Risk-based screening and overdiagnosis

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Breast cancer screening effects

- Current thinking is to present absolute benefits and harms of screening
- Rather high absolute rates of overdiagnosis and low absolute rates of breast cancer deaths prevented have recently been quoted

Absolute benefit- number needed to screen

- How many women do we need to screen to save one life from breast cancer?
- Screening sceptics tend to quote very large figures for the number needed to screen to save one life- typically 1,500-2,000 needed to screen for ten years
- These figures are miscalculated for two reasons
  - They confuse numbers invited with numbers screened (typically 75% of number invited)
  - They confuse years of follow-up with years of screening

Results at 20 years follow-up in the Two-County trial

Quantity	Study group	Control group
No. randomised	77,080	55,985
Br. Ca. deaths	319	334
Rate/1000	4.14	5.97
Deaths prevented	141	-
Number screened	65,518	-
Number needed	465	
Mammograms/life	1,499	-

Notes

- We use the intention to treat estimate of the absolute benefit but calculate the screening activity rather than the invitation activity which obtained the benefit
- We had seven years of screening but 20 years of follow-up
- Screening 1,000 women for ten years would save three lives

Need for long follow-up

- If we had carried out the analysis at 6 years, we would have found 1,800 needed to screen to prevent one death
- At ten years, the figure would have been 800
- For estimation of absolute benefit of screening, long term follow up is essential

The UK Breast Screening Programme

- Started 1988-90, ages 50-64, now 50-70
  - Planned extension 47-73
- Three-yearly, two-view mammography
- We have data on breast cancer mortality in England from 1976-2004
- Consider mortality split by
  - Age: 50-69 vs other age groups
  - Epoch 1973-88, 1989-94, 1995-2004

Mortality by age group and epoch

Age group	Breast cancer deaths/1,000/year by epoch		
	1976-88	1989-94	1995-2004
<50	0.09	0.09	0.08
50-69	0.98	0.93	0.71
70+	1.71	1.92	1.74
RR 50-69	1.00	0.84*	0.72*

* Relative to 1976-88 and other two age groups, $p<0.001$

Mortality reduction

- Net reduction of 28% in 50-69 age group, NOT observed in other groups ($p<0.001$)
- Corresponds to a total of 14,856 breast cancer deaths avoided
  - On average 4 million women screened for 13 years
- For 1000 women screened for ten years, 2.9 breast cancer deaths prevented

