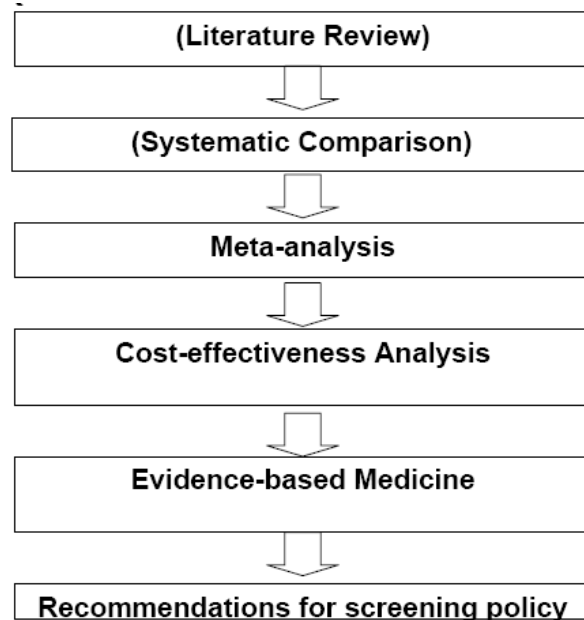


## Module II Study Design for Evaluation of Disease screening

### -Experimental Design

#### 2.1 Synthesis Science on Evidence-Based Medicine



Meta-analysis, decision analysis, and economic evaluation are integrated as “synthesis science”

#### Task Force Ratings

##### 1. Strength of Recommendations

- (1) There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination
- (2) There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination
- (3) There is insufficient evidence to support the recommendation that the condition be specifically considered in a periodic health examination, but recommendations may be made on other grounds

(4) There is fair evidence to support the recommendation that the condition be excluded in a periodic health examination

(5) There is good evidence to support the recommendation that the condition be excluded in a periodic health examination

## **2. Quality of Evidence**

I: Evidence obtained from at least one properly randomized controlled trial

II-1: Evidence obtained from well-designed controlled trials without randomization

II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

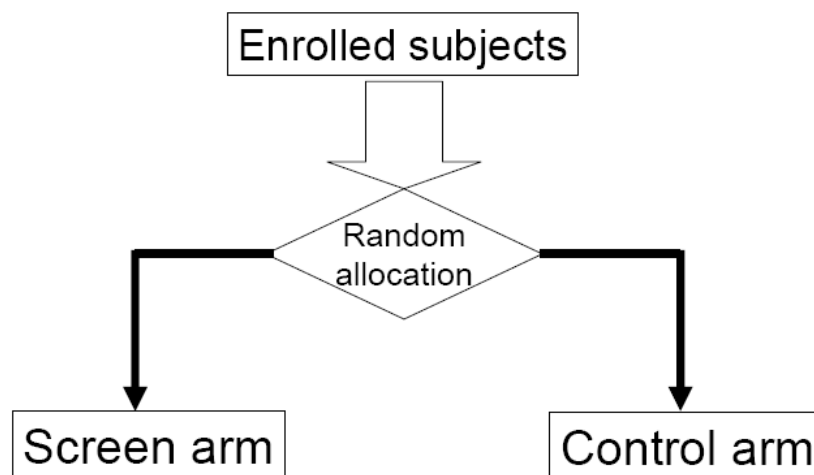
II-3: Evidence obtained from multiple time series with or without the intervention.

III: Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

## 2.2 Randomized Controlled Trial (RCT)

### Study design

## Randomized Controlled Trial (RCT)



## 2.2 Breast Cancer

### 2.2.1 Swedish Two-county Randomized Screening Trial

**2.2.1.1 Cluster Randomization:** The Swedish Two-County Randomized Screening Trial (RCT) is a population-based study, which was randomized by population cluster (communities with typically about 3000 women in the appropriate age group) rather than by individual. Clusters were randomized with in blocks designed to be approximately homogeneous in demographic terms. In Östergötland county, one cluster in each block of two was randomized to invitation to screening. In Kopparberg county, two clusters in each block of three were randomized to screening invitation. (*Ref. Laszlo Tabar, et al. Reduction in mortality from breast cancer after mass screening with mammography. The Lancet. April 15. 1985. pp1829-32*)

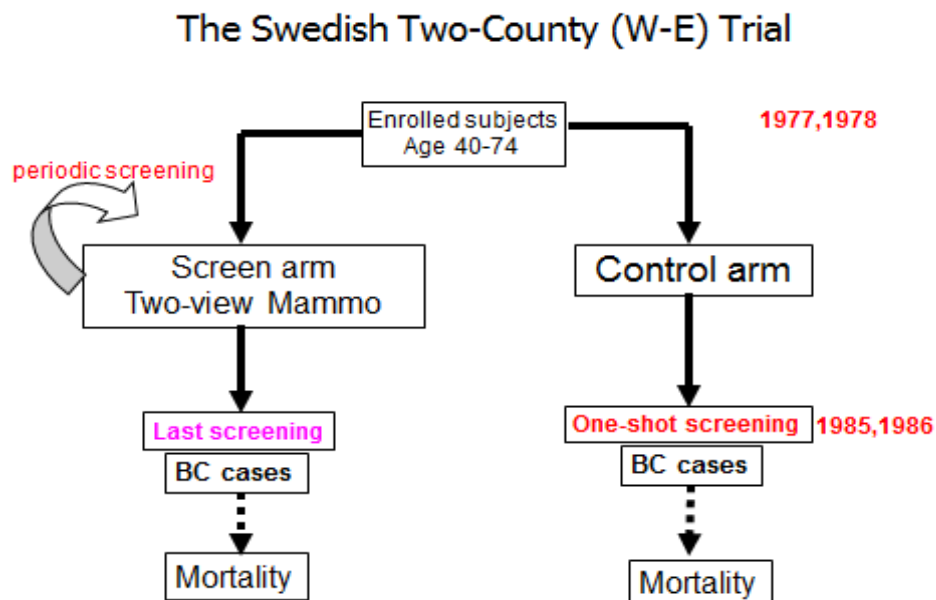
## Basic characteristics of five randomised trials in Sweden

Characteristic	Malmö	Kopparberg (W)	Östergötland (E)	Stockholm	Gothenburg
Study area	Municipality	Province	Province	Southern part	Municipality
Randomisation	Individual	Cluster	Cluster	Cluster	Individual (40-49) Cluster (59-59)
Cluster		Municipality, parish, taxdistrict	Municipality, parish	Day of birth	Day of birth

**2.2.1.2 Study subjects in two arms:** A total of 77,080 women were randomized to screening invitation (hereafter referred to as the active study population, [ASP]) to be compared with 55,985 women recruited as controls (passive study population, [PSP]). Subjects were aged 40 to 74, and the two groups had similar but not identical age distributions. Screening began in October 1977 in Kopparberg and in May 1978 in Östergötland. Subjects eligible for the trial were identified from the Swedish national population registry and those in the ASP received a personal letter of invitation to screening. Women aged 40 to 49 were invited to screening, on average, every 24 months. Women aged 50 to 74 were invited every 33 months (on average).

The study design is slightly different from HIP (Health Insurance Plan) trial that is offered for only a limited time in the intervention group. In the Two-County Trial, after the initial publication of mortality results in 1985 screening was offered to the control group. This was after four rounds of screening in women aged 40 to 49 years, after three rounds in women aged 50 to 69, and after two rounds in those aged 70 to 74. All breast cancers in both arms of the trial diagnosed between randomization and the end of the first

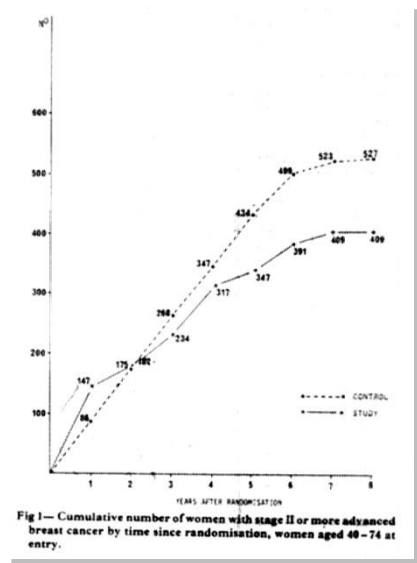
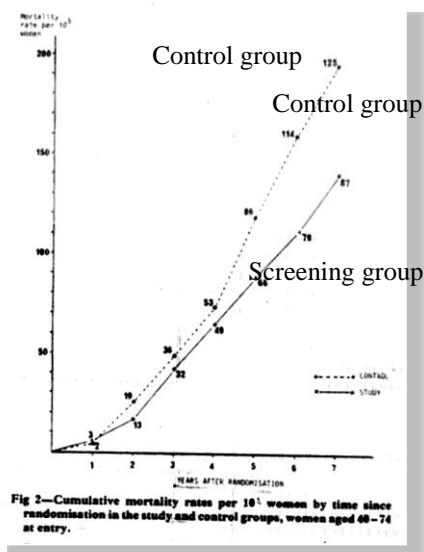
screen of the controls were included in analysis of the trial results. The closing date for each cluster in the ASP was taken as the date of completion of the first screen of the controls in the corresponding cluster in the PSP.



