International Cancer Screening Network (ICSN)
Oxford, June 23-25, 2010

Methodological approaches for the estimate of overdiagnosis in mammography screening: the cumulative incidence method and the Florence city (Italy) experience

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Overdiagnosis and breast cancer

"Detection of in situ or invasive breast cancers that would have never clinically surfaced in the absence of screening"

It's the combination of two causes:

1. the natural history of the disease (detection of not progressive cancers)

2. the presence of competing causes of death (detection of potentially progressive cancer in a woman who is going to die from other causes in the near future)

Paci and Duffy, Breast Cancer Research, 2005

A clear distinction must be done between:

Excess of incidence due to lead time, during thescreening period **needed** for reducing breast cancer mortality

and

overdiagnosis, i.e. the detection of cancers at screening that would never have clinically surfaced in the absence of screening

In the service screening context the possible reasons for an observed excess of incidence are:

1) increasing incidence trend before the start of service screening;
2) peak in incidence due to prevalence screening;
3) peak of incidence in subsequent screening
4) a small peak due to women at first screening (new entry for age or migration) in the subsequent rounds;
5) a shift in the age-incidence curve due to lead time;
6) overdiagnosis.

Can we disantangle overdiagnosis from excess of incidence?

Paci and Duffy, Br Cancer Res, 2005

Measures of overdiagnosis

- ➔ Overdiagnosis in a population invited to screening
- ➔ Increase risk of having a BC diagnosis for women undergoing screening
- ➔ % of screen detected cases that are overdiagnosed

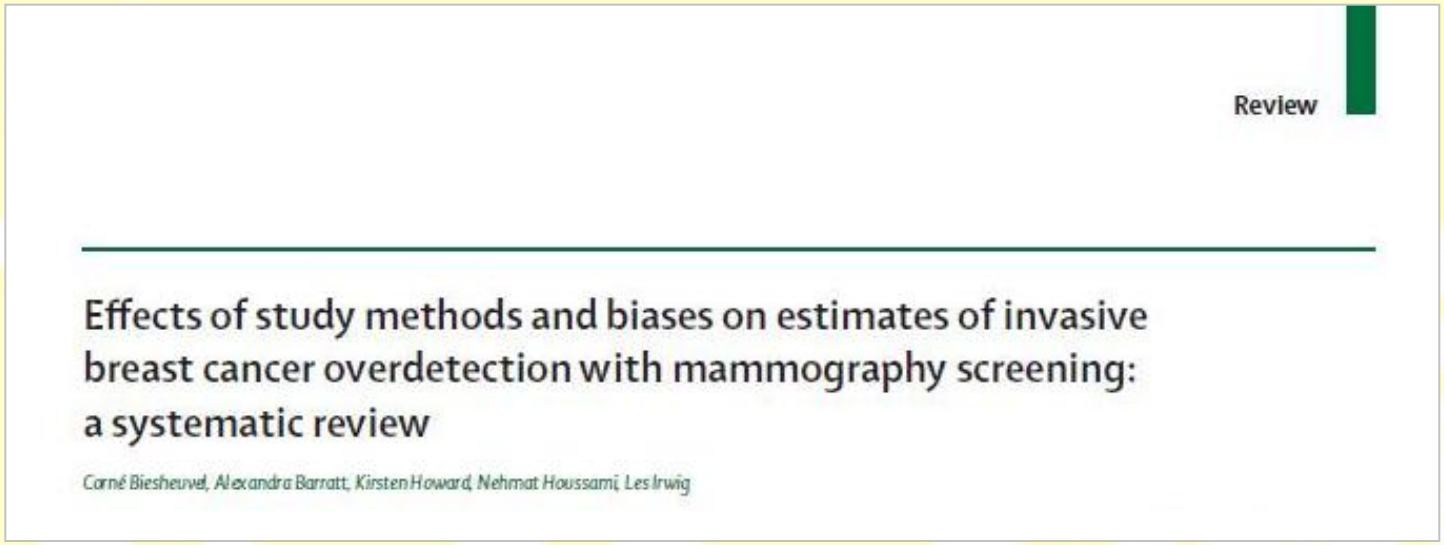
.. IN ORDER TO ESTIMATE OVERDIAGNOSIS WE NEED :

Analysis of a fixed cohort: Invited to screening or actually screened.

Comparison group: Women with the same age who are not screened (not invited) over the same time period with a similar underlying risk of breast cancer (randomised trial).
If figures are derived from observational data, adjustments for different breast cancer risk are needed (es. time trends).

Long follow up : Sufficient follow-up after the last screen (5 years or more) – cumulative-incidence method; otherwise lead-time bias should be adjusted for with statistical methods.

