Terapia preventiva del cancro: stato dell'arte

Ente Ospedaliero Ospedali Galliera Genova
Ospedale di rilievo nazionale e di alta specializzazione

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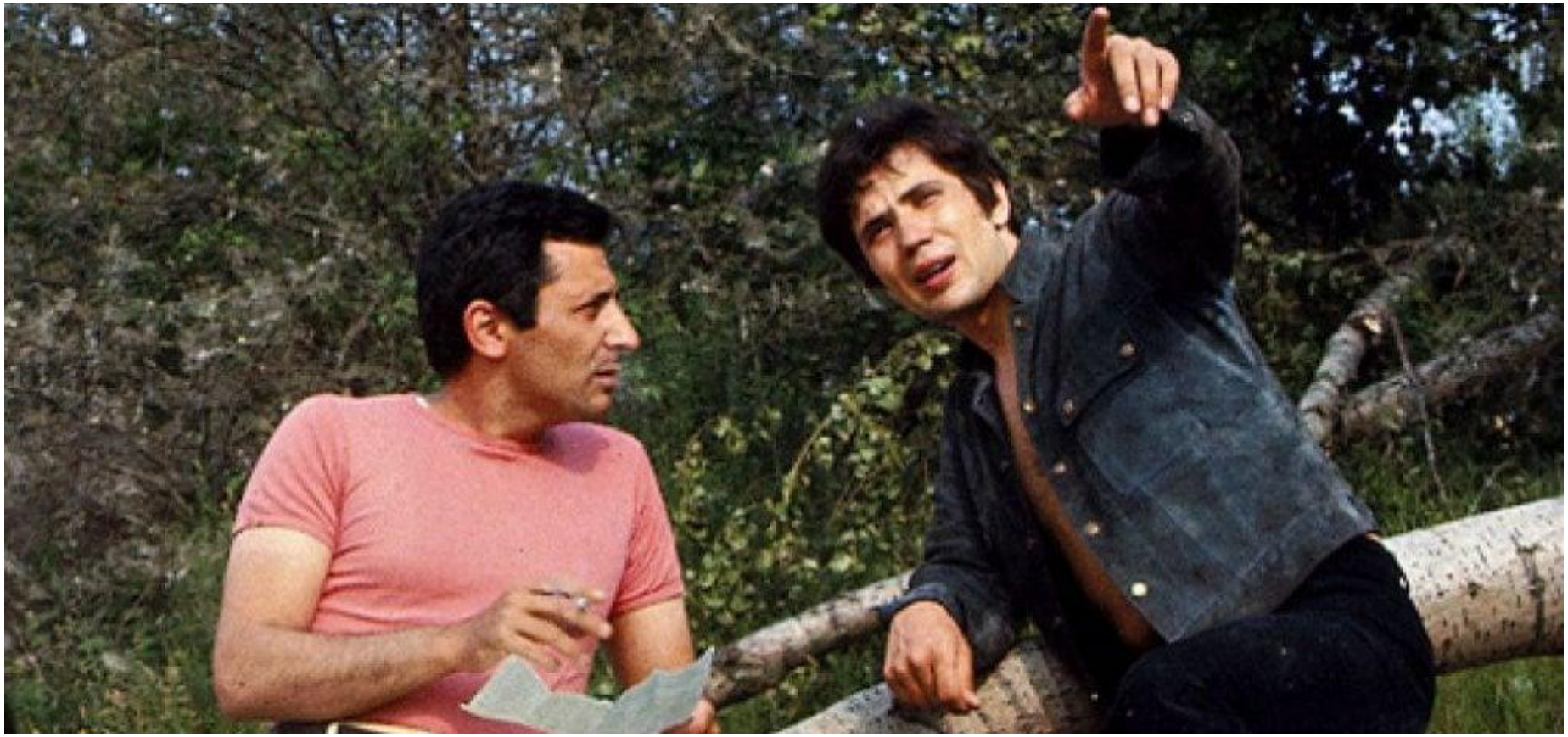
Queen Mary University of London

Lucio Battisti, '29 settembre' e l'Equipe 84: una storia lunga 51 anni



RANK	NAME	ORGANIZATION	H-INDEX	CITATIONS
1	Sigmund Freud	University of Vienna	269	488396
2	Graham Colditz	Washington University in St Louis	264	256415
3	Eugene Braunwald	Brigham and Women's Hospital;	246	290831
4	Ronald C Kessler	Harvard University	245	263006
5	Pierre Bourdieu	Centre de Sociologie Européenne; France	242	528228
7	Solomon H Snyder	Johns Hopkins University	240	216313
6	Michel Foucault	Collège de France	237	690001
8	Robert Langer	MIT	232	216122
9	Bert Vogelstein	Johns Hopkins University	230	315600
10	Eric Lander	Broad Institute Harvard MIT	225	294683

Future of Oncology: Early Detection and Prevention

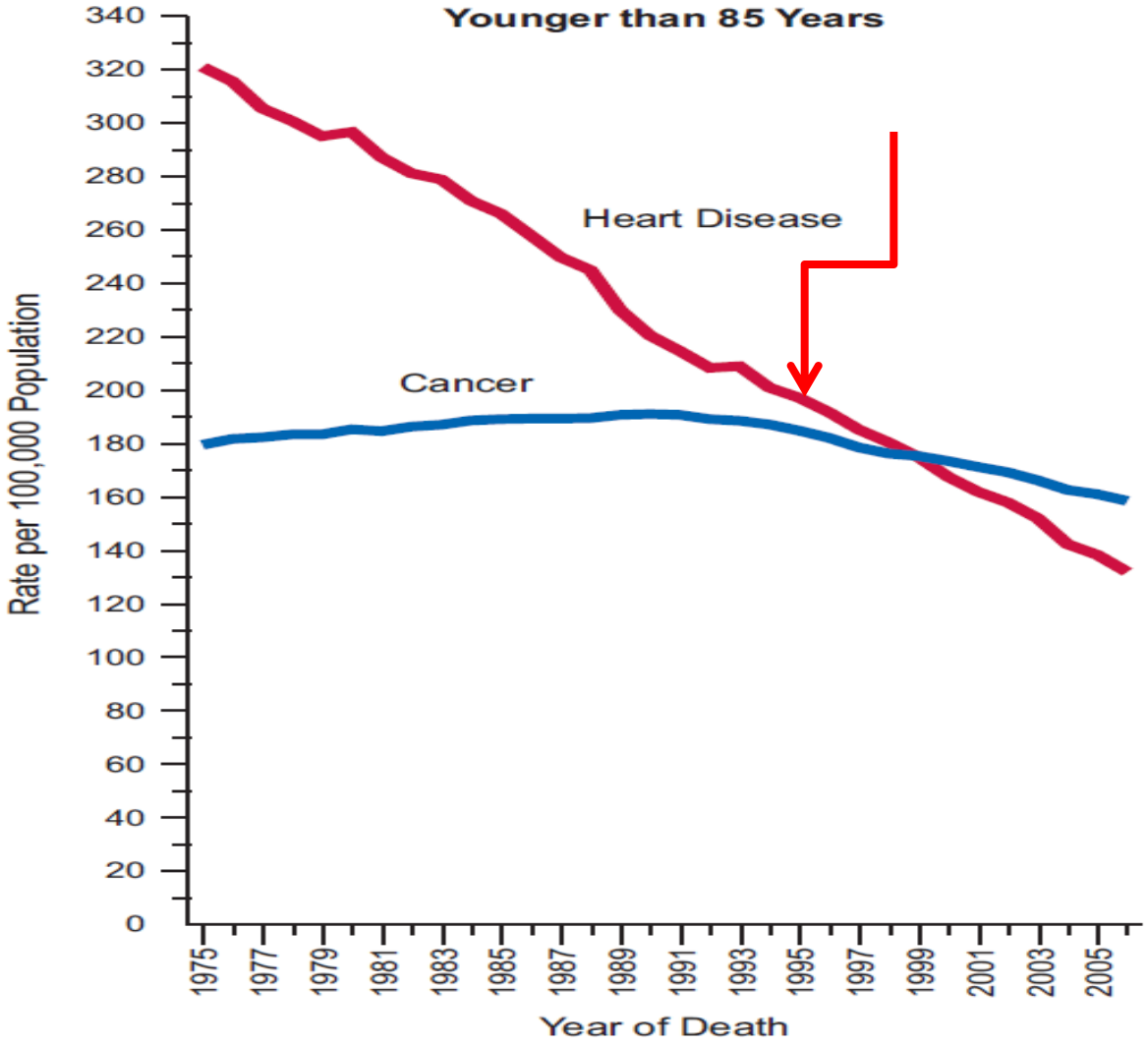
Asked about the future of oncology Dr. Vogelstein responded: "Now that we understand so much about the genetic basis of cancer, I'm optimistic we'll make progress in the years to come. But I also think that we need to readjust our efforts and spend more of our resources and intellectual energy on prevention and early detection."

> "It took us about 2 months to realize we had discovered a cancer gene [p53] that was likely involved in most cancers in the world, and that was going to start a revolution in cancer research, which it did.
>
> — *Bert Vogelstein, MD*

He continued: "We now spend an inordinate amount of our efforts developing drugs to fight metastatic disease. It's certainly critical, but I'd like to see about 50% of our efforts directed to early detection and prevention. I think heart disease serves as a good analogy. In cardiology, the focus over the past half century has been on prevention, not treating massive infarcts or strokes. In cancer, we've taken the opposite approach."

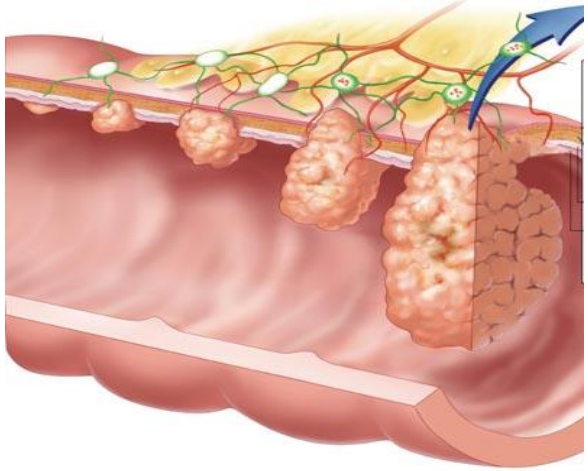
http://www.ascopost.com/issues/june-3-2017-narratives-special-issue/at-the-forefront-of-cancer-genetics-bert-vogelstein-md-calls-for-focus-on-early-detection-and-prevention/

Lesson from cardiovascular medicine:
Placing resources on therapeutic prevention (ACEi, ARB, BB, statins, aspirin, etc) has resulted in a significant reduction of cardiovascular death