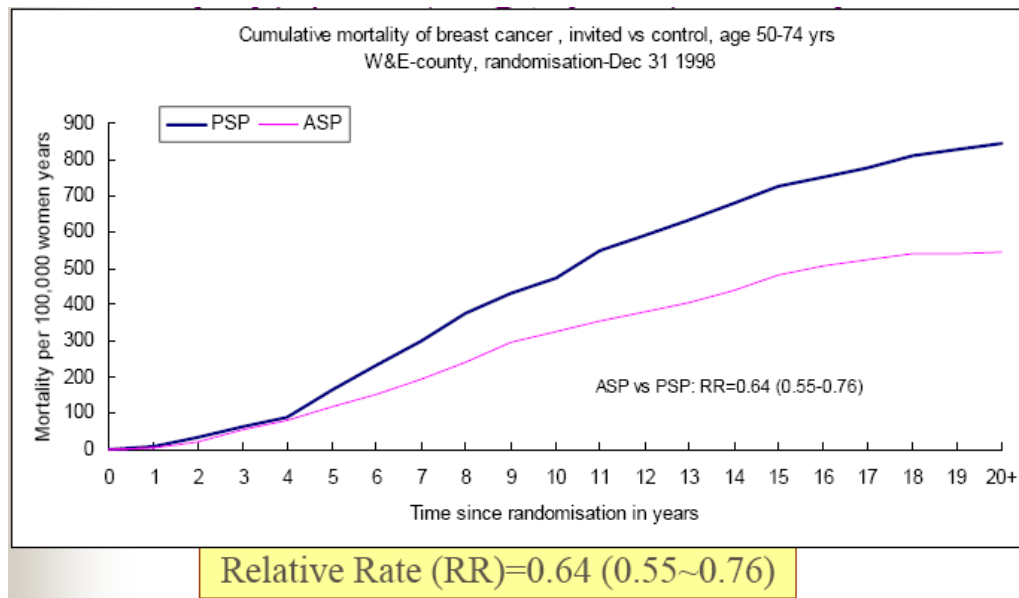
### 2.2.1.3 Comparison of Cumulative Mortality in 1985

## Overall

## Surrogate endpoint



## Mortality Results of Long-term Follow-up for breast cancer



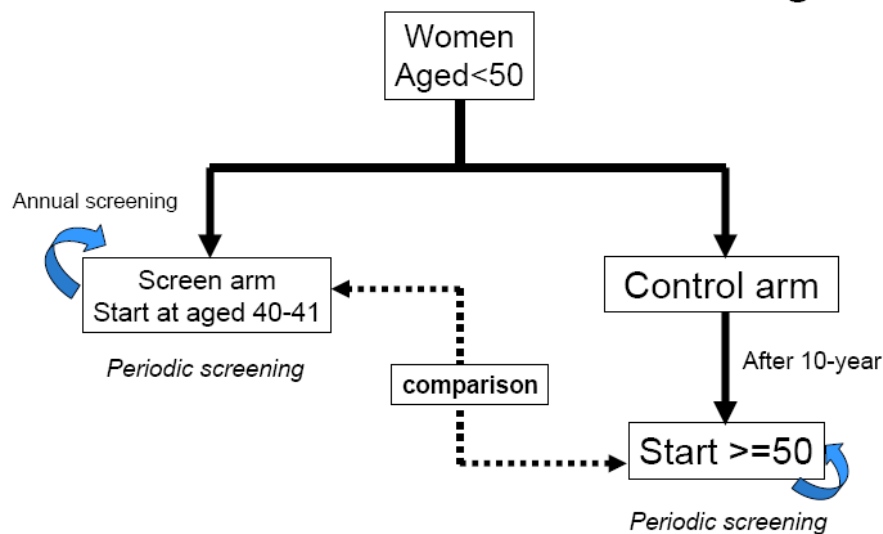
### 2.2.2 Breast cancer screening for Young women

(Ref: Moss, S. M., H. Cuckle, et al. (2006). "Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial." *Lancet*.**368**(9552): 2053-2060.)

The efficacy of screening by mammography has been shown in randomised controlled trials in women aged 50 years and older, but is less clear in younger women. A meta-analysis of all previous trials showed a 15% mortality reduction in invited women aged 40–49 years at study entry, but this finding could be due in part to screening of women after age 50 years. The Age trial was designed to study the effect on mortality of inviting women for annual mammography from age 40 years. 160 921 women aged 39–41 years were randomly assigned in the ratio 1:2 to an intervention group of annual mammography to age 48 years or to a control group of usual medical care.

The trial was undertaken in 23 NHS breast-screening units in England, Wales, and Scotland. The primary analysis was based on the intention-to-treat principle and compared mortality rates in the two groups at 10 years' follow-up.

## Delayed screen design- UK breast cancer screening



	Number of women	Women years	All cause deaths		Breast cancer deaths		Rate ratio (95% CI) intervention vs control group
			n	Rate per 1000 women years	n	Rate per 1000 women years	
Intervention	53 884	578 390	960	1.66	105	0.18	0.83 (0.66–1.04)
Control	106 956	1 149 380	1975	1.72	251	0.22	

Table 2: Mortality from all causes and from breast cancer in the intervention and control groups

At a mean follow-up of 10.7 years there was a reduction in breast-cancer mortality in the intervention group, in relative and absolute terms, which did not reach statistical significance (relative risk 0.83 [95% CI 0.66–1.04],  $p=0.11$ ; absolute risk reduction 0.40 per 1000 women invited to screening [95% CI –0.07 to 0.87]).

	Number of women	Women years	All cause deaths		Breast cancer deaths		Rate ratio* (95% CI) attenders vs control arm
			n	Rate per 1000 women years	n	Rate per 1000 women years	
Attenders	36 538	394 473	495	1.25	68	0.17	0.76 (0.51–1.01)
Non-attenders	17 346	183 917	465	2.53	37	0.20	

\* Adjusted for rates in non-attenders.

**Table 3: Mortality in attenders and non-attenders at first screen in intervention group**

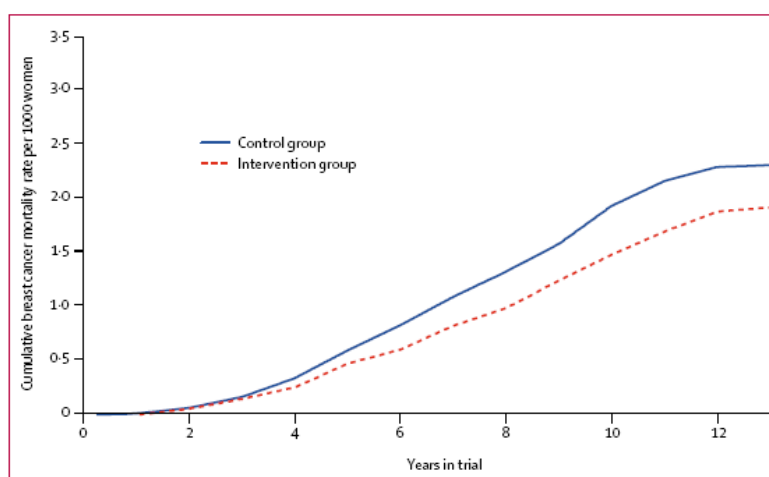


Figure 2: Cumulative breast cancer mortality

Mortality reduction adjusted for non-compliance in women actually screened was estimated as 24% (RR 0.76, 95% CI 0.51–1.01).



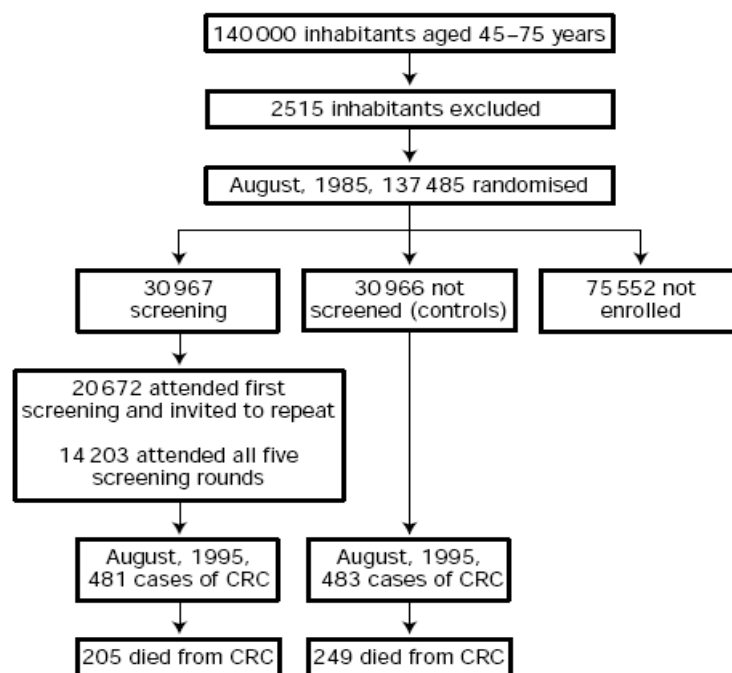
## 2.2.3 Colon Cancer Screening

(Ref:Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996; 348(9040): 1467-71.

Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996; 348(9040): 1472-7.)

### 2.2.3.1 Trial in Denmark

Population-based randomized control trial with FOBT, Denmark



	Screening group					Controls
	Positive test	Before invitation*	Non-responders†	Interval cancers‡	Total	
<b>Stage of CRC</b>						
Dukes' A	48	5	21	31	105 (22%)	54 (11%)
Dukes' B	43	9	66	46	164 (34%)	177 (37%)
Dukes' C	19	1	35	35	90 (19%)	111 (23%)
Distant spread	8	3	60	27	98 (20%)	114 (24%)
No classification	2	0	13	9	24 (5%)	27 (5%)
<b>Total CRC</b>	<b>120</b>	<b>18</b>	<b>195</b>	<b>148</b>	<b>481</b>	<b>483</b>
<b>Adenoma ≥10 mm</b>	<b>270</b>	<b>7</b>	<b>39</b>	<b>97</b>	<b>413</b>	<b>174</b>

\*Had CRC diagnosed or died after randomisation but before first invitation. †Invited to first round but did not respond. ‡Had a negative FOB test at first screening round but had a diagnosis of CRC made between screenings (includes two patients who refused further examination after a positive test).

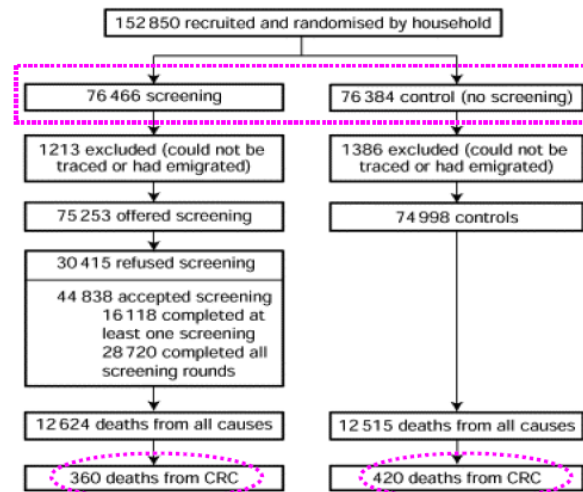
	Screening group	Control group
<b>Observation time in years</b>	281 883	281 328
<b>CRC</b>		
Number of patients	481	483
Incidence rate (per 1000 person-years)	1.71	1.72
Incidence ratio (95% CI)	1.00 (0.87–1.13)	..
<b>Death from CRC</b>		
Number of deaths	182	230
Mortality rate	0.65	0.82
Mortality ratio (95% CI)	0.79 (0.65–0.96)	..
<b>Death from CRC and complications from treatment</b>		
Number of deaths	205	249
Mortality rate	0.73	0.89
Mortality ratio (95% CI)	0.82 (0.68–0.99)	..
<b>Death from all causes</b>		
Number of deaths	6228	6303
Mortality rate	22.09	22.40
Mortality ratio (95% CI)	0.99 (0.95–1.02)	..

Controls are the reference group.

During the 10-year study, 481 people in the screening group had a diagnosis of CRC, compared with 483 unscreened controls. There were 205 deaths attributable to CRC in the screening group, compared with 249 deaths in controls. CRC mortality, including deaths attributable to complications from CRC treatment, was significantly lower in the screening group than in controls (mortality ratio 0.82 [95% CI 0.68–0.99])  $p=0.03$ )

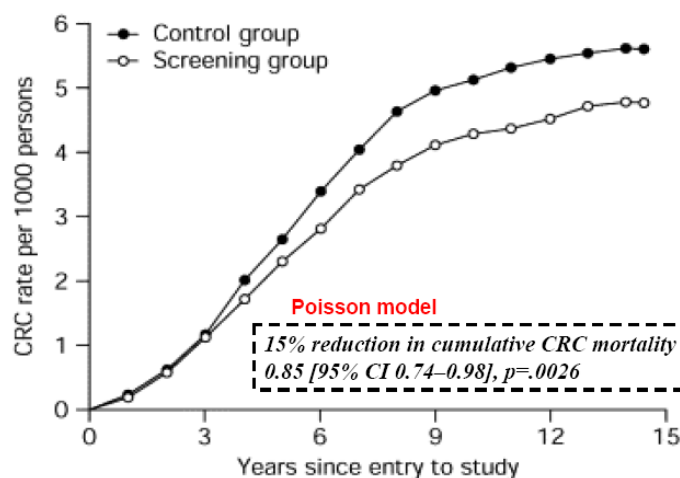
### 2.2.3.2 Trial In Nottingham

Population-based,  
randomized control trial with FOBT, UK



Hardcastle JD. *Lancet* 1996; 348: 1472–77.

### Comparison of CRC mortality



Median follow-up was 7.8 years (range 4.5–14.5). 360 people died from CRC in the screening group compared with 420 in the control group—a 15% reduction in cumulative CRC mortality in the screening group (odds ratio=0.85 [95% CI 0.74–0.98],  $p=0.026$ ).

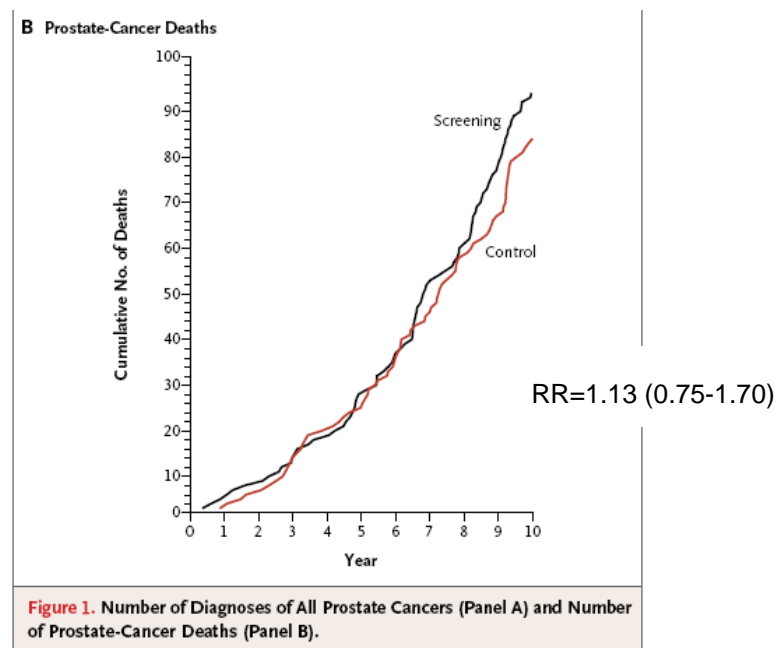
## 2.2.4 Prostate Cancer Screening

(Ref:

1. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. The New England journal of medicine. 2009; **360**(13): 1310-9.
2. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. The New England journal of medicine. 2009; **360**(13): 1320-8.
3. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. The New England journal of medicine. 2012; **366**(11): 981-90.)

### 2.2.4.1 PLCO trial in USA

76,693 men were randomly assigned at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years.

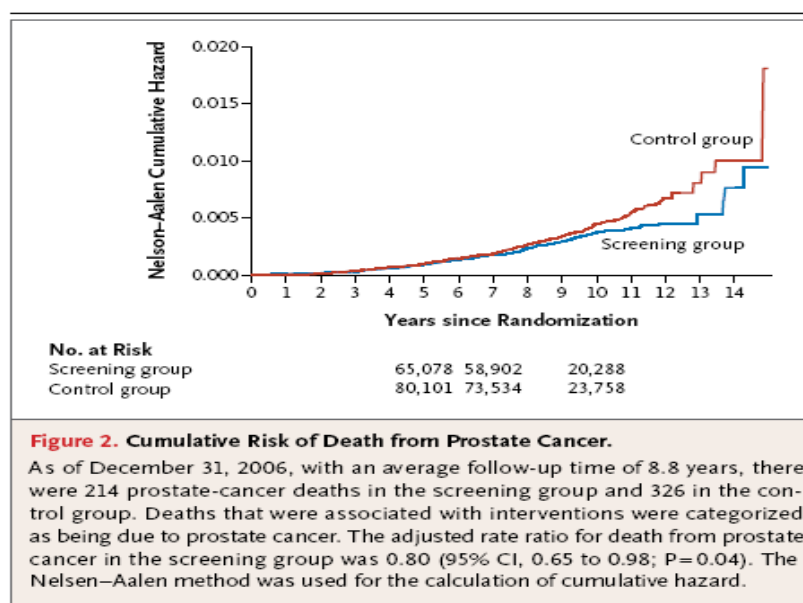


After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70).

