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University Medical Center Rotterdam

Le dépistage, est-il responsable du surdiagnostic? Comment le mesurer?

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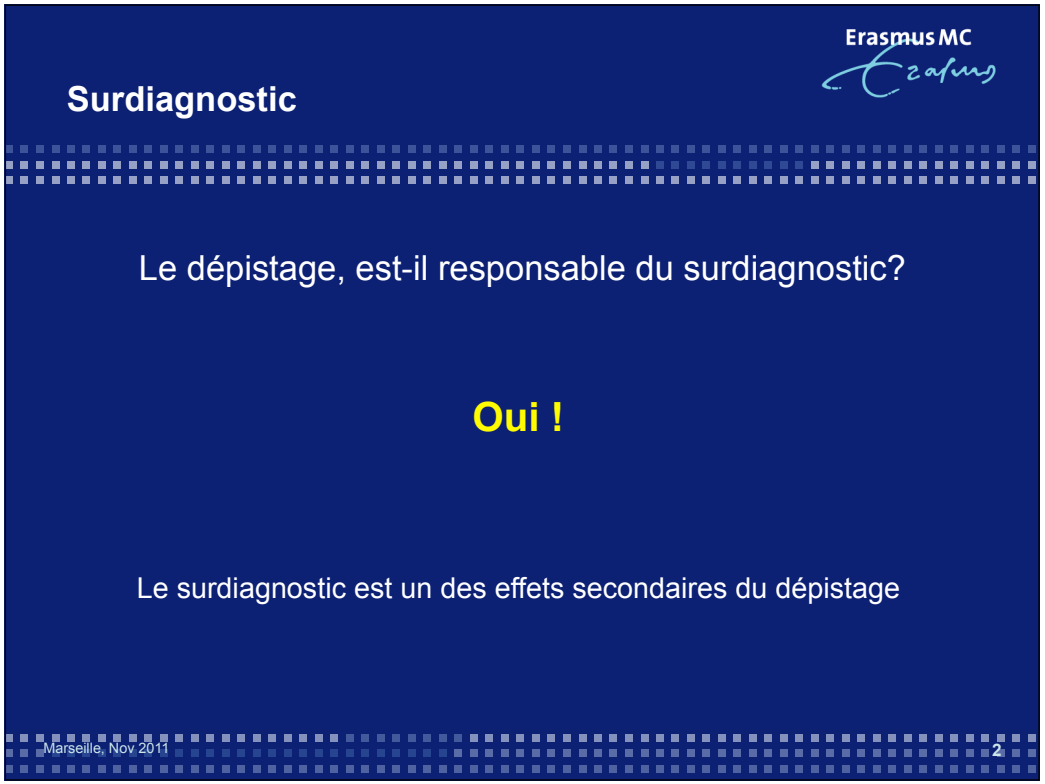
In my presentation I would like to discuss with you one of the downsides of breast cancer screening, namely, over-diagnosis.



Let's start with the definition of over-diagnosis.

In our study, we defined over-diagnosis as the detection of a pre-clinical breast cancer by screening, that WOULD NEVER have been diagnosed if no screening had taken place.

With other words, screening will detect harmless, irrelevant cancers.

It can occur when a woman has a slowly or non-progressing breast cancer

It can occur when a woman has a screen-detected breast cancer, but she dies of something else then breast cancer

It can occur (in theory) when a pre-clinical breast cancer regresses, but it is not known if and to which extent this happens

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Screening: implications for individual health status

Phase	Favourable	Unfavourable
Screening offer		(slight) worry
Screening test		(slight) burden
Test negative	reassurance	
Test positive		(stronger) worry
Assessment negative	reassurance	
Assessment positive		strong worry, label “ill”
Treatment		burden and risk
Possible outcome	longer life, better quality of life due to smaller treatment	no gain in life-years, lower quality of life due to treatment, overtreatment

