



WHO Collaborating Centre for cancer early
detection and screening

Determinanti della sovradiagnosi: carcinomi mammari indolenti o regressivi

Nereo Segnan

IARC Senior Visiting Scientist

Torino, 3 dicembre 2014

PREVENZIONE SERENA



Overdiagnosis

Duffy SW et al.
(2010)

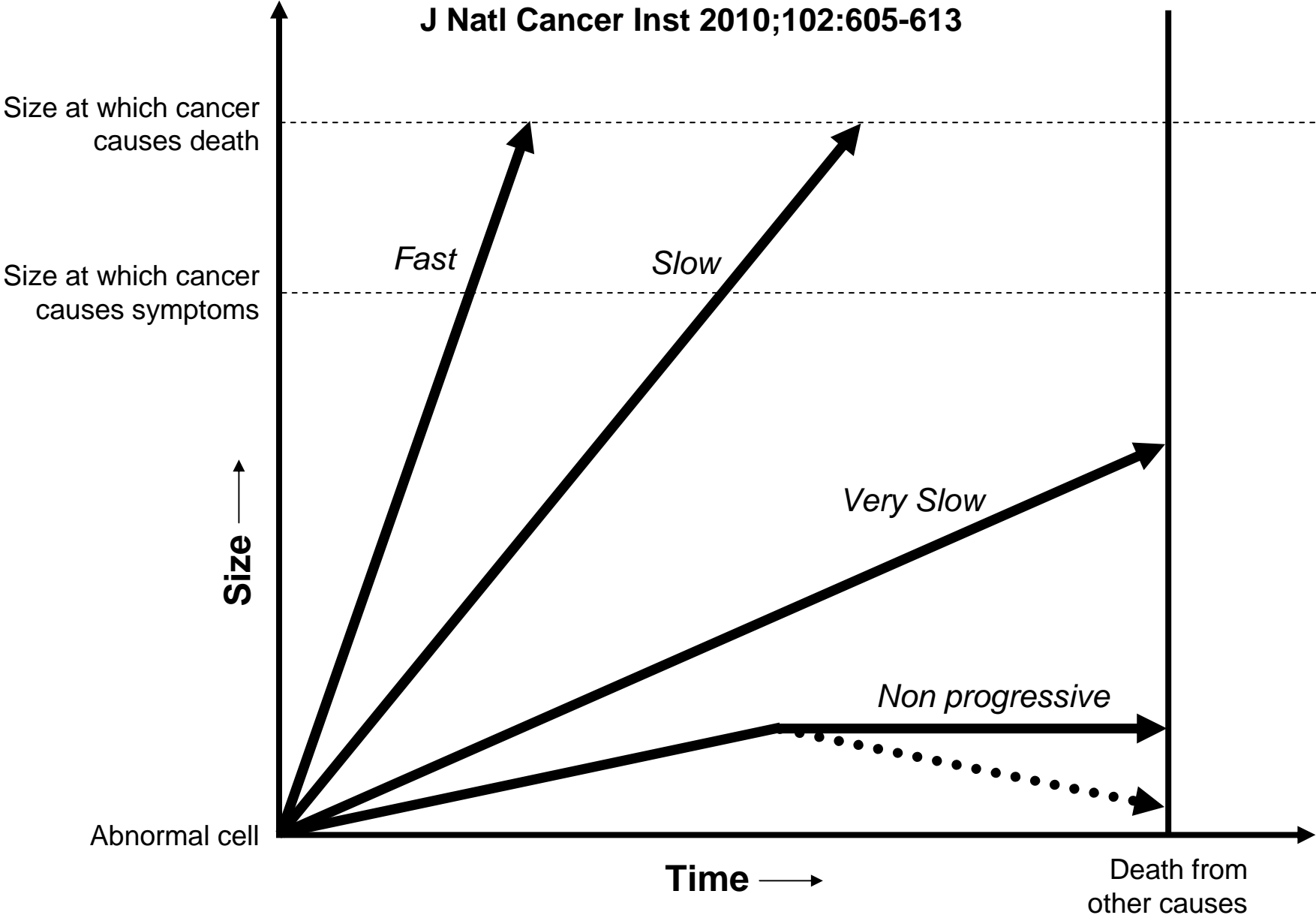
the diagnosis of a cancer as a result of screening that would not have been diagnosed if in the woman's lifetime had screening not taken place

Sovradiagnosi

Solo nello screening , nei casi
asintomatici o anche nei casi
clinici?