#### 2.2.4.2 ERSCP Trial

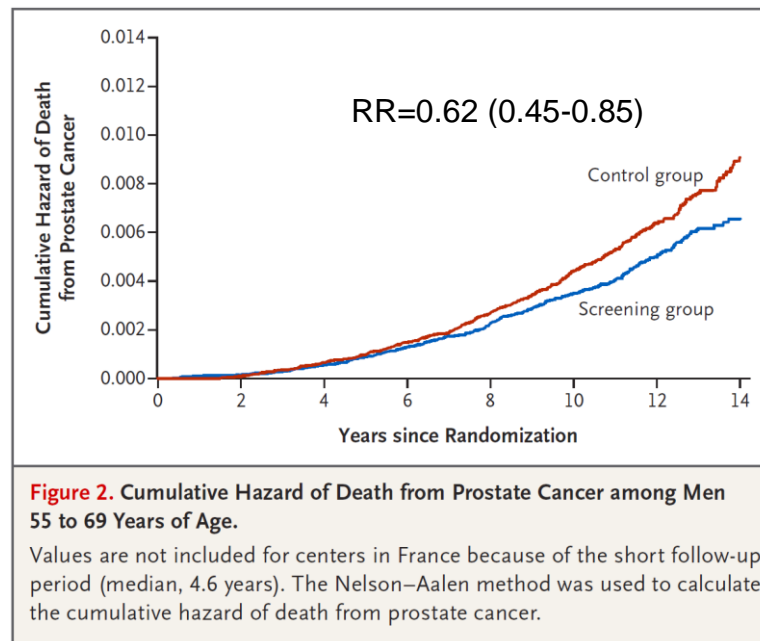
(Ref: Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. The New England journal of medicine. 2009; **360**(13): 1320-8.)

182,000 men between the ages of 50 and 74 years were randomly assigned through registries in seven European countries for inclusion in our study. The men were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening.



The rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% confidence interval [CI], 0.65 to 0.98; adjusted P=0.04).

#### 2.2.4.3 ERSCP Trial-11 years follow-up



After a median follow-up of 11 years in the core age group, the relative reduction in the risk of death from prostate cancer in the screening group was 21% (rate ratio, 0.79; 95% confidence interval [CI], 0.68 to 0.91; P=0.001), and 29% after adjustment for noncompliance.

#### 2.2.4.4 Lung Cancer Screening—Continuous Screen design

(Ref: Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. Journal of the National Cancer Institute. 2000; **92**(16): 1308-16.)

## ARTICLES

### Lung Cancer Mortality in the Mayo Lung Project: Impact of Extended Follow-up

*Pamela M. Marcus, Erik J. Bergstralh, Richard M. Fagerstrom, David E. Williams, Robert Fontana, William F. Taylor, Philip C. Prorok*

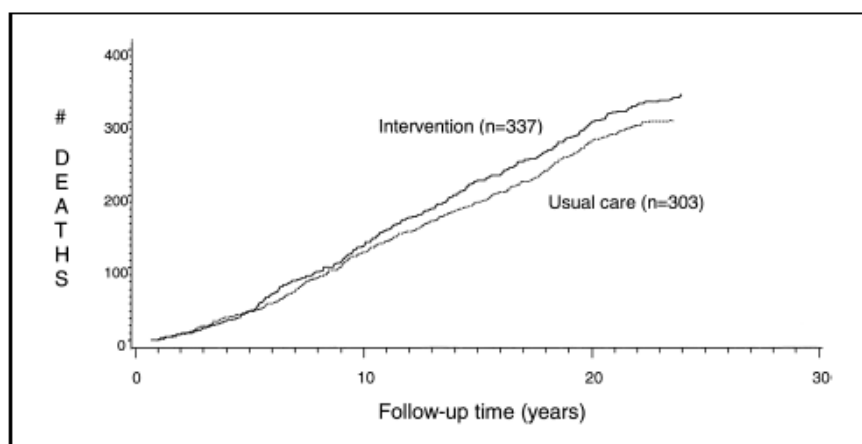
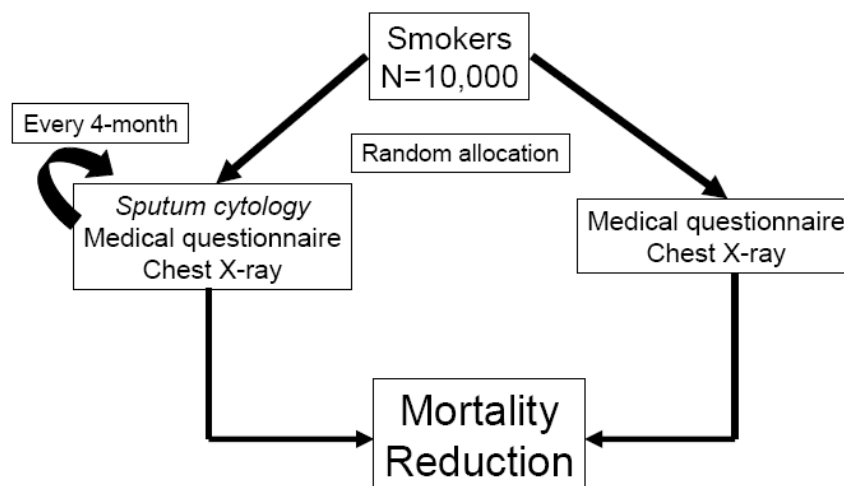


Table 2. Mortality in the Mayo Lung Project, as of December 31, 1996

Cause of death*	Deaths, No. (%)		Mortality rate (95% confidence interval) per 1000 person-years	
	Intervention arm (n = 4607)	Usual-care arm (n = 4585)	Intervention arm (76 760.7 person-years)	Usual-care arm (76 772.4 person-years)
Lung cancer	337 (7)	303 (7)	4.4 (3.9–4.9)	3.9 (3.5–4.4)
Causes other than lung cancer	2148 (47)	2133 (47)	28.0 (26.8–29.2)	27.8 (26.6–29.0)
Cancers other than lung cancer	403 (9)	391 (9)	5.3 (4.8–5.8)	5.1 (4.6–5.6)
Chronic obstructive pulmonary disease	156 (3)	149 (3)	2.0 (1.7–2.4)	1.9 (1.6–2.3)
Ischemic heart disease	816 (18)	816 (18)	10.6 (9.9–11.4)	10.6 (9.9–11.4)
Other respiratory causes	60 (1)	44 (1)	0.8 (0.6–1.0)	0.6 (0.4–0.8)
Other	712 (15)	733 (16)	9.3 (8.6–10.0)	9.5 (8.9–10.3)
All causes	2493 (54)	2445 (53)	32.5 (31.2–33.8)	31.8 (30.6–33.1)

Lung cancer mortality was 4.4 (95% confidence interval [CI] = 3.9–4.9) deaths per 1000 person years in the intervention arm and 3.9 (95% CI = 3.5–4.4) in the usual-care arm (two-sided P for difference = .09). Extended follow-up of MLP participants did not reveal a lung cancer mortality reduction for the intervention arm.

#### **2.2.4.5 Screening for Chronic Disease**

**(Ref:** Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. *Lancet*. 2012; **380**(9855): 1741-8.)

In a pragmatic parallel group, cluster-randomised trial, 33 general practices in eastern England were randomly assigned by the method of minimisation in an unbalanced design to: screening followed by intensive multifactorial treatment for people diagnosed with diabetes (n=15); screening plus routine care of diabetes according to national guidelines (n=13); and a no-screening control group (n=5). The study population consisted of 20,184 individuals aged 40-69 years (mean 58 years), at high risk of prevalent undiagnosed diabetes, on the basis of a previously validated risk score. In screening practices, individuals were invited to a stepwise programme including random capillary blood glucose and glycated haemoglobin (HbA(1c)) tests, a fasting capillary blood glucose test, and a confirmatory oral glucose tolerance test. The primary outcome was all-cause mortality. All participants were flagged for mortality surveillance by the England and Wales Office of National Statistics. Analysis was by intention-to-screen and compared all-cause mortality rates between screening and control groups.