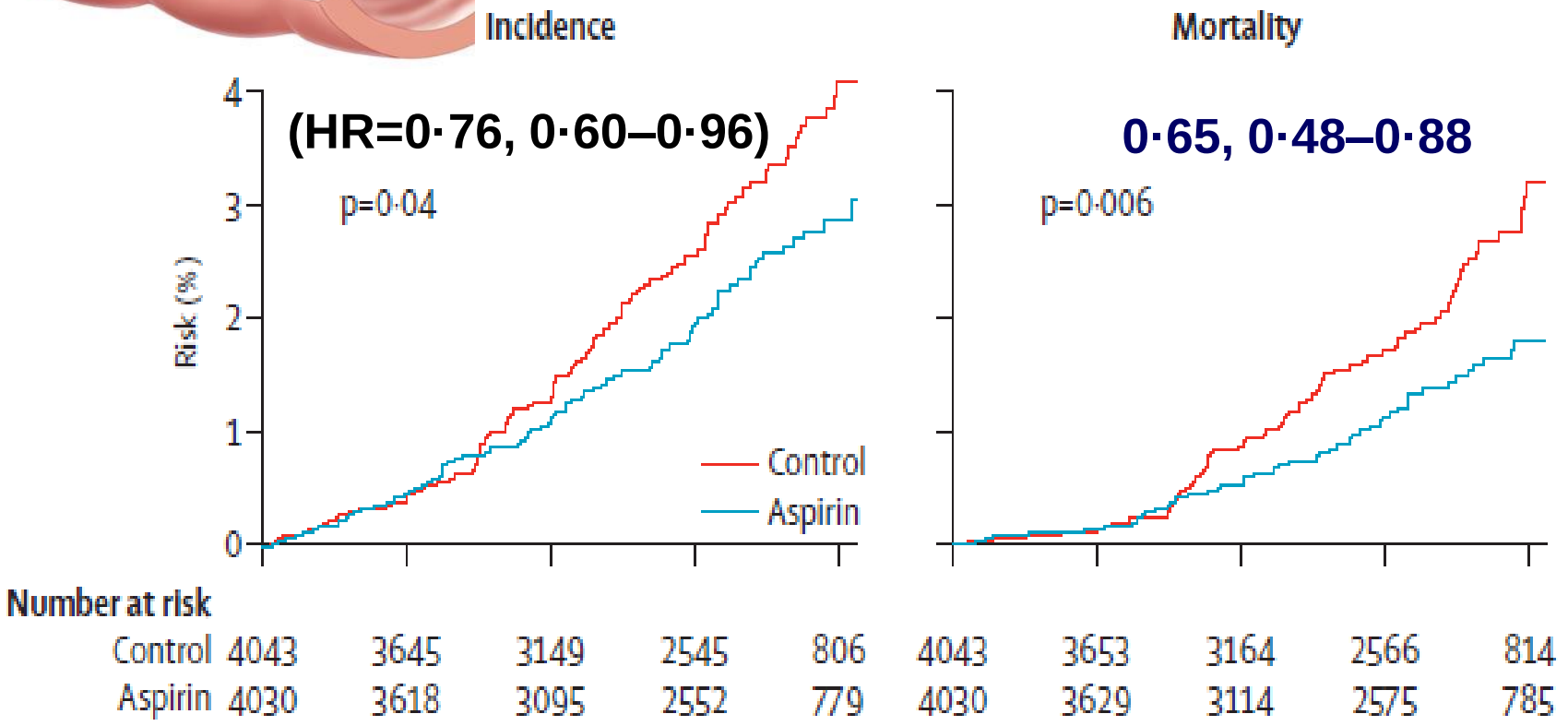


CA
A Cancer Journal for Clinicians

From Jemal, A. et al. CA Cancer J Clin 2010;60:277-300.

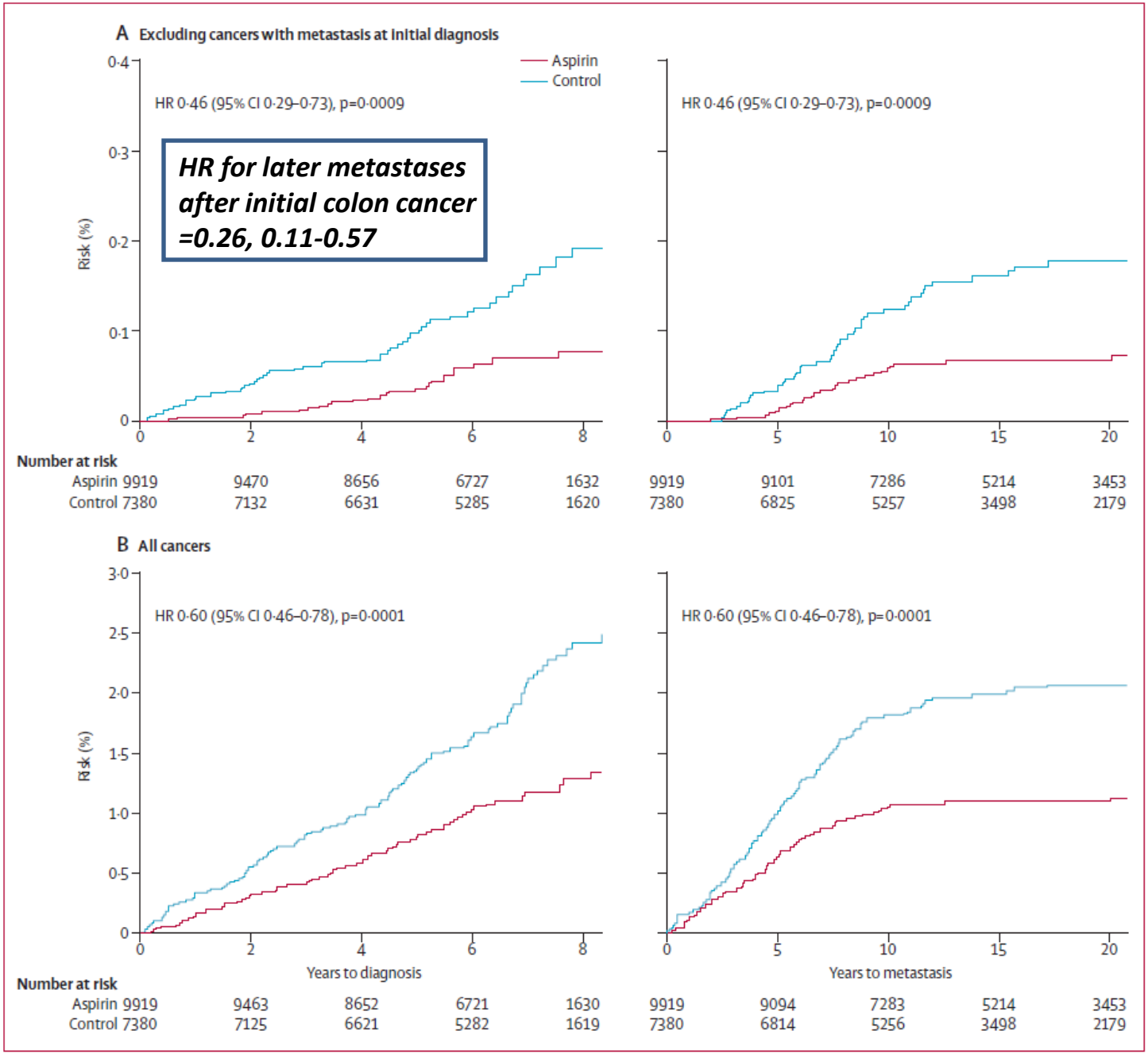


Effect of low dose aspirin (75-300) on CRC



Rothwell et al Lancet 2010

Effect of aspirin on risk of any adenocarcinoma with metastasis



Rothwell et al Lancet 2012; 379: 1591–601

Aspirin and Lung Cancer Prevention

Number of lung cancers	0-10 year follow-up		10-20 year follow-up		0-20 year follow-up	
	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value
326	0.68 (0.50-0.92)	0.01	0.75 (0.55-1.02)	0.07	0.71 (0.58-0.89)	0.002

Lung cancer-specific mortality rates were reduced by 29% (95% CI, 11%-42%) in the aspirin group in the 20-year period after trial initiation. No trend with dose above 75 mg/day was observed, but the effect on all cancers was more evident in adenocarcinomas and was present in both smokers and nonsmokers.

Rothwell et al. *Lancet* 2011

Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials

Peter M Rothwell, Nancy R Cook, J Michael Gaziano, Jacqueline F Price, Jill F F Belch, Maria Carla Roncaglioni, Takeshi Morimoto, Ziyah Mehta

Interpretation Low doses of aspirin (75–100 mg) were only effective in preventing vascular events in patients weighing less than 70 kg, and had no benefit in the 80% of men and nearly 50% of all women weighing 70 kg or more. By contrast, higher doses of aspirin were only effective in patients weighing 70 kg or more. Given that aspirin's effects on other outcomes, including cancer, also showed interactions with body size, a one-dose-fits-all approach to aspirin is unlikely to be optimal, and a more tailored strategy is required.

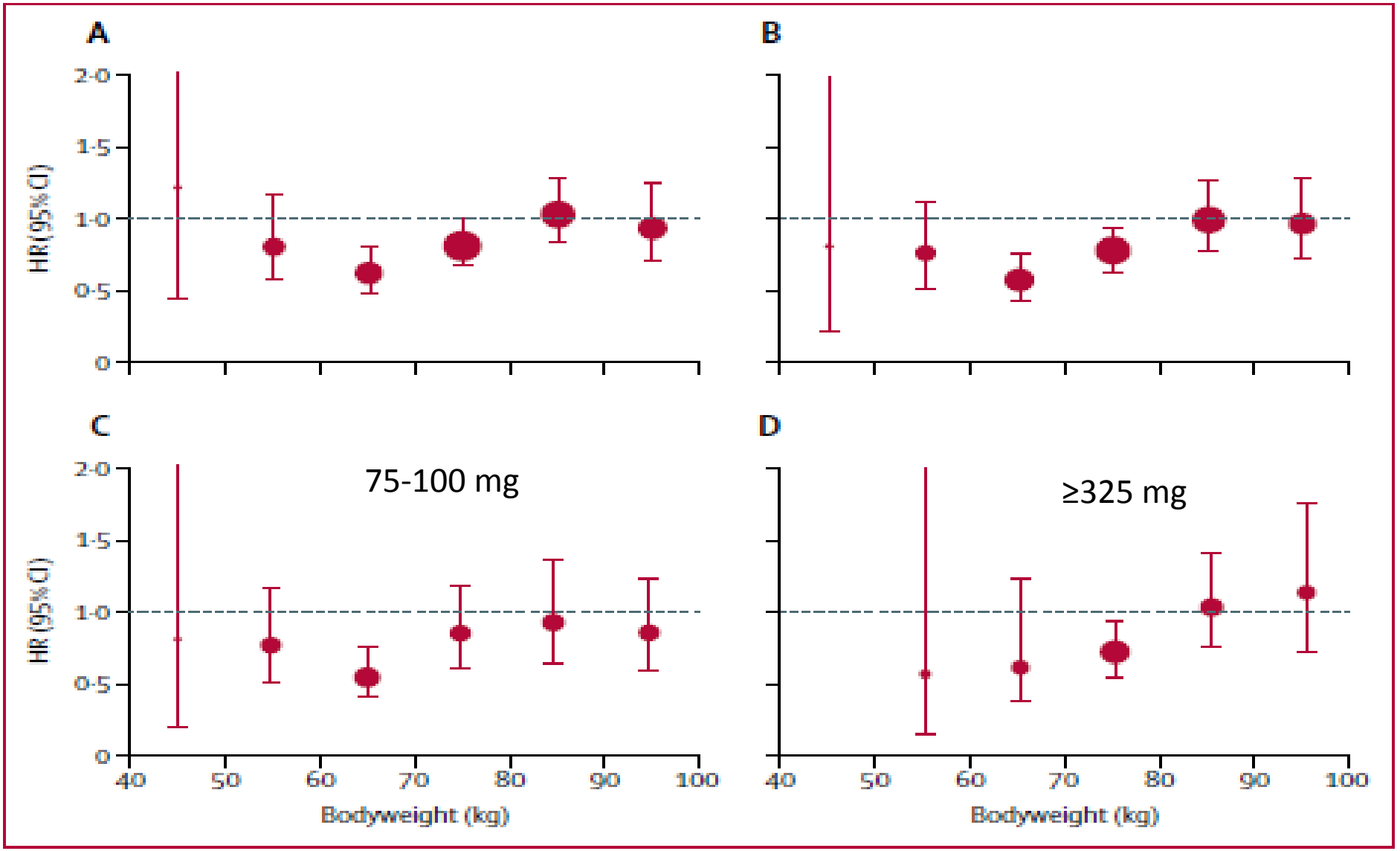


Figure 5: Effect of aspirin versus control on 20-year risk of colorectal cancer, stratified by aspirin dose and age
The size of the circles representing the point estimates of the HRs is proportional to the inverse of the variance of the estimate. The analysis included the five trials[15-19] with post-trial follow-up data and data on bodyweight. (A) Included participants treated with any dose and of any age. (B) Included participants treated with any dose who were younger than 70 years. (C) Included participants treated with 75–100 mg aspirin who were younger than 70 years. (D) Included participants treated with ≥325 mg aspirin who were younger than 70 years. HR=hazard ratio.

Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial

Janusz A Z Jankowski, John de Caestecker, Sharon B Love, Gavin Reilly, Peter Watson, Scott Sanders, Yeng Ang, Danielle Morris, Pradeep Bhandari, Stephen Attwood, Krish Ragunath, Bashir Rameh, Grant Fullarton, Art Tucker, Ian Penman, Colin Rodgers, James Neale, Claire Brooks, Adelyn Wise, Stephen Jones, Nicholas Church, Michael Gibbons, David Johnston, Kishor Vaidya, Mark Anderson, Sherzad Balata, Gareth Davies, William Dickey, Andrew Goddard, Cathryn Edwards, Stephen Gore, Chris Haigh, Timothy Harding, Peter Isaacs, Lucina Jackson, Thomas Lee, Peik Loon Lim, Christopher Macdonald, Philip Mairs, James McLoughlin, David Monk, Andrew Murdock, Iain Murray, Sean Preston, Stirling Pugh, Howard Smart, Ashraf Soliman, John Todd, Graham Turner, Joy Worthington, Rebecca Harrison, Hugh Barr, Paul Moayyedi

Interpretation High-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely improved outcomes in patients with Barrett's oesophagus.

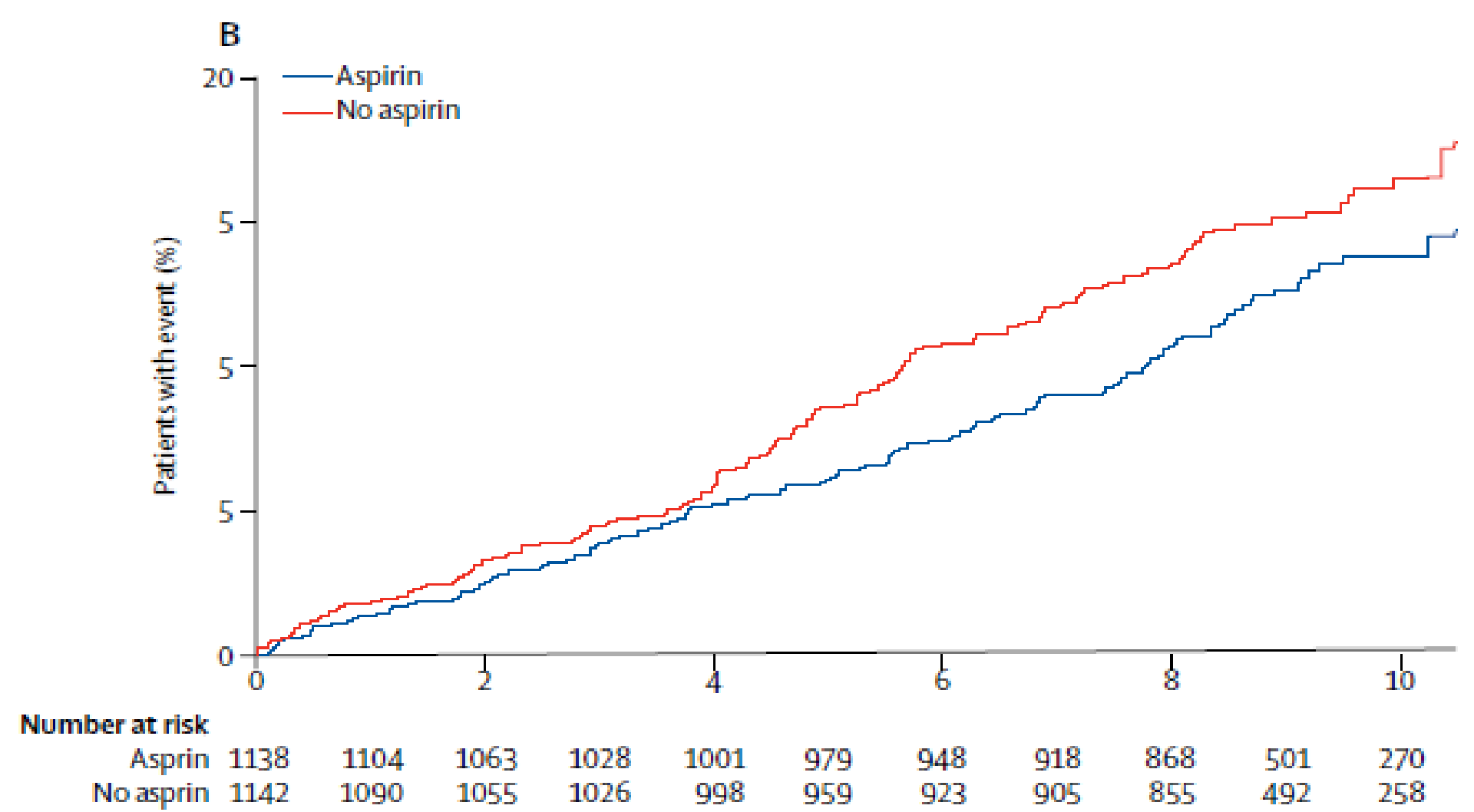
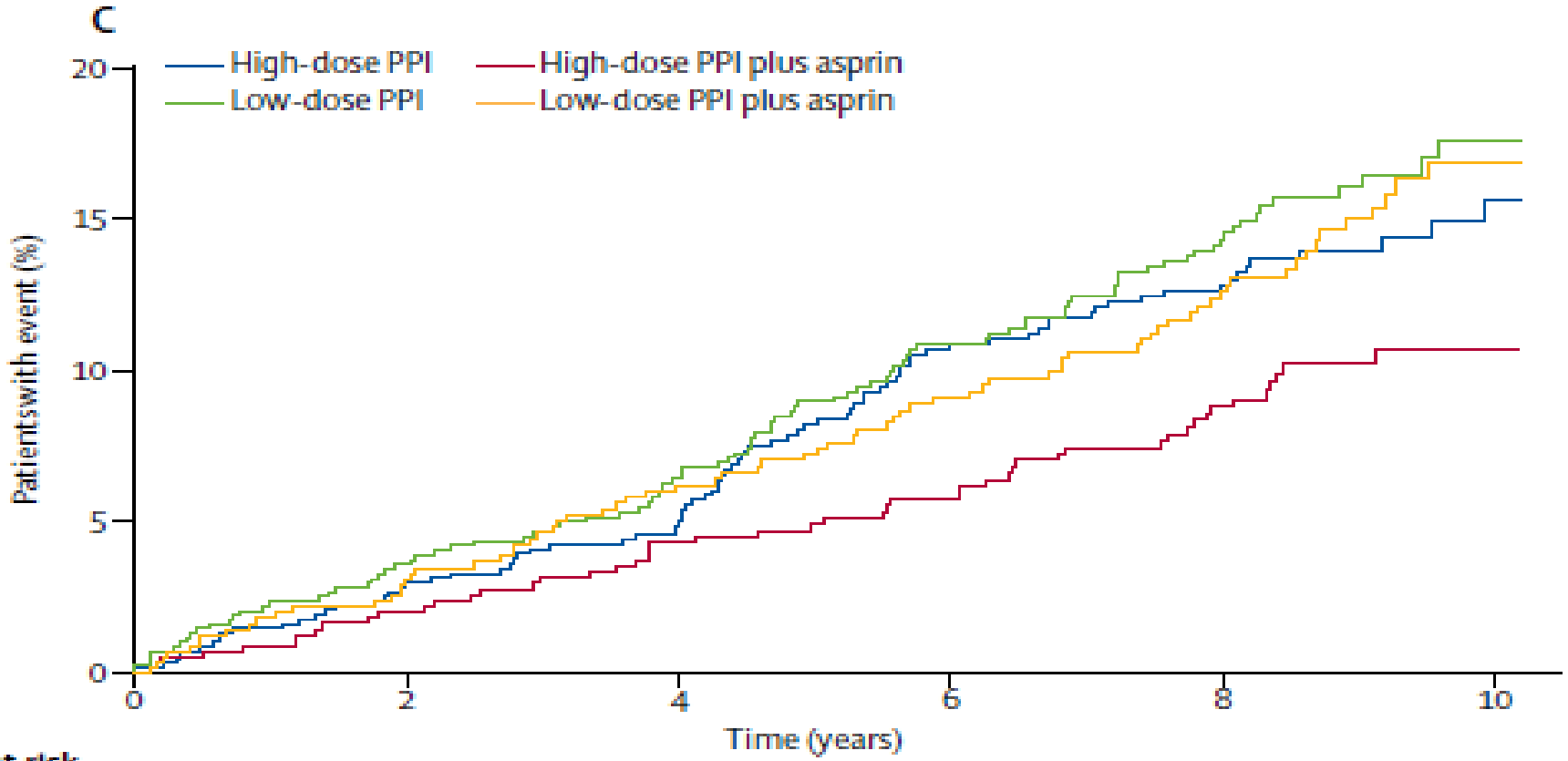


Figure 2: Event-free survival

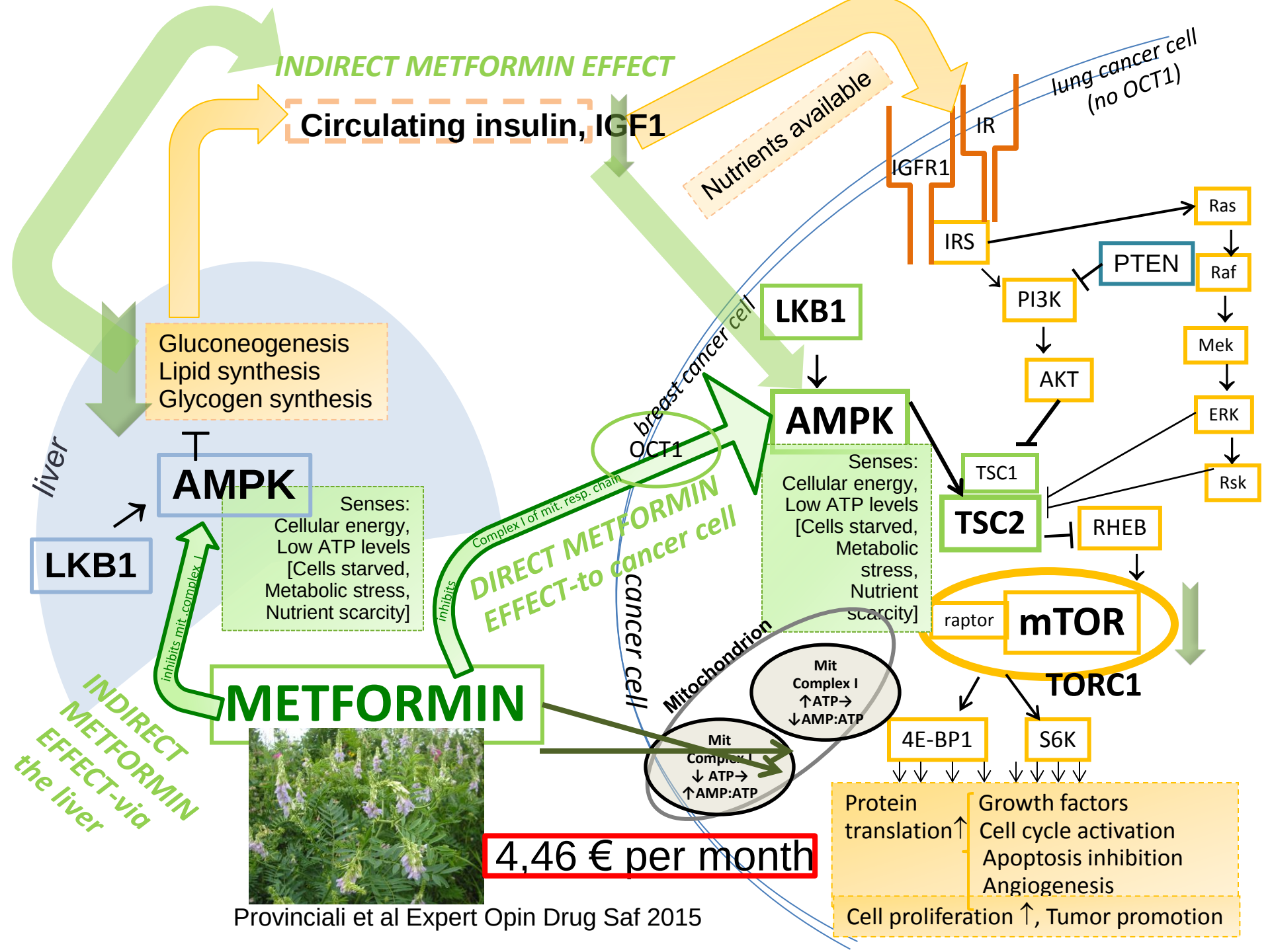
Curves show survival until the composite endpoint events (high-grade dysplasia, oesophageal adenocarcinoma, all-cause mortality) in the (A) high-dose PPI and low-dose PPI groups, (B) the aspirin and no aspirin groups, and (C) all four treatment groups. PPI=proton-pump inhibitor.



