Gynaecological Cancer Screening Update

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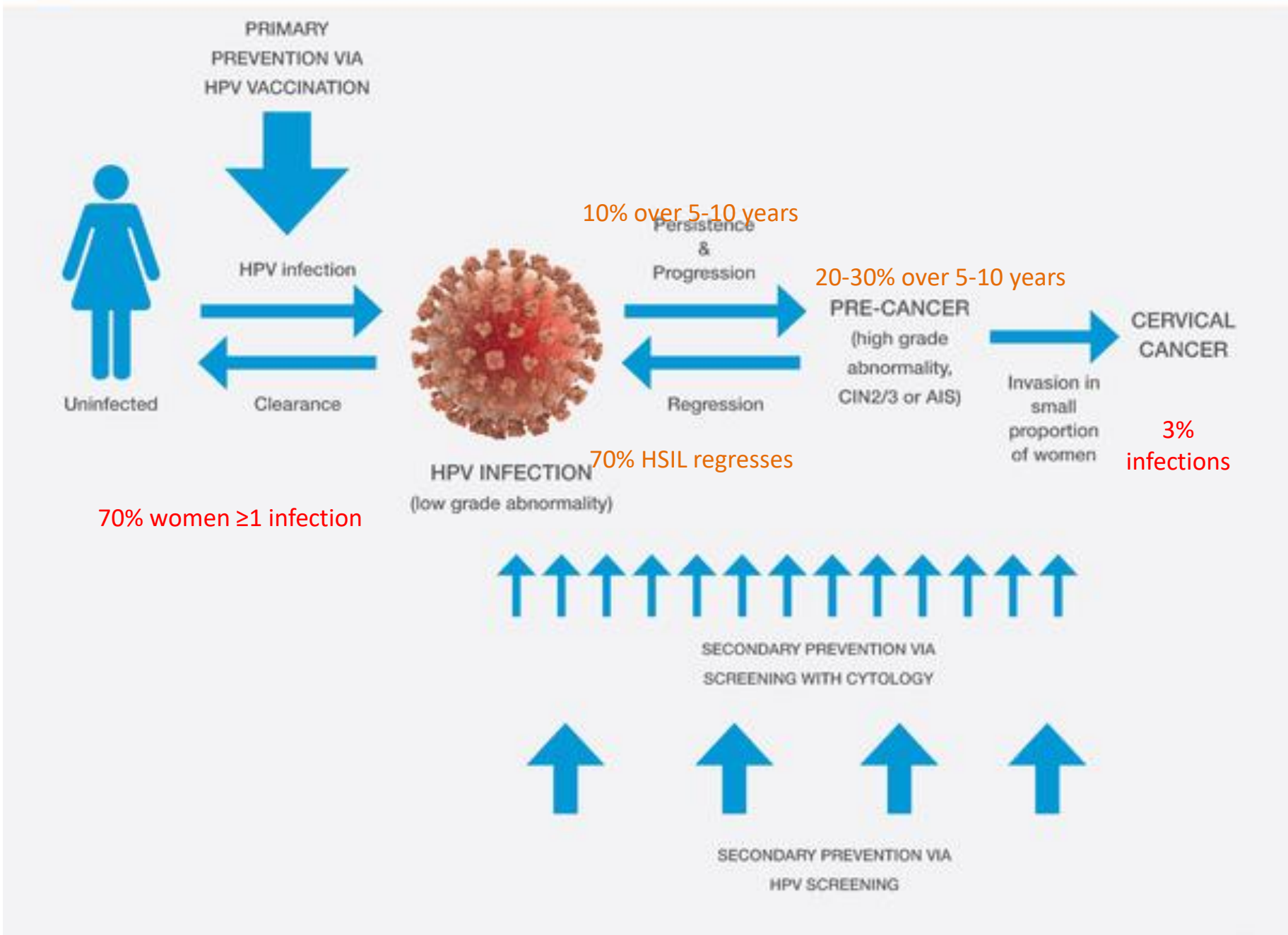
RHH

