

# Overdiagnosis and overtreatment: how to face them?

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Bologna 30 gennaio 2014

# Overdiagnosis

Duffy SW et al.  
(2010)

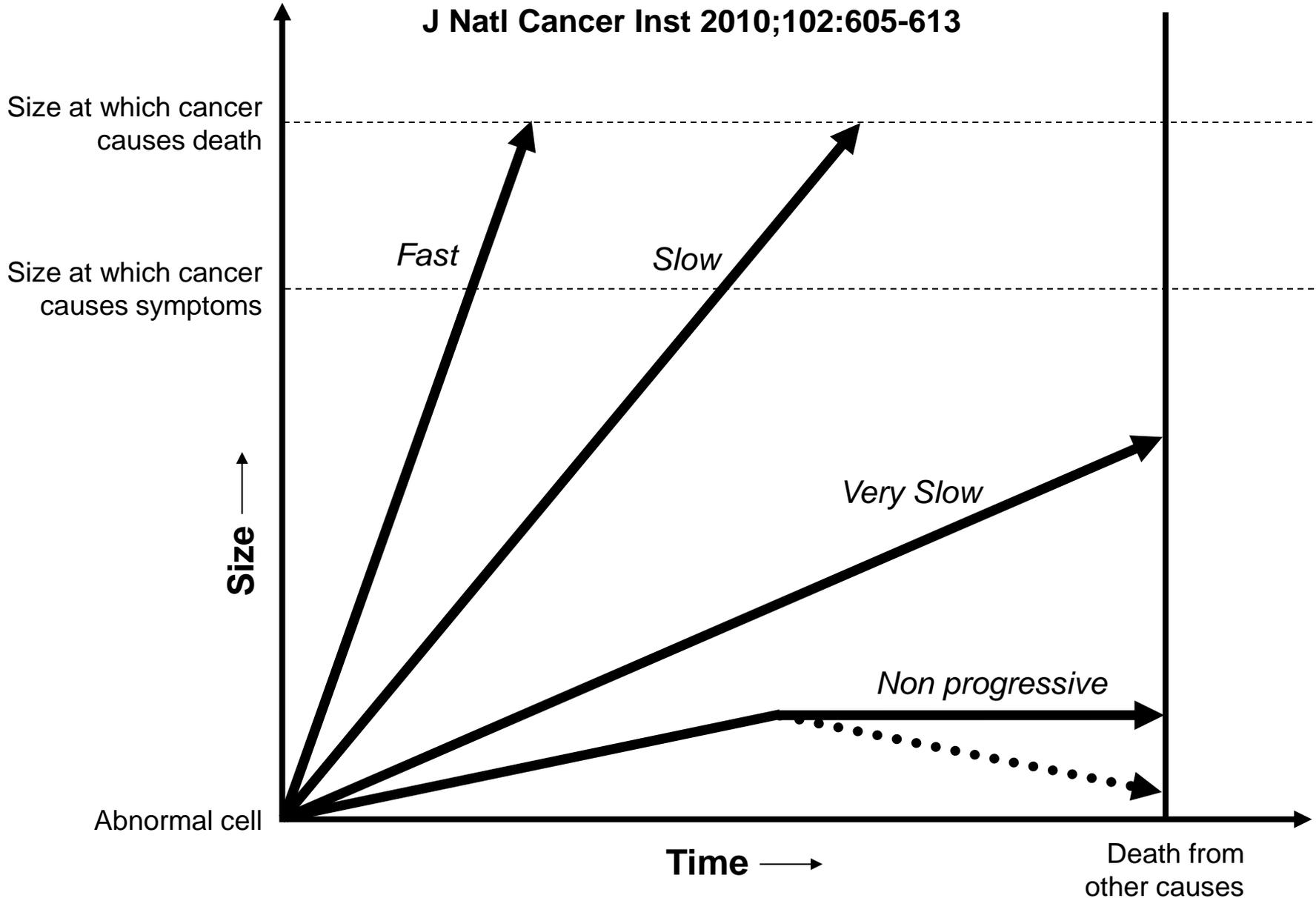
the diagnosis of a cancer as a result of screening that would not have been diagnosed if in the woman's lifetime had screening not taken place

# Overdiagnosis

Only in screening?

