Overdiagnosis of Clinically Irrelevant Cancer


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Summary

1. Short introduction to breast cancer
2. Growth rates
   - How to calculate tumor growth
   - When does dissemination starts?
3. Observed incidence when screening is not compensated by decline after screening
4. Alternative explanations to the incidence increase
5. What is lead time?
6. What is overdiagnosis?
7. Three methods to adjust overdiagnosis for lead time (early diagnosis)
8. Conclusion
1. Short introduction to breast cancer

The Edwin Smyth papyrus
Primary tumor
2. The two most natural units for measuring tumor growth:

1. the **number of cell divisions** after the appearance of the first tumor cell which is measured by studying the absorption rate of radioactive elements

2. the tumor **volume doubling time**, is calculated from two or more volumes observed by X-ray

Tumor volume doubling time is the same as the number of cell divisions when there is no cell death.
When does dissemination start?

Volume doubling times:
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 (1mg), 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 (1g), 31, 32, 33, 34, 35, 36, 37, 38, 39, dead.


Window of opportunity (sojourn time): Mammography can maximally move time of diagnoses 2 doubling times but on average time of diagnosis is moved 1 doubling time (lead time)
Surgical treatment

1. Stage I (no metastases): Lumpectomy is equally efficient as radical mastectomy

2. Stage II (lymphatic metastases): Centennial node surgery + breast surgery

3. Stage III (huge local tumors): Drugs

4. Stage IV (distant metastases): Drugs

Primary effect is on stage I-II disease
Oncological treatment

1. Cytotoxins

2. Tamoxifen (anti-estrogene) – stops growth of metastatic disease

3. Herceptin (Trastuzumab) - monoclonal antibody blocking of HER2 receptors

Primary effect of 2-3 is on metastatic disease
Prerequisites for screening to work

1. That time of diagnosis can be moved sufficiently much backward

2. That treatment is more effective on an earlier time – note that treatment with cancer drugs primarily is effective on metastatic disease – it does not prevent dissemination of metastases

In theory: screening should not work
Results of 8 randomized mammography screening trials

- No reduction in total mortality
- 10-20% reduction in breast cancer mortality
- But no reduction in total cancer mortality
- 30% increase in breast cancer rates when screening

There is a disease reservoir of DCIS

Prevalence of DCIS by number of slides per breast

<table>
<thead>
<tr>
<th></th>
<th>Number of slides per breast</th>
<th>Prevalence of DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartlow et al, 1987</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Kramer et al, 1973</td>
<td>40</td>
<td>4.3</td>
</tr>
<tr>
<td>Nielsen et al, 1984</td>
<td>95</td>
<td>14.3</td>
</tr>
<tr>
<td>Nielsen et al, 1987</td>
<td>275</td>
<td>39</td>
</tr>
</tbody>
</table>
Detection rate at screening has increased dramatically

Detection rates have increased because of: double view, computer assisted reading, ultrasound, MR and 3D mammography without any decline in the rate of interval cancer.

Incidence rate in the second year after a screening is 140 per 100,000 which is the incidence rate in mid 1980s.

* Miller et al (CBCSS-2), CMAJ 1992
** Evaluering av prøveprosjektet, 1999-2000
*** Skaane et al, Radiology 2013
3. Observed incidence when screening


Incidence after screening

Ignored and not studied until Zahl, Strand & Mæhlen (BMJ 2004) reported that the fall after age 69 years accounted for only 1/20th of the observed incidence increase when screening women aged 50-69 years. We called the unaccounted increased for overdiagnosis.
The MISCAN model predicts

Figure: Expected breast cancer incidence in 2-year age categories
Solid line = not screened, dotted line = screened.

Boer et al, Lancet 1994
In reality: Areal A = 20 \cdot Areal B
Invasive breast cancer incidence in Fife, Scotland

Vaidya. BMJ 2004; 339: b2587 (rapid responses)
This has caused a huge incidence increase in all countries with screening and only in the screened age group.

Time Magazine, February 8, 2002
4. Alternative explanations of the incidence increase when screening

A. Underlying incidence increase

B. Increased use of hormone replacement therapy

C. Earlier diagnosis
A. Underlying incidence increase
The randomized WHI study reported almost no effect of HT on the breast cancer incidence.

The model is controversial: “the authors do not discuss artefacts that can arise in ecological data and age-period-cohort analyses when non-linearities are present—problems that were noticed only after the method was introduced.”

Michels (editorial) BMJ 2012
Before 2001: Breast cancers incidence increased from 180 to 290 per 100,000

After 2001: Breast cancer rate > 300 per 100,000, while use of HT has dropped 80%

Zahl & Mæhlen, Tidsskr Nor Lægeforen 2012.
C. Can it be explained by earlier diagnosis?

Statisticians say

1. Lead time for breast cancer when screening with mammography is 2-7 years

2. Lead time for prostate cancer is 3-12 years when screening with PSA
5. What is lead time?

How to estimate clinical lead time: $T_c$

We call the annual per cent incidence reductions compared with the background incidence in a control group $pr_1$, $pr_2$, $pr_3$ and $pr_4$, respectively. It is largest in the first year after screening, that is, $pr_1 > pr_2 > pr_3 > pr_4$. The clinical lead time (in years) is then calculated approximately as the weighted average:

$$T_c = 0.5 \times pr_1 + 1.5 \times pr_2 + 2.5 \times pr_3 + 3.5 \times pr_4) / S,$$

where $S = (pr_1 + pr_2 + pr_3 + pr_4)$. Note that this estimate is not inflated by including overdiagnosed tumours and this is a novel method.
Estimated clinical lead time

Clinical lead time in the Norwegian Mammography Screening program is 1.06 year.