Overview

- Cervical Screening
  - NCSP renewal
    - Key changes
    - Rationale
  - Vaccination

- Ovarian Cancer Screening
  - UKC-TOCs
  - Ca125s

Figure 2.1. HPV to cervical cancer



Acknowledgment: Adapted from Schiffman M, 2005.[93]

HPV Vaccination

- HPV 16 and 18
  - 70% all cervical cancer
  - 90% all anal cancer
  - Majority of vulval, vaginal and penile cancers
  - Majority of HPV related oropharyngeal cancers
- HPV 31, 33, 45, 52, and 58
  - Additional 20% of cervical cancer
- HPV 6 and 11
  - 90% of all genital warts
- HPV vaccine
  - Guardasil
    - 16, 18, 6, 11
    - 2007 girls 12-13 (70% uptake)
    - 2013 boys 12-13
    - Potential to prevent 70-80% of cervical cancers
  - Nonovalent
    - 2018
    - Expected to prevent 90% of cervical cancers

- Women aged 18-24 pre and post vaccine rollout
  - Prevalence of vaccine type HPV on smears reduced from 29% to 7%
    - Prevalence of HPV is reduced by 78%
  - Rapid decline in genital warts
    - >90% reduction in under 21s who were vaccinated (2004-2011)
    - No new genital wart diagnoses in vaccinated women <21 in 2011
- Adult vaccination
  - Catch up <24yo
  - MSM
  - Selected women ≥25yo
    - >20% efficacy after 25yrs
    - 97% efficacy at 10-14years

Screening

Starting age 25

5 yearly speculum, HPV and “reflex” LBC

- If HPV negative cytology is not performed
- If HPV positive Reflex LBC is processed

HPV 16/18 positive

- Straight to colposcopy regardless of LBC

Other HPV

- LBC negative or LSIL
  - Repeat in 12/12
    - Positive >LSIL – colposcopy
    - Positive ≤ LSIL - repeat again 12/12
      - If 3x HPV other and ≤LSIL refer to colposcopy
      - Ie if persistent HPV ≥2 years
    - Negative – return to 5 yearly screening
- LBC >LSIL
  - Straight to colposcopy

Exit testing

- Negative test age 70-74 discharge from screening programme

Rationale for triage based on HPV

Cumulative 10 year incidence of ≥ CIN3

- 17.2% for women with a positive oncogenic HPV test result (type 16)
- 13.6% for women with a positive oncogenic HPV test result (type 18)
- 3% for women with a positive oncogenic HPV test result (not 16/18)
- 0.8% for women in whom oncogenic HPV is not detected.

Cytology

- LSIL (5% of PAP smear reports)
  - 20% HGSIL
  - <1% SCC
  - 90% of LG will resolve/clear
- pHSIL
  - 40-50% HGSIL
  - 1-3% SCC
- HSIL
  - 80% HGSIL
  - 1-3% SCC
  - 20-30% will progress to SCC