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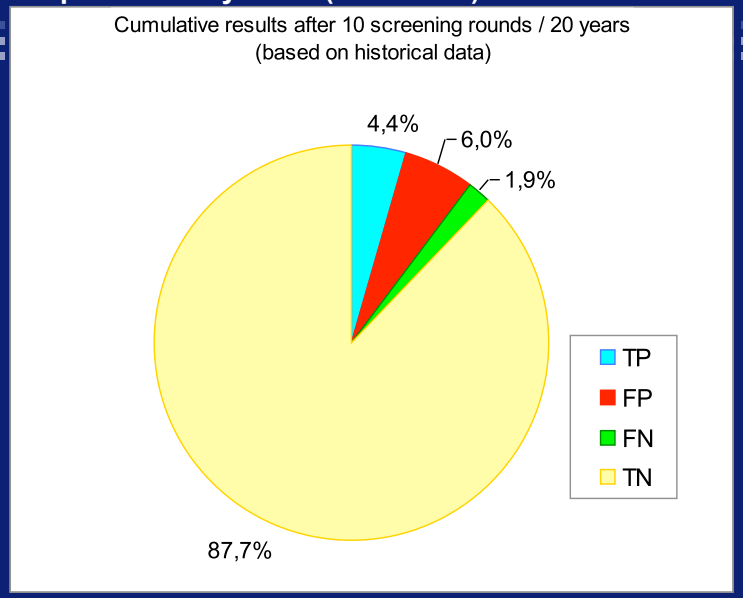
Benefits and harms:
Exemple dépistage du cancer du sein aux Pays-Bas (2005)

	Cancer du sein	Pas de cancer	
Mammo positive	50	100	150
Mammo negative	20	9 830	9 850
	70	9 930	10 000

25	Ont un bon pronostic même sans dépistage
7	Meurent du cancer du sein dépisté
13	Survivent grâce au dépistage (en moyenne 15 ans de plus)
5	N'auraient jamais eu un cancer du sein du vivant sans dépistage
50	

Benefits and harms: 20 ans d'expérience Pays-Bas (1990-2009)



Overdiagnosis - Surdiagnostic

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Overdiagnosis is the detection of a pre-clinical cancer by screening, that would never have been diagnosed in the woman's lifetime if no screening had taken place

Surdiagnostic est le dépistage précoce d'un cancer qui ne serait jamais devenu manifeste du vivant sans dépistage.

Il inclut:

- Des cancers qui croissent lentement (ou plus du tout)
- Des cancers régressifs
- Décès suite d'une autre maladie

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Taux de surdiagnostic: résultats publiés

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Morrell (Australia) *Cancer Causes Contr 2010*	30% - 42% of *all invasive* breast cancers
Biesheuvel (review) *Lancet Oncology 2007*	-4% - 54% of *all invasive* breast cancers
Zahl, (Norway) *BMJ 2004*	56% of *all invasive* breast cancers
Jorgensen (review) *BMJ 2009*	52% of all breast cancers
Zackrisson (Malmö Trial) *BMJ 2006*	10% of all breast cancers
Duffy, (TC & Gothenburg Trial) *Breast Cancer Res 2005*	1% ~~of~~ all breast cancers
De Koning (NL, modelling) *Breast Cancer Res 2005*	3% of all breast cancers

Overdiagnosis controversy

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La balance vraie du dépistage ?

- Pour chaque décès évité par le dépistage …..

0,3	femmes sont surdiagnostiquée?	(Pays-Bas, 2009)
0,5	femmes sont surdiagnostiquées?	(Duffy, JMS 2010)
2	femmes sont surdiagnostiquées?	(Moller, BMJ 2006)
10	femmes sont surdiagnostiquées?	(Gotzsche, BMJ 2009)

To put it in other words…

Would it be 1 per breast cancer death that is prevented by screening?
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So, with other words, how many women will in fact be over-diagnosed?

Pourquoi ces estimes tellement différentes?

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Programme de dépistage (organisé)

- *trial* ou *service screening* (programme nationale)
- population cible (l'âge) → *length time*
- durée de l'intervalle, taux de participation, indicateurs de prestation

Suppositions à propos de l'histoire naturelle du cancer du sein

- durée (moyenne) du stade préclinique (→ *lead time*)
- régression des tumeurs?

