Fatal side effects and cancer induced by radiotherapy of overdiagnosed breast cancer in France

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Thank you to our Conference organizers for giving the floor to an epidemiologist who survived professionally in France thanks to the support of FORMINDEP: a self funded association of health professionals and citizens that advocates for transparency in medical information and education, and for freedom from interests other than those of patients. [1,2]

Independent epidemiological research on breast cancer provided an opportunity to measure the impact of errors in current medical practice. The first criterion in health-care quality is safety: “Avoiding injuries to patients from the care that is intended to help them”. In public health, this first criterion for quality should not restrict to patients. It should also be extended to healthy people when invited to mammography screening: they might be overdiagnosed and overtreated.

The aim of this presentation is to provide incentives for changing practices in order to avoid breast-cancer overdiagnosis. The appraisal of side effects due to overtreatment by radiotherapy is intended to contribute to turn physician “in title” into physician “in reality” according to Hippocrates’ wording.[3] It is also a key information for the woman comparing benefits and harms before deciding to undergo or not to undergo mammography screening.
Since year 2002, article 26th of the French health law had been mentioning that a health professional who speaks publicly should declare his potential conflicts of interests. [4] This intent for improving transparency did not cost too much to Minister Bernard Kouchner when launching the law: there was no decree implementing the requirement of article 26 up to 2007, when FORMINDEP obtained it from the French Government. [5]

Conflicts of Interests of Bernard Junod

- Bernard Junod signed the Formindep’s Charter. He’s seeking “to act with total independence, protecting himself from interest of an industrial, commercial or financial nature.”

- Online declaration of conflicts of interests:
Evidence of similar breast-cancer mortality and evidence of overdiagnosis provided by the most reliable randomized controlled trials on mammography screening did no close the debate over the deductive “Halstedian” model versus an inductive approach leading to a “systemic” model of breast cancer. The first part of this presentation justifies the use of an empirical approach for estimating overdiagnosis.

This presentation will then focus on the investigation of the French epidemic of apparent breast cancer from year 1980 up to 2010. It provided estimates of the current yearly incidence of overdiagnosed breast cancer.

Most overdiagnosed women underwent radiotherapy. Estimate of fatal cardiac failure and of cancer of other sites, attributable to radiotherapy were obtained by attributable risks from published results on large cohorts of women treated for breast cancer in France.

The conclusion will raise some questions for further research.
The inductive approach is empirical. In 1850, when exploring the contribution of pathology to cancer diagnosis, Broca raised a fundamental question about the reliability of the biopsy for diagnosing progressive cancer disease. [6]-In the introduction of his report, he stated that histology cannot predict the progression of a tumor.

However, training in medical faculties was influenced by the Halstedian [7] model: Without treatment, breast cancer would extend locally from malignant cells, spread to surrounding tissues, and to lymph nodes; it would finally kill by distant metastases in vital organs. This model supported secondary prevention, that is early detection and treatment of the tumor, before it would spread and become symptomatic. Use of secondary prevention in medical practice postulates the reliability of testing for a progressive cancer with a biopsy. This deductive approach was supported by the perception of increase in cure due to early diagnosis and treatment, even after that pathologists like McKinnon alerted again, one hundred years later, about the limitations of the biopsy to predict the dynamic of a tumor.[8]

<table>
<thead>
<tr>
<th>Inductive</th>
<th>Deductive</th>
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<tbody>
<tr>
<td><strong>Systemic approach</strong></td>
<td><strong>Halstedian model</strong></td>
</tr>
<tr>
<td>How predictable is the biopsy when looking</td>
<td>• From one malignant cell to</td>
</tr>
<tr>
<td>progressive cancer?</td>
<td>metastases.</td>
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<tr>
<td><em>Paul Broca, 1850</em></td>
<td>• The biopsy is reliable.</td>
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<tr>
<td><em>McKinnon, 1949</em></td>
<td><em>Halsted, 1894</em></td>
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Specificity of histological examination for cancer diagnosis