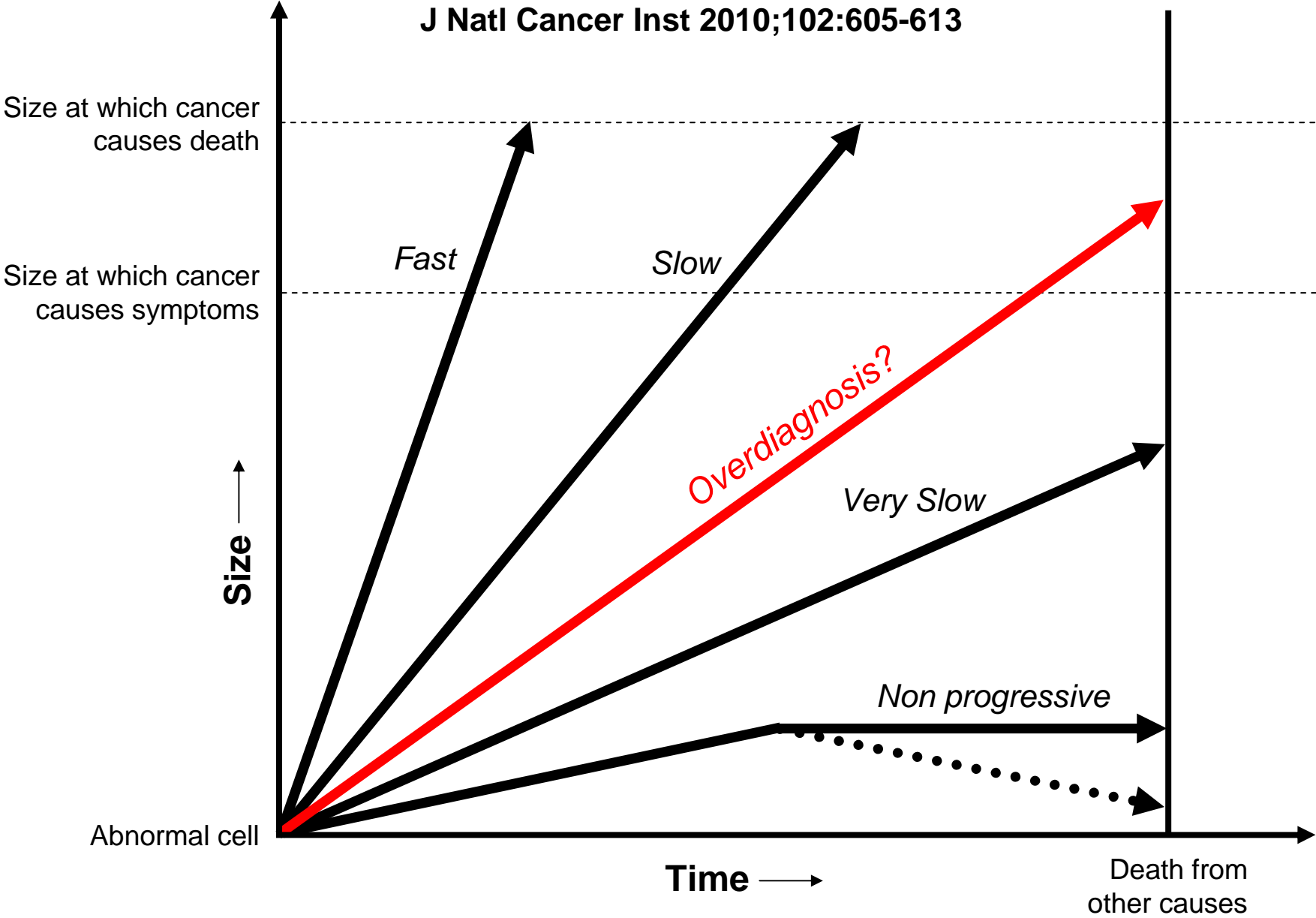
Overdiagnosis in Cancer

H. Gilbert Welch, William C. Black
J Natl Cancer Inst 2010;102:605-613



Overdiagnosis in Cancer

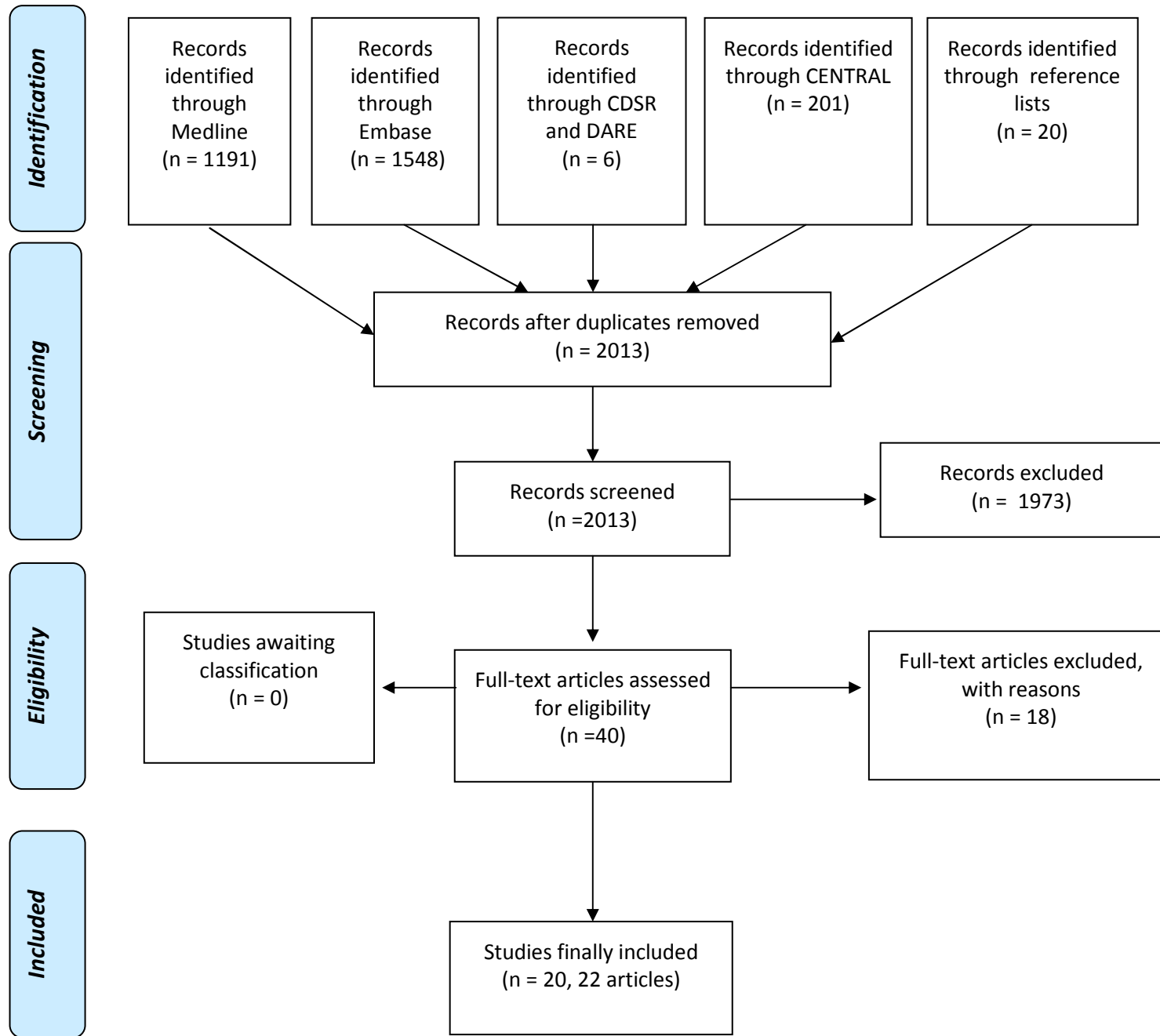
H. Gilbert Welch, William C. Black
J Natl Cancer Inst 2010;102:605-613



