Diagnosi precoce: utopia o realtà?

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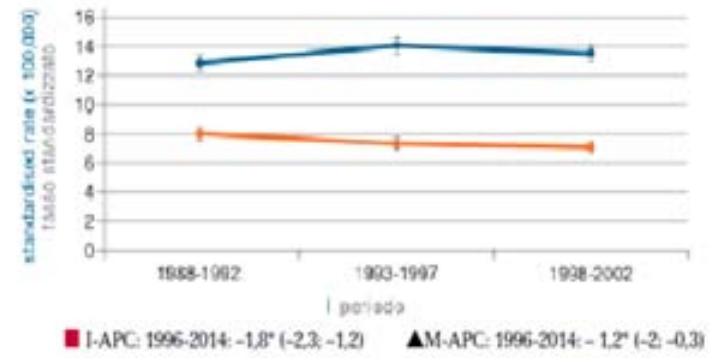
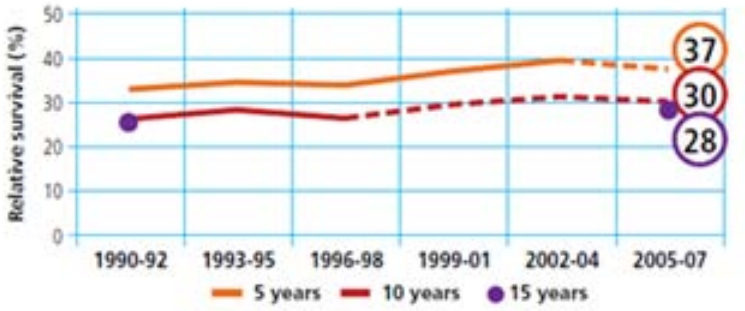
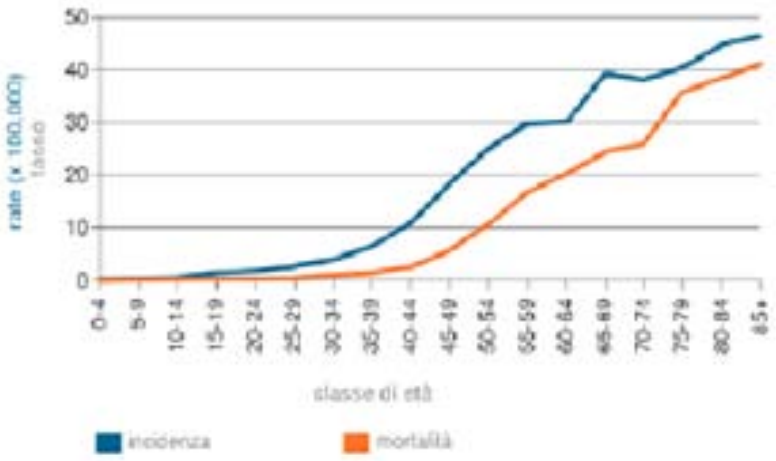
- è il 3% del totale delle diagnosi tumorali;
- è l'ottava causa di morte (4.5% dei decessi).
- 4900 nuovi casi e 3000 decessi ogni anno
- 1 donna su 100 si ammalerà di tumore nel corso della vita

- l'incidenza è sostanzialmente stabile
- la mortalità è in lieve riduzione
- la sopravvivenza relativa in lieve aumento.





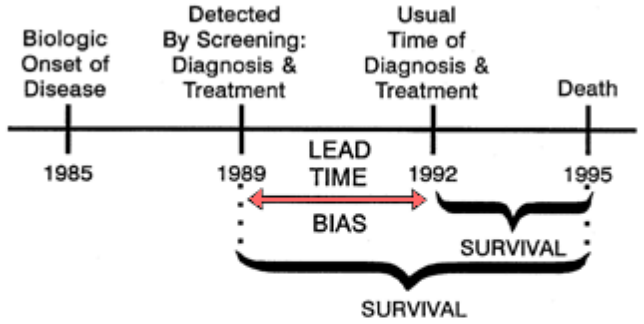
- fattori di rischio
  - genetici familiari: BRCA1/BRCA2
  - Endocrini: nulliparità
  - Ambientali: dieta, esposizione a talco ed asbesto
  - età