HPV testing is superior

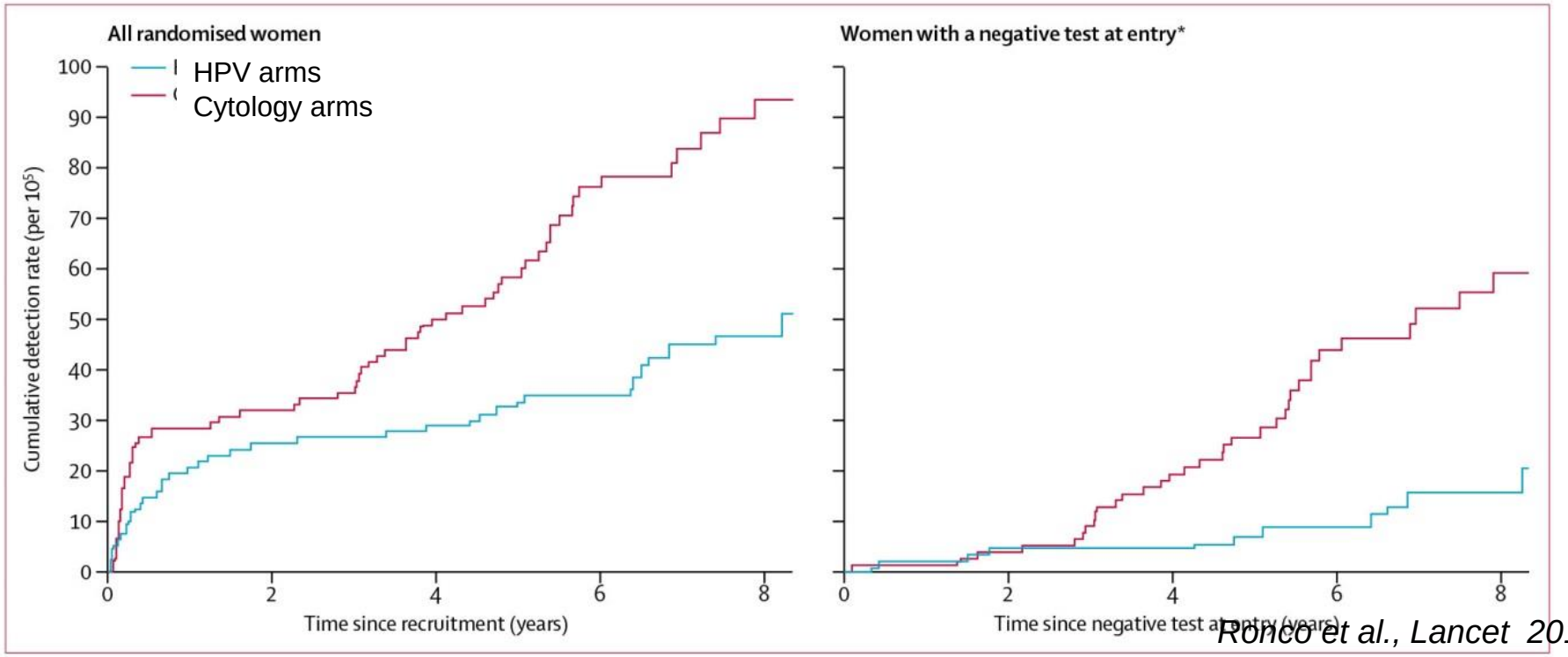
Compared to cytology starting at 18-20yo	Reduction in Cx Ca incidence and mortality >15%
Combined with colposcopy guidelines	31-36% reduction in unvaccinated cohort
	24-29% reduction in vaccinated

5 year interval is at least as effective when using HPV genotyping versus PAP cytology

Cumulative detection of invasive carcinoma

Pooled data from POBASCAM, NTCC,ARTISTIC and SWEDESCREEN (>160.000 women)

HPV as a primary screen is more effective at preventing invasive cervical cancer



Ronco et al., Lancet 2013

Figure 2: **Cumulative detection of invasive cervical carcinoma**

*Observations are censored 2·5 years after CIN2 or CIN3 detection, if any.

A negative HrHPV test provides improved protection against cervical cancer as compared to negative cytology

Starting at 25yo

Incidence of Cx Ca before 30 is very low

Cervical screening <25 has never been shown to impact rates of cancer <30

Potential harm in over treating young fertile women

HPV vaccination further reduces risk in young women

- Evidence for herd immunity for unvaccinated

Exception

- Coitarche <14yo
- Childhood sexual abuse
  - Could consider a single HPV test between 20-24 years

Self Collection

- HPV PCR testing only
- Eligibility
  - >30yrs
  - At least 2 years overdue for cervical screening
  - Or never been screened
- Offered iff speculum is declined
- Advise
  - Clinician-collected sample is more effective
  - LBC can be performed at the same time
  - This can avoid re-collections for LBC in self collection
- Negative
  - 5 yearly repeat
  - Encourage speculum
- Positive 16/18
  - Refer to colposcopy
- Positive other
  - Advise needs speculum and LBC
    - LSIL or less – repeat 12/12
    - >LSIL - colposcopy