Méthode de calcul

- *incidence-based* - modèle
- durée du follow-up
- dénominateur (population totale ou dépistée, cancers dépistés)
- invasive – in situ

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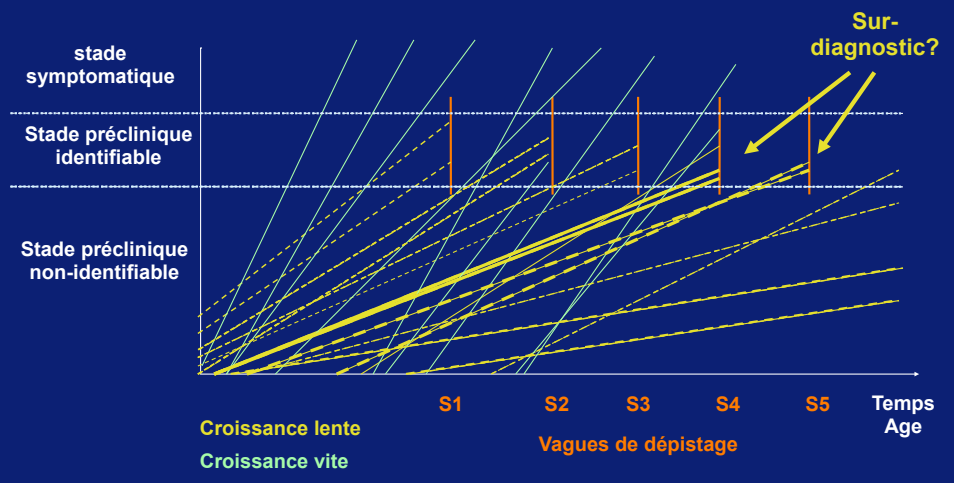
Length time


stade symptomatique
Stade préclinique identifiable
Stade préclinique non-identifiable
Sur-diagnostic?
S1
S2
S3
S4
S5
Temps Age
Croissance lente
Croissance vite
Vagues de dépistage

Méthode de calcul

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1. Basée sur des analyses d'incidence (cumulative) en fonction de l'âge

A. trial:

nombres de cancers dans le groupe intervention et le groupe contrôle

Points d'attention *(bias)*:

- taux de participation
- augmentation de l'âge moyen avec follow-up plus long (cohorte)
- contamination dans le groupe contrôle (mammographie préventive)
- dépistage plus tard dans le groupe contrôle

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Méthode de calcul

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B. Service screening:

l'incidence en fonction de l'âge entre des ans différents

- excès d'incidence dans les âges dépistés
- déficit d'incidence dans les âges suivants
- la différence entre l'excès et le déficit donne une indication pour l'ampleur de surdiagnostic

Points d'attention (*bias*):
- référence: incidence avant le début, incidence présumé
- moment de mesurer (steady state stade du programme)
- correction pour *lead time*

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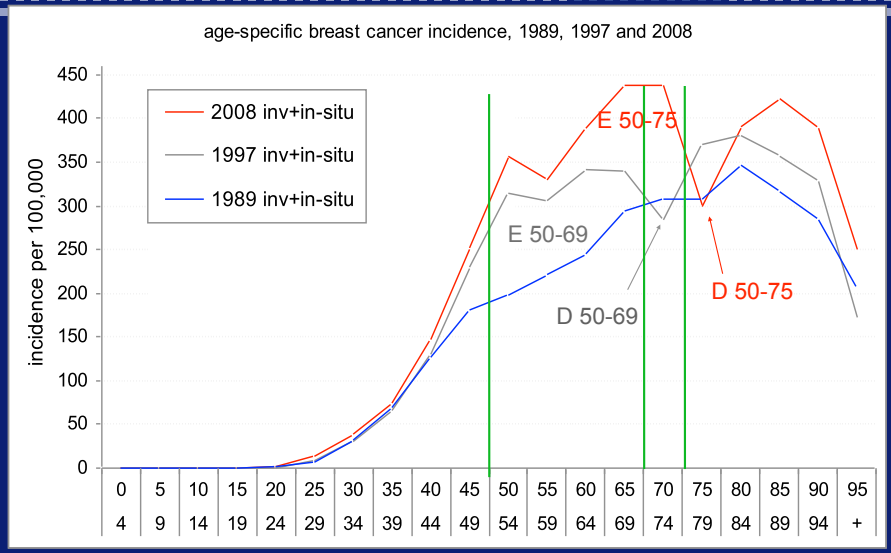
Incidence observée 1989, 1997 et 2008