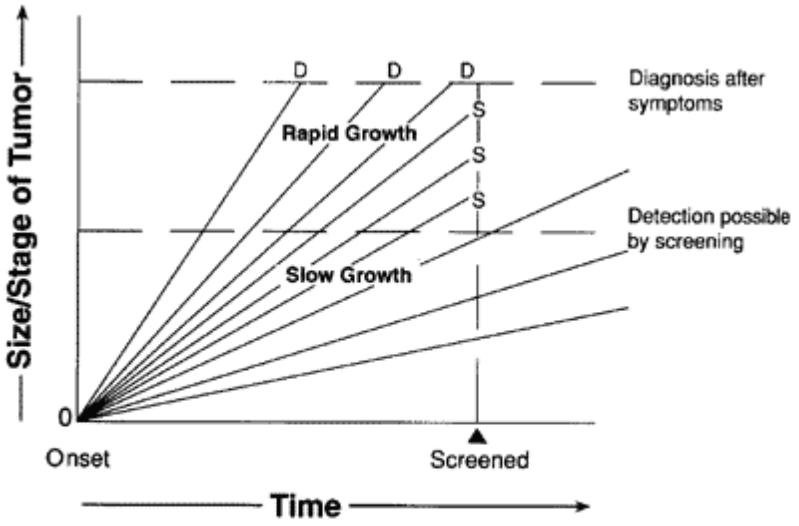


- sintomatologia aspecifica e tardiva,
  - circa il 75-80% delle pazienti presenta al momento della diagnosi una malattia in fase avanzata;
  - ben più raro (10%) è il riscontro iniziale di una neoplasia limitata agli annessi, il più delle volte scoperta occasionalmente durante i controlli ginecologici di routine.
  - nel restante 10% dei casi la diagnosi viene effettuata quando la malattia è ancora circoscritta alla pelvi.

- attualmente non sono riconosciute attività efficaci nella diagnosi precoce.

- Il confronto della prognosi di un gruppo di casi diagnosticati in uno screening con quella di casi diagnosticati normalmente non fornisce informazioni sull'efficacia dello screening
  - lead time bias
  - length time bias





- Seventeen prospective cohort studies and 3 pilot randomized controlled trials were included in this review.
  - Screening tests for cancer antigen 125 (CAI25) and ultrasound had low positive predictive values, resulting in healthy women being recalled and a false-positive rate of 0.01% to 5.8%.
  - Of every 10 000 women participating in an annual screening program with CAI25 for 3 years, 800 will have an ultrasound scan because of an elevated CAI25, 30 will undergo surgery because of an abnormal ultrasound, and 6 will have ovarian cancer detected at surgery (3 will be diagnosed at early-stage disease and have a chance of a cure).
- **Conclusion:**
  - There is insufficient evidence to support the introduction of screening for ovarian cancer in the asymptomatic general-risk postmenopausal population.
  - Screening is associated with increased rates of surgery and patient anxiety.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence Summary Report 4-6b IN REVIEW

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Context Screening for ovarian cancer with cancer antigen 125 (CA-125) and transvaginal ultrasound has an unknown effect on mortality.

Objective To evaluate the effect of screening for ovarian cancer on mortality in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Design, Setting, and Participants Randomized controlled trial of 78 216 women aged 55 to 74 years assigned to undergo either annual screening (n=39 105) or usual care (n=39 111) at 10 screening centers across the United States between November 1993 and July 2001.

Intervention The intervention group was offered annual screening with CA-125 for 6 years and transvaginal ultrasound for 4 years. Participants and their health care practitioners received the screening test results and managed evaluation of abnormal results. The usual care group was not offered annual screening with CA-125 for 6 years or transvaginal ultrasound but received their usual medical care. Participants were followed up for a maximum of 13 years (median [range], 12.4 years [10.9-13.0 years]) for cancer diagnoses and death until February 28, 2010.