Determinants of overdiagnosis

- Biology of the disease:
indolent or regressive lesions
- X ray induced cancers
- False positive cases:
diagnostic errors

PRISMA FLOW CHART. Studies on untreated cancers.



Determinants of overdiagnosis

- **Biology of the disease:
indolent or regressive lesions**
- X ray induced cancers
- False positive cases:
diagnostic errors

Untreated BCs cases: 8 cohort studies and 12 case series analyzing 3891 patients were included.

In 4 controlled cohort studies including BCs diagnosed from 1978 to 2006, the 5 years overall survival of women who refused any treatment ranged from 19% to 43%.

Overall 5 yrs survival (S) or Mortality (M)

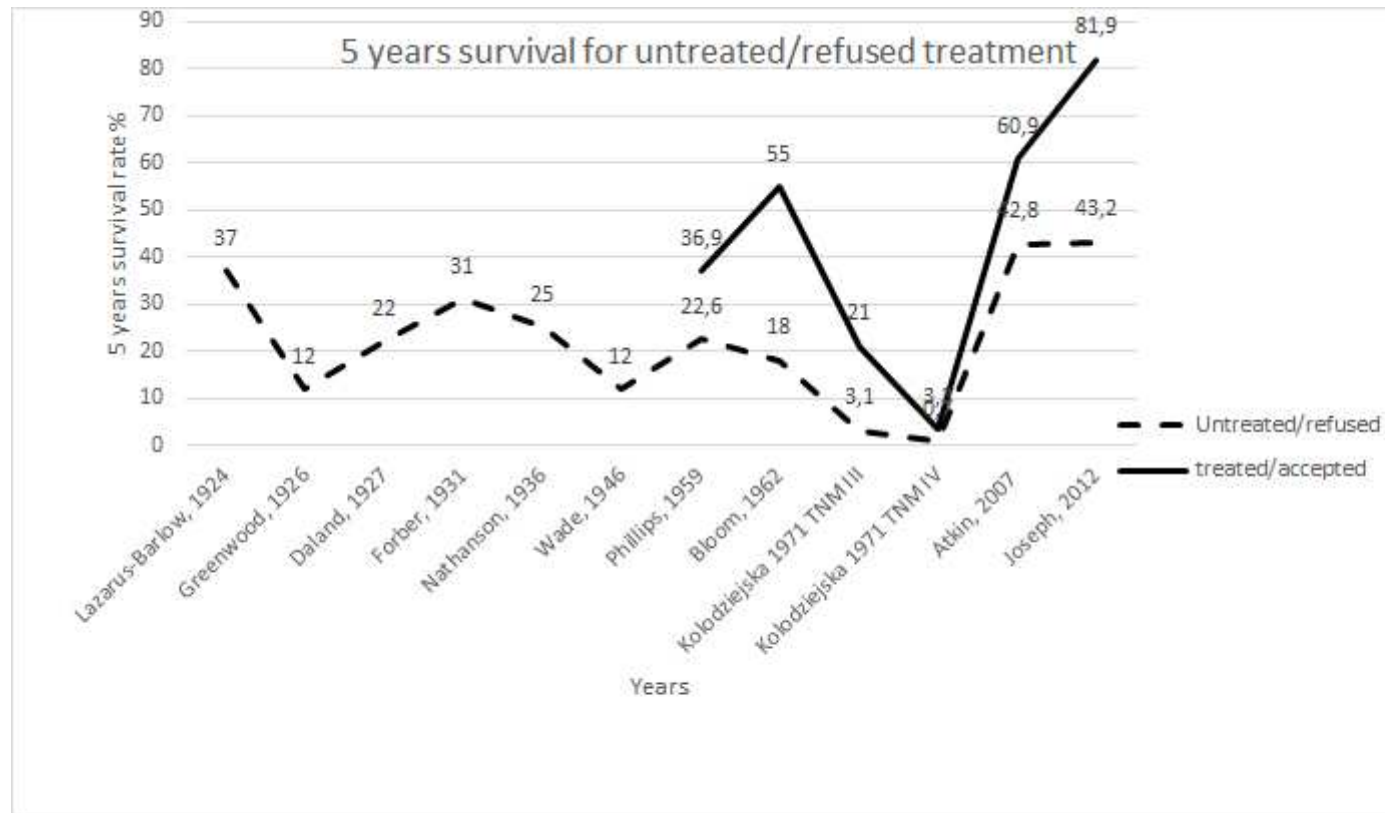
Atkin (stage 1-3)	(S) T 42.8% (S) U 60.9%
Bloom (stage 1-4)	(S) T 18% (S) U 55%
Bouchardy (stage 1-4)	(M) T 47% (M) U 81%
Kolodziejska (stage 3-4)	(S) T 17.8% (S) U 1.6%
Phillips (stage 1-4)	(S) T 36.9% (S) U 22.6%
Verkooijen (stage 1-4)	(S) T 87% (S) U 64%