Overdiagnosis controversy

Estimating overdiagnosis:

- in the screening ages, observed incidence > predicted incidence without screening ('excess');
- in the ages past the screening age, observed incidence < the predicted incidence without screening ('deficit')
- Overdiagnosis = excess – deficit

Méthode de calcul

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2. Modèle microsimulation (MISCAN)

simulation des vies individuelles basé sur des données
- démographiques (population, *life table,* mortalité)
- sur l'incidence et le traitement
- sur des risques connus
- (présumées) de dépistage

calibration en essayant de reproduire l'incidence observée

en variant les caractéristiques du dépistage, on peut comparer les effets (positives et négatives)

→ coût-efficacité
→ décisions pratiques

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Cost-effectiveness analysis Dutch programme (1990)

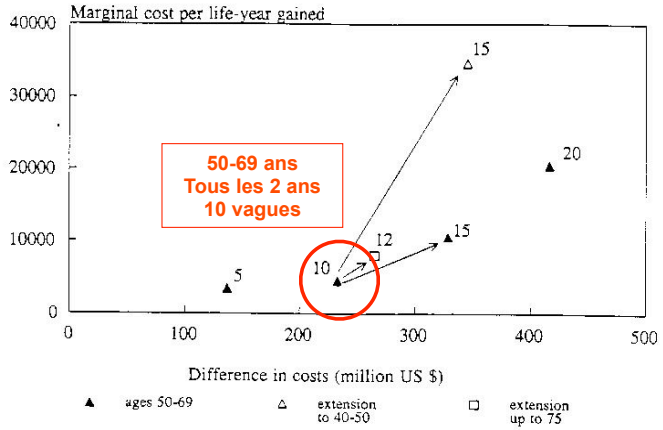

Figure 8.2 Marginal cost-effectiveness (additional US dollars per additional life-year gained) of 6 breast cancer screening policies: 5, 10, 15 or 20 invitations in the age group 50-70, 12 invitations in the age group 50-75, and 5 invitations during ages 40-49 followed by 10 invitations during ages 50-70. The corresponding differences in cost for each screening policy have been put at the horizontal axis. 5% discount rate.

Observed incidence in 1990 and predicted incidence without screening

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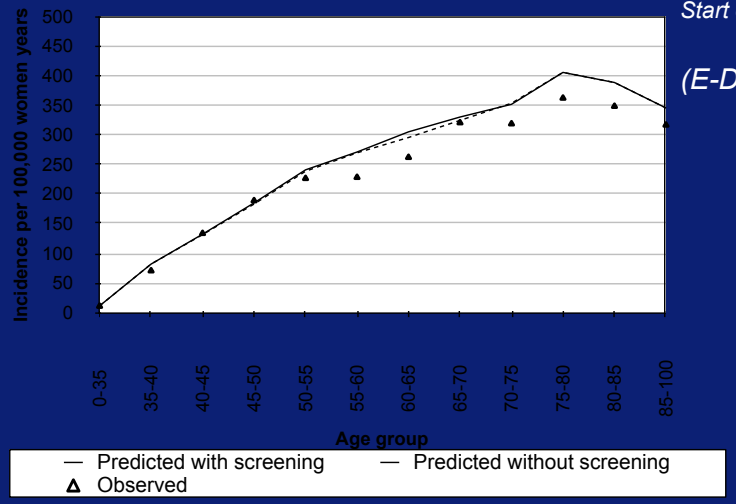