Main Outcome Measures Mortality from ovarian cancer, including primary peritoneal and fallopian tube cancers. Secondary outcomes included ovarian cancer incidence and complications associated with screening examinations and diagnostic procedures.

Results Ovarian cancer was diagnosed in 212 women (5.7 per 10 000 person-years) in the intervention group and 176 (4.7 per 10 000 person-years) in the usual care group (rate ratio [RR], 1.21; 95% confidence interval [CI], 0.99-1.48). There were 118 deaths caused by ovarian cancer (3.1 per 10 000 person-years) in the intervention group and 100 deaths (2.6 per 10 000 person-years) in the usual care group (mortality RR, 1.18; 95% CI, 0.82-1.71). Of 3285 women with false-positive results, 1080 underwent surgical follow-up; of whom, 163 women experienced at least 1 serious complication (15%). There were 2924 deaths due to other causes (excluding ovarian, colorectal, and lung cancer) (76.6 per 10 000 person-years) in the intervention group and 2914 deaths (76.2 per 10 000 person-years) in the usual care group (RR, 1.01; 95% CI, 0.96-1.06).

Conclusions Among women in the general US population, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

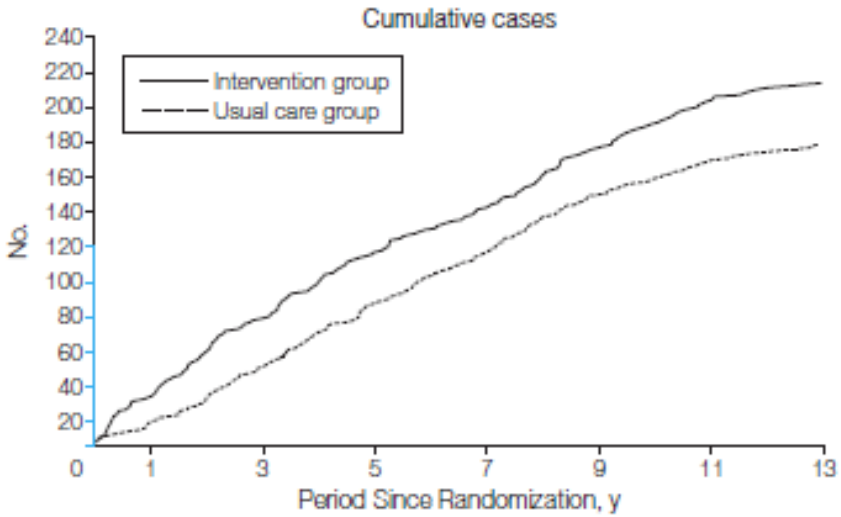
Effect of Screening on Ovarian Cancer Mortality
The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial

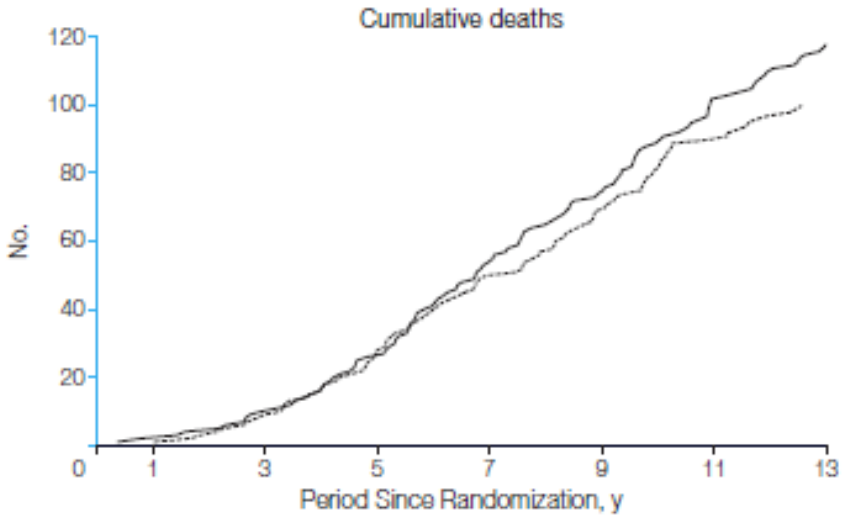
78000 donne

12 anni follow-up

risultati negativi

Lo studio PLCO – JAMA 2011





Intervention group													
Cumulative cancers	28	74	113	139	174	202	212	2	10	26	54	74	102	118
Cumulative person-years	33908	100777	166273	230393	292223	341975	371833	34210	102191	169354	235475	299372	350870	381574
Usual care group													
Cumulative cancers	13	45	83	113	146	167	176	0	9	28	50	69	90	100
Cumulative person-years	33994	101279	167380	232046	294424	344734	374976	34260	102344	169617	235836	299903	351557	382502