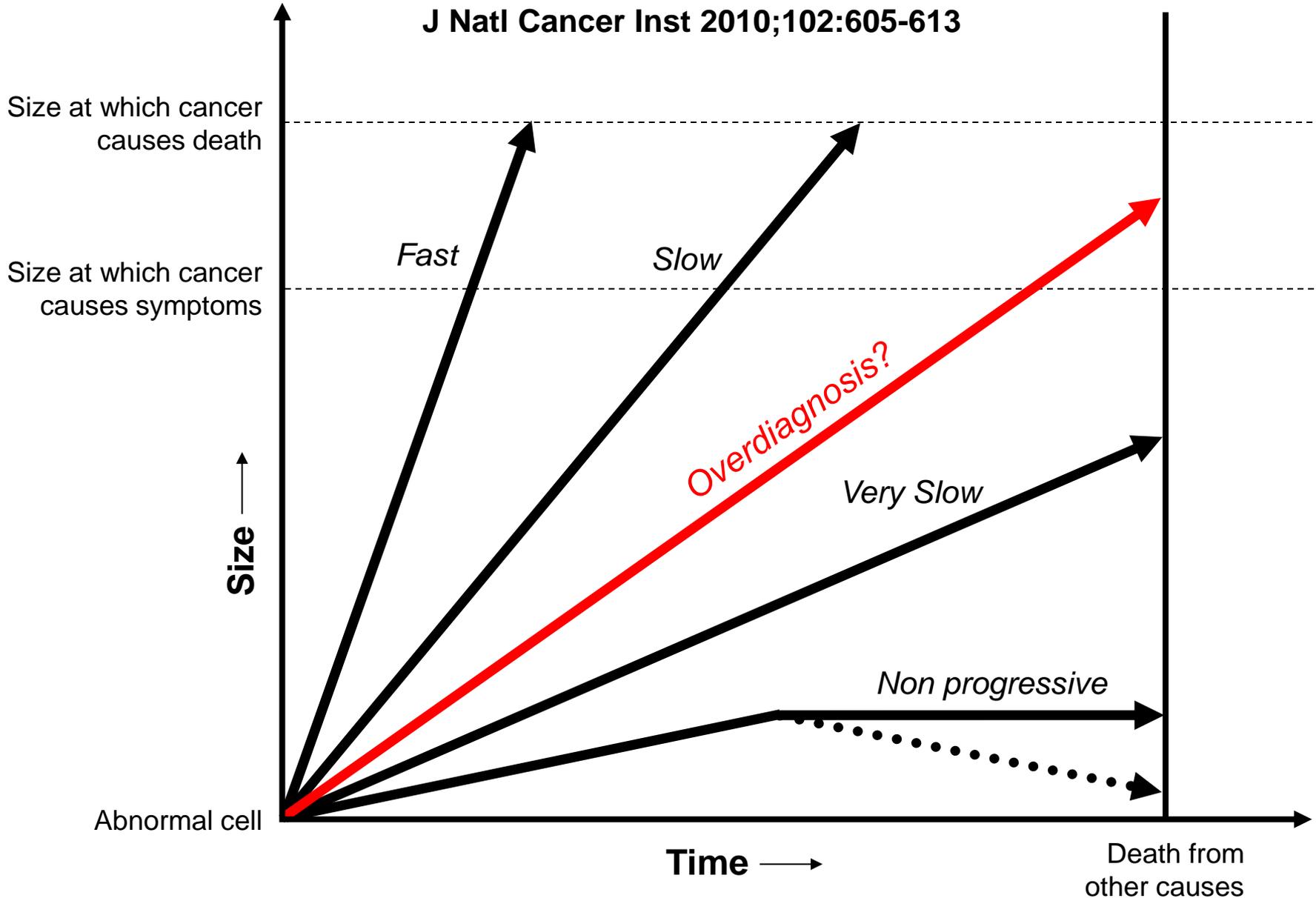
# Overdiagnosis in Cancer

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



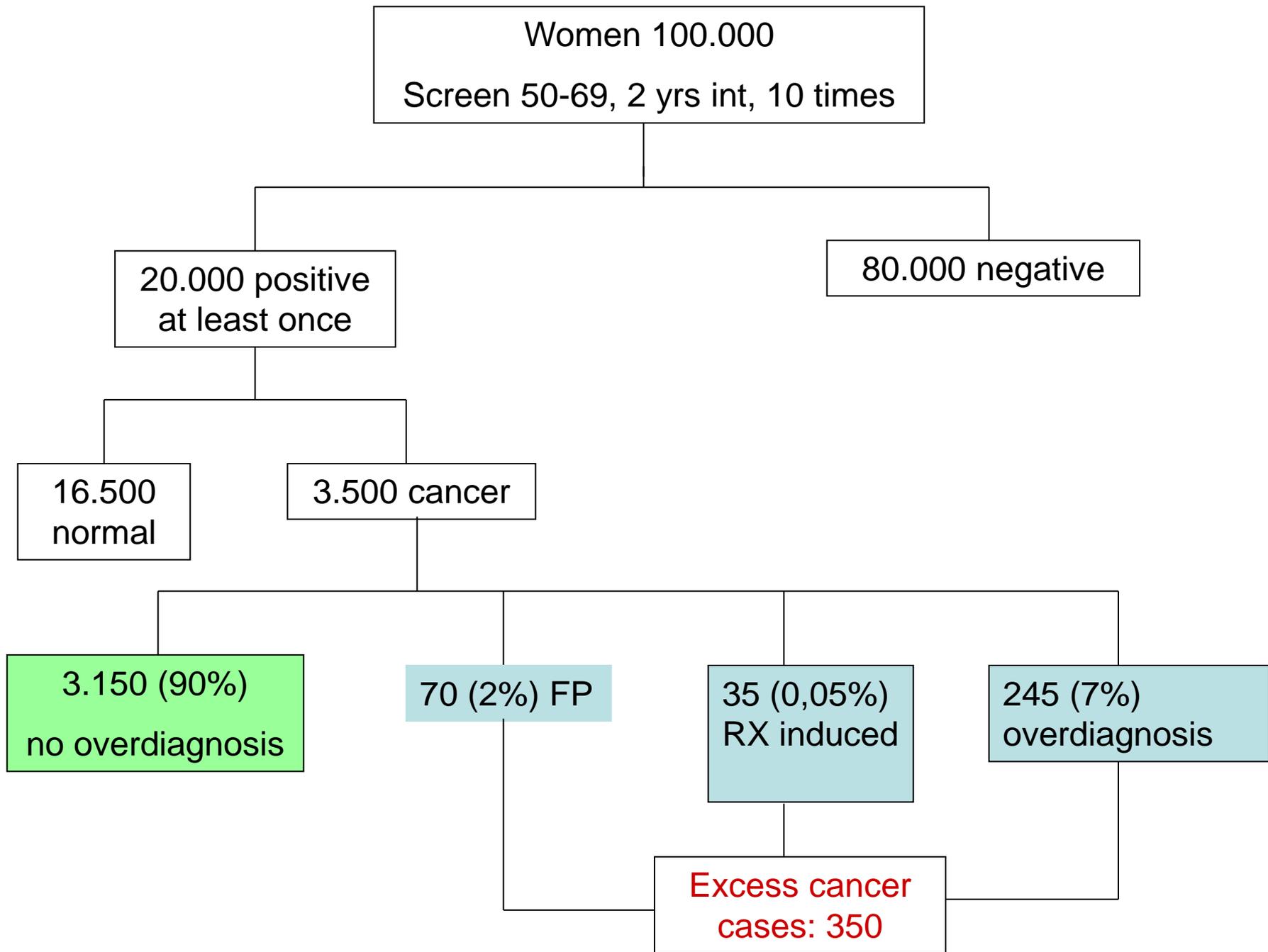
# Overdiagnosis in Cancer

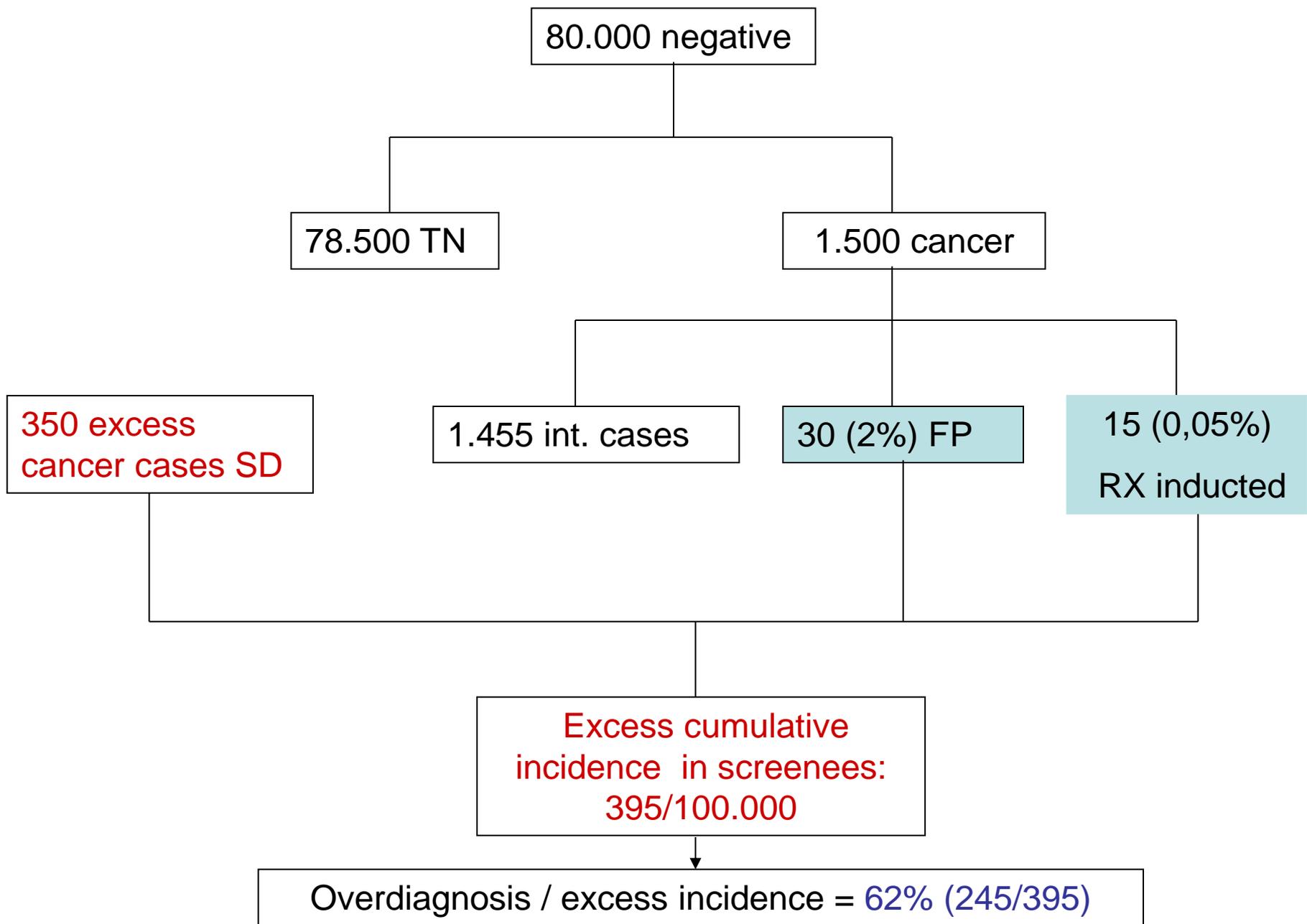
H. Gilbert Welch, William C. Black  
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# Determinants of overdiagnosis

- Biology of the disease: slow growing lesions
- Radiation induced cancers
- False positive cases: diagnostic errors





In the example about  $2/3$  of excess cancer cases may be overdiagnosed. The remaining  $1/3$  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**

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

**“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, ductalcarcinoma in situ or high-gradeprostatic 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.

# Overdiagnosis as an epiphenomenum

Nereo Segnan and Antonio Ponti

CPO Piemonte and S.Giovanni Battista University Hospital

Firenze November 6, 2010

# Overdiagnosis: some questions

## 1. Which are the determinants of overdiagnosis?

-Slow growing lesions: the speed of a neoplastic process in reaching the clinical threshold of cancer, is slower than the speed of other competing events causing death. This crucial component of overdiagnosis is due to the lead time: the longer the lead time the higher the probability of overdiagnosis.

- Which actions may reduce the rates of overdiagnosis ?

-Proposals : classify the cancer lesions taking into account not only the morphology classification, but also biomarkers as proxies of speed of progression. Do not classify as cancer lesions of unknown malignant potential, do not treat these lesions as cancer, or treat not aggressively.