Start of screening program

(E-D)/T(0) = 1.0%

Observed incidence in 1993 and predicted incidence without screening

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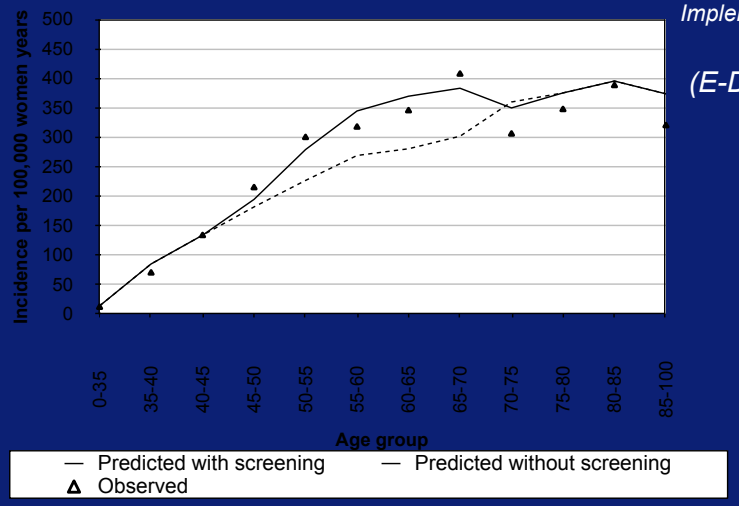
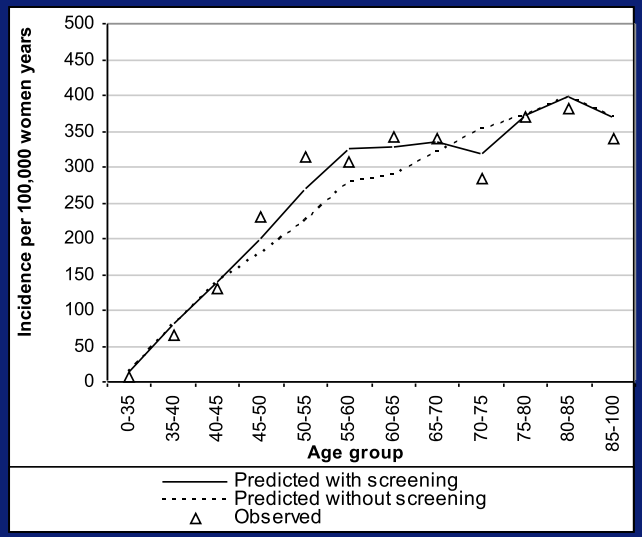


Implementation halfway

(E-D)/T(0) = 11.4%

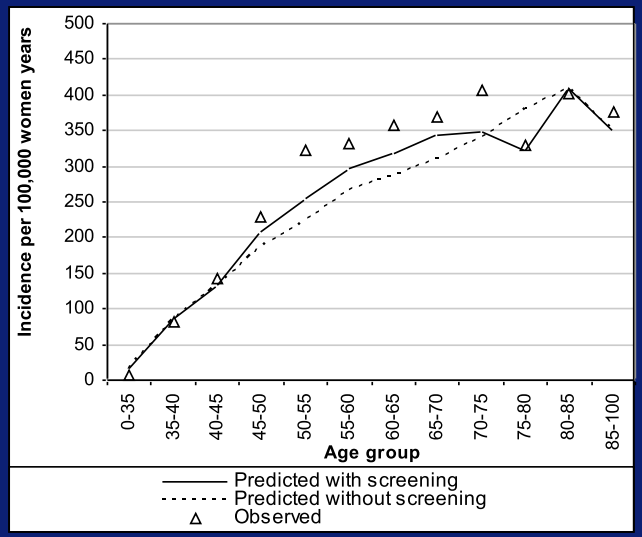
Observed incidence in 1997 and predicted incidence without screening