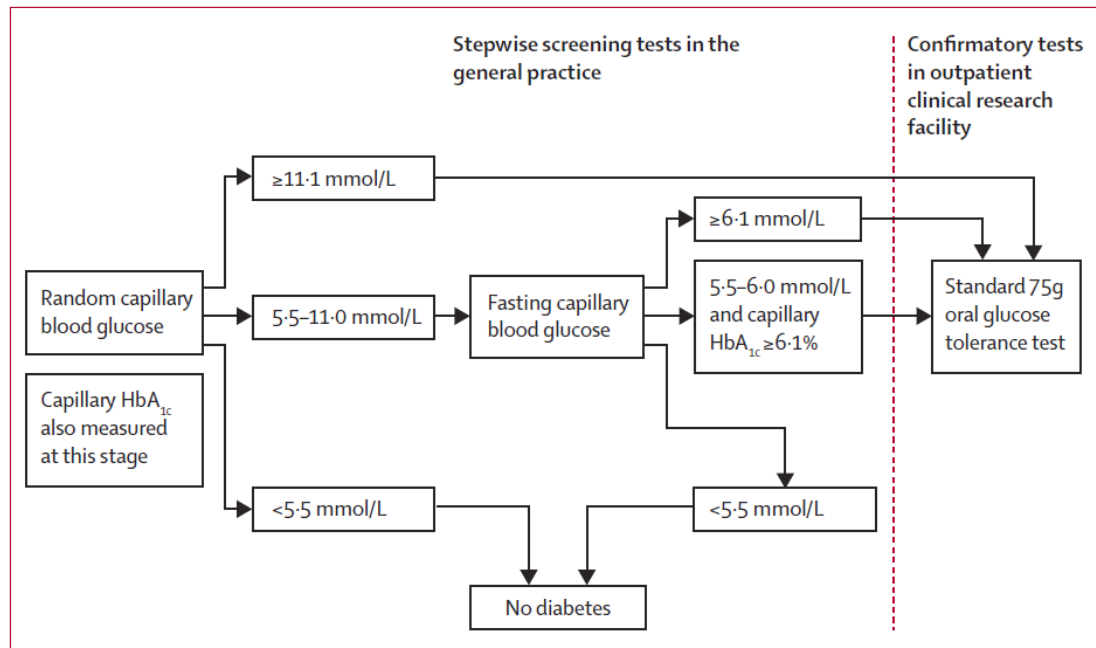


Figure 1: ADDITION-Cambridge screening and diagnostic procedure  
HbA<sub>1c</sub>=glycated haemoglobin.

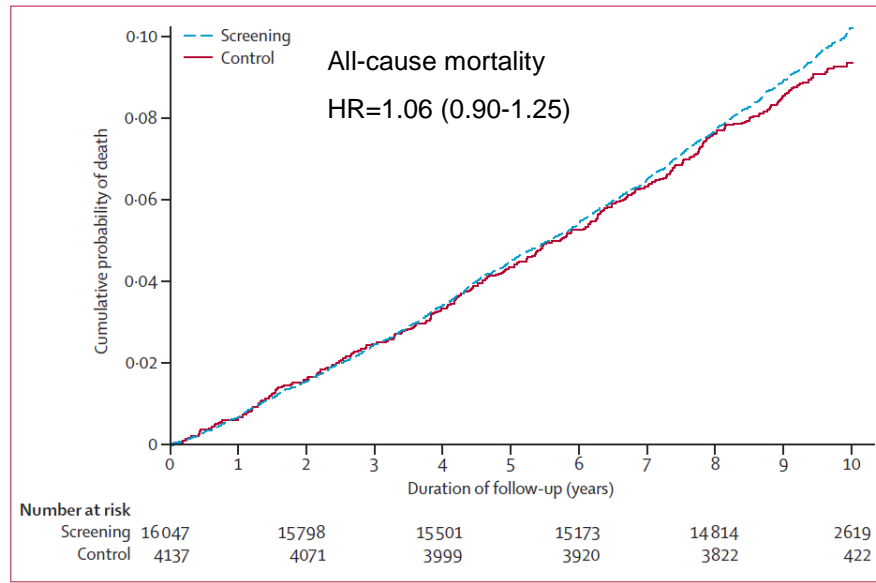
Of 16,047 high-risk individuals in screening practices, 15,089 (94%) were invited for screening during 2001-06, 11,737 (73%) attended, and 466 (3%) were diagnosed with diabetes. 4137 control individuals were followed up. During 184,057 person-years of follow up (median duration 9.6 years [IQR 8.9-9.9]), there were 1532 deaths in the screening practices and 377 in control practices (mortality hazard ratio [HR] 1.06, 95% CI 0.90-1.25). We noted no significant reduction in cardiovascular (HR 1.02, 95% CI 0.75-1.38), cancer (1.08, 0.90-1.30), or diabetes-related mortality (1.26, 0.75-2.10) associated with invitation to screening.

In this large UK sample, screening for type 2 diabetes in patients at increased risk was not associated with a reduction in all-cause, cardiovascular, or diabetes-related mortality within 10 years. The benefits of screening might be smaller than expected and restricted to individuals with detectable disease.

	No-screening control group			Screening group			Hazard ratio (95%CI)*
	Number of deaths	Person-years of follow-up	Rate per 1000 person-years (95% CI)	Number of deaths	Person-years of follow up	Rate per 1000 person-years (95% CI)	
All-cause mortality	377	38 126	9.89 (8.94-10.94)	1532	145 930	10.50 (9.99-11.04)	1.06 (0.90-1.25)
Cardiovascular mortality	124	38 126	3.25 (2.73-3.88)	482	145 930	3.30 (3.02-3.61)	1.02 (0.75-1.38)
Cancer mortality	169	38 126	4.43 (3.81-5.15)	697	145 930	4.78 (4.43-5.14)	1.08 (0.90-1.30)
Other causes of death	84	38 126	2.20 (1.78-2.73)	353	145 930	2.42 (2.18-2.68)	1.10 (0.87-1.39)

\*Accounting for clustering.

**Table 2: Incidence of death by study group and hazard ratios for mortality in the ADDITION-Cambridge trial**



**Figure 3: Cumulative incidence of death in the screening and no screening control groups in the ADDITION-Cambridge trial**

## **2.3 Meta-analysis**

### **2.3.1 Breast Cancer Screening**

**(Ref:**

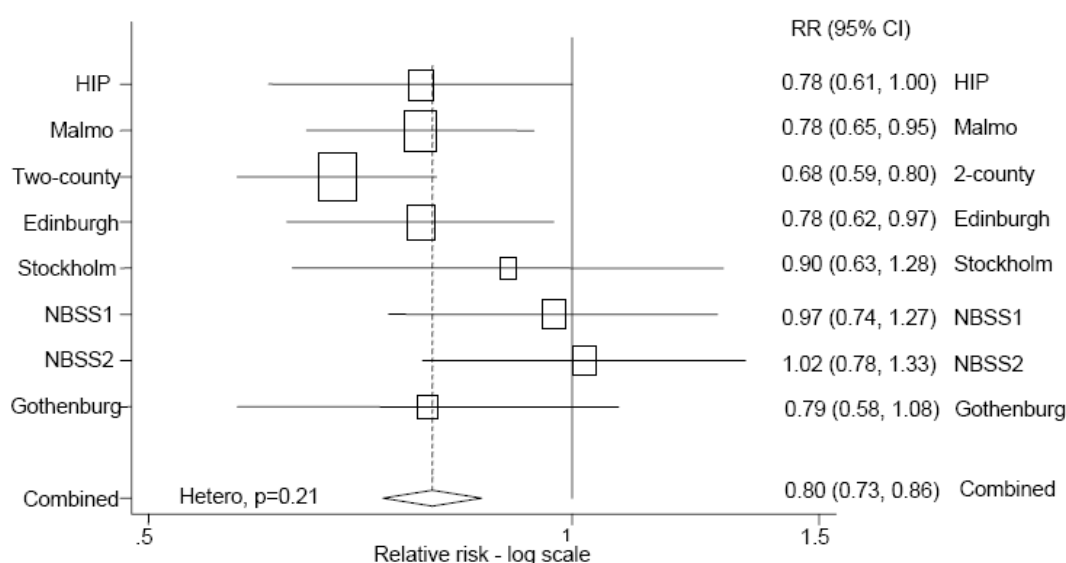
Smith RA, Duffy SW, Gabe R, et al. The randomized trials of breast cancer screening: what have we learned? Radiologic clinics of North America. 2004; 42(5): 793-806, v.

Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet. 2012; **380**(9855): 1778-86.)

#### **2.3.1.1 Results of Eight randomized controlled trails**

Eight randomized controlled trials of mammography screening have been conducted to date. In addition to evaluating the efficacy of screening with an experimental design, the trials provided investigators with access to information about breast cancers much earlier in their development than had previously been available. The trials of mammographic screening provide conclusive evidence that the policy of offering screening is associated with a significant and substantial reduction in breast cancer mortality.