Bloom: 10 yrs survival rate: **T 34%, U 3.6%**

Bouchardy: 5 yrs disease specific mortality:

T 20-40%, U 64%

Five years survival for women who received or refused treatment



Untreated BCs cases: 8 cohort studies and 12 case series analyzing 3891 patients were included. In 4 controlled cohort studies including BCs diagnosed from 1978 to 2006, the 5 years overall survival of women who refused any treatment ranged from 19% to 43%.

Occult BCs: 7 case series of 2279 autopsies were included. The prevalence of invasive BC undiagnosed during life and found in autopsies ranged from 0 to 1.4%. Ductal carcinoma in situ ranged from 0.2% to 18%.

Spontaneous regression: 2 cohort studies, 3 case reports, 1 case series were included. In the cohort studies the relative risk of regression for screen detected BCs compared with non-screened women was estimated as 1.2 and 1.1.

Prevalence of invasive breast cancer undiagnosed during life ranged from 0 to 1.4%.

DCIS ranged from 0.2% to 18%

Characteristics of studies on occult cancers found at autopsy (I)

Author, publication year	Participants characteristics	Hospital based/forensic autopsies Country	Invasive breast cancer	DCIS/LCIS
Alpers 1985 (55)(data extracted from abstract)	292 breasts ; 185 breasts from random autopsies, 63 cancer-containing breasts, and 44 breasts contralateral to cancer-containing breasts Period: not specified Mean age: not specified (range not reported)	Not specified		DCIS (unrelated to invasive breast carcinoma, if present) in cancer-containing breasts: 33/63(52.5%) In breasts contralateral to cancer-containing breasts: 21/44 (47.7%) In breasts from random autopsies: 11/185(5.9 %)
Bartow 1987 (56)	490 unselected, consecutive autopsies of non pregnant women older than 14performed between December 1978 and December 1983 at the New Mexico Office of the Medical Investigator. No women with clinically apparent breast carcinomas were included in the series Mean age: not reported (range 15-98)	Forensic USA	5/490 1%	1/490 (0.2%)
Bhathal 1985 (57)	207 consecutives autopsies of women. Period not specified Mean age: 60 years (range 15-97) Excluded 5 cases with: unresected but clinically known breast carcinoma; known metastatic carcinoma to the breast from a primary in the lung; previous mastectomies for breast carcinoma	Forensic Australia	3 (1.4%) radial scar, considered by some to be a precursor of infiltrating ductal carcinoma: 16(7.7%)	27 (13%)

Characteristics of studies on occult cancers found at autopsy (II)

Author, publication year	Participants characteristics	Hospital based/forensic autopsies Country	Invasive breast cancer	DCIS/LCIS
Giarelli 1986 (58)	517 unselected consecutive series of autopsies done on women older than 35 years between January and August 1985 Mean age : not specified (range 35-90)	Forensic Italy	8 (1.5%)	
Imaida 1997 (59)	510 unselected autopsy cases from a medical center for the elderly between 1982 and 1994 in Nagoya C Geriatric Hospital Mean age : not reported (range 48-113)	Hospital based Japan	0/510	Not assessed
Kramer 1973 (60)	70 autopsies of over 70 years of age women dying from causes other than mammary cancer	Hospital based UK	1/ 70 (1.4%)	4/70(5.7%)
Nielsen 1984 (61)	83 consecutive, unselected female autopsy cases performed from November 1976 to May 1977 median age 67 years (range, 22 to 89 years). Exclusion criteria: younger than 20 years	Forensic Denmark	1/83 (1.2%)	14/83 (16.8%)
Nielsen 1987 (62)	110 consecutive medico legal autopsies on Caucasian Danish women, performed from October 1983 to July 1984 at the University Institute of Forensic Medicine in Copenhagen. Mean age 39 years (range 20-54). Exclusion criteria : women younger than 20 years and older than 54 and extensive injury to one or both breasts.	Forensic Denmark	1/110 (0.9%)	20/110 (18.2%)

Determinants of overdiagnosis

- Biology of the disease:
indolent or regressive lesions
- X ray induced cancers
- False positive cases:
diagnostic errors