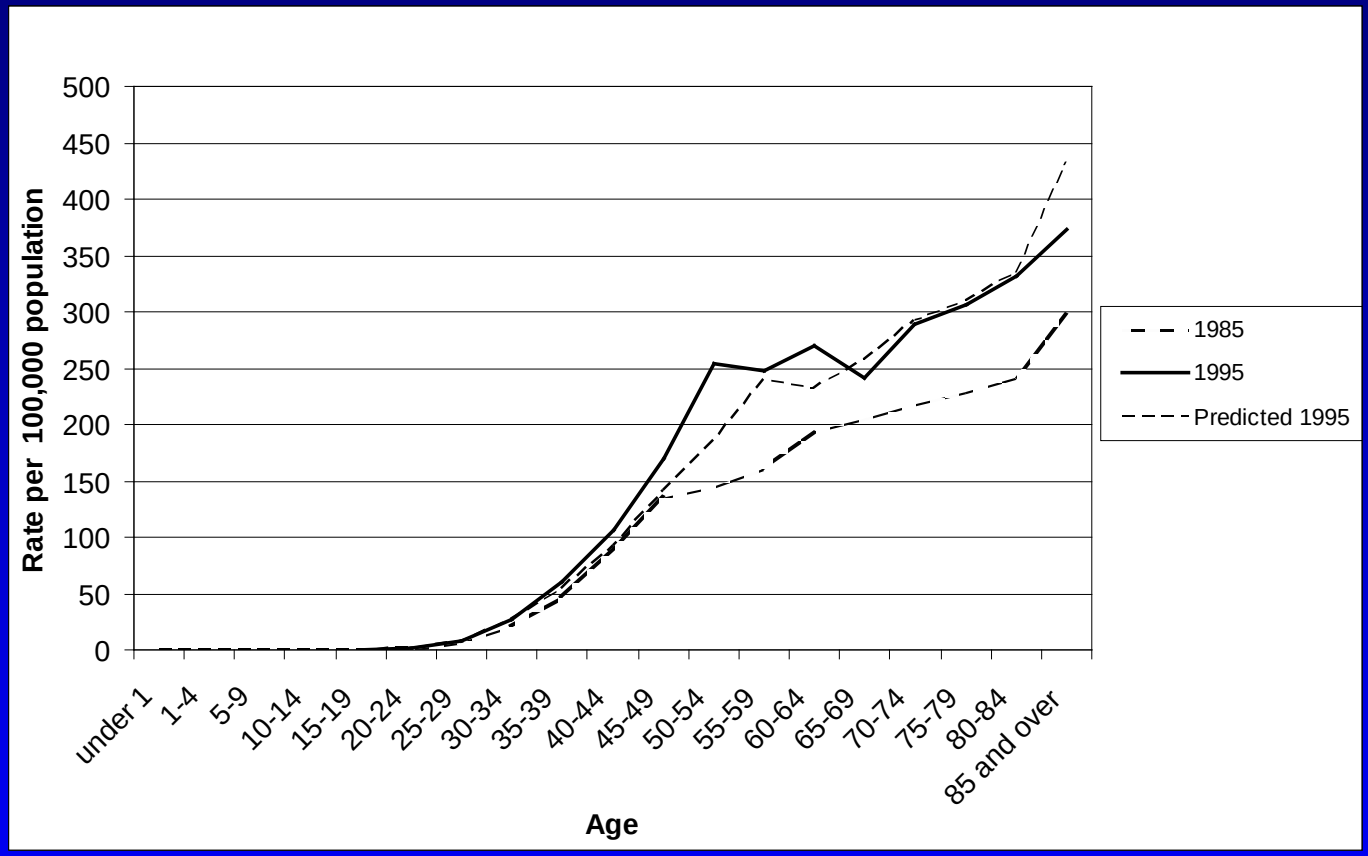
Overdiagnosis

- Defined as the diagnosis by screening of cancer which would not have arisen in the lifetime of the host had screening not taken place
- Invariably, an excess incidence is observed when screening is introduced
- Only part of this is due to overdiagnosis

Sources of excess incidence

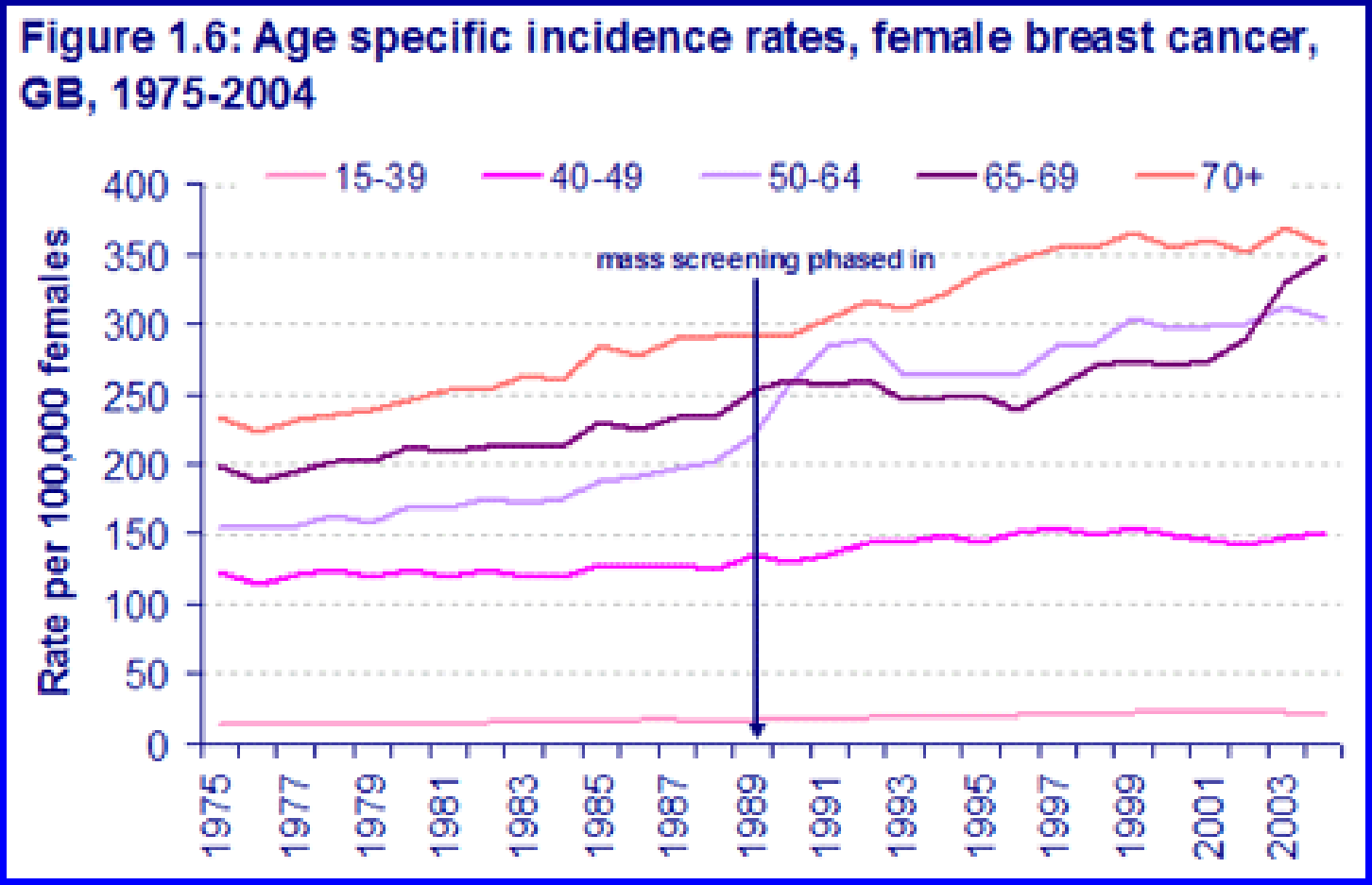
1. Pre-existing trend of increasing incidence
2. Bringing forward of future higher rates by lead time in the presence of existing increasing incidence trend
3. Excess due to lead time of large harvest of prevalence screen tumours at start of programme
4. Continuing age-specific excess due to advance in age at diagnosis
5. Continuing excess from prevalence screens of those reaching the lower age limit for screening
6. Overdiagnosis