## RCT results for breast screening



Overall, 20% reduction in breast cancer mortality associated with invitation to screening mammography

### 2.3.1.2 Independent UK Panel Review

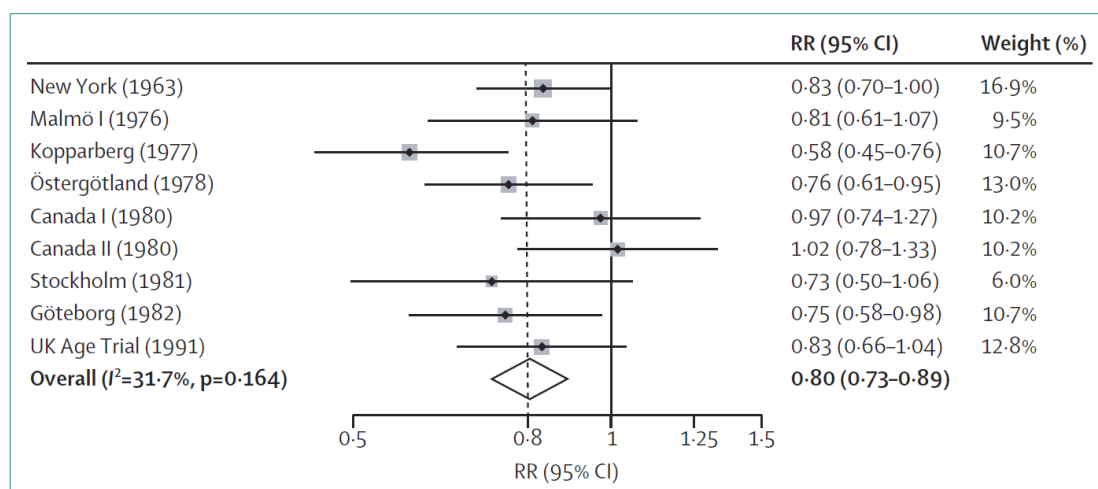


Figure 1: Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials

In a meta-analysis of 11 randomised trials, the relative risk of breast cancer mortality for women invited to screening compared with controls was 0.80 (95% CI 0.73—0.89), which is a relative risk reduction of 20%.

### 2.3.1.3 Meta-analysis for young women

(Ref: Report of the Organizing Committee and Collaborators FM, Falun, Sweden. Breast-cancer screening with mammography in women aged 40-49 years. Swedish Cancer Society and the Swedish National Board of Health and Welfare. International journal of cancer. 1996; **68**(6): 693-9.)

For some years, there has been a perceived need for more information on the effect of screening for breast cancer in women aged 40 to 49. Our approach was to gather the most recent data on screening in this age group, to assess the following quantities: the likely benefit in mortality terms, measures of screening performance and arrest of tumour progression through screening, costs and public-health implications, and prospects for future screening and research. A collaborative meeting was held in Falun, Sweden, for which data were gathered in advance from all the randomized trials of breast-cancer screening that included women in this age group, and all identifiable substantial databases on service screening of women aged 40 to 49. Updated results from the Swedish overview of mammographic screening trials indicated relative mortality associated with invitation to screening of 0.77 (95% confidence interval 0.59-1.01). Combining all population-based randomized trials gave the relative-mortality figure of 0.76 (0.62-0.93), and combining all trials gave 0.85 (0.71-1.01).

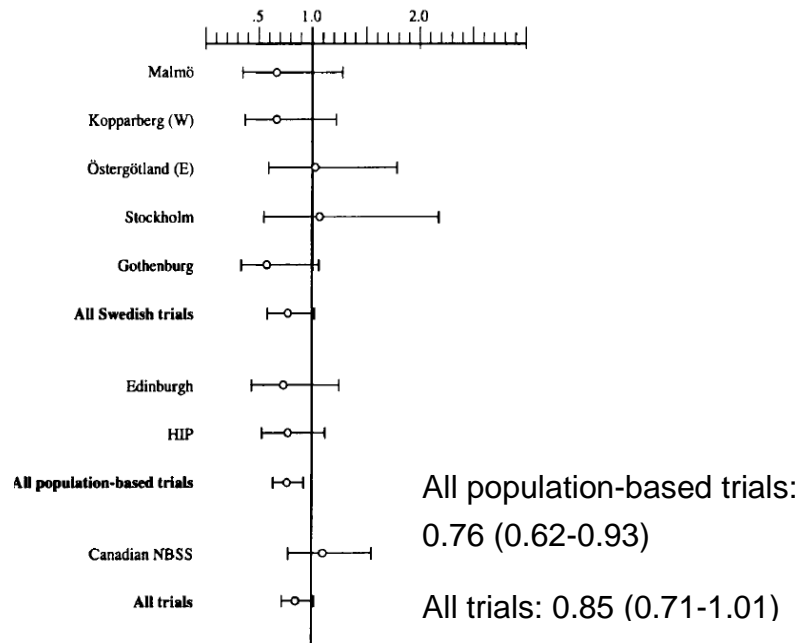


FIGURE 1 – Relative mortality in the age group 40 to 49 from breast cancer in randomized trials of breast-cancer screening (invitation vs. no invitation), with overall results from the Swedish trials, all population-based trials, and all trials.

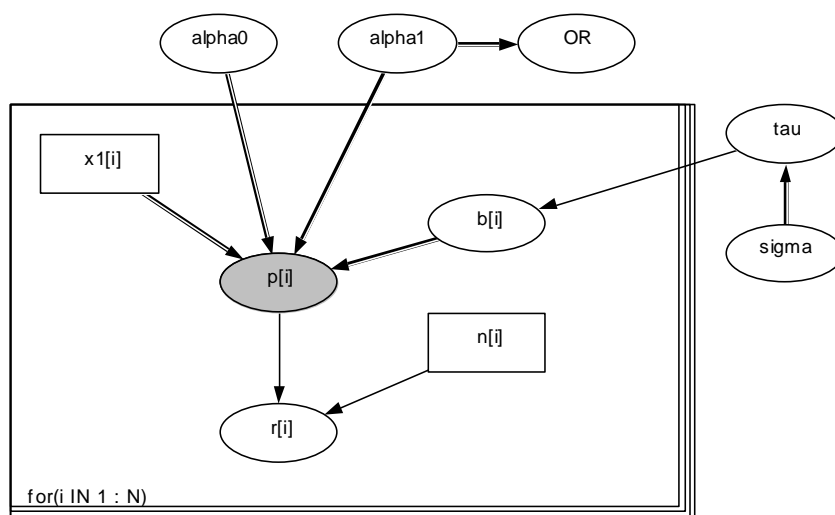
## Result from SAS

0.84 (0.71-0.99) [M-H test]

0.84 (0.71-1.00) [Logit method]

## Result from Bayesian analysis

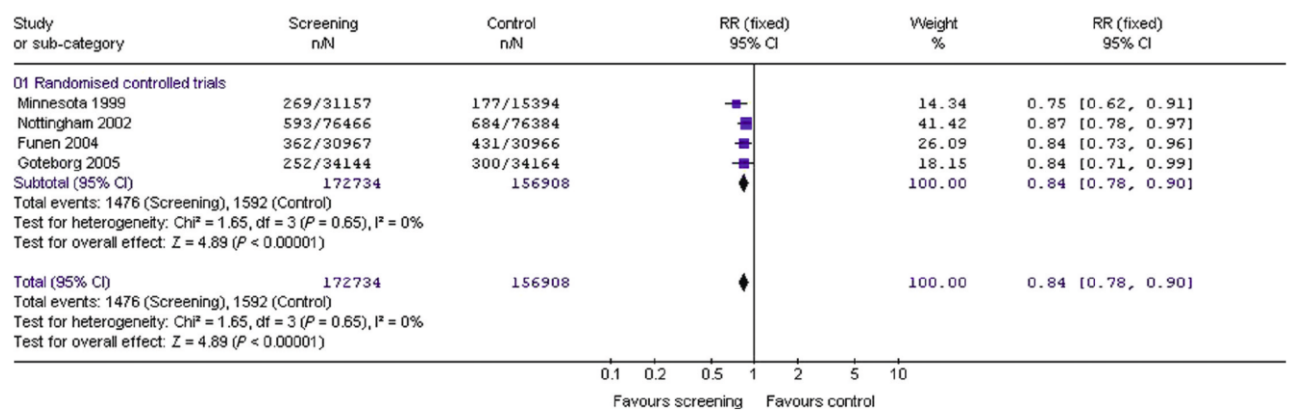
name:  $p[i]$  type: logical link: logit  
value:  $\alpha_0 + \alpha_1 * x1[i] + b[i]$



OR=0.78 (0.52-1.07)

### 2.3.2 Colorectal Cancer Screening

(Ref: Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. The American journal of gastroenterology. 2008; **103**(6): 1541-9.)