Lo studio PLCO – JAMA 2011

Major Complications Associated With Diagnostic Evaluation for Ovarian Cancer

	No. (%)		
	Intervention Group		Cancer Cases in Usual Care Group (n = 176)[b]
	No Cancer, Surgical Follow-up (n = 1080)[a]	Cancer (n = 212)[b]	
Women with complications	163 (15)	95 (45)	91 (52)
Total complications[c]	**222** (100)	**140** (100)	**143** (100)
Infection	89 (40)	32 (23)	37 (26)
Direct surgical	63 (28)	69 (49)	61 (43)
Cardiovascular or pulmonary	31 (14)	26 (19)	27 (19)
Other	39 (18)	13 (9)	18 (12)

[a] Includes only women who had a false-positive screening result for ovarian cancer during the screening phase of the trial.
[b] Includes women diagnosed with cancer during the screening phase or follow-up.
[c] Some women had more than 1 complication.

Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial *Lancet* 2016; 387: 945–56

Summary

Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

Methods In this randomised controlled trial, we recruited postmenopausal women aged 50–74 years from 13 centres in National Health Service Trusts in England, Wales, and Northern Ireland. Exclusion criteria were previous bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, and active non-ovarian malignancy. The trial management system confirmed eligibility and randomly allocated participants in blocks of 32 using computer-generated random numbers to annual multimodal screening (MMS) with serum CA125 interpreted with use of the risk of ovarian cancer algorithm, annual transvaginal ultrasound screening (USS), or no screening, in a 1:1:2 ratio. The primary outcome was death due to ovarian cancer by Dec 31, 2014, comparing MMS and USS separately with no screening, ascertained by an outcomes committee masked to randomisation group. All analyses were by modified intention to screen, excluding the small number of women we discovered after randomisation to have a bilateral oophorectomy, have ovarian cancer, or had exited the registry before recruitment. Investigators and participants were aware of screening type. This trial is registered with ClinicalTrials.gov, number NCT00058032.

Findings Between June 1, 2001, and Oct 21, 2005, we randomly allocated 202 638 women: 50 640 (25·0%) to MMS, 50 639 (25·0%) to USS, and 101 359 (50·0%) to no screening. 202 546 (>99·9%) women were eligible for analysis: 50 624 (>99·9%) women in the MMS group, 50 623 (>99·9%) in the USS group, and 101 299 (>99·9%) in the no screening group. Screening ended on Dec 31, 2011, and included 345 570 MMS and 327 775 USS annual screening episodes. At a median follow-up of 11·1 years (IQR 10·0–12·0), we diagnosed ovarian cancer in 1282 (0·6%) women: 338 (0·7%) in the MMS group, 314 (0·6%) in the USS group, and 630 (0·6%) in the no screening group. Of these women, 148 (0·29%) women in the MMS group, 154 (0·30%) in the USS group, and 347 (0·34%) in the no screening group had died of ovarian cancer. The primary analysis using a Cox proportional hazards model gave a mortality reduction over years 0–14 of 15% (95% CI −3 to 30; p=0·10) with MMS and 11% (−7 to 27; p=0·21) with USS. The Royston-Parmar flexible parametric model showed that in the MMS group, this mortality effect was made up of 8% (−20 to 31) in years 0–7 and 23% (1–46) in years 7–14, and in the USS group, of 2% (−27 to 26) in years 0–7 and 21% (−2 to 42) in years 7–14. A prespecified analysis of death from ovarian cancer of MMS versus no screening with exclusion of prevalent cases showed significantly different death rates (p=0·021), with an overall average mortality reduction of 20% (−2 to 40) and a reduction of 8% (−27 to 43) in years 0–7 and 28% (−3 to 49) in years 7–14 in favour of MMS.