Implementation finished

(E-D)/T(0) = 5.6%

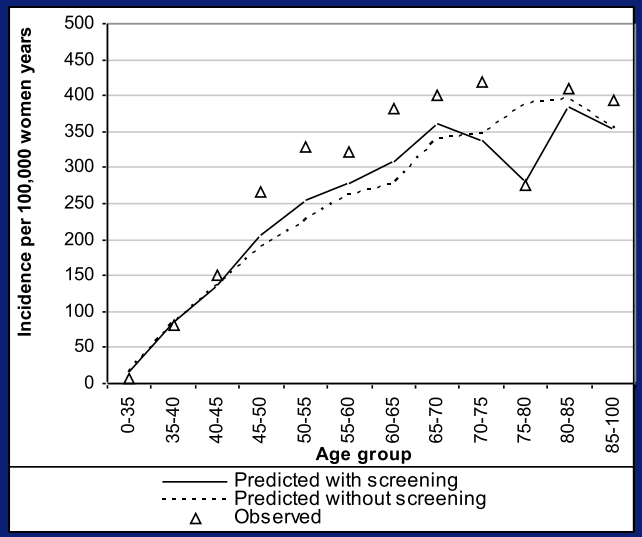
Observed incidence in 2002 and predicted incidence without screening



Steady state

(E-D)/T(0) = 4.7%

Observed incidence in 2006 and predicted incidence without screening



Steady state

(E-D)/T(0) = 2.8%

Long follow up necessary!!

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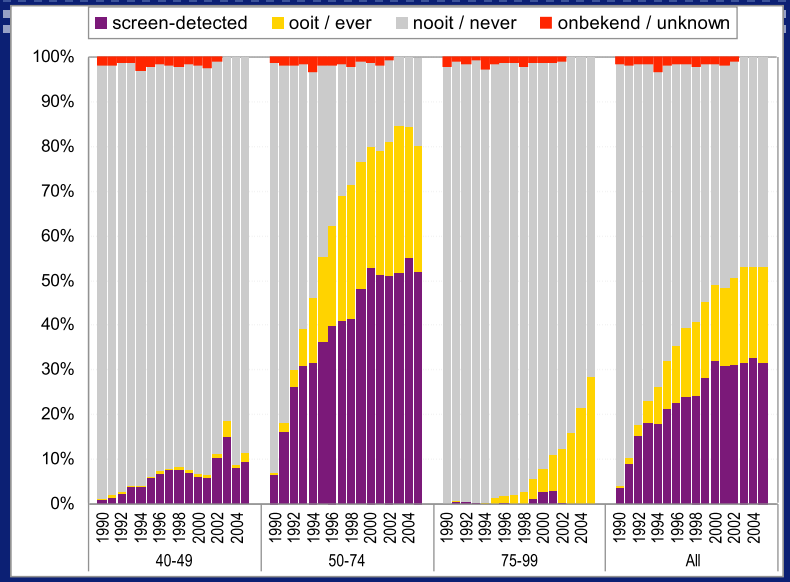
Results: population at risk in 2006

Estimate	Method	Description
2.8%	(E-D)/ T0 0 -100	All predicted breast cancers
3.6%	(E-D)/ T0, age 49-100	Method by Zackrisson et al.
5.0%	(E-D)/ T0, age 49-69/74	Method by Jørgensen et al.
9.7%	T1, 49-69/74/ T0, 49-69/74	Method by Zahl et al.
4.6%	(E-D)/ T1, age 49-69/74	Method by Duffy et al.
8.9%	(E-D)/ SD	All screen-detected breast cancers

Distribution (%) cancer du sein selon méthode de détection



Synthèse (1)

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- Surdiagnostic inévitable
- Calcul complexe, approximations

  Résultat dépend

  de la phase du programme / durée follow-up

  de l'incidence présumé sans dépistage

  du dénominateur choisi

Option alternative (NL): terminer le programme (dépistage organisé)

Mais: il y a toujours le dépistage individuel (DI)

le DI cause des effets pareils comme le DO

(qualité? évaluation?)