Number at risk											
High-dose PPI	698	668	644	629	616	587	563	552	523	260	128
High-dose PPI plus aspirin	572	554	530	516	503	493	477	459	432	242	135
Low-dose PPI	699	665	650	629	608	586	565	551	522	249	130
Low-dose PPI plus aspirin	566	550	533	512	498	486	471	459	436	259	135

Figure 2: Event-free survival

Curves show survival until the composite endpoint events (high-grade dysplasia, oesophageal adenocarcinoma, all-cause mortality) in the (A) high-dose PPI and low-dose PPI groups, (B) the aspirin and no aspirin groups, and (C) all four treatment groups. PPI=proton-pump inhibitor.



Provinciali et al Expert Opin Drug Saf 2015

Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial

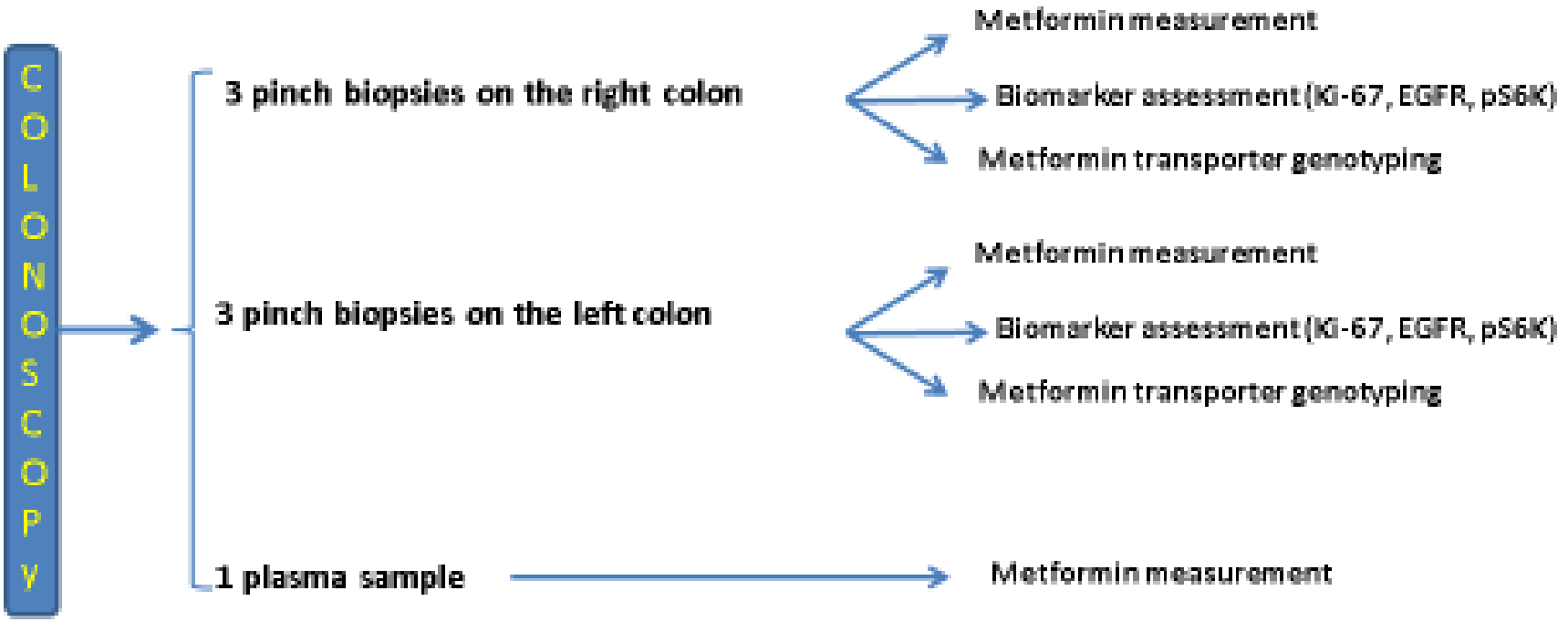
Higurashi T et al. ***Lancet Oncol 2016; 17: 475–83***

	Metformin (n= 79)	Placebo (n=72)	Results
All polyps	27 (38%)	35 (56.5%)	RR=0.67 (95% CI, 0.47-0.97) p=0.034
Adenoma	22 (30.6%)	32 (51.6%)	RR=0.60 (95% CI, 0.39-0.62)

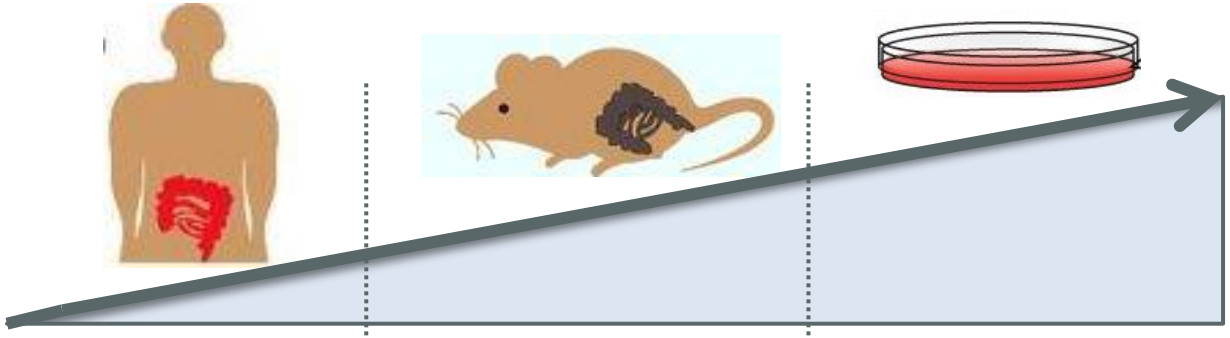
Metformin, very low dose 250mg/day!

Pre-ASAMET pilot study

Hypothesis: metformin accumulates in the colonic mucosa
Methods: metformin quantification in plasma and colonic tissue of 13 volunteers candidates to screening colonoscopy



Concentrations of metformin used in clinical and preclinical studies



therapeutic dose
250-2250 mg/die
[0.005-0.045] mM

2-45 x therapeutic dose
750 mg/kg/die
[0.145 mM]

25 →1000 x therapeutic dose
[1-50] mM

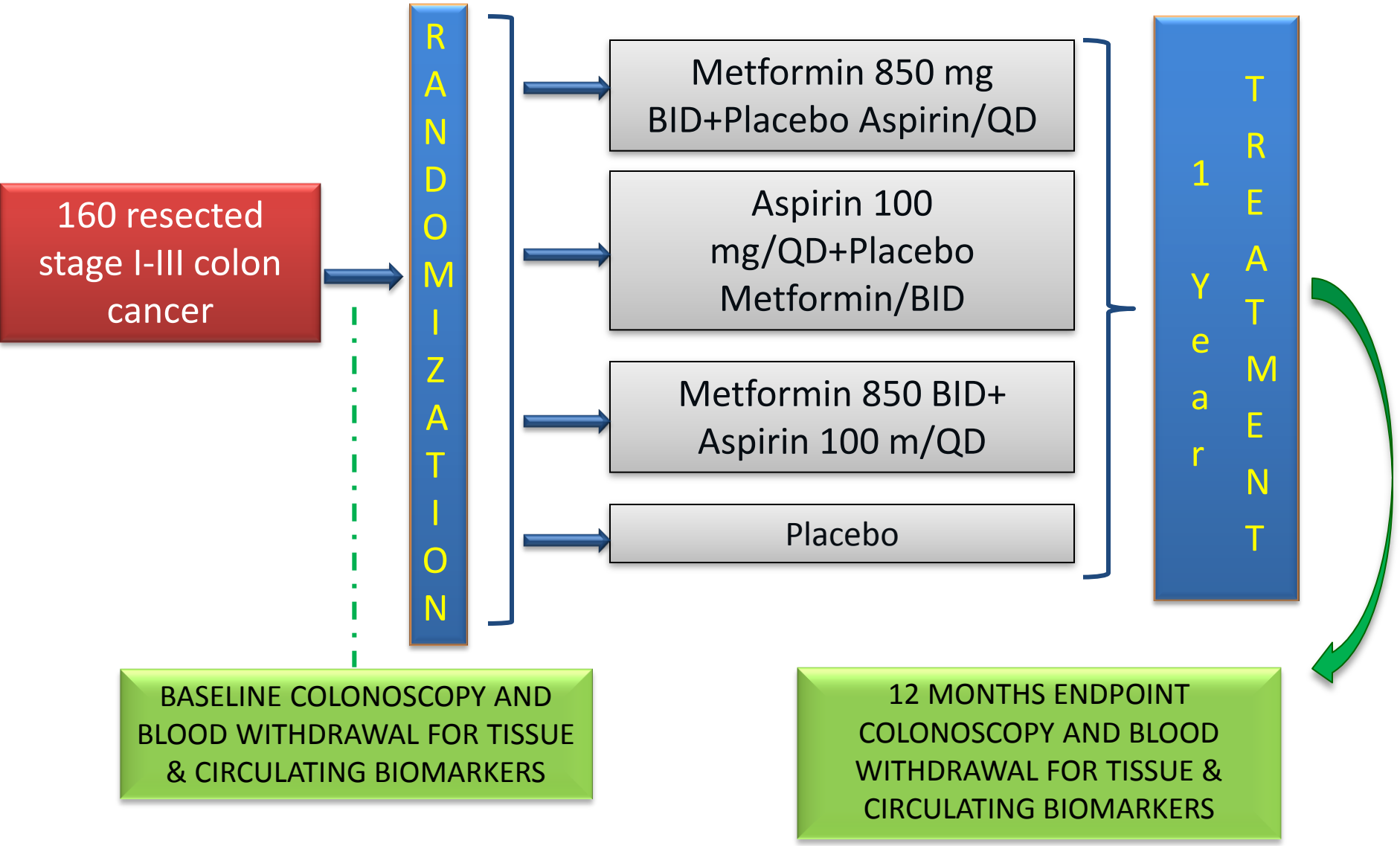
Plasma/tissue metformin concentrations
(Mean and range)

Plasma (mmol/L)	Right colon unwashed (mmol/kg)	Right colon washed (mmol/kg)	Left colon unwashed (mmol/kg)	Left colon washed (mmol/kg)	Average tissue (mmol/kg)
0.0025 ($5x10^{-5}$-0.017)	**0.36** (0.008-1.75)	**0.36** (0.007-1.79)	**0.41** (0.047-1.86)	**0.35** (0.041-1.89)	**0.37** (0.026-1.82)

Metformin can attain ~150 fold higher colonic tissue levels than in plasma.

Paleari L., et al . Gastroenterology, 2018,154(5):1543-1545.

Study Design ASAMET Trial



Determina 29 novembre 2017

Inserimento del medicinale per uso umano **“Tamoxifene”** nell’elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n.648, per il trattamento preventivo del carcinoma mammario in donne ad alto rischio.
(Determina n.1980/2017/DG)

7-12-2017 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA *Serie generale* - n. **286**

Determina 29 novembre 2017

Inserimento del medicinale per uso umano **“Raloxifene”** nell’elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale, ai sensi della legge 23 dicembre 1996, n.648, per il trattamento preventivo del carcinoma mammario in donne in post-menopausa ad alto rischio.
(Determina n.1979/2017/DG)

ID:

Age is 45-yrs.

Age at menarche 11-yrs.

Age at first birth 31-yrs.

Premenopausal.

Height is 1.65 m.

Weighs 60 kg.

HRT used more than 5-yrs ago.