Test of Cure

Co-test (HPV and LBC)

- 12 months post treatment
- Colposocopy is no longer necessary
- LBC or HPV <12/12 is not indicated
- Can be performed by GP
- Annually until two-consecutive negative tests

Follow usual guidelines for any abnormalities

Screening after hysterectomy

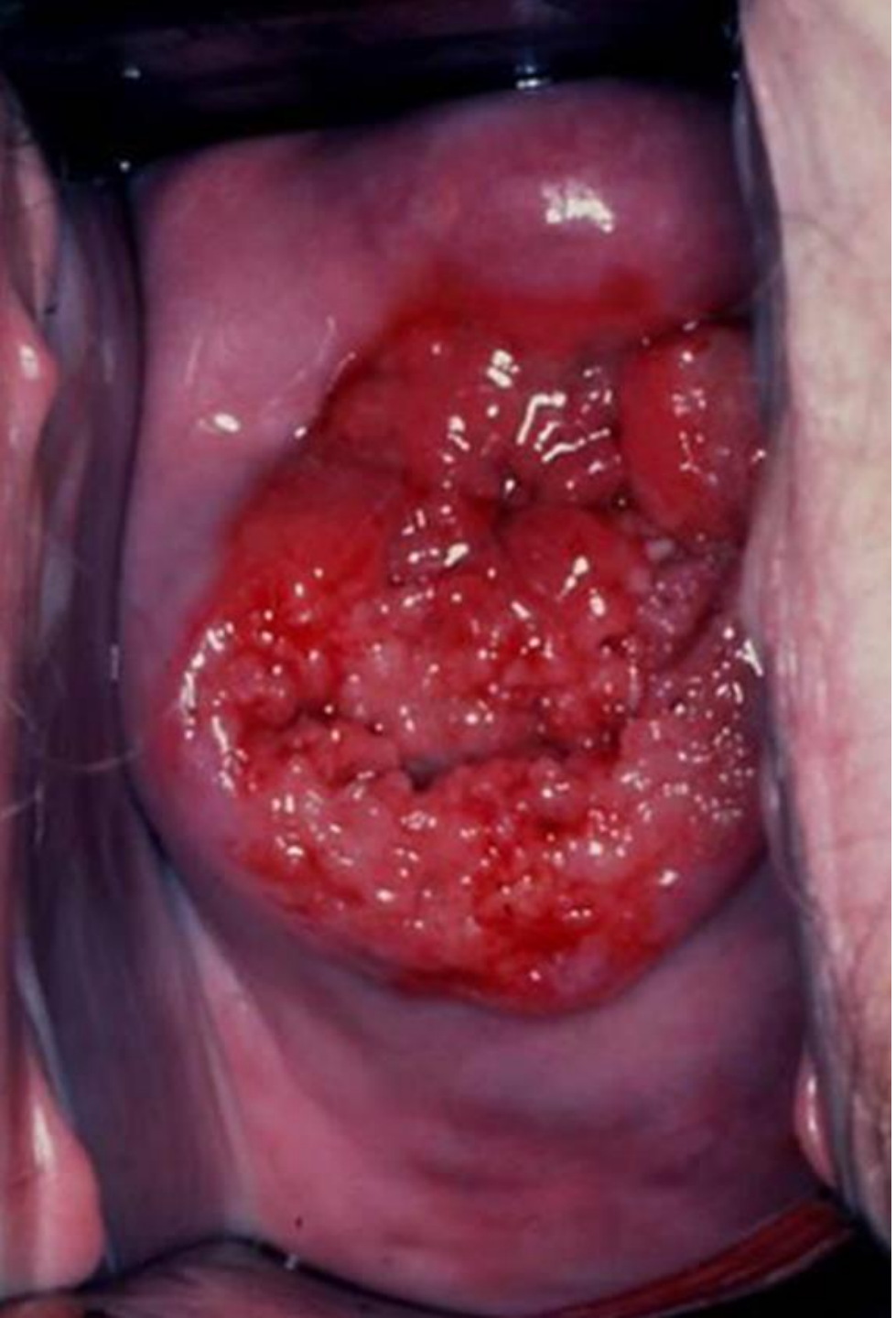
Normal smear history, benign pathology	No further screening
No smear history and benign pathology	Yearly HPV test from vault until two consecutive negative
Previously treated dysplasia but no pathology on hysterectomy specimen	Test of cure completed – no further screening required Otherwise annual co-test on vaginal vault until two consecutive negative results
Unexpected cervical dysplasia on hysterectomy	Yearly co-test until two consecutive negative results
Hysterectomy as definitive treatment for HG dysplasia	Yearly co-test until two consecutive negative results
Hysterectomy for AIS	Yearly co-test forever
Sub-total hysterectomy	Normal screening guidelines