**Figure 1.** Effects of screening with Hemoccult on mortality from CRC (fixed effects model).

Combined results from the four eligible RCTs indicated that screening had a 16% reduction in the relative risk (RR) of CRC mortality (RR 0.84, 95% confidence interval [CI] 0.78-0.90). There was a 15% RR reduction (RR 0.85, 95% CI 0.78-0.92) in CRC mortality for studies that used biennial screening. When adjusted for screening attendance in the individual studies, there was a 25% RR reduction (RR 0.75, 95% CI 0.66-0.84) for those attending at least one round of screening using the FOBT. This review confirms previous research demonstrating that FOBT screening reduces the risk of CRC mortality.

### 2.3.3 Lung Cancer

(Ref: Chien CR, Chen TH. Mean sojourn time and effectiveness of mortality reduction for lung cancer screening with computed tomography. International journal of cancer. 2008; **122**(11): 2594-9.)

TABLE III – ESTIMATED MEAN SOJOURN TIME AND SENSITIVITY OF INDIVIDUAL TRIALS

Author	Gohagan <i>et al.</i> <sup>13,1</sup>	Henschke <i>et al.</i> <sup>14</sup>	Diederich <i>et al.</i> <sup>16</sup>	Sone <i>et al.</i> <sup>17</sup>	Pastorino <i>et al.</i> <sup>19</sup>	Novello <i>et al.</i> <sup>29</sup>
MST (year) <sup>2</sup>	2.53	3.86	1.38	1.68	2.02	2.13
MST: 95%CI	1.50–3.88	3.42–3.99	0.63–3.18	1.06–3.02	1.06–3.63	0.96–3.75
Sensitivity (%) <sup>2</sup>	97	99	89	97	97	96
Sensitivity: 95%CI	70–99	97–99	51–99	80–99	74–99	63–99

95% CI, 95% confidence interval.

<sup>1</sup>Arm of computed tomography only. <sup>2</sup>Means sojourn time, median.

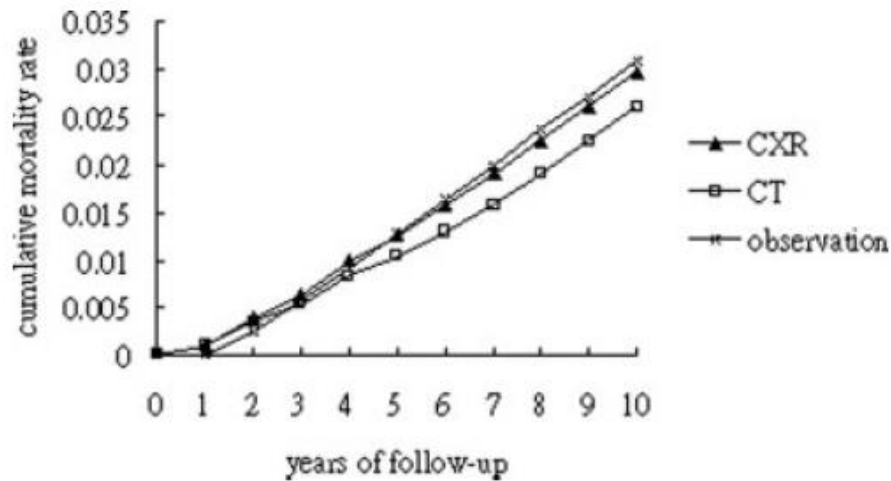


FIGURE 2 – Cumulative mortality rate among 3 study arms in NELSON-like setting.

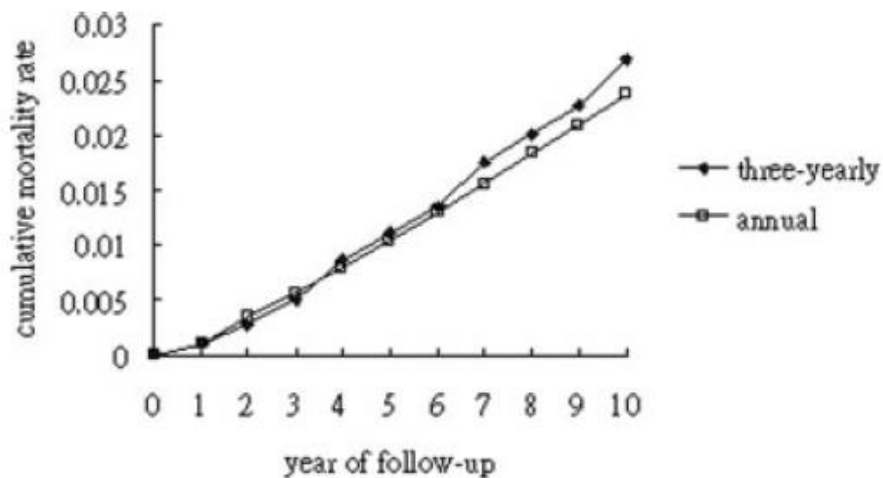


FIGURE 3 – Comparison of cumulative mortality rates between 2 different screening schedules (3-yearly program vs. annual program) by CT.

By simulating the scenario similar to NELSON study, CT screen may gain an extra of 0.019 year of life expectancy per person, yields 15% mortality reduction (relative risk (RR): 0.85, 95% confidence interval



[95%CI: (0.58-1.01)]. Approximate 23% [RR: 0.77, 95%CI: (0.43-0.98)] mortality reduction would be achieved by annual CT screening program. The mortality findings in conjunction with higher sensitivity and shorter MST estimate given data on prevalent and incident (2nd) screen may provide a tentative evidence, suggesting that annual CT screening may be required in order to be effective in reducing mortality before the results of randomized controlled studies available.

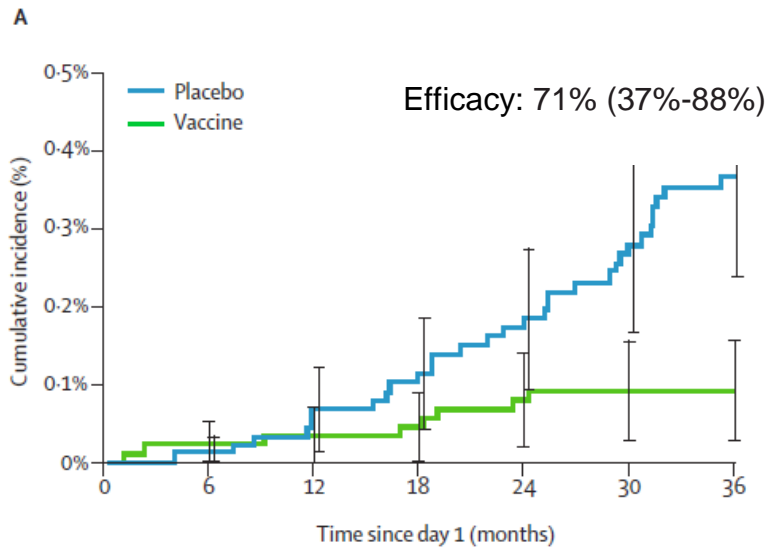
### 2.3.4 Cervical Cancer Screening

(Ref:

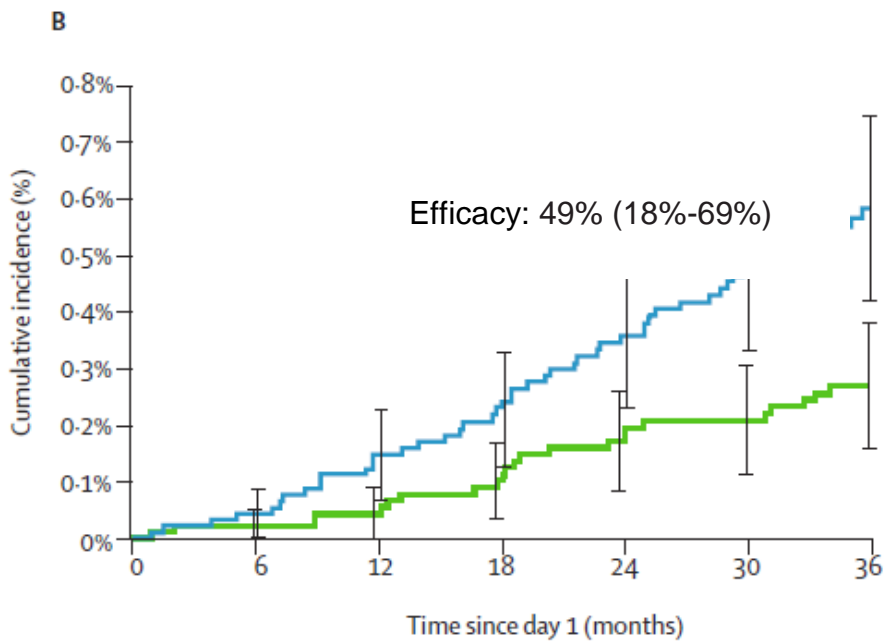
1. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet*. 2007; **369**(9574): 1693-702.
2. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet*. 2007; **369**(9576): 1861-8.)