Lifetime Radiation induced cases per 100,000 Mammography screening

Studies	Country	Radiation-induced cases	Radiation-induced deaths
Mattson et al 2000	Sweden	Screening 40-49 years: 12 to 53 cases Screening 40-69 years: 16 to 76 cases	Screening 40-49 years: 5 to 24 deaths Screening 40-69 years: 7 to 31 deaths
Léon et al 2001	Spain	Screening 45-65 years: 20 to 36 cases Screening 50-65 years: 11 to 26 cases	Screening 45-65 years: 10 to 18 deaths Screening 50-65 years: 5 to 13 deaths
Law and Faulkner 2001	UK	Screening 30-34 years: 8 cases Screening 40-44 years: 7.5 cases Screening 50-54 years: 6 cases Screening 60-64 years: 4 cases	<i>na</i>
Berrington and Reeves 2005	UK		Starting screening At 30: 72 deaths At 40: 50 deaths At 50: 11 deaths
HPA 2011	UK	Screening 40-47 years: 61 to 110 cases Screening 47-73 years: 28 to 60 cases	Screening 40-47 years: 4 to 10 deaths Screening 47-73 years: 2 to 50 cases
Hendrick 2010	US	<i>na</i>	20 to 25 cancer deaths
O'Connor et al 2010	US	Screening 40-80 years: 56 (DM) to 71 (SFM) cases Screening 50-80: 21 (DM) to 27 (SFM) cases Screening 40-49: 35 (DM) to 44 (SFM)	Screening 40-80 years: 15 (DM) to 19 (SFM) deaths Screening 50-80 years: 6 (DM) to 7 (SFM) deaths Screening 40-49 years: 9 (DM) to 11 (SFM) deaths
Yaffe and Mainprize 2011	Canada	Screening 40-49 years: 59 cases Screening 40-74: 86 cases	Screening 40-49 years: 7.6 deaths Screening 40-74 years: 10 deaths
de Gelder et al 2011	Netherlands	Screening 40-74 years: 17 cases Screening 50-74 years: 7.7 cases	Screening 40-74 years: 3.7 deaths Screening 50-74: 1.6 deaths
Hauge et al 2013	Norway	Until 85 or 105	10 cases (from 1.4 to 36)

Determinants of overdiagnosis

- Biology of the disease:
indolent or regressive lesions
- X ray induced cancers
- False positive cases:
diagnostic errors

False positive cases

- Misclassification Benign to Malignant (MBM) and k statistic:
 - 16 studies assessed the reproducibility of two or more readings of the same specimen among pathologists or cases selection for a second opinion, from 1951 to 2012.
 - MBM of non palpable lesions at Core Biopsy ranges from 4.39% to 0.25% (3 studies). At surgical excision it was estimated as 0.69% and 1.17% (2 studies). Among studies not reporting the type of lesion or/and the type of specimen MBM ranges from 0.57 % to 4.84% (6 studies).
 - In the studies including a consecutive or random or representative sample of all biopsies median k value was: 0.83 (range 0.61-0.98) for the 5 studies analyzing CB; 0.93 (range 0.86-0.94) for the 3 studies analyzing SE; 0.78 (range 0.35-0.91) in 5 studies not reporting the type of specimens

Diagnostic variability

European multicentric project “Eunice”

(www.qtweb.it/eunice/)

Screen detected cases 2005-2007

24 Areas age 50-69

(subsequent tests)

Further Assessment: 1.2%-10.5%

DCIS: range 4%-23% of screen detected cancers

DCIS: range 0.1-1.1 per 1000 screening tests

Invasive cancers DR: 2.4-6.8 per 1000 tests



Treatment variability

European multicentric project “Eunice”
(www.qtweb.it/eunice/)

Screen detected cases 2005-2007
24 Areas age 50-69
(subsequent tests)