Immunodeficiency

Screening every 3 years with HPV and reflex LBC

Refer to colp for any positive HPV

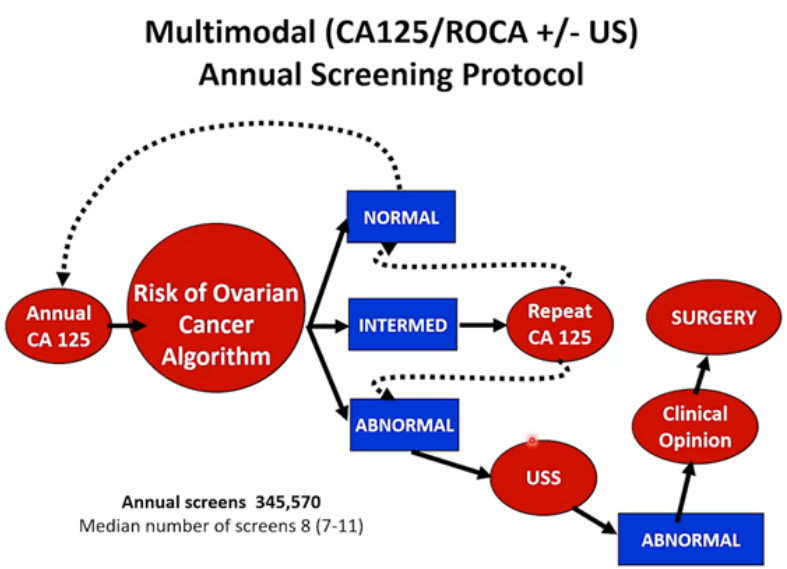
Colposcopy of the whole lower genital tract

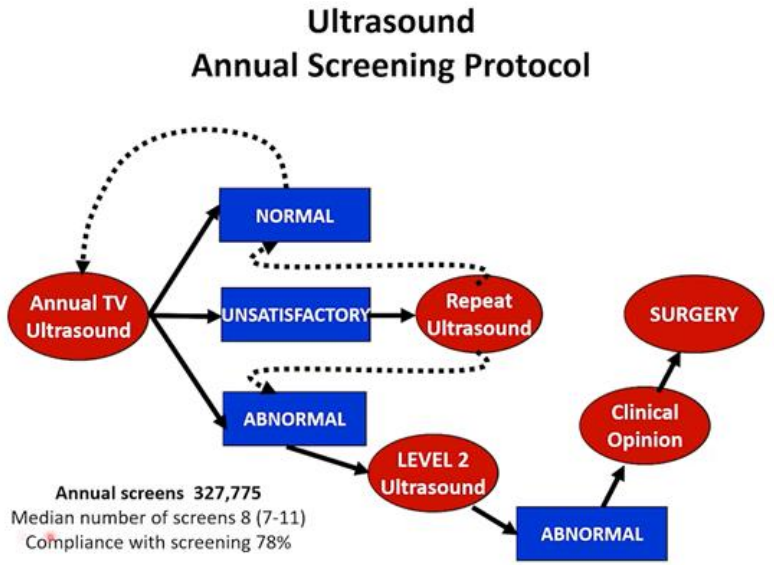


Abnormal Vaginal Bleeding

- Symptomatic women should have a co-test
  - Some cancers are HPV negative or “negative”
- Do not delay due to the presence of blood
  - LBC performs better than smears
  - HPV testing can proceed
- If persistent symptoms refer to colposcopy regardless of screening