Lead time and age



The dotted line shows UK incidence of breast cancer in 1985, the solid line 1995 and the dashed line the expected incidence in 1995 from pre-1985 trends

Incidence by age, UK



Age-period analysis of English incidence, 1974-2003

1. Poisson regression to estimate log-linear trends in incidence 1974-88, for age groups <45, 45-49, 50-64, 65-69, 70+
2. Calculation of expected numbers 1989-2003, along with relative risks
3. Divided expected numbers and relative risks by the relative risk for ages <45, to take account of non-linear effects

Observed and expected cases

Age	Observed cases	Expected cases	O-E
45-49	42,962	40,467	2,495
50-64	168,253	145,706	22,547
65-69	47,044	49,844	-2,800
70+	168,656	184,837	-16,181

Overdiagnosis?

- At ages 45-64 there was a 25,042 excess of cases
- At ages 65+ there was an 18,981 deficit
- The overall excess was 6,061
- 3% (6,061/184830) of the cases diagnosed at ages 45-64 were overdiagnosed
  - Approximately 1.2 per 1,000 screened for 10 years

Benefit/harm balance

- For every 2 lives saved, less than one overdiagnosed case
- There are other harms (false positives etc), but these are well tolerated
- Claims of 6 times as many overdiagnosed cases as lives saved clearly do not apply

DCIS

- The overdiagnosis figures are for invasive cancers only
  - Past DCIS figures for trend calculation were not available
- However
  - estimation from the 2-county trial including in situ gave similar benefit-harm balance
  - Even if we assume that DCIS cases are 4 times more likely to be overdiagnosed than invasive, lives saved would still outnumber overdiagnosis

Overdiagnosis and risk-based screening

- There is overdiagnosis in breast screening but it is outweighed by the benefit in lives saved
- No room for complacency
- Would risk based screening have implications for overdiagnosis?

Data sources

- Cohort study in Sweden
  - Risk by invasion and histological grade
- Case-control study of breast cancer in Singapore
  - Risk by detection mode (screen/symptomatic)
- Case-control study of breast density within UK breast screening programme
  - Risk by grade and detection mode

Swedish Cohort Study

Risk factor	RR for			
	DCIS	Grade 1	Grade 2	Grade 3
Dense breasts	1.4	1.7	1.2	1.5
Nulliparity	2.0	1.3	0.9	1.4
Late first birth	2.5	1.5	1.2	2.0
High BMI	1.6	1.0	2.9	0.7
Family history	0.8	1.4	1.9	1.9
Mother affected	-	1.7	1.6	3.3

Singapore Case-Control Study

Risk factor	OR for	
	Screen-detected cancer	Symptomatic cancer
Density (per 10%)	1.4	1.2
Nulliparity	1.8	1.4
Early menarche	1.2	0.7
High BMI	1.0	1.3
Family history	2.1	3.1
Late first birth	0.9	1.6

UK Case-Control Study

Tumour category	OR for Wolfe P2/DY
DCIS	1.8
Invasive	1.5
Grade 1	1.6
Grade 2	1.2
Grade 3	2.2
Prevalence screen	1.4
Incidence screen	1.3
Interval cancers	2.1

Tentative implications

- Family history more associated with aggressive invasive disease and symptomatic tumours
- Density results mixed but some indication of stronger association with grade 3 invasive and symptomatic disease
- Screening intensity based on these factors (especially FH) would probably not exacerbate overdiagnosis

Thank you