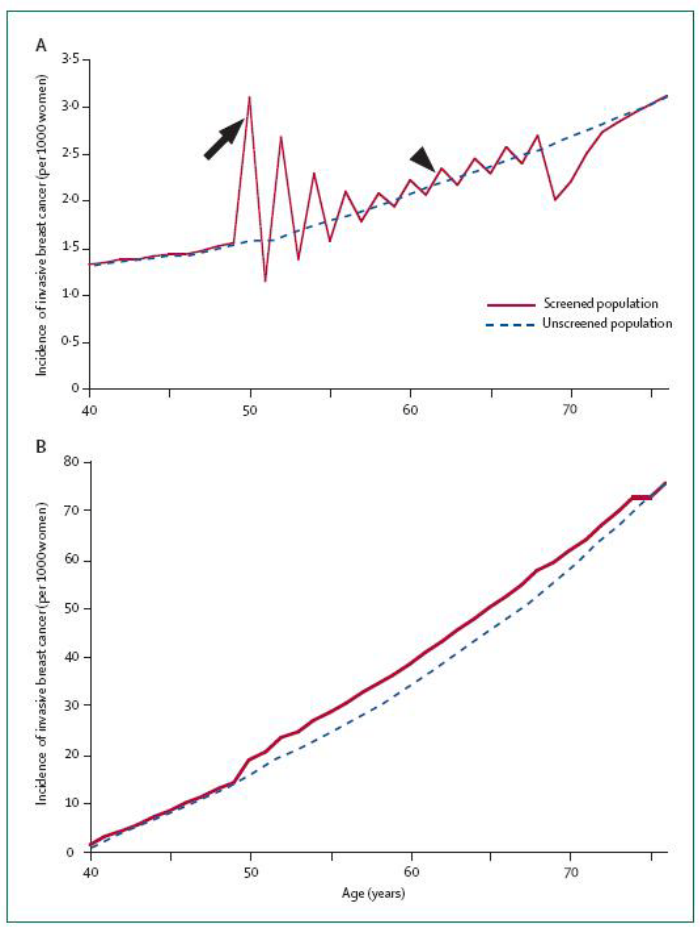
METHODS TO ESTIMATE OVERDETECTION:



A) "The theoretically most robust method to estimate overdetection is the **cumulative-incidence approach** with data from a randomised controlled trial, in which there is more than several years of follow-up after screening stops, and the control group is never screened."

B) "If there is little or no follow-up after the last screen, there will be lead-time bias that should be adjusted for statistical methods, otherwise the estimate of overdetection will be too high." **(adjusted for lead-time method)**

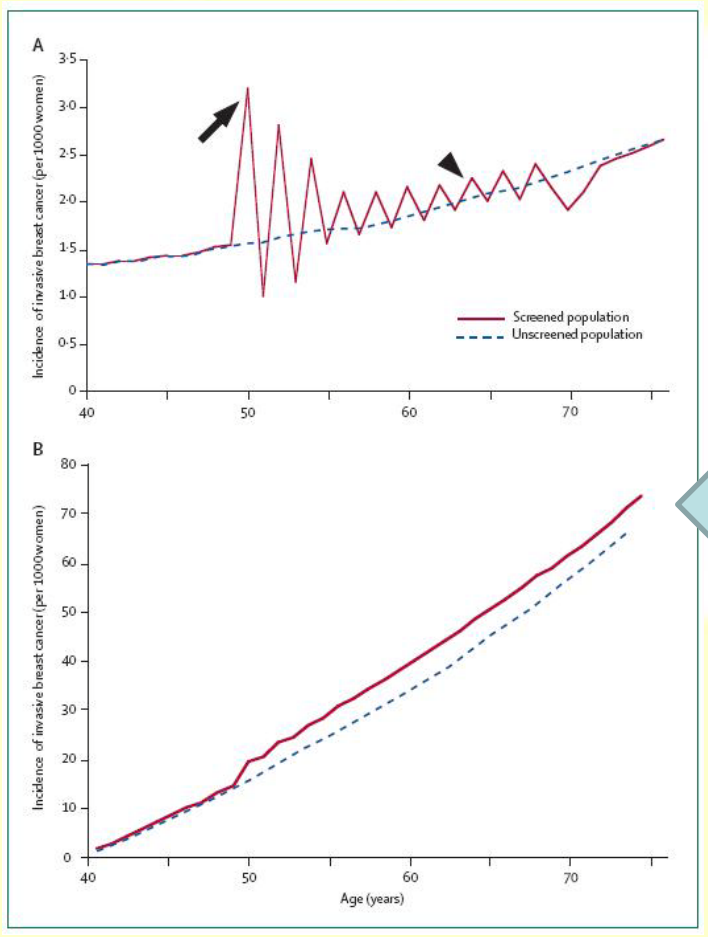
Figure 1.
Effect of biennial screening of women 50-68 years on incidence of invasive breast cancer in the absence of overdiagnosis.



Several years after the screening end, if there is no overdiagnosis, the cumulative incidence will be identical in the two groups.

Biesheuvel et al, Lancet Oncology, 2007

Figure 2.
Effect of biennial screening of women 50-68 years on incidence of invasive breast cancer in the presence of overdiagnosis.



Cumulative incidence method:

The comparison of cumulative incidence in the two groups several years after screening stops is a valid estimate of overdiagnosis

Biesheuvel et al, Lancet Oncology, 2007

APPLICATION OF THE CUMULATIVE-INCIDENCE METHOD TO FLORENTINA DATA:

EUROPEAN JOURNAL OF CANCER 45 (2009) 3166–3171

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

An estimate of overdiagnosis 15 years after the start of mammographic screening in Florence

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Objective: To evaluate the degree of overdiagnosis of breast cancer 15 years after the introduction of mammographic service screening in Florence in the year 1991.

Method: Cumulative incidence method.

Measure: The measure of overdiagnosis is the ratio of cumulative incidence of breast cancers in the invited group at least 5 years after the last screen to that in the non-invited group.

Invited group (observed):

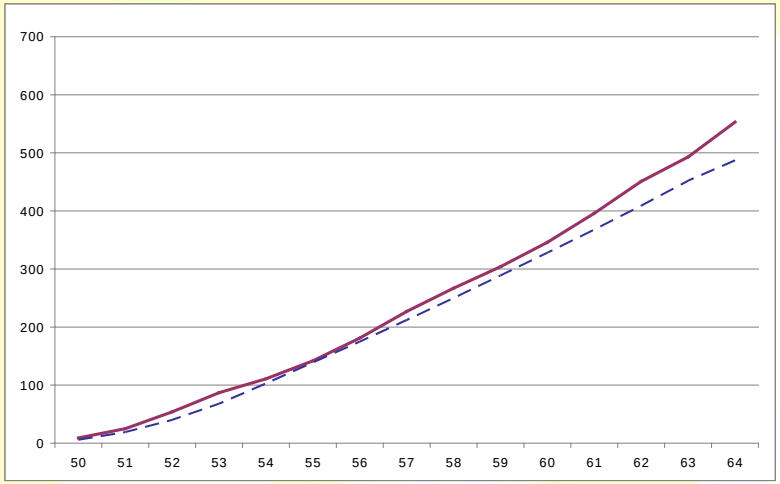
Cohort of women aged 50-69 at the beginning of service screening (61.568 women) and follow up for breast cancer incidence between 1991 and 2004.