Volpara® Volumetric Density: 20%.

Risk after 10 years is 16.8%.

10 year population risk is 2.3%.

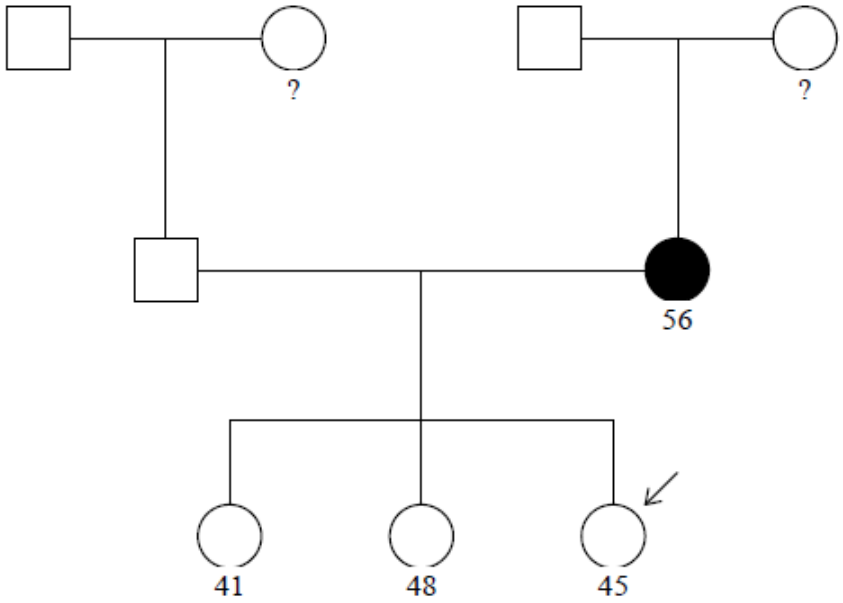
Lifetime risk is 65.5%.

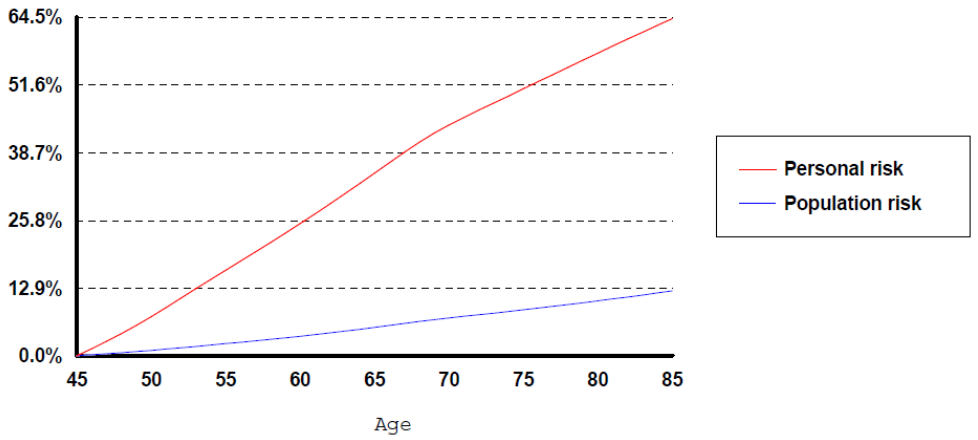
Lifetime population risk is 12.3%.

Probability of a BRCA1 gene is 0.17%.

Probability of a BRCA2 gene is 0.38%.

Proliferative benign disease from biopsy.





SERM meta-analysis on individual data from 306.307 women-years in 9 double blind trials. Breast cancer. Cuzick et al Lancet 2013

HR=0.62 (0.56-0.69)

HR=0.69 (0.53-0.90)

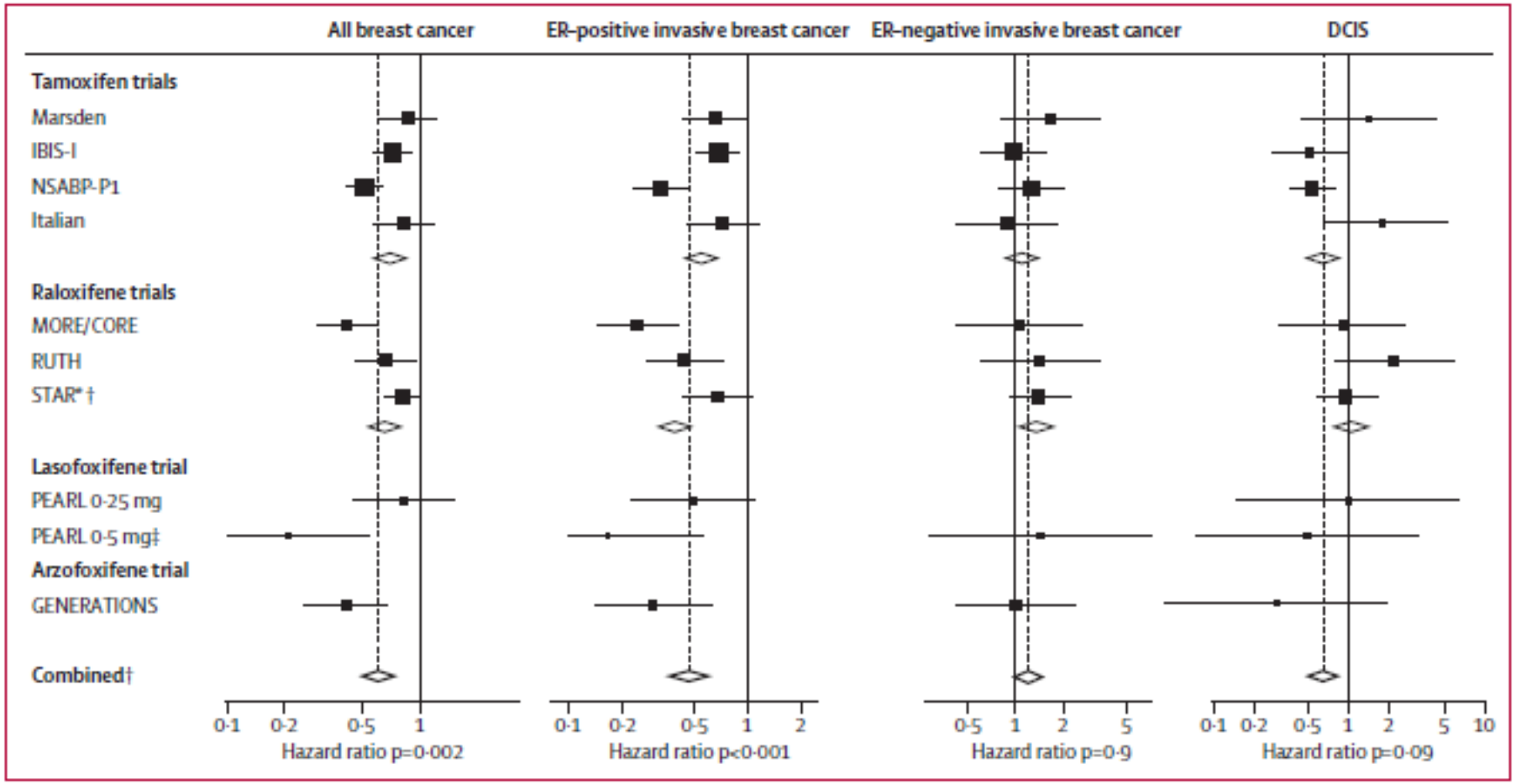
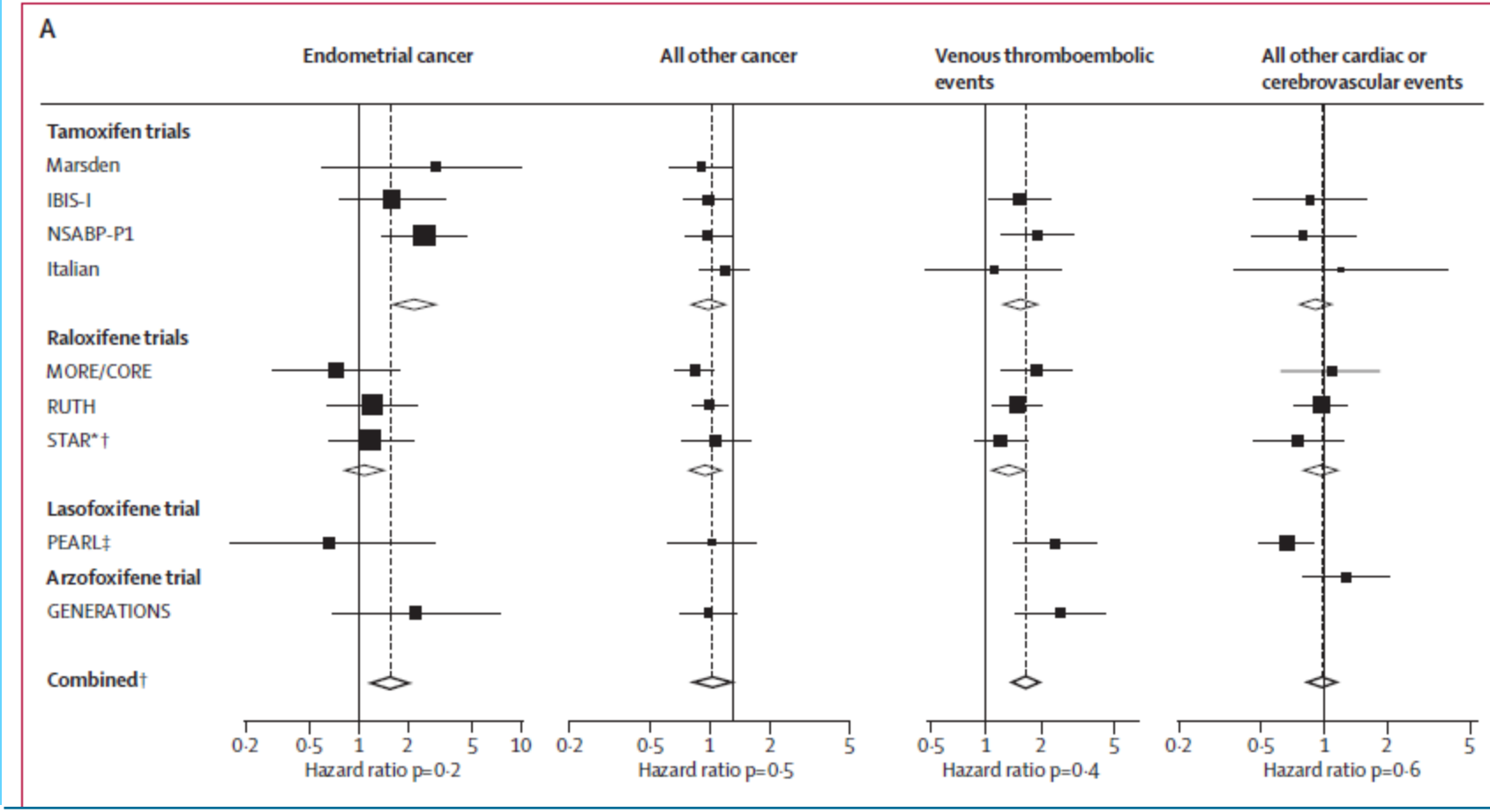