- Study the survival by stage and prognostic biomarkers. Modulate the therapy according to.

## Recommendation n° 4

### **Mitigate overdiagnosis.**

Strategies to reduce detection of indolent disease include reducing low-yield diagnostic evaluations appropriately, reducing frequency of screening examinations, focusing screening on high-risk populations, raising thresholds for recall and biopsy, and testing the safety and efficacy of risk-based screening approaches to improve selection of patients for cancer screening. The ultimate goal is to preferentially detect consequential cancer while avoiding detection of inconsequential disease.

# Overdiagnosis: some questions

## 1. Which are the determinants of overdiagnosis?

-In screen detected cancers the proportion of slow growing lesions is larger than the proportion of fast growing lesions compared with clinical detected cancers, due to length bias. This also increases the likelihood of overdiagnosis.

Which actions may reduce the rates of overdiagnosis ?

**Proposals: use longer interval between screening episodes, reconsider the trade off between interval cases and overdiagnosis.**

**-Study by modelling the PYLG according to different screening intervals**

# Overdiagnosis: some questions

## 1. Which are the determinants of overdiagnosis?

Diagnostic error: the accuracy of the screening and of the related diagnostic process is limited by the intrinsic characteristics of the tests and exams which are adopted. The reproducibility of the classification scales may be enhanced.