Non-invited group (expected):

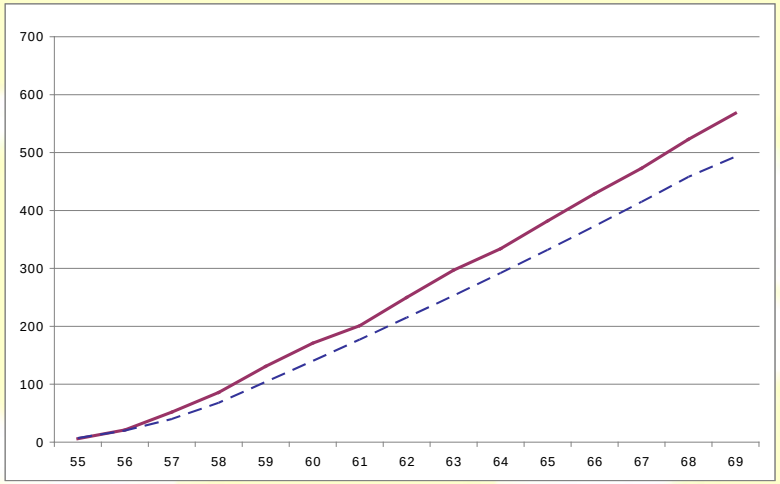
A Poisson regression model (with age and calendar year) was fitted to Florentine pre-screening incidence data (1986-1990) and the annual trend was forced to 1.2% (pooled estimate in North-Central Italy).

FIGURE 2. Invited (observed) and non-invited (expected) cumulative breast cancer cases by age at the beginning of service screening:

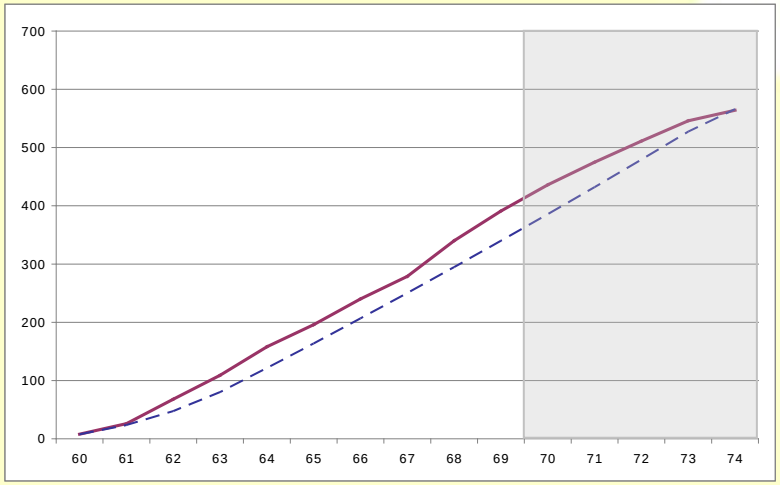
a) 50- 54 years



b) 55-59 years



c) 60-64 years



d) 65-69 years

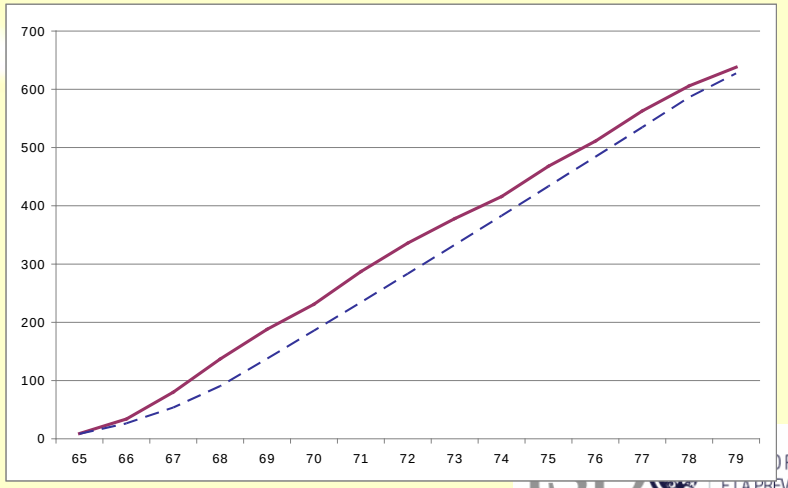


TABELLA 1.

Incidence excess and estimate of overdiagnosis by birth cohort.

Age at the start of service screening	Years of screening	Incidence excess (95%CI) in the last year of screening	Years after screening stopped	Estimate of overdiagnosis (95%CI)
50-54	**15**	1.15 (1.06 to 1.24)	**0**	n.e.
55-59	**15**	1.15 (1.06 to 1.25)	**0**	n.e.
60-64	**10**	1.15 (1.04 to 1.27)	**5**	1.00 (0.92 to 1.08)
65-69	**5**	1.36 (1.18 to 1.57)	**10**	1.02 (0.94 to 1.10)

1.01 (0.95 – 1.07)
for in situ and invasive cases

Sensitivity analysis

In order to assess how our estimate of overdiagnosis depends upon pre-screening trend estimates, we performed a sensitivity analysis assuming the most extreme scenario: **the absence of incidence trend**.