Benign surgical biopsies: 0.34-1.4 per 1000 screening tests
B/M ratio 0.09-0.38

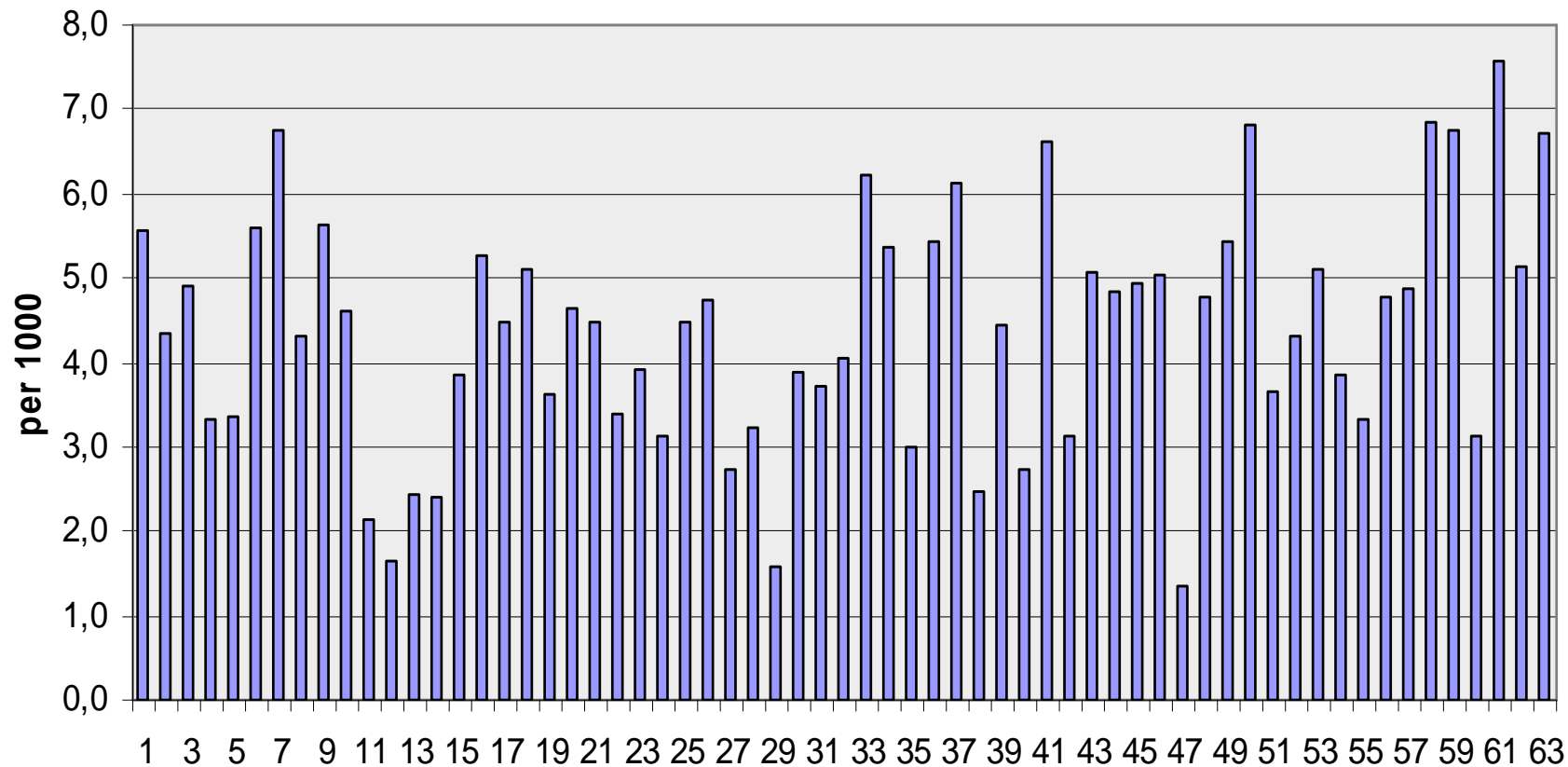
Mastectomy rate: 0.5-1.8 per 1000 screening tests

Breast conservation surgery: 32%-90% of screen detected cancers

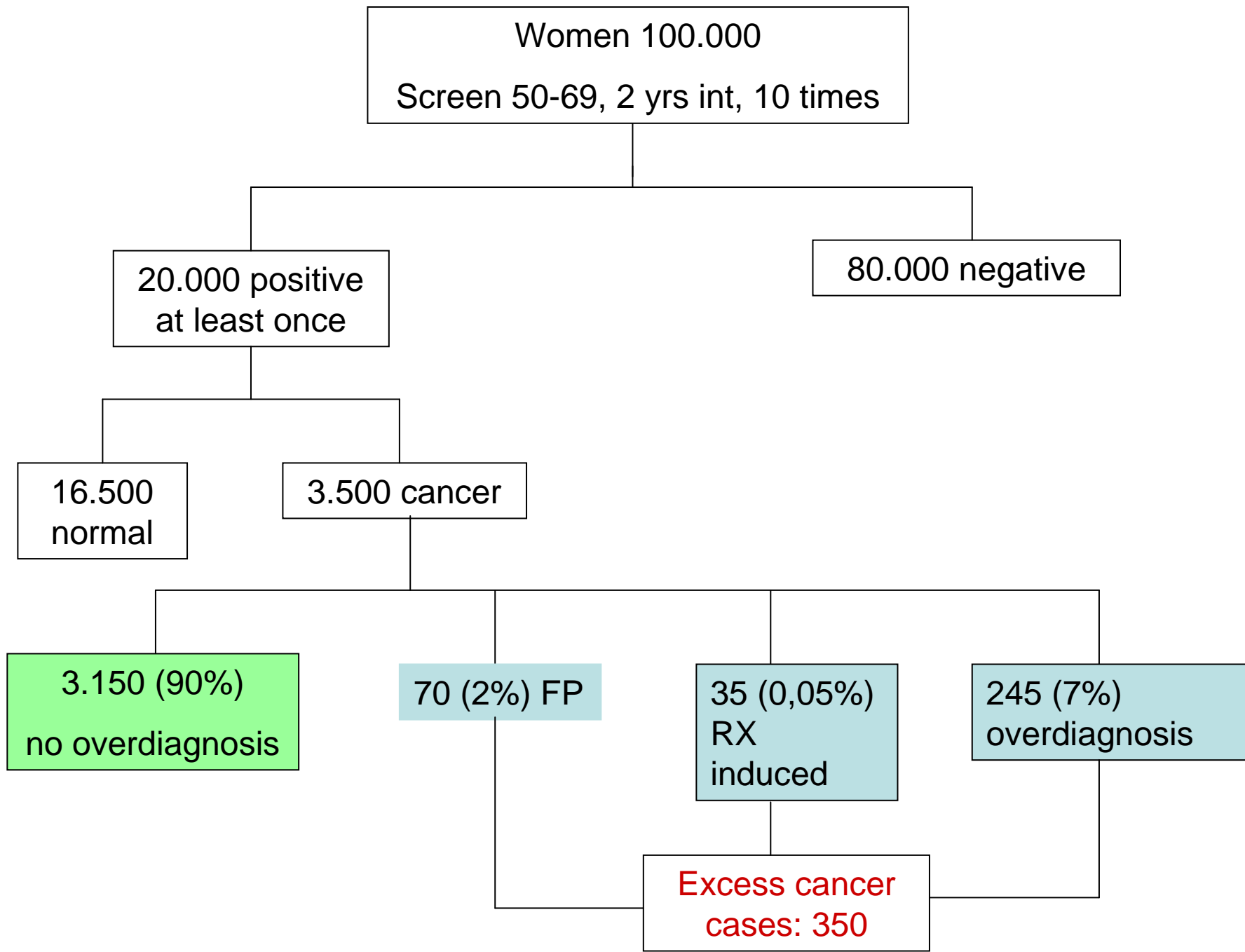


50-69 yrs, Age Std Breast Cancer DRs - Northern Italy 2011.