**Which actions may reduce the rates of overdiagnosis ?**

Training and quality controls may reduce the errors due to the interpretation of the test and to poor/absent quality controls. The compliance to guidelines and to standards as well as the magnitude of the diagnostic errors should be estimated.

# Diagnostic variability

**Italian multicentric project “Impatto”**

**Population-based 1988-2006**

**11 Areas age 50-69**

**Non screen detected cancers**

**DCIS: range 4%-9% of all cancers**

**MI: range 0.9%-2.7% of all cancers**

# Diagnostic variability

**European multicentric project “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

# Overdiagnosis: some questions

## 1. Which are the determinants of overdiagnosis?

-For some neoplasias (DCIS grade 1 and 2 or invasive or micro-invasive, low grade cancer smaller than 1 cm or 1.5 cm) treatment (surgery, radiotherapy chemotherapy) is performed without knowing the fatality rates of conditions:

- the hiatus between morphology and biology of cancer seems to increase in spite of many available biomarkers and prognostic factors: the use of biomarkers seems to work only in one direction i.e. when more effective treatment can be offered according to biological characteristic of the neoplasia. Not in the other, i.e. when the biomarkers may identify slow growing, not aggressive lesions.

- the variability of treatment in different screening programs may enhance the harms of overdiagnosis

# Treatment variability

**European multicentric project “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

# Treatment variability

**Italian multicentric project “Osservatorio Nazionale Screening  
- QT”**

**Screen detected cases 2006-2008 (any test)**

**40 Areas age 50-69**

**Pre-operative diagnosis 12.5%-96.8% of screen detected cancers**

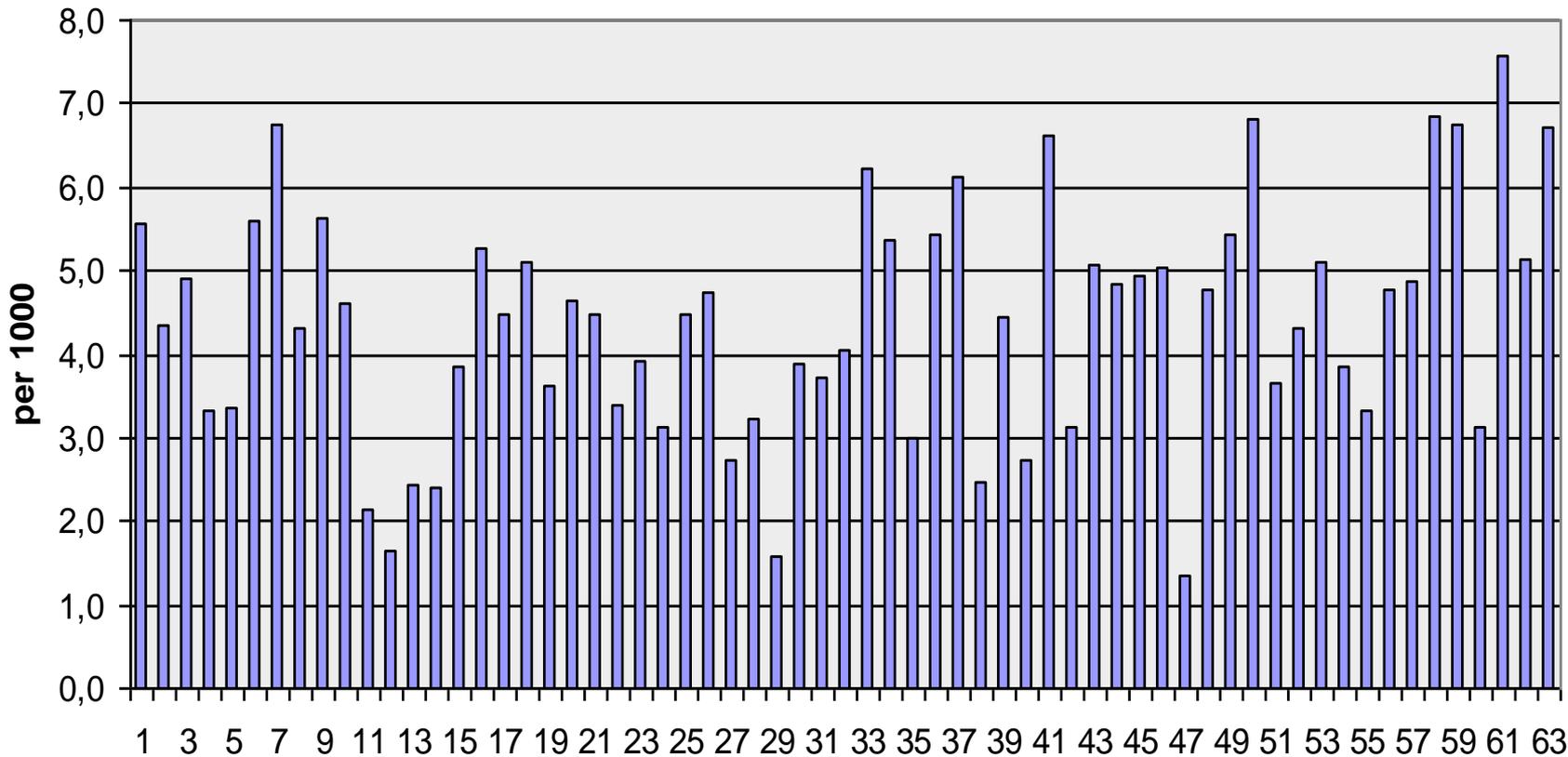
**Breast conservation surgery: 75%-97.9% of DCIS  $\leq$  20mm**

