McGuire

Lead Researchers Regional Centres

Keith Godfrey / Tito Lopez
Karin Williamson
David Oram
Jonathon Herod
Robert Woolas
Tim Mould
John Murdoch
Mourad Seif
Nazar Amso
Simon Leeson
Stephen Dobbs
Ian Scott / Howard Jenkins
Derek Cruickshank

Outcomes review committee

Naveena Singh (Chair)
Elizabeth Benjamin
Martin Widschwendter
Karina Reynolds

Coordinating centre team

Andy Ryan
A Gentry-Maharaj
Tindie Kalsi
Matthew Burnell
Susan Davies
Chloe Karpinskyj
Julie Taylor
Danielle Margolin
Sophia A
Mariam Habib
Aarti Sharma
Sarah Lewis
Rachel Halett
Jeremy Ford
Anne Dawnay
Richard Gunu
Sheila Spicer

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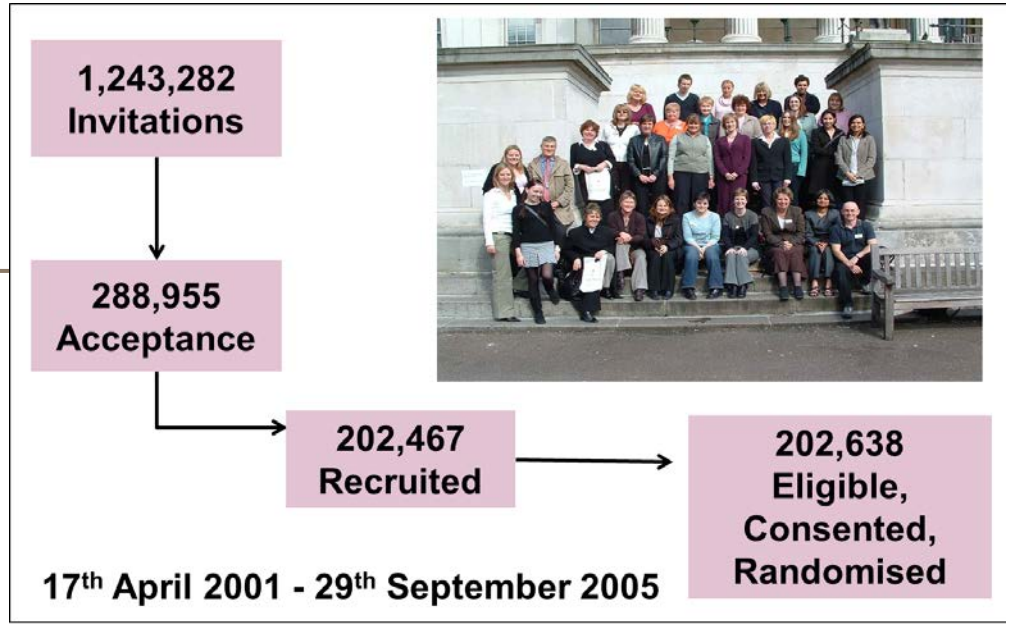
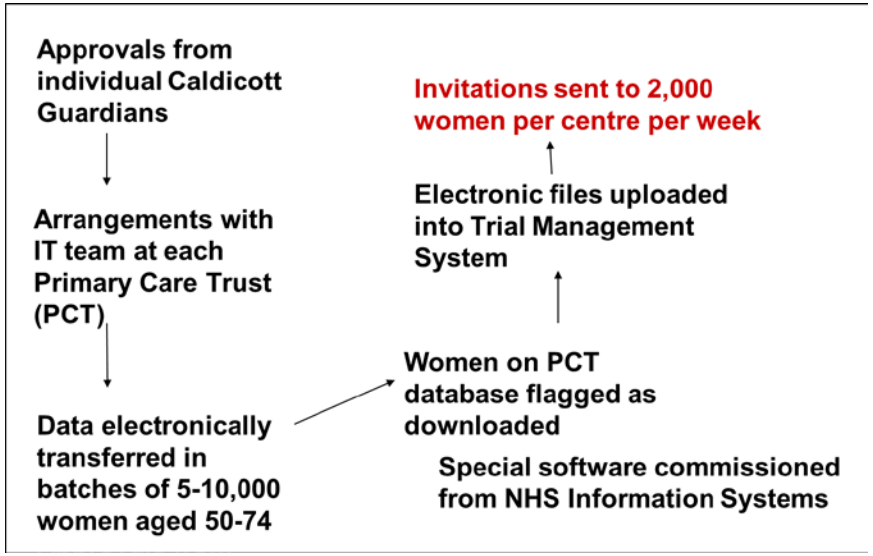
Increasing efficiency of recruitment and completeness of follow-up - electronic health record linkage



Identifying eligible participants to invite to screening trials using and registry data

Follow up to ascertain outcomes
In UKCTOCS data linkage using National Health Service number resulted in complete follow-up for primary outcome in 98.9% of participants



Menon U et al BMJ 2019

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Incorporating healthy volunteer effect into sample size calculations in screening trials