Subsequent screenings 63 Programmes (ONS survey)



Screening programmes



- Around 10% of invasive breast cancers are not symptomatic during the life of women but detectable post mortem.
- Detecting all in situ breast cancers during lifetime, would increase the cumulative risk of in situ and invasive breast cancers up to 20-25%, twice the lifetime cumulative breast cancer risk.
- One out of 5 breast cancer if untreated would be alive after 5 years.
- Two studies conducted by the same group suggested that 1-2 screen detected breast cancers out of 10 may regress.

- Around 10% of invasive breast cancers are not symptomatic during the life of women but detectable post mortem.
- Detecting all in situ breast cancers during lifetime, would increase the cumulative risk of in situ and invasive breast cancers up to 20-25%, twice the lifetime cumulative breast cancer risk.
- One out of 5 breast cancer if untreated would be alive after 5 years.
- Two studies conducted by the same group suggested that 1-2 screen detected breast cancers out of 10 may regress.

- Around 1% of benign breast lesions may be classified as malignant in the final diagnosis

- The variability in breast cancer detection rates at screening suggests that the misclassification benign to malignant could be higher

Women invited / screened for 20 years starting at age 50

	EUROSCREEN review (screening interval 2 years)	UK Independent review (screening interval 3 years)
Mortality reduction	28% (invited) 42% (screened)	20% (invited) 25% (screened)
Absolute mort. benefit (lives saved)	1 / 127 (screened)	1 / 235 (invited) 1 / 180 (screened)
Over-diagnosis	6.5% of incident ca. in absence of screening	11% of incident ca. since start of screening
FP (non invasive inv.)	17%	
FP (invasive inv.)	3%	



For every 10000 women screened since age 50 for 20 years:

	EUROSCREEN review (screening interval 2 years, follow up till age 79)	UK Independent review (screening interval 3 years)
Cases diagnosed	710	
BC deaths expected	300 (190 IBM)	
Lives saved	80	56
Over-diagnosed cases	40	168
LS : OD	1 : 0.5	1 : 3



**“Overdiagnosis and Overtreatment in
Cancer. An Opportunity for
Improvement”**

Esserman LJ, Thompson IMJ, Reid B
JAMA August 28, 2013 Volume 310, Number 8

Recommendations:

- 1. Physicians, patients, and the general public must recognize that overdiagnosis is common and occurs more frequently with cancer screening.**
- 2. Change cancer terminology based on companion diagnostics.**
- 3. Create observational registries for low malignant potential lesions.**
- 4. Mitigate overdiagnosis.**
- 5. Expand the concept of how to approach cancer progression.**