Interpretation Although the mortality reduction was not significant in the primary analysis, we noted a significant mortality reduction with MMS when prevalent cases were excluded. We noted encouraging evidence of a mortality reduction in years 7–14, but further follow-up is needed before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening.

200000 donne

11 anni follow-up

qualche speranza

Lo studio UKCTOCS LANCET 2016

Screening Strategy

Level I screen (CA125). Women in the screen arm underwent an annual serum CA125 assay interpreted using the ROC calculation. On the basis of the risk value, patients were allocated to one of three groups and managed as detailed below:

Normal risk (< one in 2,000). Patients were informed that their results were normal.

Intermediate risk (one in 2,000 to one in 500). Patients were recalled for a repeat venipuncture. The interval of recall varied between 6 weeks and 6 months and was inversely related to the risk estimate. Management following repeat testing depended on the recalculated risk value, which incorporated the latest CA125 result.

Elevated risk (> one in 500). Patients were recalled for a level II screen.

Level II screen (TVS and CA125). Women underwent a scan of their ovaries and serum CA125 assay. On the basis of the results of these tests, they were managed as presented in Table 2.

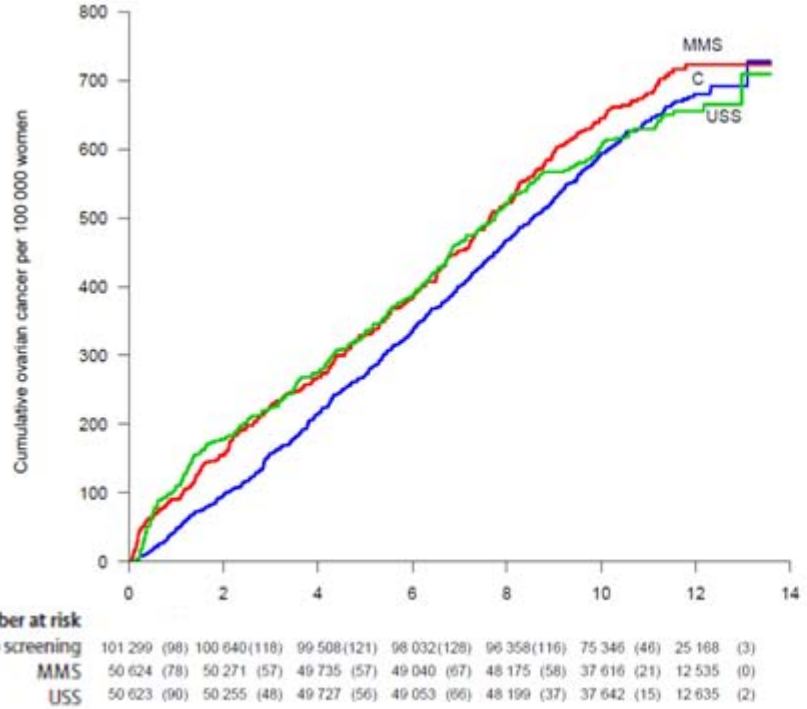
Normal scan and risk less than one in 25. Patients were informed that their results were normal.

Normal scan and risk one in 25 to one in five. Serum CA125 was repeated and the risk reassessed. Subsequent management was determined by the same risk criteria as described above for level 1 screens.

Equivocal or unsatisfactory scans irrespective of the risk value or normal scan with risk more than one in five. TVS and CA125 were repeated after ruling out other conditions associated with a CA125 elevation. The patient was referred for surgery if the scan findings were persistently equivocal or became abnormal.