**Breast conservation surgery: 78%-100% of invasive cancers  $\leq$   
20mm**

**SLN only 63%-100% of cancers pN0**

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

## Subsequent screenings 63 Programmes ( ONS survey)



Screening programmes

## Recommendation n°3

### **Create observational registries for low malignant potential lesions.**

Providing patients and clinicians with pathologic diagnosis and information related to disease prognosis is crucial to informed decision making, including comfort with alternate treatment strategies such as active surveillance. Prognosis for precancerous lesions includes the risk of development of invasive cancer, the period over which such a tumor would develop, and the prognosis of that type of tumor should it occur. Prognosis for invasive cancer includes risk and timing of development of metastatic disease and death. **Large registries for potentially indolent conditions would provide data linking disease dynamics (eg, tumor growth rate over time) and diagnostics needed to provide patients and physicians with confidence to select less invasive interventions.**

## Recommendation n°5:

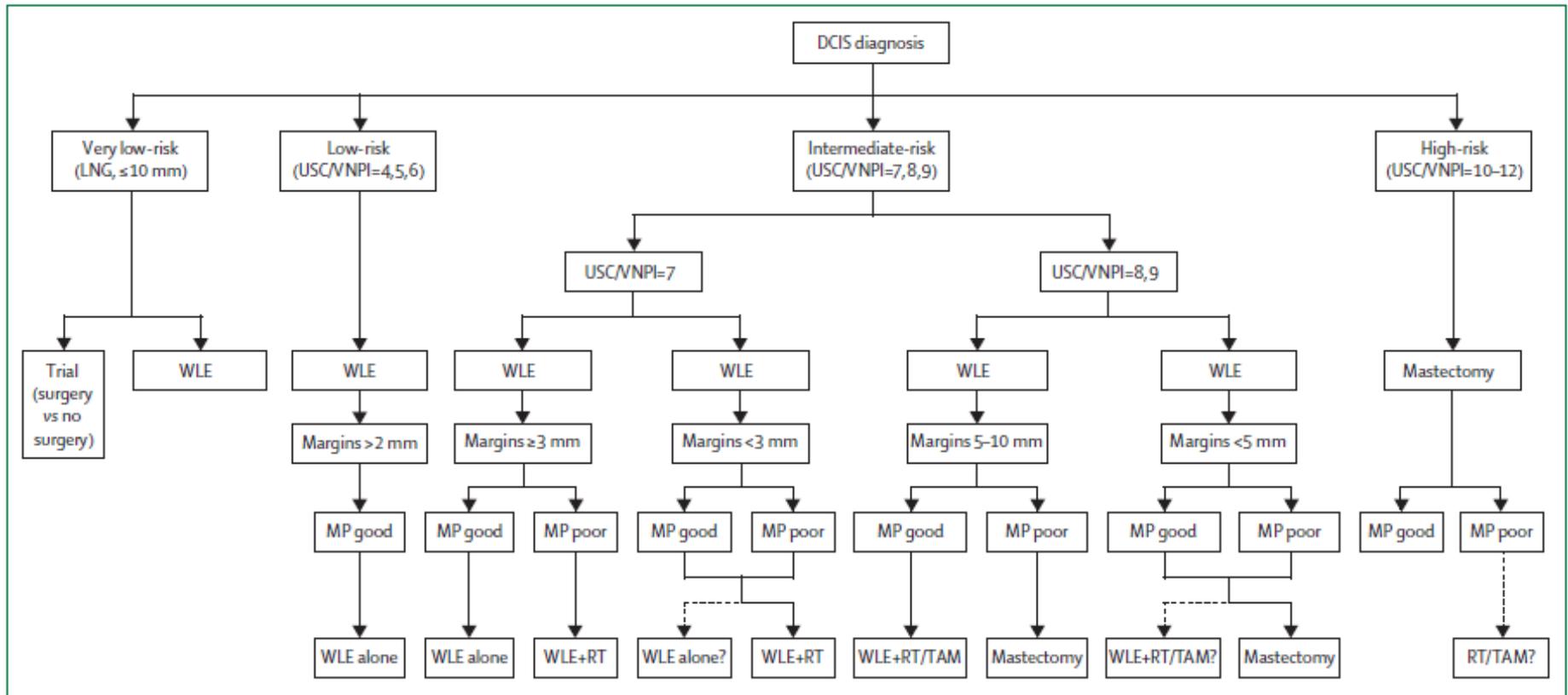
**Expand the concept of how to approach cancer progression.**

Future research should include controlling the environment in which precancerous and cancerous conditions arise, as an alternative to surgical excision.

**“Predictors of recurrence for ductal carcinoma in situ after breast-conserving surgery”**

Benson JR, Wishart G

Lancet Oncol 2013; 14: e348-57



**Figure 2: Algorithm for treatment of DCIS**

MP includes ER, PR, HER2, and Ki-67 status, and Oncotype DX score. DCIS=ductal carcinoma in situ. LNG=low nuclear grade. USC/VNPI=University of Southern California/Van Nuys Prognostic Index. WLE=wide local excision. MP=molecular profile. RT=radiotherapy. TAM=tamoxifen.

	Wide local excision	Mastectomy	TAM	RT+TAM
Very low risk	<b>X</b>			
Low Risk	<b>X</b>			
Intermediate Risk	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>
High Risk		<b>X</b>	<b>X</b>	<b>X</b>

Summary of previous algorithm: surgery alone is recommended for patients at very low risk, low risk and intermediate risk.

# Screening or treatment?

JNCI Journal of the National Cancer Institute Advance Access published July 17, 2012

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EDITORIAL

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## Is the Breast Cancer Mortality Decrease in Sweden Due to Screening or Treatment? Not the Right Question

Nereo Segnan, Stefano Rosso, Antonio Ponti

**Correspondence to:** Nereo Segnan, MD, MSc Epi, CPO Piemonte, Unit of Cancer Epidemiology, ASO S Giovanni Battista University Hospital, Via S Francesco da Paola 31, Turin 10123, Italy (e-mail: [nereo.segnan@cpo.it](mailto:nereo.segnan@cpo.it)).