UKC-TOCS

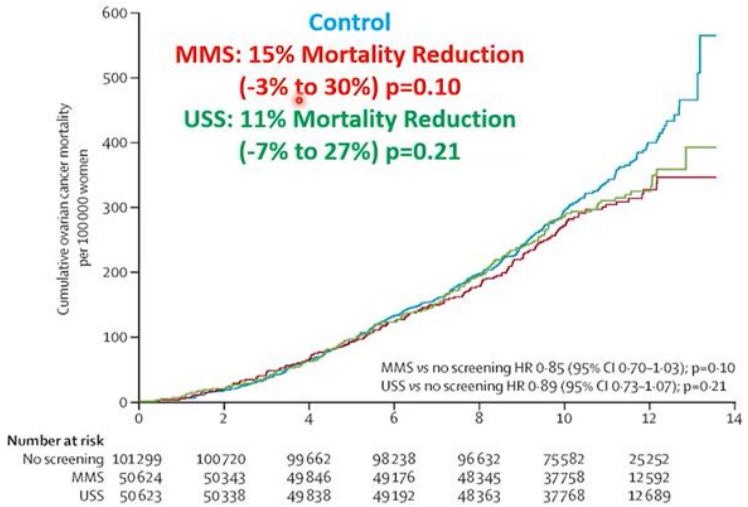




- Largest RCT to date – UKC-TOCS
  - UK Collaborative trial of ovarian cancer screening
  - Jacobs et al. Lancet 2016
    - 10 year outcomes
  - 20 year follow up closed end June 2020
    - 95% complete followup
  - Screening in post-menopausal women
  - 200,000 women – age 50-74
    - 25% yearly US
    - 25% Ca125 followed by US if raised
    - 50% no screening

UKC-TOCS Results – Lancet May 2021

UKCTOCS interim mortality analysis 2015 Lancet



Shift in Stage Distribution

	FIGO 2014 stage					Total
	I	II	III	IV	Unable to stage	
Ovarian and tubal cancers (WHO 2014 classification)*						
No screening						
Cases	212 (20·9%)	73 (7·2%)	510 (50·2%)	208 (20·5%)	13 (1·3%)	1016
Deaths	20 (9·4%)	24 (32·9%)	391 (76·7%)	174 (83·7%)	10 (76·9%)	609 (59·9%)
MMS						
Cases	155 (29·7%)	42 (8·0%)	242 (46·4%)	78 (14·9%)	5 (1·0%)	522
Deaths	23 (14·8%)	16 (38·1%)	190 (78·5%)	62 (79·5%)	4 (80·0%)	291 (55·7%)
USS						
Cases	121 (23·4%)	36 (7·0%)	253 (48·9%)	105 (20·3%)	2 (0·4%)	517
Deaths	8 (6·6%)	6 (16·7%)	188 (74·3%)	88 (83·8%)	2 (100·0%)	290 (56·1%)
Between group differences in cases compared with no screening at 9·5 years after end of screening†						
MMS	47·2% (19·7 to 81·1)	15·9% (−20·7 to 69·4)	−4·4% (−18·0 to 11·4)	−24·5% (−41·8 to −2·0)	..	..
USS	17·0% (−6·4 to 46·2)	1·1% (−32·2 to 50·6)	1·7% (−12·6 to 18·2)	3·4% (−18·2 to 30·8)	..	..