Figure 3: **All breast cancers, invasive breast cancer, and DCIS in years 0–10**

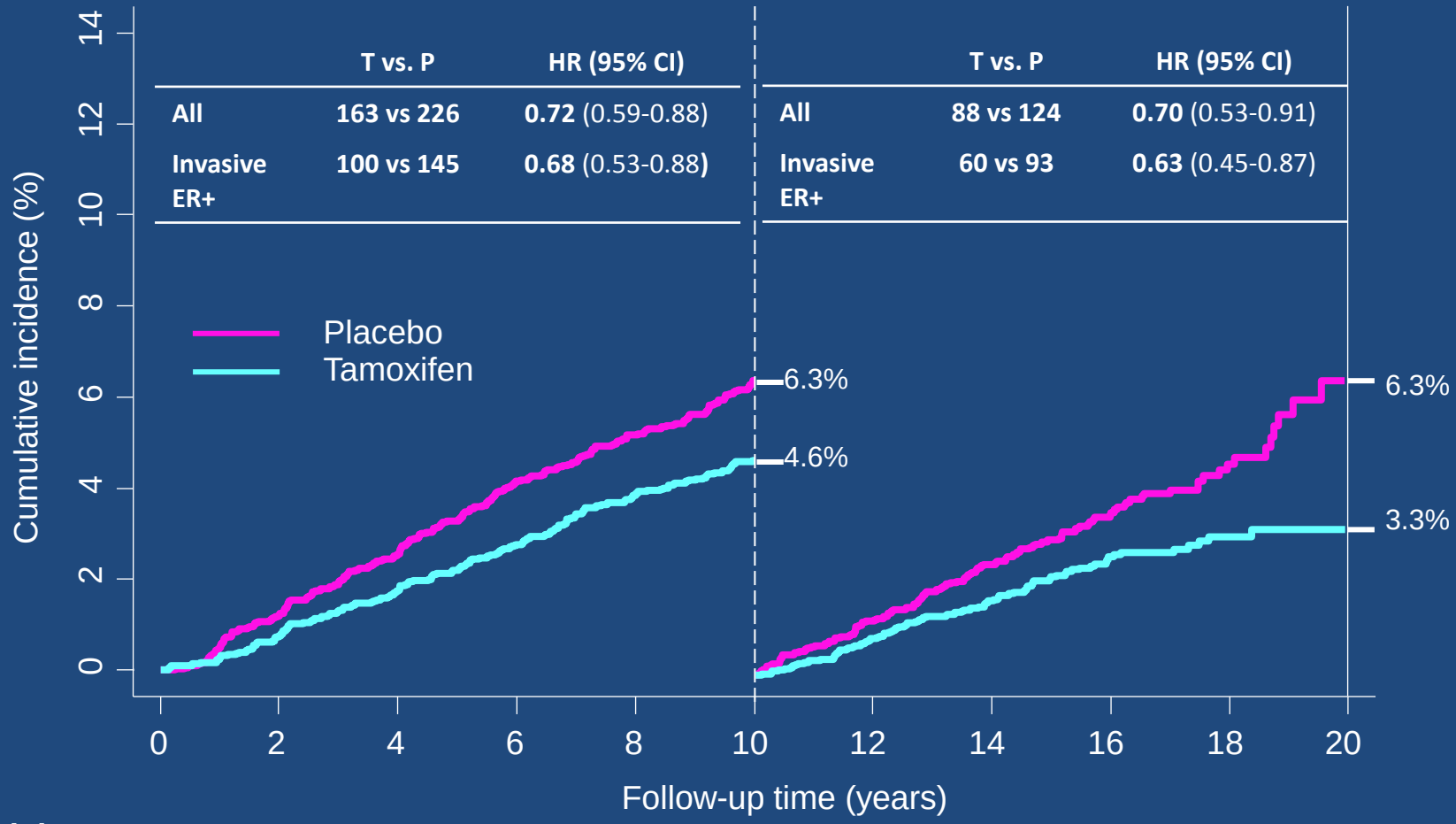
ER=oestrogen receptor. DCIS=ductal carcinoma in situ. *Adjusted by overall tamoxifen effect to give raloxifene versus placebo comparisons. †STAR data not included in comparisons. ‡Data for ER-invasive cancer are pooled.

SERM meta-analysis on individual data from 306.307 women-years
in 9 double blind trials. Serious adverse events.



Cuzick et al Lancet 2013

Cumulative incidence for all breast cancer



Number at risk

Placebo	3575	3527	3474	3410	3358	3296	3239	2850	1901	725	165
Tamoxifen	3579	3542	3495	3446	3385	3344	3293	2890	1918	748	168

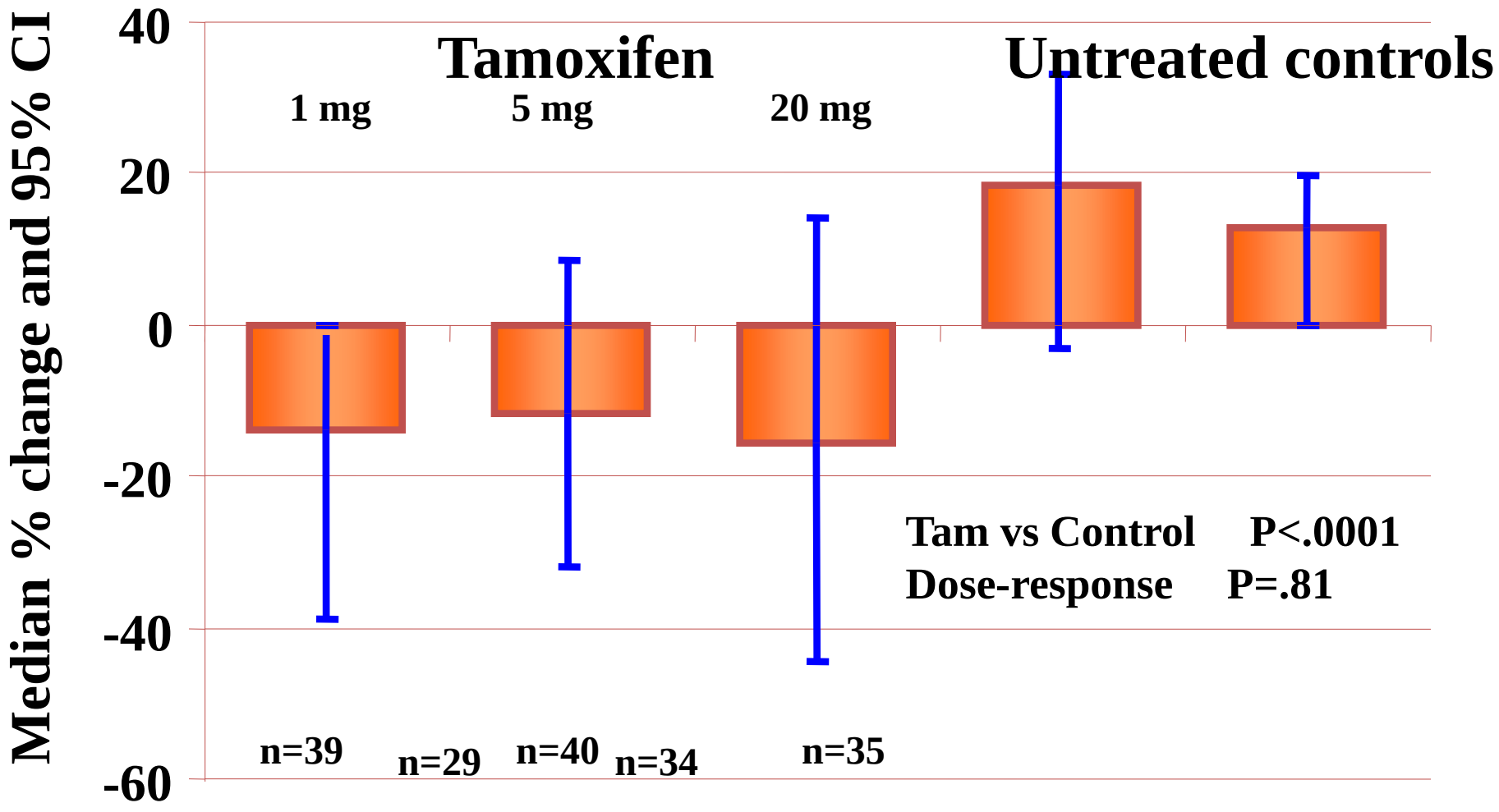
Cuzick et al Lancet Oncol 2015

Annual rates for invasive breast cancer in the NSABP-P1 trial (n=13386)

Subject characteristic	Rate per 1000 women		RR	95%CI
	Placebo	Tamoxifen		
All women	6.8	3.4	0.51	0.39-0.66
Age, y				
≤ 49	6.7	3.8	0.56	0.37-0.85
50-59	6.3	3.1	0.49	0.29-0.81
≥ 60	7.3	3.3	0.45	0.27-0.74
LCIS				
No	6.4	3.3	0.51	0.39-0.68
Yes	13.0	5.7	0.44	0.16-1.06
ADH				
No	6.4	3.6	0.56	0.42-0.73
Yes	10.1	1.43	0.14	0.03-0.47

Fisher B. et al, JNCI 1998

Lower doses of Tamoxifen have similar effects on Ki-67 change in a randomized 4-week presurgical trial



De Censi et al. JNCI 2003

Last year…

MDA2014-04-01 STUDY DESIGN

180 Postmenopausal women; confirmed Tis-2, N0-1, Mx, ER-positive breast cancer

R

- Exemestane 25mg daily
- Exemestane 25mg three times a week
- Exemestane 25mg /week

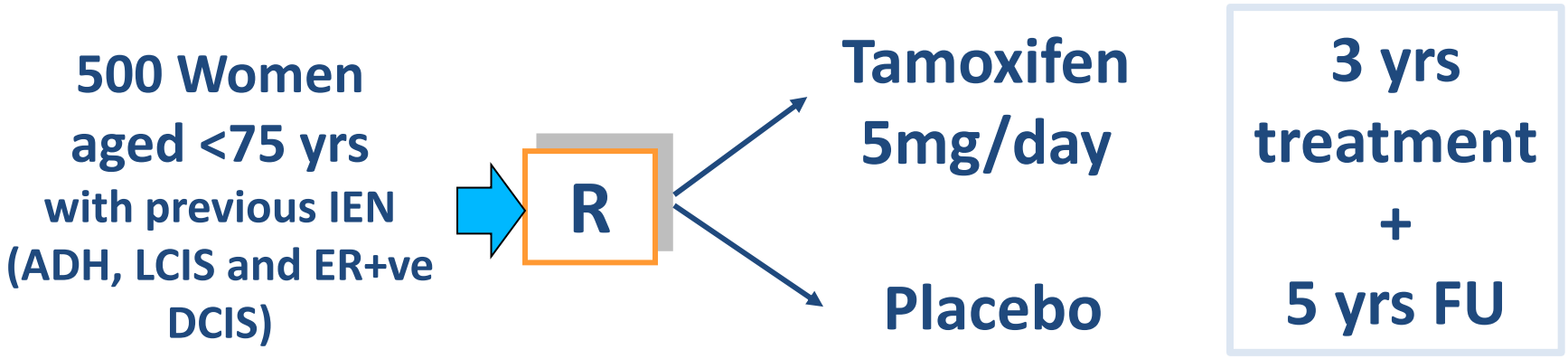
4/6 weeks

SURGERY

Multicenter Study

- European Institute of Oncology (IEO), Milan, Italy, **23**
- E.O. Galliera/ASL 3, Breast Unit, Genoa, **16**
- Columbia University Medical Center (CUMC), New York, USA, **11**
- MD Anderson Cancer Center, Houston, TX, USA, **37**
- Moffitt Cancer Center, Tampa, FL, USA, **12**