In this case, the estimate of overdiagnosis for women 60-69 years at the enrolment was **1.13 (1.07 – 1.19)**.

BENEFIT AND HARM OF BREAST CANCER SERVICE SCREENING:

Invited versus Not invited

Benefit: reduction in BC mortality = 25% (Puliti D et al, 2008)

Harm: overdiagnosis = 13% (no incidence trend)

In a population where the risk of breast cancer between 50 and 79 years is 6.5% and the risk of dying from breast cancer in the same age class is 2.5%,
inviting 1000 women:

- may prevent about 6 BC deaths (6 lives saved) out of 25 expected

- but could lead to an overdiagnosis, in the worst and most unlikely scenario, of up to 8 cases out of 65 expected in situ and invasive breast cancer cases.

→ 1 Saved life : 1 overdiagnosed cancer

Our results show that the degree of overdiagnosis estimated in service screening (1-13%) is within the range estimated in other studies, including those based on RCTs and those which use the statistical adjustment for lead time method.

	Authors	Method	Data	Estimate of overdiagnosis
cohort	Puliti, 2009	Cumulative incidence method	Florence	1-13%
	Zackrisson, 2006	Cumulative incidence method	Malmo Trial	10%
	Moss, 2005	Cumulative incidence method	Canadian trial I	11%
	Moss, 2005	Cumulative incidence method	Canadian trial II	14%
Dynamic p.	Morrell, 2010	Adjusted for lead-time method	New South Wales	30-42%
	Paci, 2006	Adjusted for lead-time method	IMPACT study	4.6%
	Paci, 2004	Adjusted for lead-time method	Florence	5%
	Jonsson, 2005	Adjusted for lead-time method	Sweden	21-52%
	Jorgensen, 2009	Analysis of incidence trends	Meta-analysis	52%

(Cohort: Puliti, Zackrisson, Moss, Moss)
(Dynamic p.: Morrell, Paci, Paci, Jonsson, Jorgensen)

Study *in progress*

- Cohort study with individual definition of screening exposure:

a) estimate of BC mortality reduction
b) estimate of overdiagnosis of breast cancer

STUDY DESIGN

Definition of the cohort

Women aged 50-69 years invited at the first round of the Florentine screening programme (1991-1993).

Follow-up for vital status and cause of death

All women were followed-up for vital status and cause of death until 31 December 2008 through the linkage with the regional mortality registry and with the list of residence.

Follow-up for breast cancer incidence

All women were followed-up for breast cancer incidence until 31 December 2007 through the linkage with the Tuscan Cancer Registry and Pathology Reports.

Definition of screening exposure

Screening exposure was defined on the basis of attendance at the firsts two rounds and the women were classified in:

1) frequent attenders, if they responded to both invitations;
2) irregular attenders, if they only responded to one invitation;
3) never attenders, if they not responded to any invitation.

For the women invited only at the first round, screening exposure was defined on the basis of the attendance at the first round.

We excluded BC occurred in the first 6 monts only from never attenders group

RESULTS: BC mortality reduction

We selected 51,063 women aged 50-69 years invited at the first screening round in Florence.

The women were classified in:

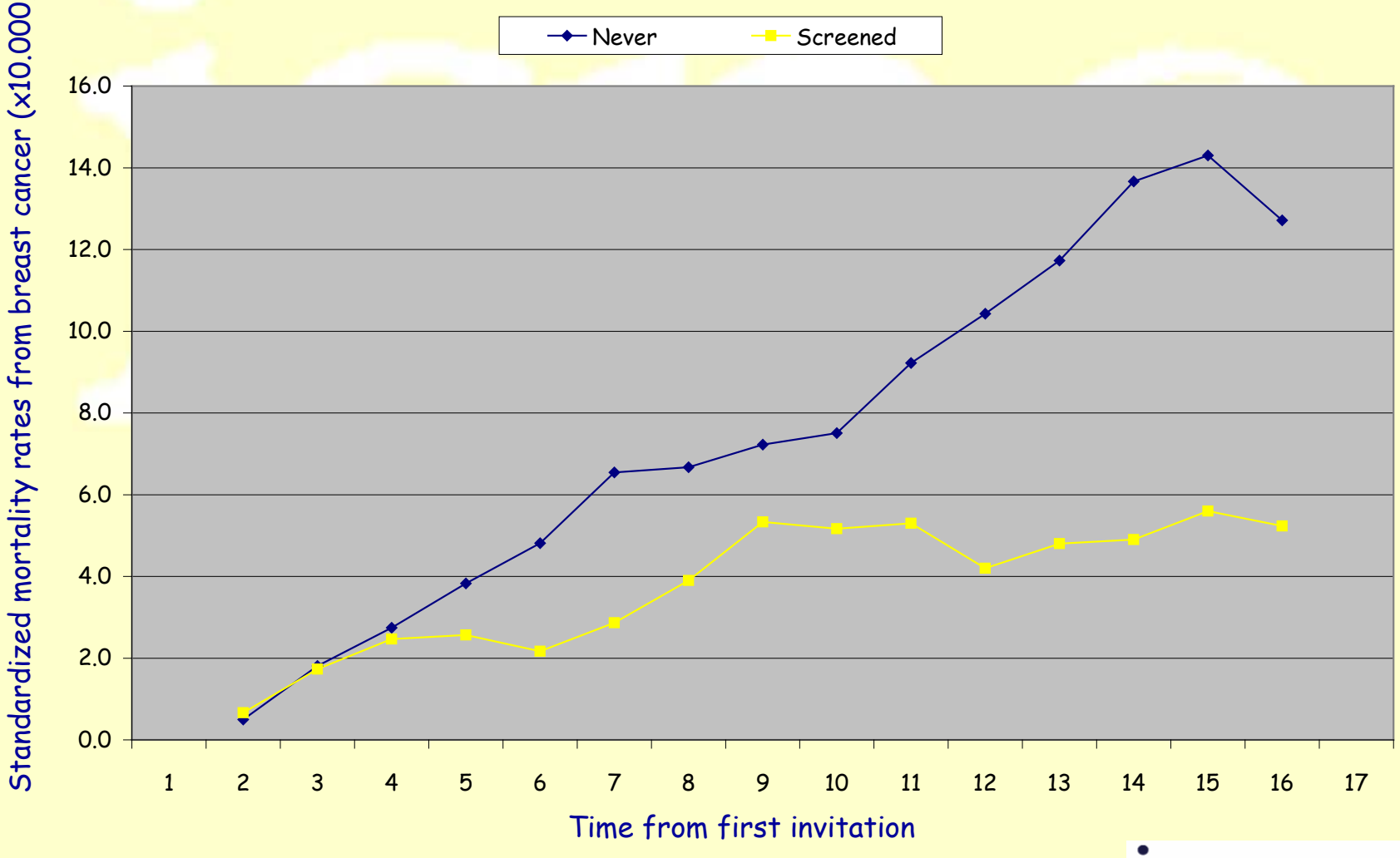
Exposure	N° (%)	Mean n° of test
Frequent	24.580 (48%)	5.1 – 7.6
Irregular	7.965 (16%)	3.1 – 5.5
Never	18.518 (36%)	0.4- 1.8