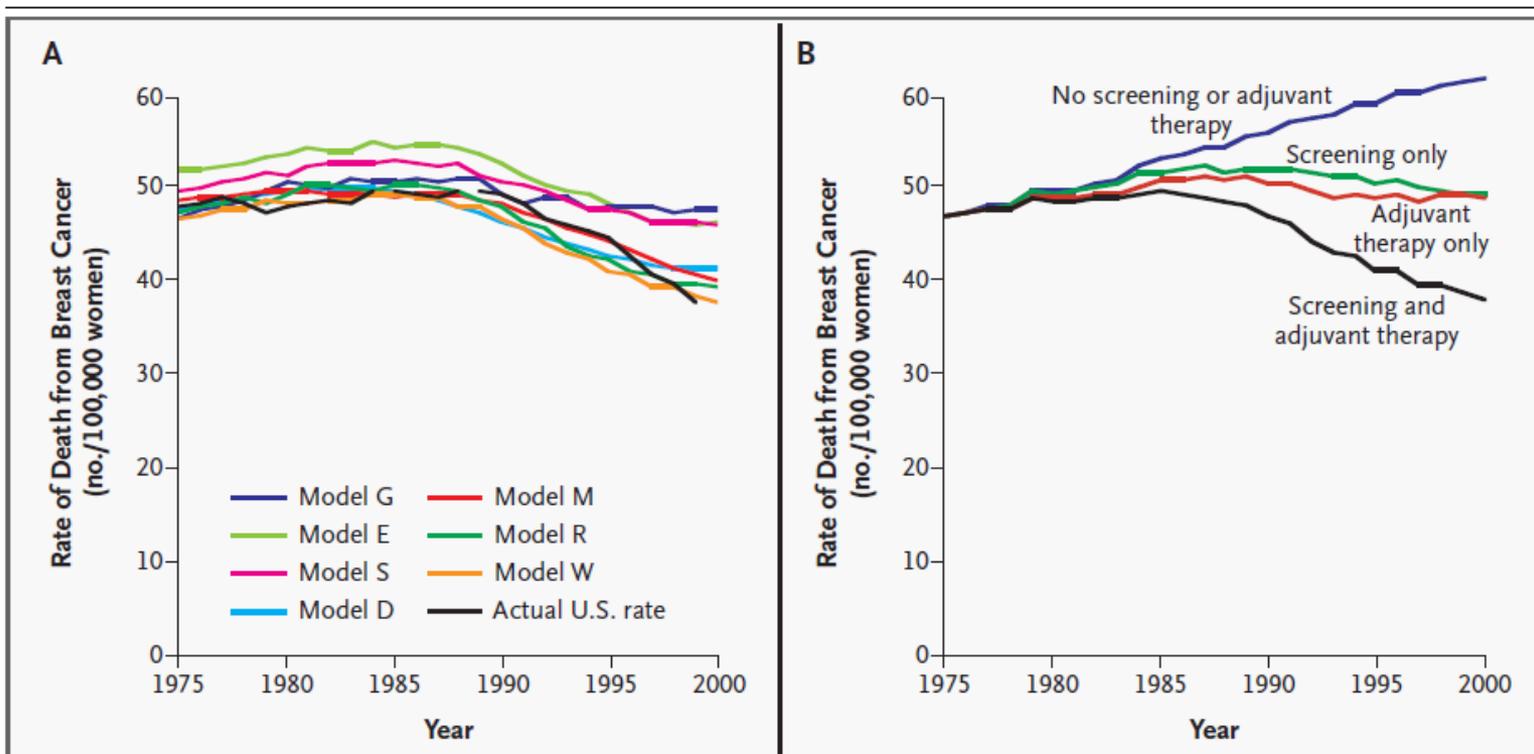
## Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer

Donald A. Berry, Ph.D., Kathleen A. Cronin, Ph.D., Sylvia K. Plevritis, Ph.D.,  
Dennis G. Fryback, Ph.D., Lauren Clarke, M.S., Marvin Zelen, Ph.D.,  
Jeanne S. Mandelblatt, Ph.D., Andrei Y. Yakovlev, Ph.D., J. Dik F. Habbema, Ph.D.,  
and Eric J. Feuer, Ph.D., for the Cancer Intervention and Surveillance  
Modeling Network (CISNET) Collaborators\*

**Table 3.** Estimated Reductions in the Rate of Death from Breast Cancer in 2000 Attributed to Adjuvant Treatments and Screening.\*

Model	Tamoxifen	Chemotherapy	Both Therapies	Screening	Overall
	<i>percent (percent of reduction)</i>				
D (Dana–Farber Cancer Institute)	6.1	6.1	12.0 (35)	22.7 (65)	32.9
E (Erasmus University Medical Center)	12.0	9.6	20.9 (58)	15.3 (42)	30.9
G (Georgetown University)	7.7	7.0	14.6 (54)	12.4 (46)	24.9
M (M.D. Anderson Cancer Center)	10.7	9.5	19.5 (65)	10.6 (35)	27.5
R (University of Rochester)	NA	NA	19.0 (72)	7.5 (28)	25.6
S (Stanford University)	8.9	6.9	14.9 (47)	16.9 (53)	29.9
W (University of Wisconsin–Madison)	12.5	8.9	20.8 (51)	20.3 (49)	38.3

\* Values are point estimates from each model; percentages in parentheses are the percentages of the overall reduction that are attributable to treatment or screening. NA denotes not applicable.



**Figure 2.** Estimated and Actual Rates of Death from Breast Cancer among Women 30 to 79 Years of Age from 1975 to 2000 (Panel A) and under Hypothetical Assumptions about the Use of Screening Mammography and Adjuvant Treatment (Panel B).

Panel A, which compares the model-based results with the actual rates in the United States from 1975 to 2000, shows the variability across the model estimates. Some of the models were calibrated according to the observed rate of death from breast cancer in the United States, and some were not. Panel B shows the results from model W (the University of Wisconsin–Madison) of estimated mortality trends for the four scenarios considered: no screening and no adjuvant treatment; base-case screening, but no adjuvant treatment; no screening, but base-case adjuvant treatment; base-case screening and adjuvant treatment. Rates in both panels are age-adjusted to the 2000 U.S. standard.

The way forward is not to increase the threshold of mammographic recall but *to stop the overtreatment of indolent lesions* such as invasive tubular carcinoma and low grade ductal carcinoma in situ, *particularly in elderly women*.

*Breast cancer is more indolent in elderly women*, with tumours being of lower histological grade and more often oestrogen receptor positive.