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Dépistage individuel (Belgique)

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L'Agence des Mutualités (Intermutualistisch Agentschap)

Campagne Borstkankerscreening 1999-2002, 2ème rapport, Bruxelles, 2004

Femmes Belges, 50-69 ans:

Couverture par « mammographie diagnostique » 2001-2002: 50%

- 80% 1 mamm., 15% 2 mamm., 5% >2 mamm.
- 79% en combinaison avec autres examens diagnostique (echographie)
  (dépistage organisé: 5%)

"Gezien het grote aantal mammografieën, kan men er nochtans van uitgaan dat de diagnostische mammografieën toch overwegend voor opsporing worden gebruikt."

« Vu le grand nombre des mammographies, il faut conclure que les mammographies diagnostiques servent en grande majorité à la détection précoce. »

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Et les bénéfices ?

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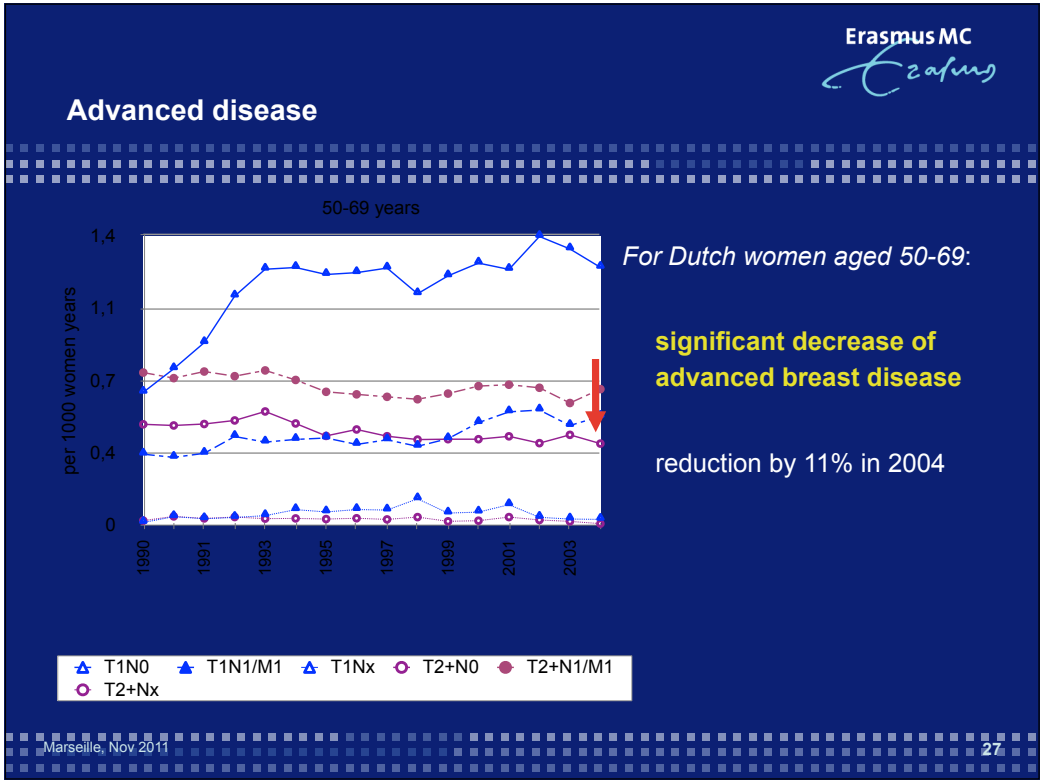
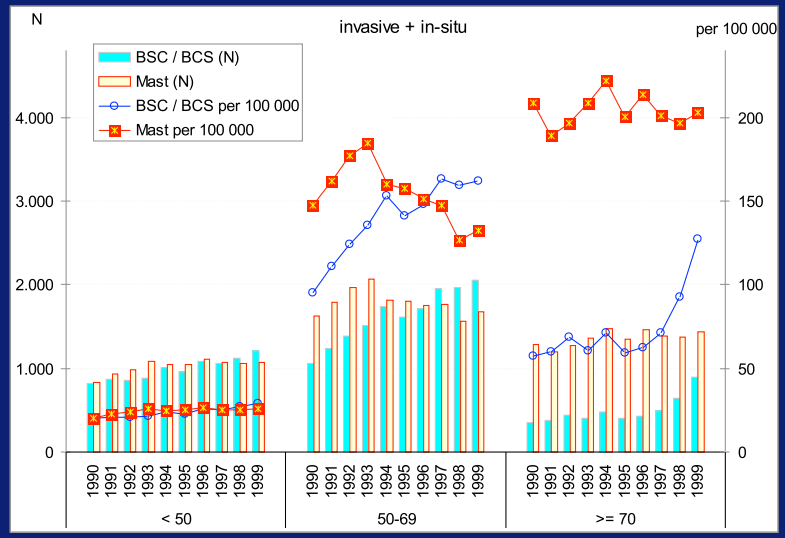