Screened (64%)

84% of "never" did not perform any test in the study period

MORTALITY RATES

The follow-up for vital status was updated at 31 December 2008 with a median follow-up of 16.5 years.



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N° of breast cancer deaths and standardized mortality rates by exposure category

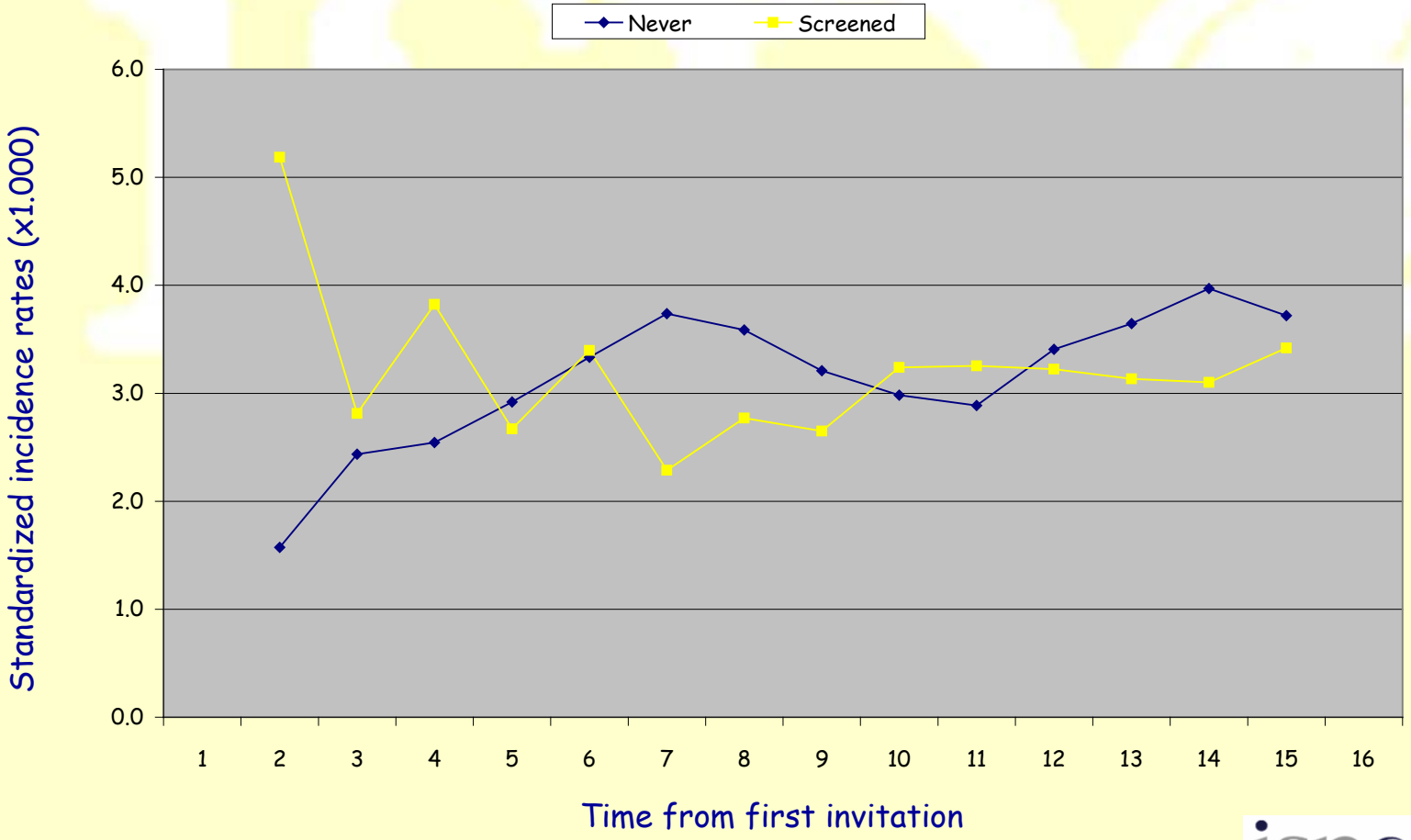
On the 16-years study period, in total we observed 9,624 deaths for whatever cause and 392 breast cancer deaths.