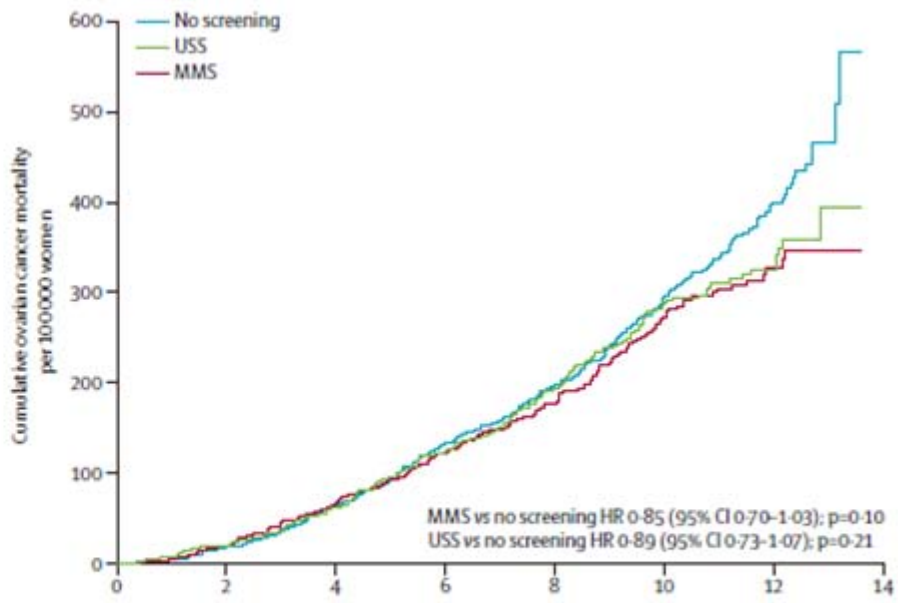
Abnormal scans irrespective of the risk value. The patient was referred to a gynecologic oncologist for assessment and possible surgical investigation.

Diverso algoritmo decisionale per la valutazione dinamica del CA125



Number at risk

No screening	101 299	(98)	100 640	(118)	99 508	(121)	98 032	(128)	96 358	(116)	75 346	(46)	25 168	(3)
MMS	50 624	(78)	50 271	(57)	49 735	(57)	49 040	(67)	48 175	(58)	37 616	(21)	12 535	(0)
USS	50 623	(90)	50 255	(48)	49 727	(56)	49 053	(66)	48 199	(37)	37 642	(15)	12 635	(2)



Number at risk

No screening	101299	100720	99662	98238	96632	75582	25252
MMS	50624	50343	49846	49176	48345	37758	12592
USS	50623	50338	49838	49192	48363	37768	12689