Tam01 trial-Study Design

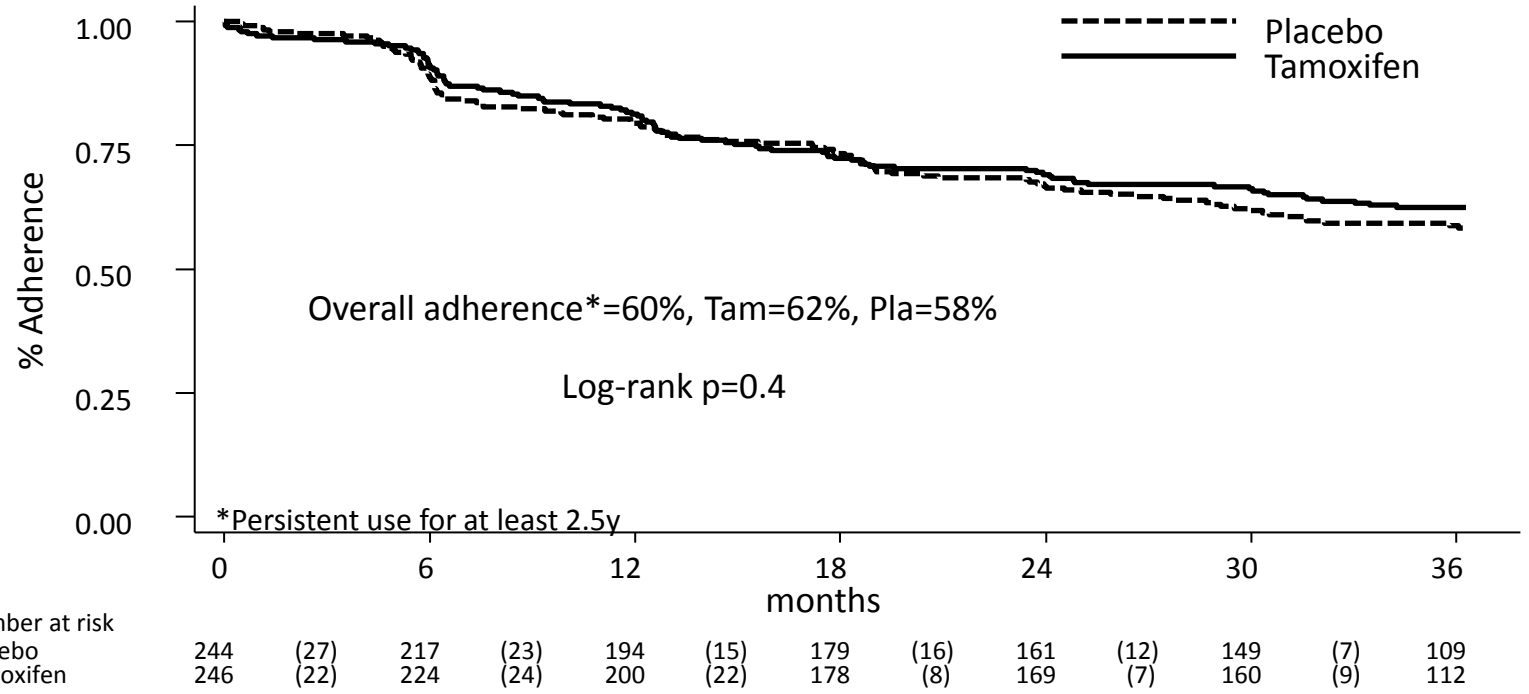


A multicenter, phase III randomized, double blind, placebo-controlled clinical trial: TAM01

Primary endpoint: Incidence of breast cancer
Secondary: association with MxD, CYP2D6 genotype and tam metabolites

- **500 subjects enrolled from 14 centers**
- **Median followup 5.1 years**
- **1600 person years**
- **Events: 43**

Supplemental figure 3



SABCS 2018

Effects of volume CT lung cancer screening

Mortality results of the NELSON randomised-controlled population-based screening trial

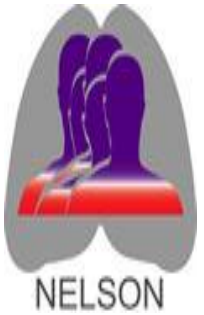
Harry J. de Koning, MD PhD

PI NELSON
Professor & Deputy Head
Department of Public Health
Erasmus MC, University Medical Center Rotterdam, the Netherlands

Background

- **The National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality for annual screening over three years with low dose CT to chest radiography**
- **The trial recruited 53,454 persons at high risk (59% men)**
- **In a post-hoc analysis, there was weak evidence of a differential benefit by gender: RR=0.92 for men, versus RR=0.73 for women (p=0.08), and a slightly smaller point estimate**
- **Differential effect by gender was found consistent with the natural history of lung cancer by histology, with a potential greater advancement (lead time) by CT screening in women than in men**
- **Except for the NLST, no other RCT has published mortality benefits**

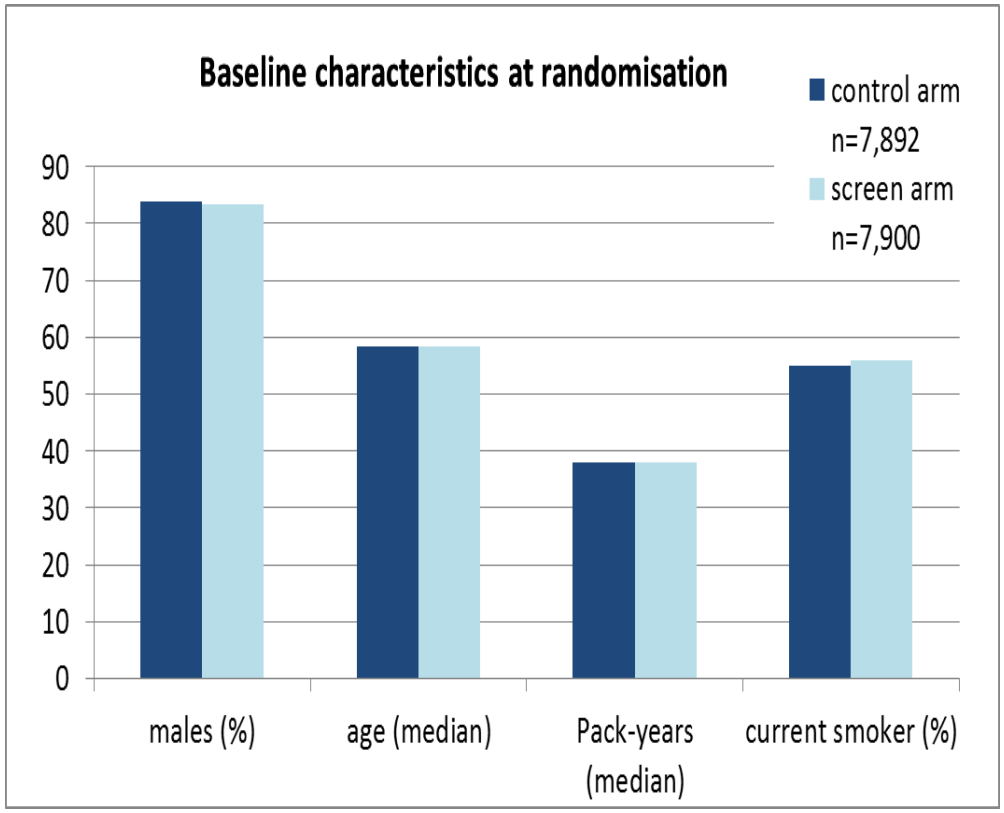
NELSON - trial ISRCTN 63545820

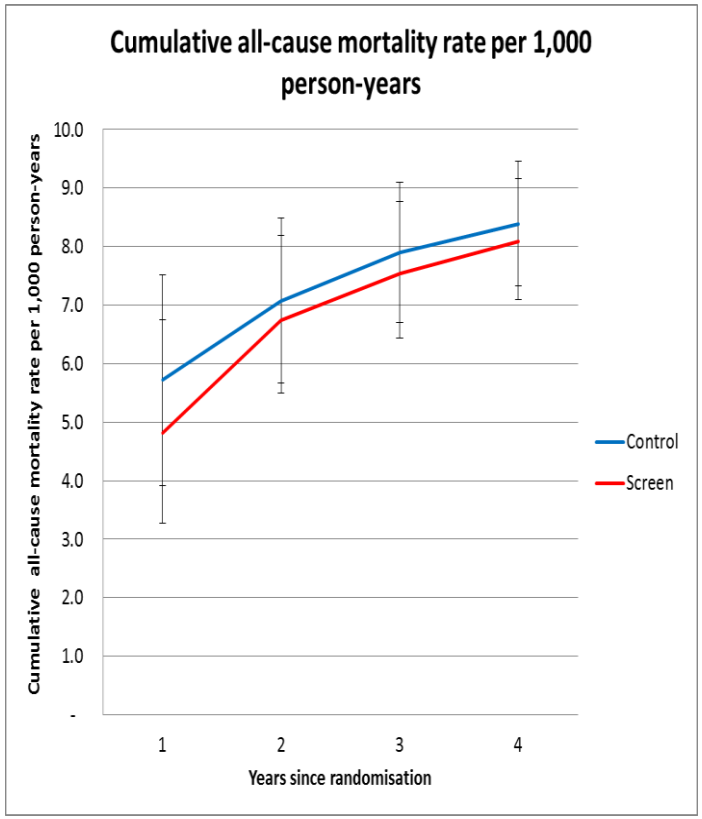


- **Randomized Controlled Trial**
- **Recruitment through population-based registries**
- **CT screening vs. no screening**
- **Different screening intervals**
- **Volume & Volume Doubling Time of nodules**
- **Central reading of CT images**
- **Expert causes of death committee &**
- **Follow up through national registries**

Trial, initially powered (80%) for high risk **males**, to detect a lung cancer mortality reduction of ≥ 25% at 10 years after randomization (individual FU)

And includes a small subgroup of women (16%)


Baseline characteristics at randomisation
control arm n=7,892
screen arm n=7,900
90
80
70
60
50
40
30
20
10
0
males (%)
age (median)
Pack-years (median)
current smoker (%)


Cumulative all-cause mortality rate per 1,000 person-years
Cumulative all-cause mortality rate per 1,000 person-years
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
-
1
2
3
4
Years since randomisation
Control
Screen

	Year 1	Year 2	Year 4	Year 6.5	Year 10
	CT screening	CT screening	CT screening	CT screening	
Screen arm n=7,900					
	n=7,557	n=7,295	n=6,922	n=5,279	
	95.6% uptake	92.3% uptake	87.6% uptake	66.8% uptake	
Control arm n=7,892	**Usual care (no screening)**				

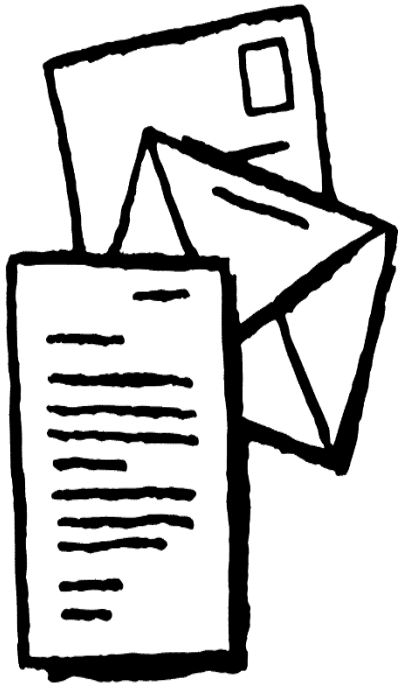
NATIONAL LINKAGES
- Statistics Netherlands/ Belgium
- Dutch/ Belgium Cancer Registry
- Centre for Genealogy

CAUSE OF DEATH REVIEW

	screening uptake	indeterminate test result	positive test result (final result)	lung cancer detection (participants)	positive predictive value positive test result
ROUND 1	7,557 (95.6%)	1,451 (19.2%)	197 (2.6%)	70 (0.9%)	36%
ROUND 2	7,295 (92.3%)	480 (6.6%)	131 (1.8%)	55 (0.8%)	42%
ROUND 3	6,922 (87.6%)	471 (6.8%)	165 (2.4%)	75 (1.1%)	45%
ROUND 4	5,279 (66.8%)	101 (1.9%)	105 (2.0%)	43 (0.8%)	41%
TOTAL	**27,053 (85.6%)**	**2,503 (9.3%)**	**598 (2.2%)**	**243 (0.9%)**	**41%**

Message indeterminate screening test result

"We have observed a very small abnormality in your lung (5–10 mm long). Such a small abnormality is often detected in many persons and it usually represents a small scar or a minor inflammation. Therefore, at this moment there is no need for any further investigations. However, in order to see whether there has been any change in this abnormality, a new CT scan of the lungs will be made after 3 to 4 months."