A study of 448 women with breast cancer estimated that 90% of the doubling times were between 69 and 1622 days with a median of 260 days

“Sensitivity” of our method

Including 5% tumours with 5 years clinical lead time increased the estimated clinical lead time by 0.14 years; assuming a 1% annual underlying incidence increase added only 0.01 year to the estimate; assuming a 50% higher incidence reduction after screening increased the estimate by 0.06 year, and combining all three extreme assumptions increased the estimate by 0.18 year.
Model-based lead time: $T_M$

$$f(t) = \lambda \int_a^t k(t-u)x^m(u)\,du$$

Vito Volterra, 1913

This formula can be used to estimate lead time when
i) all tumors grow and
ii) there are no competing causes of deaths

$T_M = T_C \times (1-p) + T_O \times p$


The relationship between clinical and model-based lead time

\[ T_C = 1 \text{ year} \]

**Table 2. Calculated model-based lead time for a combination of clinical tumours (all with lead time of 1 year) and overdiagnosed tumours**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Overdiagnosis</th>
<th>Model-based lead time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>10%</td>
<td>1.8</td>
</tr>
<tr>
<td>Lead time for overdiagnosed tumours is 10 years</td>
<td>30%</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td>4.7</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>10%</td>
<td>3.2</td>
</tr>
<tr>
<td>Lead time for overdiagnosed tumours is 25 years</td>
<td>30%</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>70%</td>
<td>10.9</td>
</tr>
</tbody>
</table>

The level of overdiagnosis varies from 10 to 70% and the lead times for overdiagnosed tumours are 10 and 25 years, respectively.

6. What is overdiagnosis?

Overdiagnosis is the detection of a disease that in the absence of screening would not have been diagnosed within the patient's lifetime.
Three methods for «adjusting overdiagnosis» for lead time

1. Adjusting for earlier diagnosis of clinical cancers

   Observed 530 more cancers than expected
   Observed 14 less after age 69

   \[
   \frac{945 + 530 - 14}{945} = 1.54
   \]

   This is adjustment for earlier diagnosis

   Zahl & Mæhlen, BMJ 2004, Tidsskr Nor Legeforen 2012
2. Calculating the proportions A and B based on a lead time model. Overdiagnosis: \( \frac{A}{A+B} \) or \( \frac{A}{A+B+C} \)

Note: Only data from the screening period are used in the calculation – they could have included data after screening has stopped.
Ruth Etzioni and colleagues

Lead time when screening for prostate cancer with PSA varies from 3-12 years, and this corresponds to estimates of overdiagnosis varying from 23-42%.


If $B = 0$, then it is 100% overdiagnosis.
<table>
<thead>
<tr>
<th>Overdiagnosis</th>
<th>Where?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>At incidence screen, only 4% of DCIS</td>
<td>Two-County Trial and UK, Netherlands, Australia and the USA</td>
<td>Eur J Cancer 2003; 39:1746-54</td>
</tr>
<tr>
<td>zero (Markov models)</td>
<td>Two-County Trial</td>
<td>Radiol Clin North Am 2004; 42:793-806</td>
</tr>
<tr>
<td>around 5%</td>
<td>Firenze</td>
<td>J Med Screen 2004; 11:23-7</td>
</tr>
<tr>
<td>around 1%(*)</td>
<td>Two-County Trial and the Gothenburg Trial</td>
<td>Breast Cancer Res 2005; 7:258-65</td>
</tr>
<tr>
<td>4.8% (2 rounds plus following intervals)</td>
<td>Copenhagen</td>
<td>Breast J 2006; 12:338-42</td>
</tr>
</tbody>
</table>
“The lead-time effect can be seen for age 50, year 1, for example, as

$$410 + 0.86 \times 410 + 0.64 \times 420 + \cdots + 0.07 \times 561 = 1,812.$$"

i.e. they assume that there is 86% and 64% reduction in the breast cancer rate in the first and second year after a screening. Truth is that it was about 0% in Fife, Scotland.
Model checking: Are there many overdiagnosed tumors with long $T_{0D}$?

After the screening period, you can actually check if there are many tumors with long lead time by

A) Study if there are any decline after screening has stopped like we do or Vaidya did in Fife, Scotland.
B) Alternatively, you can study if slow-growing tumors accumulate over time

Zahl et al, Arch Int Med 2009
Zahl et al, Lancet Oncol 2011
Smith-Bindman et al, JAMA 2003
3. The «dilution method»

If you add cancers detected after screening has stopped at age 69 to both the screening and the control group, you will get a function that tend to the life time risk when all are dead.

Example (Norway): 55% incidence increase from age 50 to 59 years, whereof 5% of 55% is earlier diagnosis of clinical relevant cancers.

Problems with the dilution method

• Estimates depend on i) how long you are screening and ii) how long you follow-up after screening has stopped.

• It is not the life time risk (unless you follow the cohorts until all are dead at age 100). Impractical method.

• “…the Panel thinks that the best estimate of overdiagnosis for a population invited to be screened is roughly 11%, defined as the excess incidence in the screening population as proportion of the long-term expected incidence.”

• “11% of something that is not defined” cannot be the best estimate??

• If both groups are screened after age 59 (which is also adjusting for lead time – see the red curve), then you get almost identical estimates (curves that tend to zero), even though the proportion of overdiagnosed tumors in the population is constant over time.

(Actually this is a test of cancer regression).
Conclusions

1. Model-based lead time has no medical interpretation (in contrast to lead time for clinical relevant tumors where it means earlier diagnosis)

2. Tumors with long lead times mainly exist in the head of some statisticians

3. Overdiagnosis adjusted for model based lead-time are not comparable from studies to studies

4. And cannot be compared with overdiagnosis adjusted for clinical relevant tumors = adjusting for earlier diagnosis
HIT
Not less late stage disease