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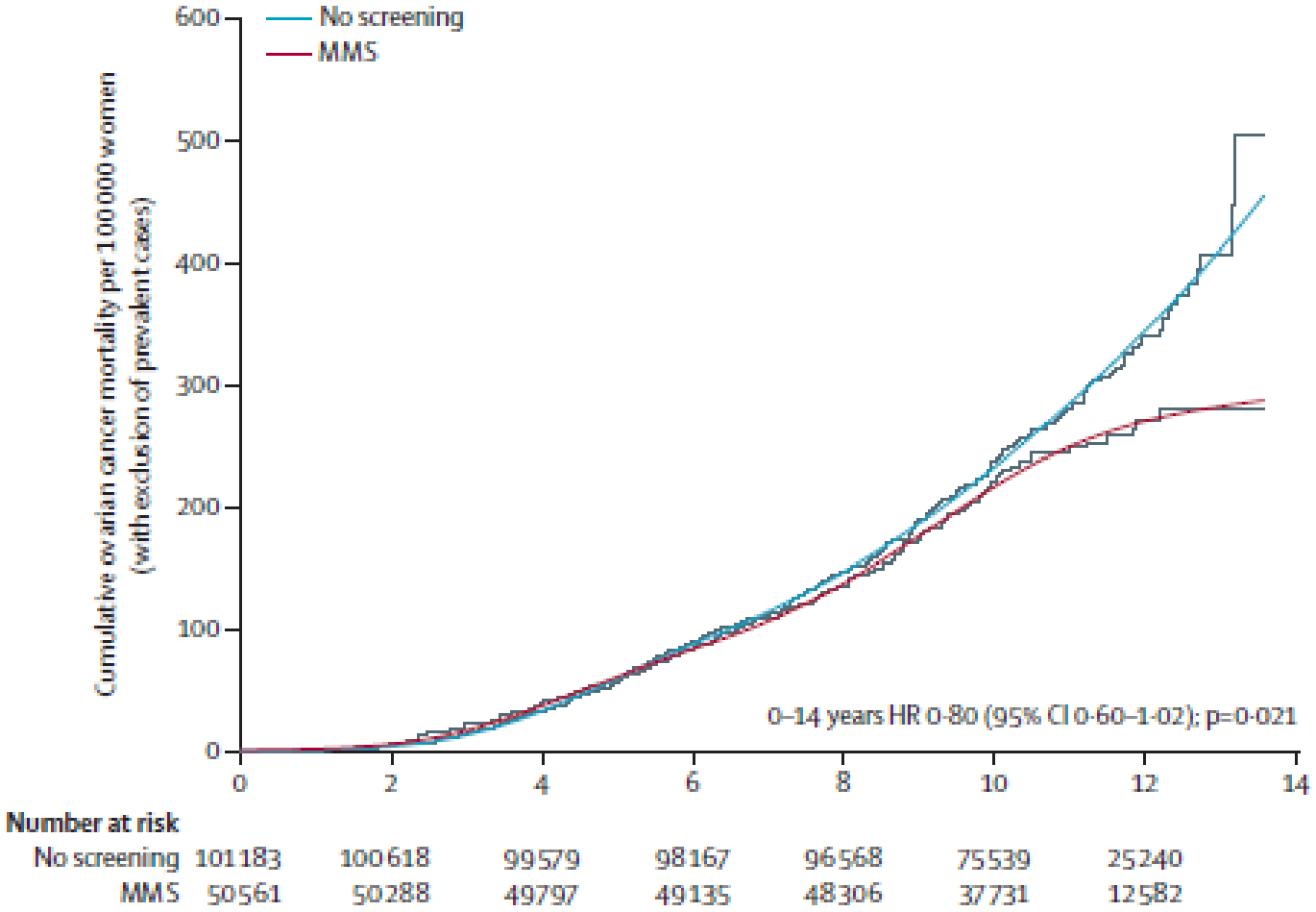

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Complications related to screening			
MMS		*USS*	
Complication type	No. of women	Complication type	No. of women
Bruising	13	Pain	20
Pain	8	Cystitis/infection	11
Haematoma	3	Discomfort	5
Fainting	1	Bruising	2
Cystitis/infection	1	Fainting	1
Other	4	Other	22
Total	**30**	**Total**	**61**
Rate	**8·6/100 000**	**Rate**	**18·6/100 000**
Complications related to screen-positive surgery			
MMS		*USS*	
Complication type	No. of women	Complication type	No. of women
Anaesthetic	1	Injury to hollow viscus (4 GI, 3 bladder, 4 ureter)	11
Injury to hollow viscus (2 GI, 1 bladder)	3	Haemorrhage	11
Haemorrhage	2	Anaesthetic/Myocardial Infarction	3
Deep Vein Thrombosis	1	Hernia	6
Bowel obstruction	4	Deep Vein Thrombosis/Pulmonary Embolism	3
Wound breakdown - total dehiscence	1	Wound breakdown	6
Significant ileus	1	Bowel obstruction	4
Uterine perforation	1	Wound/supravaginal haematoma	4
Infection	1	Infection	6
		Pain - ward readmission/further operation	3
Total	**15**	**Total**	**57**
Rate	**3·1% (15/488)**		**3·5% (57/1634)**
GI – Gastro Intestinal. In women who had more than one complication, the most serious was reported.			

Complications related to screening and screen-positive surgery in women with benign or normal adnexa

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- At a median 11 years' follow-up of the 202 638 women allocated to annual screening by either USS, MMS, or to no screening,
  - **the primary outcome of death due to ovarian cancer was not significantly different.**
  - **further analyses suggested that there may be a late survival advantage from screening, but longer follow-up is needed**.
- importance of science-based priority setting
- very large-scale, publicly funded, randomised trials are needed