Mortality in women recruited to UKCTOCS

Average time per woman on trial at censoring (1 June 2009) = 5.55 years

Standardized Mortality Ratios (SMR) for all cause mortality = 37%

MORTALITY CAUSE	Expected mortality	Observed Mortality	SMR
Cancers Overall	4419	2469	55.90%
Lung Cancer	1020	499	48.90%
Breast Cancer	813	349	42.90%
Colorectal Cancer	415	218	52.60%
Pancreatic Cancer	244	195	79.80%
Oesophagus Cancer	111	85	76.40%
Stomach Cancer	85	64	75.10%
N-H Lymphoma	194	88	45.40%
Leukaemia	107	49	45.90%
Uterine Cancer	120	63	52.30%
Bladder Cancer	68	32	46.70%
Mental Behaviours Deaths	127	9	7.10%
Nervous System Deaths	344	92	26.80%
Circulatory Deaths	3208	999	31.10%
Respiratory Deaths	1179	261	22.10%
Digestive Deaths	688	187	27.20%

Had to extend screening and follow-up

Burnell M et al. Trials 2011

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Implementing screening strategies

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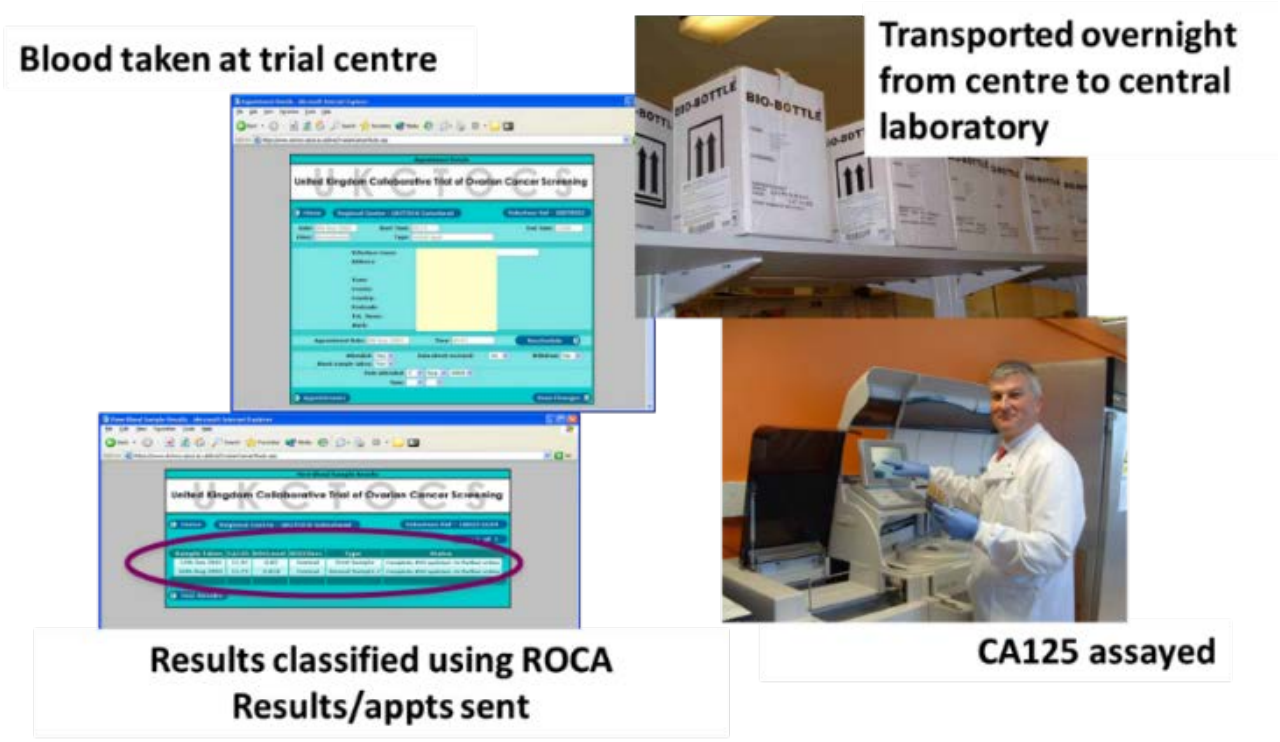
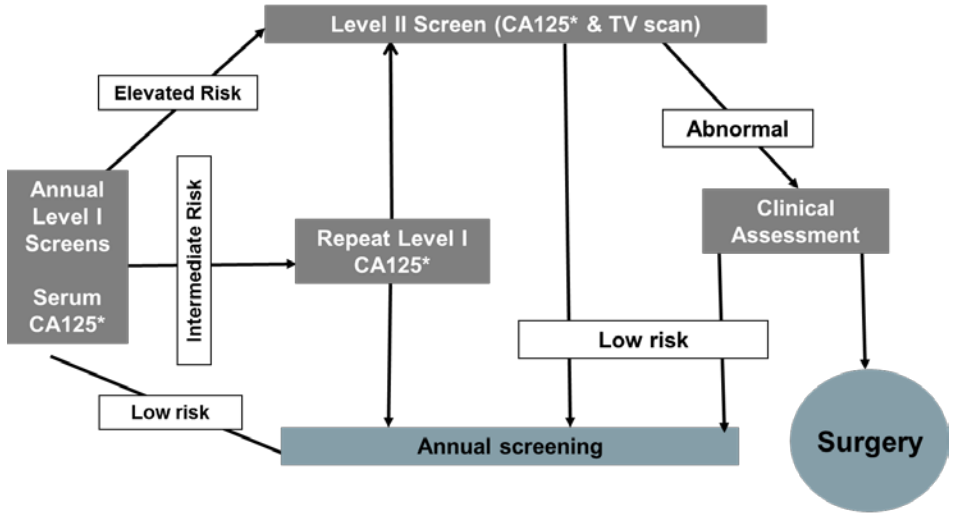
Median number of screens 8

Multimodal Screening (MMS)





* Risk of Ovarian Cancer Algorithm