2.3.4.1 Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials

18 174 women (16-26 years) were enrolled and randomised to receive either quadrivalent HPV6/11/16/18 L1 virus-like-particle vaccine or placebo at day 1, and months 2 and 6.



A. Time to HPV16-related or HPV18-related VIN2-3 or VaIN2-



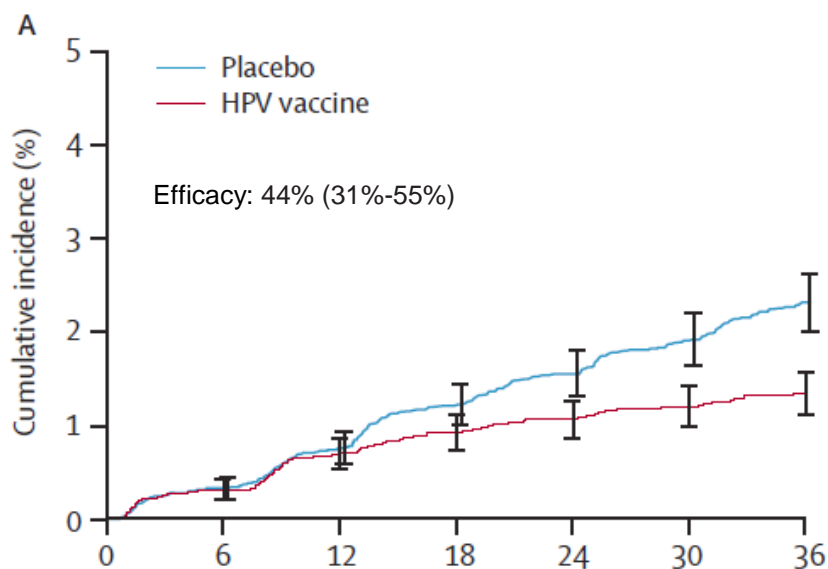
B. Time to any VIN2-3 or VaIN2-3, irrespective of causal HPV type.

The mean follow-up time was 3 years. In the intention-to-treat population (which included 18 174 women who, at day 1, could have been infected with HPV16 or HPV18), vaccine efficacy against VIN2-3 or VaIN2-3 associated with HPV16 or HPV18 was 71% (37-88). The vaccine was 49% (18-69)

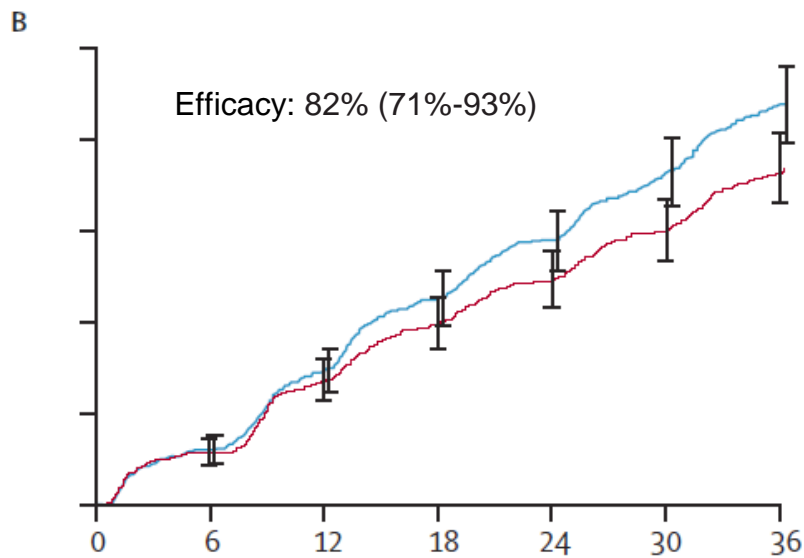
effective against all VIN2-3 or ValN2-3, irrespective of whether or not HPV DNA was detected in the lesion.

#### 2.3.4.2 Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials

20,583 women aged 16-26 years were randomised to receive quadrivalent HPV6/11/16/18 vaccine (n=9087), its HPV16 vaccine component (n=1204), or placebo (n=10 292). Mean follow-up was 3.0 years (SD 0.66) after first dose.



A. Cumulative plot of time to HPV16/18-related CIN2/3 or AIS.



B. Cumulative plot of time to any CIN2/3 or AIS due to any HPV type

In an intention-to-treat analysis of all randomised women (including those who were HPV16/18 naive or HPV16/18-infected at day 1), efficacy was 44% (95% CI 31-55); all but one case in vaccine recipients occurred in women infected with HPV16 or HPV18 before vaccination. In a second intention-to-treat analysis we noted an 18% reduction (95% CI 7-29) in the overall rate of CIN2/3 or AIS due to any HPV type.

Administration of HPV vaccine to HPV-naive women, and women who are already sexually active, could substantially reduce the incidence of HPV16/18-related cervical precancers and cervical cancer.

## 2.4 Epidemiological evaluation

### 2.4.1 Primary endpoint evaluation

- Mortality Reduction
- Incidence Reduction– Screening for pre-cancerous lesion

### 2.4.2 Cumulative incidence (CI)

(A) Simple CI

$$CI_{(0,1)} = \frac{1}{12}$$

$$CI_{(0,5)} = \frac{5}{12} \quad \text{for } t(\text{follow-up time}) < 5.5 \text{ days}$$

(B) Life-Table method (Non-parametric method)

$$CI_{(0,1)} = \frac{1}{12 - \frac{1}{2}} = 0.087$$

We can get the following table.

k	Time interval ( $t_{k-1}, t_k$ )	Population at risk	Incident cases	Death	$CI_k$	$CI_{(t_0, t_k)}$
1	(0, 1)	12	1	1	0.087	0.087
2	(1, 2)	10	1	2	0.111	0.188
3	(2, 3)	7	2	3	0.364	0.484
4	(3, 4)	2	1	0	0.500	0.742
5	(4, 5)	1	0	1	0.000	0.742
Total	(0, 5)	-	5	7	-	-

$$CI_{(t_0, t_2)} = 1 - (1 - 0.087)(1 - 0.111) = 0.188$$

$$\text{General formula: } CI_{(t_0, t_k)} = 1 - \prod_{k'=1}^k (1 - CI_{k'})$$

### (C) Exponential Method (Parametric Method)

We need the parameter of hazard rate ( $\lambda$ ) for defining the exponential distribution ( $S(t) = e^{-\lambda t}$ )

$$F(t) = 1 - S(t)$$

$$= 1 - e^{-\lambda t}$$

$$CI_{(t_0, t)} = 1 - e^{-ID \times \Delta t}$$

Approximate method:  $CI_{(t_0, t)} = ID \times \Delta t$

#### ※Optional

Maclaurin series ( $e^x = 1 + x + \frac{x^2}{2!} + \frac{x^3}{3!} + \dots$ ).

$$\text{When } ID \text{ or } \Delta t \text{ is small, } CI_{(t_0, t)} = 1 - e^{-ID \times \Delta t} = 1 - \left\{ 1 - ID \times \Delta t + \underbrace{\frac{(-ID \times \Delta t)^2}{2!} + \frac{(-ID \times \Delta t)^3}{3!} + \dots}_{\text{ignore}} \right\} = ID \times \Delta t$$

$$\widehat{ID}_1 = \frac{1}{11} = 0.091$$

$$\widehat{CI}_{(0, 1)} = 0.087$$

$$\widehat{ID}_2 = \frac{1}{8.5} = 0.118$$

$$\widehat{CI}_{(0, 2)} = 1 - \exp[-0.091 \times (1) - 0.118 \times (1)] = 0.188$$

⋮

$$CI_{(t_0, t_k)} = 1 - \exp \left[ - \sum_{k'=1}^k ID_{k'} (\Delta k') \right]$$

k	Time interval	Cell (CT)	time	Incident cases	$ID_k$	$CI_{(t_0, t_k)}$
1	(0, 1)	11		1	0.091	0.087
2	(1, 2)	8.5		1	0.118	0.188
3	(2, 3)	4.5		2	0.444	0.480
4	(3, 4)	1.5		1	0.667	0.733
5	(4, 5)	0.5		0	0.000	0.733
Total	(0, 5)	26		5	0.192	-

If we assume a constant ID(=0.192), we get 62%CI during 5-year period by using  $1 - e^{-0.192 \times 5} = 0.62$  .

## 2.5 Statistical Model

### Poisson regression model

$$\log(\mu) = \log(\text{person} - \text{years}) + \alpha + \beta x + \varepsilon$$

where  $x = 1$  for the screening group, and  $x=0$  for the control group

$$H_0: \beta = 0$$

$$H_1: \beta \neq 0$$