*Specificity: ability to exclude non-progressive cancer*

- Lack of specificity recognized when histology was introduced in the 19th century:
  - ~300 pages of P. Broca devoted to “pseudo-cancers”
  - Major book of H. Lebert about cancer disease and curable disease confused with cancer
- Systematic search for breast-cancer at autopsy yielded more invasive “cancer” and much more “ductal carcinoma in situ” than expected from registry data
- Histology fails to provide evidence of progression

Paul Broca won the Portal prize for his 600 pages report. The first part was entitled “malignant tumors”; the second part was entitled “pseudo-cancer”. In 1852, Lebert published a 800 pages book about “cancer disease and curable disease confused with cancer”. [9]

Autopsy studies with systematic biopsies in the breast yielded more invasive and much more ductal cancer in situ than expected from registry data. [10-13]

According to distinguished experts, like Bernard Fisher, the reliability of the biopsy for taking decision in cancer management might be compared to the faithfulness of what you would imagine that follows in a film from a snapshot.[14]
Here is a published graphical representation of time trend of breast-cancer incidence and breast-cancer mortality in France. [15]

The deductive interpretation was the following: Increase in incidence over time resulted from environmental factors and/or to a longer lead time due to earlier diagnosis. Time trend of breast-cancer mortality would then result from increasing successful treatment of earlier diagnosed breast cancer. This interpretation was intuitively supported by clinical studies showing that screened patients had better survival.

The discrepancy between incidence and mortality observed in year 1980 was mainly attributable to breast self-examination: breast awareness was already fashionable. Mammography screening strengthened the difference between incidence and mortality during subsequent years.

The inductive approach provided a different interpretation: Time trend of better survival was due to increase in overdiagnosed cases. This resulted from lower specificity of the biopsy following breast self-examination and/or mammography screening.
Lower case fatality rate was observed among women diagnosed with breast cancer who practiced breast self-examination; but large comparative studies provided evidence that screening by breast self-examination did not modify the risk of breast-cancer death in the population. [16] The failure of breast self-examination for reducing the mortality due to breast cancer in the population should have already pointed towards overdiagnosis. Overdiagnosis would explain why observed survival was longer among women practicing breast self-examination and diagnosed with breast cancer: overdiagnosed cases increased survival because they did not die from breast cancer!

Another explanation of the better survival of women diagnosed when practicing breast self-examination was the lead time due to earlier diagnosis.

### Failure of screening by breast self-examination (BSE)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Women practicing BSE</th>
<th>Women without practice of BSE</th>
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<tbody>
<tr>
<td>Case fatality rate(^a)</td>
<td>18.2 %</td>
<td>29.0 %</td>
</tr>
<tr>
<td>Breast-cancer mortality(^b)</td>
<td>1.04 %</td>
<td>1.03 %</td>
</tr>
</tbody>
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\(^a\) Meta-analysis of available studies among patients – more than 5 years of follow-up

\(^b\) Result obtained in large populations in the UK

*Source: Hackshaw Ak, Paul EA. British Journal of Cancer 2003*
Deductive models made use of lead time for explaining discrepancies in time and space distribution of breast cancer morbidity. Changes in lead time distribution when improving the sensitivity of tumor detection by mammography screening resulted in “prevalent cases” considered as correctly diagnosed. Speculative assumptions about lead time of 4 years or more and faithfulness to a real increase in breast-cancer incidence over time precluded the possibility to get a fair appraisal of overdiagnosis.