Lancet Oncol 2014; 15: 1332–41

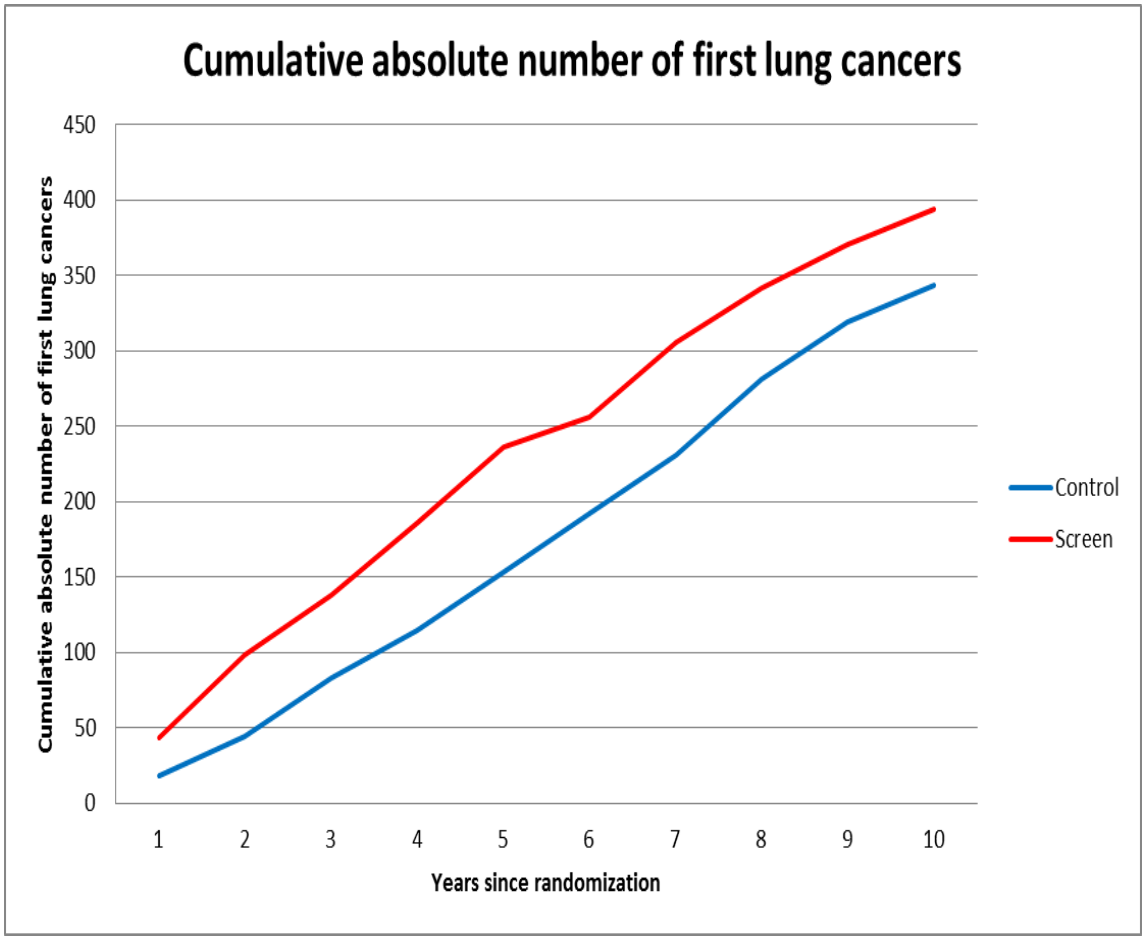
Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening

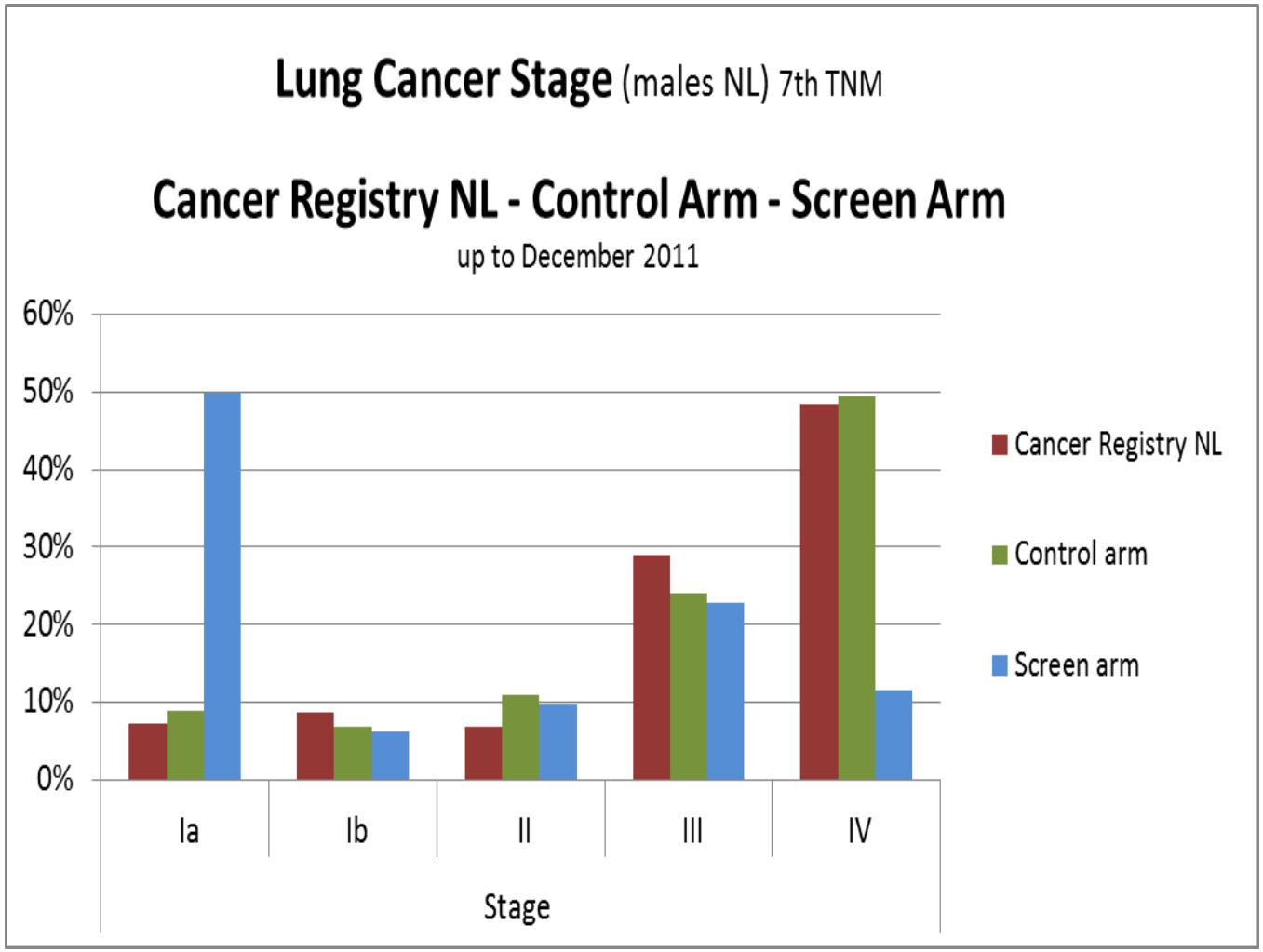
Nanda Horeweg*, Joost van Rosmalen*, Marjolein A Heuvelmans, Carlijn M van der Aalst, Rozemarijn Vliegenthart, Ernst Th Scholten, Kevin ten Haaf, Kristiaan Nackaerts, Jan-Willem J Lammers, Carla Weenink, Harry J Groen, Peter van Ooijen, Pim A de Jong, Geertruida H de Bock, Willem Mali, Harry J de Koning*, Matthijs Oudkerk*

Lancet Oncol 2016; 17: 907–16

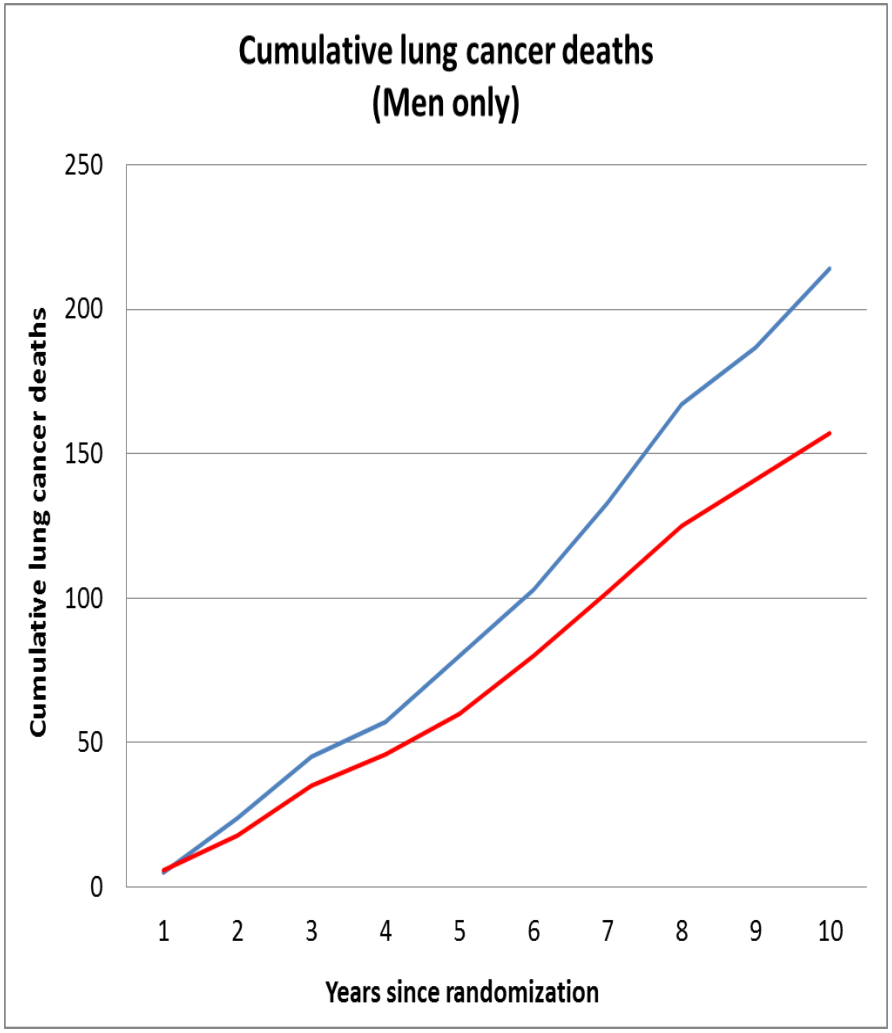
Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial

Joan E Walter, Marjolein A Heuvelmans, Pim A de Jong, Rozemarijn Vliegenthart, Peter M A van Ooijen, Robin B Peters, Kevin ten Haaf, Uraujh Yousaf-Khan, Carlijn M van der Aalst, Geertruida H de Bock, Willem Mali, Harry J M Groen, Harry J de Koning, Matthijs Oudkerk


Cumulative absolute number of first lung cancers
Cumulative absolute number of first lung cancers
450
400
350
300
250
200
150
100
50
0
1
2
3
4
5
6
7
8
9
10
Years since randomization
Control
Screen



Yousaf-Khan et al., in preparation



Control arm:
214 lung cancer deaths

Screen arm:
157 lung cancer deaths

Lung cancer mortality rate ratio (95% CI)	Year 8	Year 9	Year 10
MALES	**0.75** P=0.015 (0.59-0.95)	**0.76** P=0.012 (0.60-0.95)	**0.74** P=0.003 (0.60-0.91)
FEMALES	**0.39** P=0.0037 (0.18-0.78)	**0.47** P=0.0069 (0.25-0.84)	**0.61** P=0.0543 (0.35-1.04)

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

FU 94% complete year 10

NELSON Volume CT screening

- **MALES at high risk for lung cancer have a reduced risk of dying from lung cancer of 26% in the screen arm compared to the male control arm (95% CI 9-40%)**
- **In WOMEN, reductions are consistently more favourable: 39-61%**
- **These results are more favourable than the NLST-results & suggest gender differences**
- **Volume CT lung cancer screening of high risk former and current smokers results in low referral rates (2.3%), and a very substantial reduction in lung cancer mortality (in both genders)**

conclusions

- Aspirin ready for prime time for cancer prevention with some dose adjustement
- Metformin at low dose for CRC prevention?
- Tamoxifen at low dose may change clinical practice in women with IEN
- Lung cancer screening with spiral CT ready for large scale implementation