47.2% increase in Stage I in MMS

24.5% decrease in Stage IV in MMS

No Mortality difference

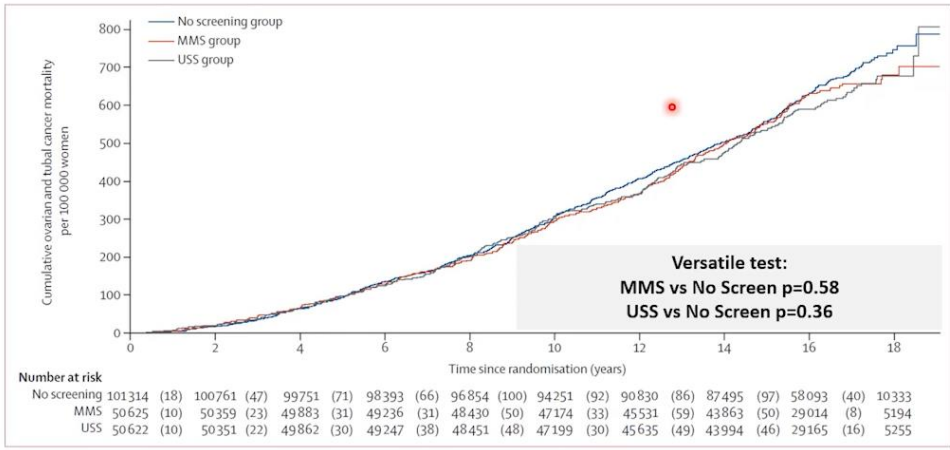


Figure 3: Kaplan-Meier cumulative mortality for ovarian and tubal cancer per 100 000 women
MMS=multimodal screening. USS=ultrasound screening. *Royston-Parmar model based estimates of the effect of screening (appendix p 10).

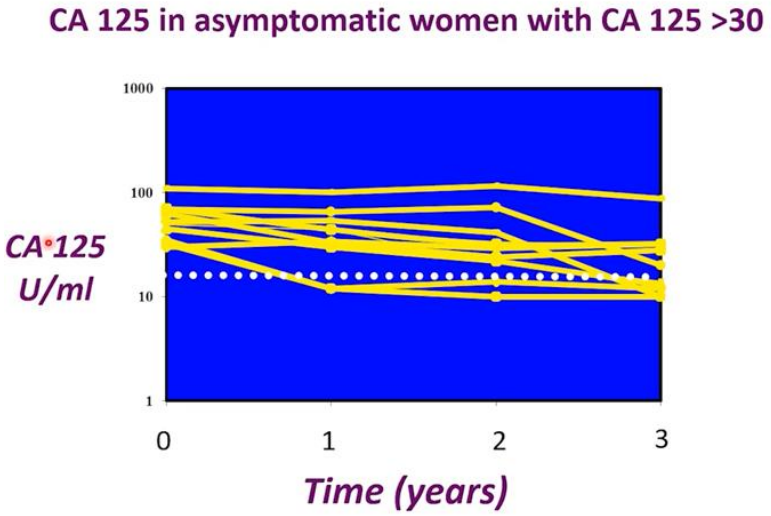
At 18 years after randomisation Royston-Parmar estimates of survival difference per 100,000 women: MMS 36.7 (CI -65 to +138) / USS 52.9 (-48 to +153)

Harms of Screening

- 10:1 Benign:Malignant surgeries in UKC-TOCs
- 20:1 in other studies
  - 15% surgical complication rate
- Interesting findings
  - 5% rates of abnormal scans
  - 1.4% abnormal Ca125
  - PPV for scan, Ca125 or both
    - 1, 4, 25%

UKC-TOCS Other Findings

- Other findings
  - Ca125 if raised in women without ovarian cancer tends to stay the same level or reduce
  - Ca125 in women with an eventual diagnosis rises exponentially
- Early diagnosis does not change mortality
  - This was shown in asymptomatic women
  - Therefore what is the benefit to education campaigns surrounding early symptoms?
- We are a long way off ovarian cancer screening
  - Even if we found a pre-clinical marker we would need another 20year RCT to show a benefit



Thank you – Questions?