Exposure	BC deaths	Person-years	STD rates (x10.000)	SRR (95%CI) adjusted*
Never	208	264.636	7.3	1
Screened	184	503.961	3.6	0.53 (0.43 – 0.66)

* Adjusted for age, deprivation index , marital status, and previous breast examination

RESULTS: estimate of overdiagnosis

We selected 26,514 women aged 60-69 years invited at the first screening round in Florence.



N° of breast cancer cases and standardized incidence rates by exposure category

On the 15-years study period, we observed 1182 breast cancer (1110 invasive and 72 in situ)

Esposure	Cases	Person-years	STD rates (x1000)	SRR (95%CI) adjusted*
Never	438	142.542	2.99	1
Screened	744	216.325	3.44	1.15 (1.02 – 1.30)

* Adjusted for age, deprivation index, marital status, and previous breast MX

For invasive cases only: 1.10 (0.97-1.24)

BENEFIT AND HARM FOR A SCREENED WOMAN:

Screened versus Never

Benefit: reduction in BC mortality = 47%

Harm: overdiagnosis = 15%

In a population where the risk of breast cancer between 50 and 79 years is 6.5% and the risk of dying from brteast cancer in the same age class is 2.5%, screening 1000 women:

- may prevent about 12 BC deaths (12 saved lives) out of 25 expected

- could lead to an overdiagnosis of 10 cases out of 65 expected

→ 1 saved life : 1 overdiagnosed cancer

- Thank you !

Adjusted for lead-time cumulative incidence method

(Paci et al, J Med Screen 2004; Paci et al, Br Cancer Res, 2006)

If there's little or no follow-up after the last screen (5 years or more), there will be lead-time bias that should be adjusted for statistical methods.

Assuming an exponential distribution for the *sojourn time*, the probability that a tumour currently detected at screening in the pre-cinical phase would have of progressing to the clinical phase within the next n years is as follows:

$$\int_0^n \lambda \cdot e^{-\lambda x} dx = 1 - e^{-\lambda n}$$

thus, it is possible to calculate the probability that each screen-detected case would have been identified clinically each year after detection until the end of the study period.

Number of corrected for lead time cases =

- n° of observed incidence cases
- n° of screen-detected cases in that year
+ estimated n° of SD cases that would have arisen clinically in that year.

Estimate of overdiagnosis

The corrected-for-lead-time cases should be compared with the predicted number in the absence of screening.
The percentage excess after correction for lead time is an indicator of overdiagnosis, given the lead time estimate.

(Paci et al, J Med Screen 2004; Paci et al, Br Cancer Res, 2006)