This coupled with a *decreased life expectancy* means that overdiagnosis is likely to become more of a problem with the proposed extension of screening to women in their 70s.

Evans A, Cornford E, James J. Breast screening overdiagnosis.  
Stop treating indolent lesions.  
BMJ. 2009 Aug 11;339

# Conclusions

More than 3 years ago we suggested interventions and studies aiming to reduce the overdiagnosis and the related overtreatment of breast cancer.

Proposals to mitigate overdiagnosis :

- Improve accuracy: Multicentre study on diagnostic reproducibility, 2nd opinion on borderline lesions.
- Reduce radiation inducing cancer: Xray generation and dosimetry, technical quality controls.
- Decrease screening intensity for low risk women (3 vs 2 years interval)
- Stop to treat indolent lesions: do not refer screen positive women to breast units that do not agree on conservative, not aggressive treatment protocols.

European Commission Working Group on Breast Screening Pathology: J.P. Sloane (Chairman)  
 I. Amendoeira · N. Apostolikas · J.P. Belloq  
 S. Bianchi · W. Boecker · G. Bussolati · D. Coleman  
 C.E. Connolly · V. Eusebi · C. De Miguel · P. Dervan  
 R. Drijkonigen · C.W. Elston · D. Faverly · A. Gad  
 J. Jacquemier · M. Lacerda · J. Martinez-Penuela  
 C. Munt · J.L. Peterse · F. Rank · M. Sylvan  
 V. Tsakraklides · B. Zafrani

**Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas**

**Table 1** Consistency of making overall diagnoses expressed as  $\kappa$  statistics (*AH* Atypical ductal hyperplasia, *In situ/micro* in situ or microinvasive carcinoma, *Invasive* invasive carcinoma)

Round	Diagnosis				
	Benign	ADH	In situ/ micro	Invasive	Overall
1	0.66	0.17	0.83	0.96	0.79
2	0.73	0.29	0.91	0.95	0.87
3	0.83	0.33	0.87	0.97	0.86
4	0.50	0.29	0.84	0.91	0.80
All 4	0.74	0.27	0.87	0.94	0.84

## OVERDIAGNOSIS: some definitions

<p>Martinez-Alonso M et al. (2010)</p>	<p>screening may cause overdiagnosis when it detects tumours which would never have been diagnosed during a lifetime without screening because of the lack of progressive potential or death from other causes</p>
<p>Duffy SW et al. (2010)</p>	<p>the diagnosis of a cancer as a result of screening that would not have been diagnosed in the woman's lifetime had screening not taken place</p>
<p>de Roos MA et al. (2007)</p>	<p>because DCIS is a non-obligatory precursor to invasive carcinoma, and so has a relatively benign nature, screen-detected DCIS represents an overdiagnosis</p>
<p>Olsen AH et al. (2006)</p>	<p>overdiagnosis may be thought of as an extreme form of length bias, where the tumour develops so slowly that it would never have given rise to symptoms in the lifetime of the host</p>

# The debate

Screening may reduce deaths from the target cancer but may increase deaths from other causes, most likely because of overdiagnosis, an increasingly recognized risk of cancer screening.

Recognition of the discrepancy between the expected and the actual impact of screening and recognition of overdiagnosis as a source of harm may be critical for understanding and projecting the potential impact of cancer screening programs.

Newman DH.

Screening for breast and prostate cancers: moving toward transparency.

J Natl Cancer Inst. 2010 Jul 21;102(14):1008-11

Overdiagnosis — along with the subsequent unneeded treatment with its attendant risks — is arguably the most important harm associated with early cancer detection.

The impact of false-positive test results is largely transitory, but the impact of overdiagnosis can be life-long and affects patients' sense of well-being, their ability to get health insurance, their physical health, and even their life expectancy.

In general, there is no right answer for the resulting trade-off between the potential to avert a cancer death and the risk of overdiagnosis. Instead, the particular situation and personal choice have to be considered.

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**Benefits**

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One woman will avoid a breast cancer death (36)

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**Harms**

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Between two and 10 women will be overdiagnosed and treated needlessly  
Between five and 15 women will be told that they have breast cancer earlier than they would otherwise yet have no effect on their prognosis  
Between 200 and 500 women will have at least one "false alarm" (50–200 will be biopsied)

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\* Among one thousand 50-year-old women undergoing annual mammography for 10 years. See Supplementary Technical Appendix (available online).

Draft balance sheet for screening mammography in 50-year-old women, among 1000 50-year-old women undergoing annual mammography for 10m years.

The Welch and Black study is not “bad news,” but “good news” because it points a way forward. First, we must accept that population screening and diagnostic scans detect substantial numbers of indolent tumors and benign lesions in addition to potentially lethal disease. Second, we must resolve that we can and must address the problem.

Recognition of this fact may help us to set better thresholds for intervention and more appropriate screening intervals. If less frequent screening is as effective as more frequent screening and results in fewer diagnostic procedures, this should be welcome news and embraced, not dismissed out of fear.

Esserman L, Thompson I.  
Solving the overdiagnosis dilemma.  
J Natl Cancer Inst. 2010 May 5;102(9):582-3

## Overdiagnosis and mammography screening

*The question is no longer whether, but how often, it occurs*

The information that will probably influence most women's choice will be data on the trade-off between the number of deaths from breast cancer avoided and the number of cancers overdiagnosed.

More research is needed to confirm or dispute this assertion and to determine how sensitive women's choices are to various estimates of the trade-off.

Welch HG.

Overdiagnosis and mammography screening.

BMJ. 2009 Jul 9;339

The way forward is not to increase the threshold of mammographic recall but *to stop the overtreatment of indolent lesions* such as invasive tubular carcinoma and low grade ductal carcinoma in situ, *particularly in elderly women*.

*Breast cancer is more indolent in elderly women*, with tumours being of lower histological grade and more often oestrogen receptor positive.

This coupled with a *decreased life expectancy* means that overdiagnosis is likely to become more of a problem with the proposed extension of screening to women in their 70s.