Last year, Zahl and colleagues published a key paper in the British Journal of Cancer.[17] It will be available free of charge next October, two weeks from now. This paper provided evidence that clinically relevant lead time in screened cohorts was about one year. It only explained a fraction of observed “prevalent cases”. Actually, lower specificity of the biopsy following mammography screening yielded overdiagnosed cases among observed prevalent cases.
Our concern today is more serious for women than Galileo’s view about respective movements of sun and earth in the universe. Last year, Per-Henrik Zahl, Peter Gøtzsche and Karsten Jørgensen published the major paper quantifying clinically relevant lead time observed in Norway where opportunistic screening was unlikely. The paper corrected errors in the deductive models minimizing overdiagnosis by making use of inflated lead time. Our colleagues were dealing with a major concern we all share in this conference: people’s health. One year after Galileo provided evidence-based correction of wrong models, in 1611, he was welcomed as a hero in Rome.

Let us on our turn warmly applause Per-Henrik’s venue to this conference in Oxford!

Thank you! Now, we are ready to face the disaster due to screening in France.
Empirical investigation of an epidemic was best taught by Alexander Langmuir at the Centers for Control Disease. [18] His inductive approach used to take the big picture before interpreting observed facts. Here is the conventional way to provide epidemic curves: crude numbers of new cases per year. Each pair of columns provides the yearly number of specific death and of diagnosis observed every 5th calendar year. [19,20]

For lung cancer, screening was not a common practice in France. Lung cancer diagnosis and death due to lung cancer were highly correlated. There were about 12000 more lung cancer death in 2010 than in 1980. They were mainly attributable to increasing tobacco consumption during previous decades. For breast cancer and for prostate cancer, death occurrence did not change much.

For breast cancer, occurrence of diagnosis was already much higher than death in 1980. As mentioned previously, overdiagnosis due to breast self-examination might explain such a large difference. Since 1980, mammography screening and PSA had been increasing in France. There were about 30000 more invasive breast cancer diagnosis and 45000 more diagnoses of prostate cancer in 2010 than in 1980. For breast and for prostate, the increase in screening was correlated with higher discrepancies between diagnosis and death frequency. This was mainly reflecting overdiagnosis.
There was not only a discrepancy between breast-cancer incidence and breast-cancer mortality. Four French registries published the time trend of early, and late stage breast-cancer incidence.[21]

Incidence of late stage diagnosis did not change substantially whereas incidence of early stage increased with increasing screening. According to this result, increase in breast cancer incidence would be mainly attributable to overdiagnosis among early stage tumors.
Computation of overdiagnosed breast cancer among women aged 35 or more in 2010

Procedure

- Get an incidence of clinically relevant cases in 1980
- Apply incidence of clinically relevant cases in 1980 to women aged 35 or more in 2010
- Subtract previous result from observed incident diagnoses to get overdiagnosed cases in 2010

The computation of overdiagnosed breast cancer among women aged 35 or more in 2010 made use of available data before mammography screening was common in France. Incidence of clinically relevant cases was estimated from the data available in 1980. Then, age-specific incidence rates of clinically relevant cases were applied to women aged 35 or more in 2010. The difference between the observed incident cases and the expected number of clinically relevant cases in 2010 provided the estimate of the overdiagnosed breast cancer cases we were looking for.
Three background data are provided here before estimating the number of clinically relevant cases.

The risk of death due to any cause was declining strongly from 1980 to 2010 in France. It was 34% lower in 2010 than in 1980. [19]

But the risk of death due to breast cancer did not change as much. It was 6% lower in 2010 than in 1980. This decline might be explained by treatment improvements. It does not support the hypothesis of an increase in incidence of clinically relevant cases.

The last background data give an appraisal of the increase in the practice of mammography in France. In 2000, there were about 8 times more mammography machines than in 1980.[22]
Let us come now to the question: What was the incidence of clinically relevant tumors according to age in 1980?

This slide shows the discrepancy between breast-cancer incidence and breast-cancer mortality by age in 1980.[23]

As mentioned previously, breast self-examination was common in France. It contributed to overdiagnosis due to the lack of specificity of the biopsy.