Application of the adjusted for lead time method to the IMPACT dataset

Breast Cancer Research, 2006

Available online http://breast-cancer-research.com/content/8/6/R68

Research article

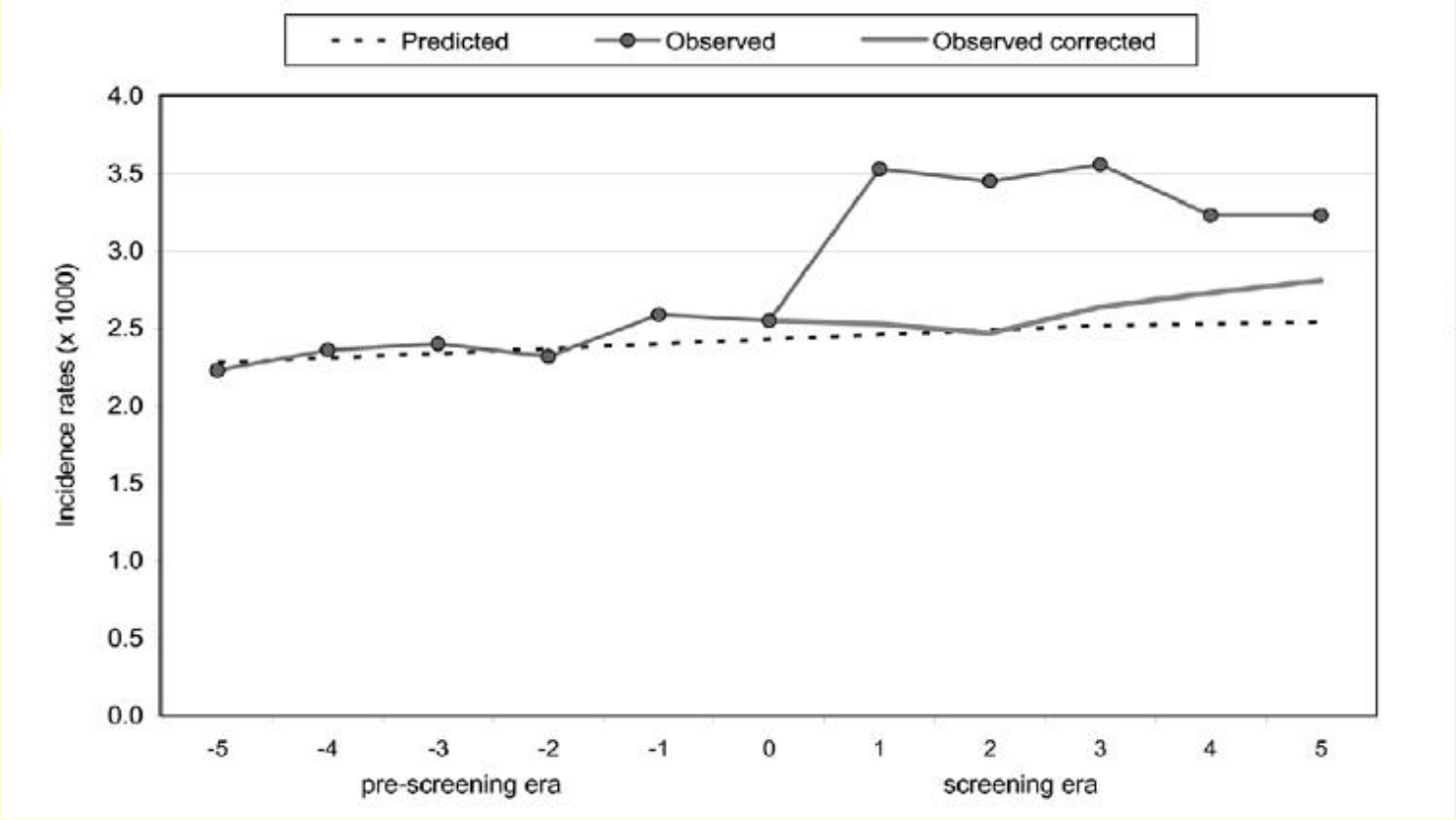
Open Access

Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy

Eugenio Paci[1], Guido Miccinesi[1], Donella Puliti[1], Paola Baldazzi[2], Vincenzo De Lisi[3], Fabio Falcini[4], Claudia Cirilli[5], Stefano Ferretti[6], Lucia Mangone[7], Alba Carola Finarelli[8], Stefano Rosso[9], Nereo Segnan[10], Fabrizio Stracci[11], Adele Traina[12], Rosario Tumino[13] and Manuel Zorzi[14]

Breast cancer incidence rates predicted, observed and observed corrected for lead time.

Age: 50-74 years. Data: Impact study (Firenze, Torino, Parma, Ferrara, Modena e Romagna)



Excess ratio: 4.6% (2% - 7%) all carcinomas (invasive and in situ)

3.2% (1% - 6%) only invasive carinomas

Person-years

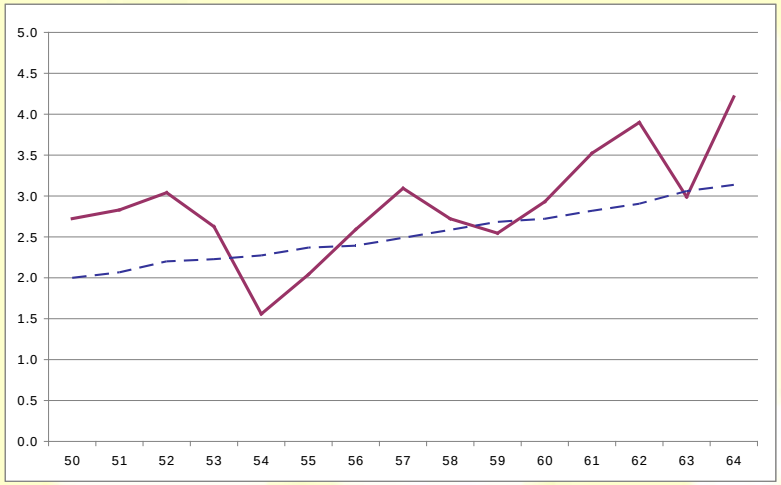
For each woman we calculated the person-years at risk to experiment the event (breast cancer diagnosis/ breast cancer death):

Date of first invitation

Date of the event
Date of death
Date of migration
Date of study end

FIGURE 1. Invited (observed) and non-invited (expected) incidence breast cancer rates by age at the beginning of service screening:

a) 50-54 years



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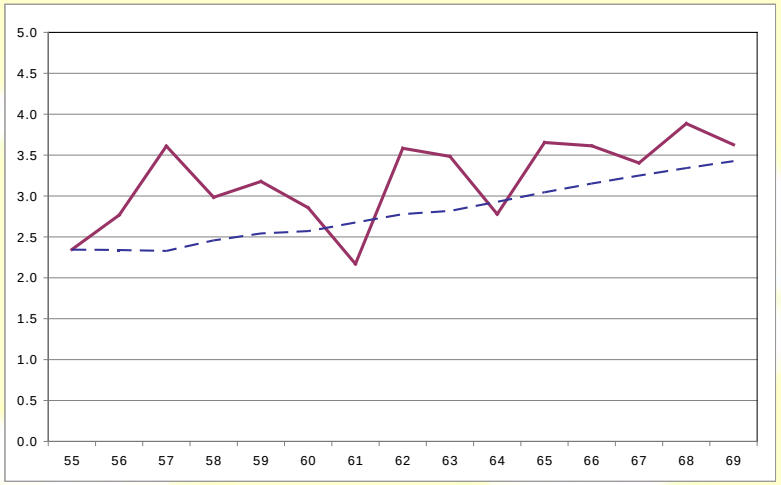