We found three main outcomes in women aged 50-69:

1) A strong increase of incidence rates in the early 1990s, particularly of DCIS and small lymph node negative invasive cancers.
2) That at the end of implementation in 1997 half of the breast cancers were detected by screening, and a quarter of all breast cancers in the total population; and
3) We found a significant of advance disease incidence rate of 12.1% in 1997 compared with 1989.

We conclude from our results that organised breast cancer screening has indeed the potential to reduce breast cancer mortality.

Traitement chirurgical: tous les cancers du sein (Pays-Bas)



Mortalité du cancer du sein avant / après le début du programme de dépistage dans les communes hollandaises (50-69 ans)

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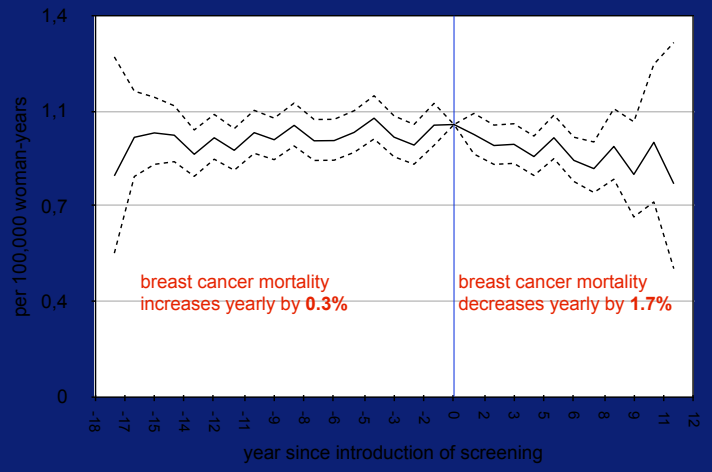

Otto et al.
Lancet 2003

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Case control analyses Breast Screening Europe

			Cases	Controls	RR
UK	Fielder	2004	419	717	**0.75**
UK	Allgood	2008	284	568	**0.52**
Iceland	Gabe	2007	226	902	**0.65**
Italy	Puliti	2008	657	2,772	**0.55**
Netherlands	Otto	2011	755	3,739	**0.51** (0.45 unadjusted)

Synthèse (2)

- Réduction de mortalité par le dépistage? Oui!
- Réduction de mortalité par dépistage toujours le résultat d'une diagnose précoce *en combinaison* avec un traitement efficace

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Breast cancer screening justified?

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Prerequisites:

Decrease in rate of advanced disease ✓
Decrease in cancer mortality ✓

Good performance of screening test / programme ✓
- limited amount of interval cancers –

- Limited amount of overdiagnosis and overtreatment ✓
  - - increase in breast cancer in screening ages must be
  - counterparted by a decrease in breast cancer at later age -

- ***Favourable balance between benfits and harms!***

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- Declaration:
- No conflict of interest.