Evans A, Cornford E, James J. Breast screening overdiagnosis.  
Stop treating indolent lesions.  
BMJ. 2009 Aug 11;339

## Overdiagnosis: some questions

**2. Which is the likelihood of a woman with a positive screening mammography of being classified as a (overdiagnosed) breast cancer case in different screening programmes?**

**If the variability is significant, which proportion of non reproducible (overdiagnosed) cancer cases is avoidable, adopting more reliable classifications and more stringent protocols for diagnosis and treatment ?**

## Overdiagnosis: some questions

- Which and how many cases are referred for assessment in the screening programmes?
- How breast cancer cases are classified in breast cancer screening programmes?
- How many DCIS are detected?
- Which biomarkers are measured and how are they used for deciding about the treatment?
- Which quality controls are adopted for reducing the diagnostic errors especially for borderline cases?
- Which and how many cases are treated and how?

## Overdiagnosis: some questions

### PROPOSALS:

- Utilize available/accessible data set to compare the adopted classifications and the diagnostic and treatment protocols, and the EU breast cancer screening quality assurance guidelines.
- Try to estimate the avoidable fraction of breast cancer overdiagnosis, achievable with more reliable classification, and more stringent quality controls.

## Overdiagnosis: some questions

### 3. Which is the trade-off between mortality reduction and overdiagnosis?

The harms of overdiagnosis depend on the side effects of treatment and on psychological impact of being a cancer patient. Which are, how frequent, and how severe are these side effects?

Reducing, minimizing the harms would change the overdiagnosis weight. It would be meaningful to characterize the estimates of 1:1, 1:2,5 case of overdiagnosis for avoided death, describing what harms the overdiagnosed cases experienced, and how much the life has been prolonged for the others.

## Overdiagnosis: some questions

### 3. Which is the trade-off between mortality reduction and overdiagnosis?

In practice, given that it would be not possible to identify the overdiagnosed cases (a part the false positive due to diagnostic errors) and the survivors, thank to screening, among all breast cancer survivors, which are the criteria for defining and weighting the harms of overdiagnosis and the benefits for survivors?

**Study the population values and preferences. Make possible the informed decision. Respect the individual decision**

# Overdiagnosis: some questions

## PROPOSALS:

RCTs comparing no therapy or limited, less aggressive therapy to the conventional one. When surgery alone (and FU) could be recommended?

RCTs with different treatments

# Conclusion

- These are some of the problems that we should be aware of.
- We are not able to solve these problems
- If we can make clear or (unlikely) if we can solve some of them we have to take into account the overall context of unanswered questions.

## Recommendation n° 1:

**Physicians, patients, and the general public must recognize that overdiagnosis is common and occurs more frequently with cancer screening.**

Overdiagnosis, or identification of indolent cancer, is common in breast, lung, prostate, and thyroid cancer. Whenever screening is used, the fraction of tumors in this category increases. By acknowledging this consequence of screening, approaches that mitigate the problem can be tested.

# Assumptions – screened population

- 100,000 women - 50 years of age - 10 screen episodes every 2 years
- Mortality follow up until 79 years
- Incidence follow up until 72 years
- Cumulative incidence 50-72 yrs 5%
- Screening programme sensitivity 70%
- No overdiagnosis 90%
- Diagnostic error 2%
- RX induced cancers 0.15%
- 10 years mortality 27%
- Prevented deaths 20%

# “Overdiagnosis” in unscreened persons

Which is the risk of not necessary treatment ( cancers that would not cause the death if left untreated plus false positive cancers ) in unscreened, symptomatic women?

92-342 cases ( 1 year relative survival – observed survival 2%, 5 years relative survival – observed survival 7%) plus 92 FP: 184-334 excess cases of unnecessary treatment

**Table. Change in Incidence and Mortality of Cancers Over Time From 1975 to 2010 as Reported in Surveillance, Epidemiology and End Results<sup>1</sup>**

Change <sup>a</sup>	Incidence			Mortality		
	Per 100 000		%	Per 100 000		%
	1975	2010 <sup>b</sup>		1975	2010 <sup>b</sup>	
<b>Example 1</b>						
Breast <sup>c</sup>	105.07	126.02	20	31.45	21.92	-30
Prostate	94	145.12	54	30.97	21.81	-30
Lung and bronchus <sup>d</sup>	52.26	56.68	8	42.56	47.42	11
<b>Example 2</b>						
Colon	41.35	28.72	-31	28.09	15.51	-45
Cervical	14.79	6.71	-55	5.55	2.26	-59
<b>Example 3</b>						
Thyroid	4.85	13.83	185	0.55	0.51	-7
Melanoma	7.89	23.57	199	2.07	2.74	32

<sup>a</sup> Example 1: Indolent and consequential tumors are identified with screening, leading to an overall increase in incidence rates. Example 2: Prescreened tumor population is more homogeneous, slower-growing but consequential. Screening substantially decreases incidence (through detection and removal of precursor lesions) and mortality. Example 3. Screening expands the population of indolent tumors, with little or no effect on the small population of more aggressive tumors.

<sup>b</sup> Represents period in which screening (except for lung cancer) is prevalent.

<sup>c</sup> At least two-thirds of the mortality reduction is believed attributable to adjuvant therapy.

<sup>d</sup> The National Lung Screening Trial conducted among individuals at risk for lung cancers shows that the proportion of stage I detected tumors is more than 2-fold higher than the decrease in the higher-stage tumors, accounting for its inclusion in example 1

From: **Overdiagnosis and Overtreatment in Cancer: An Opportunity for Improvement**

JAMA. 2013;310(8):797-798. doi:10.1001/jama.2013.108415

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<sup>c</sup> At least two-thirds of the mortality reduction is believed attributable to adjuvant therapy.<sup>2,3</sup>

<sup>d</sup> The National Lung Screening Trial conducted among individuals at risk for lung cancers shows that the proportion of stage I detected tumors is more than 2-fold higher than the decrease in the higher-stage tumors, accounting for its inclusion in example 1.<sup>5</sup>

**Figure Legend:**

Change in Incidence and Mortality of Cancers Over Time From 1975 to 2010 as Reported in Surveillance, Epidemiology and End Results