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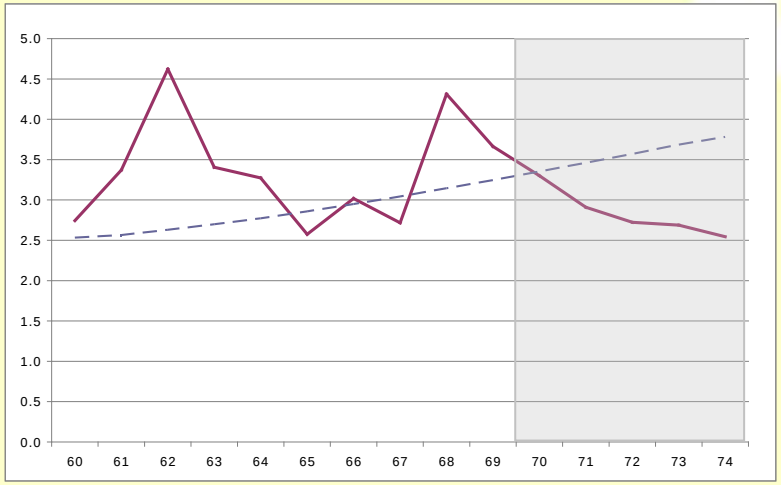
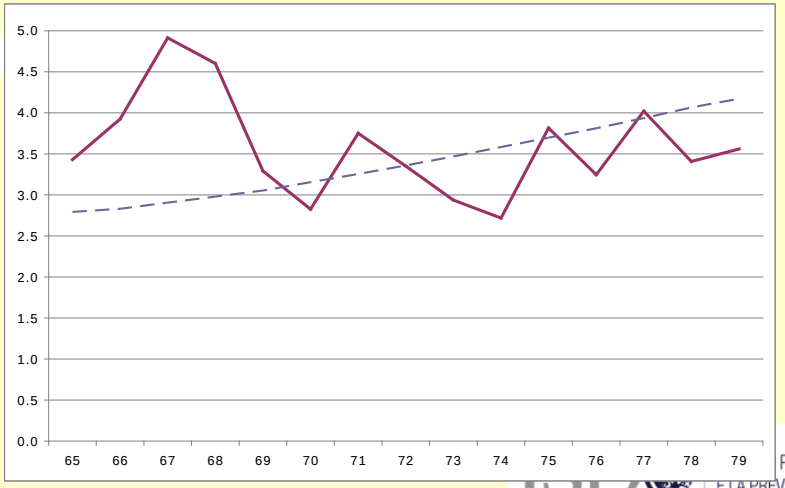
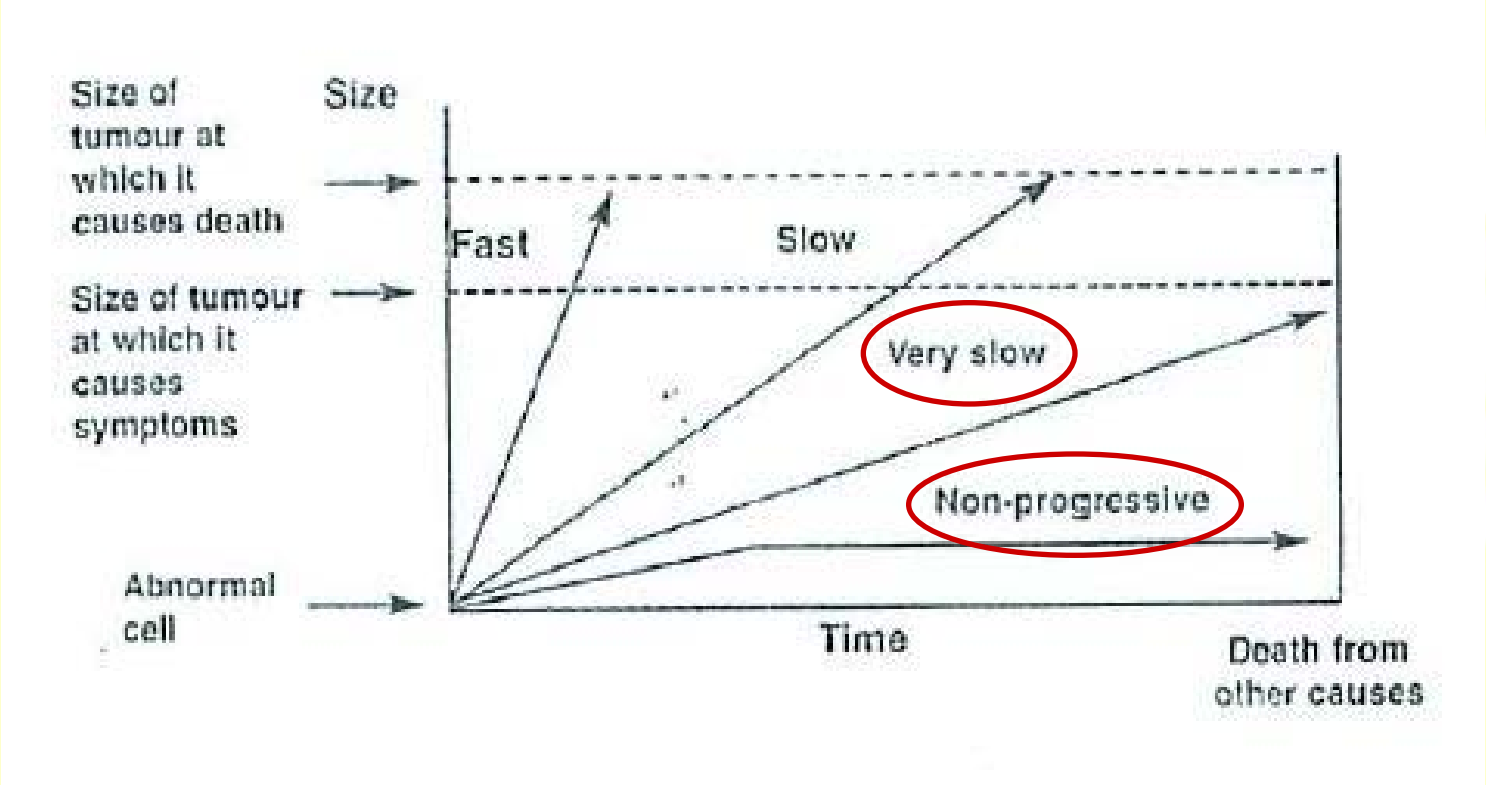


d) 65-69 years



Growth rates of cancers (IARC, 2002)



The diagnosis of these cancers (very slow and non-progressive), that Morrison (1992) have called "pseudodisease", is overdiagnosis.