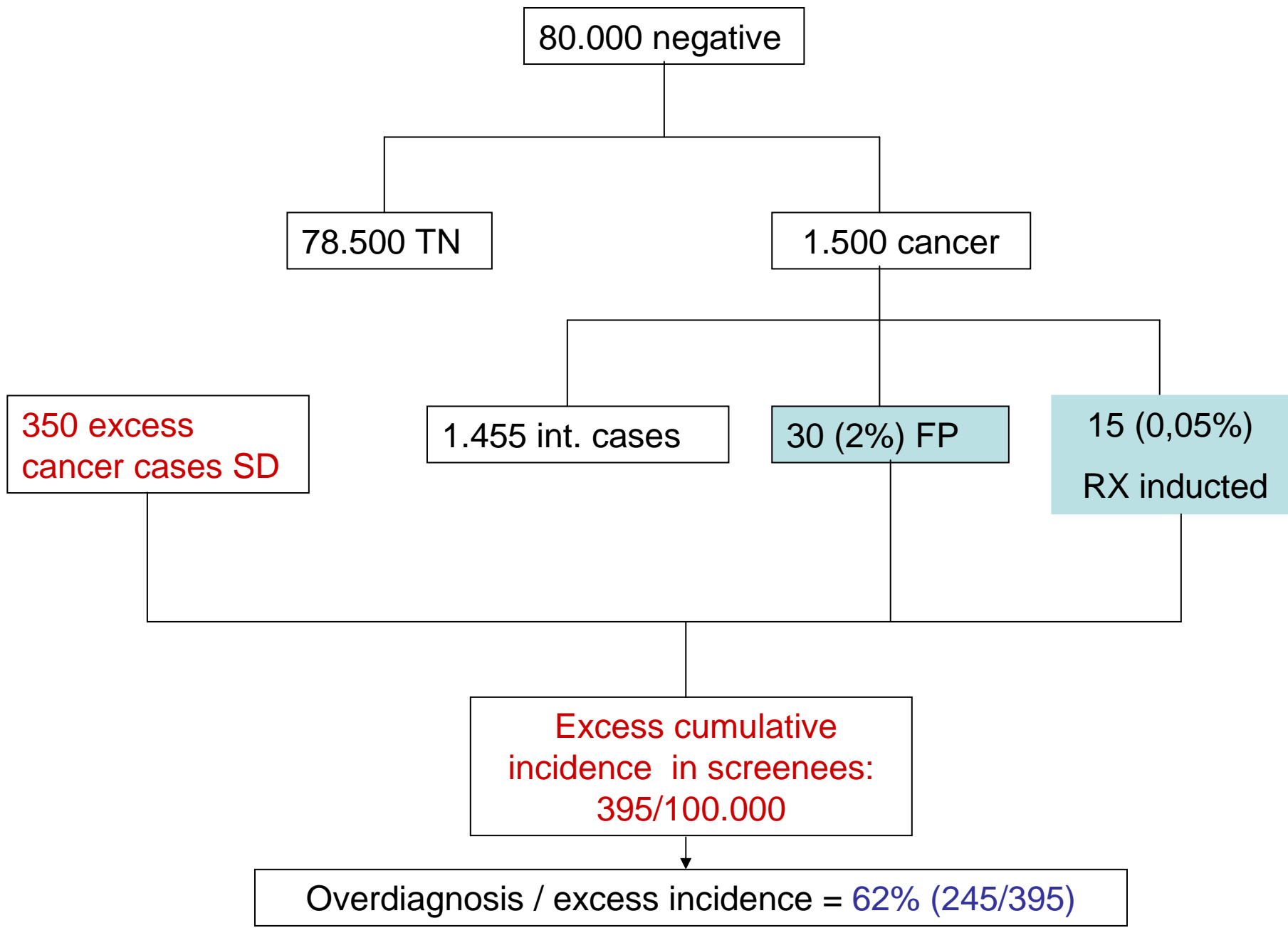
Recommendation n°2

Change cancer terminology based on companion diagnostics.

Use of the term “cancer” should be reserved for describing lesions with a reasonable likelihood of lethal progression if left untreated. There are 2 opportunities for change. First, premalignant conditions (eg, ductal carcinoma in situ or high-grade prostatic intraepithelial neoplasia) should not be labeled as cancers or neoplasia, nor should the word “cancer” be in the name. Second, molecular diagnostic tools that identify indolent or low-risk lesions need to be adopted and validated..... Another step is to reclassify such cancers as IDLE (indolent lesions of epithelial origin) conditions. A multidisciplinary effort across the pathology, imaging, surgical, advocate, and medical communities could be convened by an independent group (eg, the Institute of Medicine) to revise the taxonomy of lesions now called cancer and to create reclassification criteria for IDLE conditions.

Gruppo di lavoro

Nereo Segnan, Silvia Minozzi, Antonio Ponti,
Cristina Bellisario, Sara Balduzzi, Marien
González-Lorenzo, Silvia Gianola, Paola Armaroli



In the example about $\frac{2}{3}$ of excess cancer cases may be overdiagnosed. The remaining $\frac{1}{3}$ may be due to screening but not overdiagnosed.

Screening population cases 100.000
50-69 2 yrs int. 10 times

3500 SD

1.500 NSD

Screen
population
cases 5.000

4.655
cancers

FP 100

Overdiagnosis 245

1.257
deaths
(27%)

Prevented deaths 297
(RR 0,80)

No screen 100.000 50-69

FP 92

4.605
cancers

1.554
deaths
(34%)

Excess incidence / prevented deaths

$$395/297 = 1.33 (4:3)$$

Overdiagnosis / prevented deaths

$$245/297 = 0.82 (4:5)$$

Cohort studies of treatment refused or not received (I)

Study, year	Period	Comparison	5 yrs overall outcome (survival /mortality rate)	10 yrs survival rate	5 yrs disease specific outcome
Bloom 1962	Untreated: 1805-1933 Treated: 1936-1949	Untreated vs treated	Survival rate: Untreated: 18% Treated: 55%	Untreated: 3.6% Treated: 34%	NR
Phillips 1959	NR	Untreated vs treated	Survival rate: Untreated: 22.6% Treated: 36.9%	Untreated: 2.4% Treated: 7.1%	NR
Kolodziejska 1971	1956-1964		Survival rate: TNMIII - treated vs untreated = 21% vs 3,1% Patients with distant metastases TNM IV – treated vs untreated = 3.3% vs 0.7% Treated vs untreated total = 17.8% vs1.6%	NR	NR
Verkooijen 2005	1975-2000	Surgery refusal vs accepted	NR	NR	Disease specific survival: Refused surgery but received therapy: 81% Refused any treatment: 64% Accepted surgery 87%

Cohort studies of treatment refused or not received (II)

Study, year	Period	Comparison	5 yrs overall outcome (survival /mortality rate)	10 yrs survival rate	5 yrs disease specific outcome
Bouchardy 2003	1989-1999	No treatment vs tamoxifen/BCS/ Mastectomy/ mast+adjther/ BCS+adjther	Mortality rate: Untreated: 81% Tamoxifen: 76% BCS: 54% Mastectomy: 40% Mast+adjther: 47%	NR	Disease specific mortality: Untreated: 64.6% Tamoxifen: 53% BCS: 17,8% Mastectomy: 14.5% Mast+adjther: 26.9%
Atkin 2007	1990-2004	Surgery refusal vs accepted	Survival rate: Refused surgery: 42.8% Accepted surgery 60.9%	NR	NR
Roder 2012	1998-2005	Surgery vs declined Radiotherapy vs declined Systemic therapy vs declined			