The age-specific incidence of clinically relevant breast cancer should actually lie somewhere between the curves of breast-cancer incidence, the dotted line, and of breast-cancer mortality, the plain line.
Breast-cancer incidence amounted to 152 per 100000. The minimum rate of clinically significant tumors would be the breast-cancer mortality rate in 1980 corrected for the age distribution in 2010, that is 65 per 100000. The truth should lie somewhere between the two.

A geometric mean was used for getting the incidence of clinically relevant tumors. It amounted to 102 per 100000.

<table>
<thead>
<tr>
<th>Clinically relevant tumors</th>
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<tr>
<td><strong>Getting to true incidence per 100000 in 1980</strong></td>
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<table>
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<tr>
<th>Incidence of clinically relevant tumors in 1980 = geometric average value of breast-cancer incidence and mortality</th>
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<tbody>
<tr>
<td>Observed breast-cancer incidence(^a) : 152</td>
</tr>
<tr>
<td>Observed breast-cancer mortality(^a) : 65</td>
</tr>
<tr>
<td>Incidence of clinically relevant tumors(^b):</td>
</tr>
<tr>
<td>((152 \times 65)^{0.5} = 102)</td>
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</tbody>
</table>

\(^a\) Age-specific rates applied to women aged 35 or more in 2010  
\(^b\) Incidence applicable to women aged 35 or more in 2010
The detailed result obtained for clinically relevant tumors, overdiagnosed invasive breast cancer and overdiagnosed ductal carcinoma in situ appears on this slide.

Among women aged 35 or more, 28932 diagnoses of invasive breast cancer were found overdiagnosed, that is 60% of the 48301 observed invasive breast cancer cases in 2010.

Increase in ductal carcinoma in situ from 1980 to 2010 were also considered as overdiagnosis in 2010. [21,24]

The grand total of overdiagnosed cases in 2010 amounted to 36597.

<table>
<thead>
<tr>
<th>Overdiagnosis of breast-cancer in 2010 =</th>
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<tbody>
<tr>
<td><strong>Observed diagnoses – expected clinically relevant tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer diagnosis in 2010</td>
<td>48301</td>
</tr>
<tr>
<td>Incidence of clinically relevant tumors in 2010(^a)</td>
<td>19369</td>
</tr>
<tr>
<td>Overdiagnosed invasive breast cancer in 2010</td>
<td>28932</td>
</tr>
<tr>
<td>Increase in ductal carcinoma in situ from 1980 to 2010(^b)</td>
<td>7665</td>
</tr>
</tbody>
</table>

**Total overdiagnosed cases in 2010: 28932 + 7665 = 36597**

\(^a\) Rates of clinically relevant tumors in 1980 applied to women aged 35 or more in 2010

\(^b\) Extrapolation of published data for year 1990 and for year 2005
According to previously published data, about 80% of patients diagnosed with breast cancer were treated by radiotherapy.[25,26]

When applying this proportion to overdiagnosed cases in 2010, the total of new cases overtreated by radiotherapy was close to 30000.

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**Overdiagnosed breast-cancer cases overtreated by radiotherapy**

*Estimate for women aged 35 or more - France 2010*

<table>
<thead>
<tr>
<th>Proportion of overdiagnosed cases treated by radiotherapy:</th>
<th>80%[^1]</th>
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<tbody>
<tr>
<td>Number of overdiagnosed cases treated by radiotherapy:</td>
<td></td>
</tr>
<tr>
<td>• Invasive cancer:</td>
<td>80% × 28932 = 23146</td>
</tr>
<tr>
<td>• Ductal carcinoma in situ:</td>
<td>80% × 7665 = 6132</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>29278</strong></td>
</tr>
</tbody>
</table>

[^1]: Source:

- Kirova YM et al. *Int J Radiation Oncology Biol Phys* 2007
Result of long term risk of cardiovascular death attributable to radiotherapy in France were published in 2011. According to these results, radiotherapy of overdiagnosed women in 2010 would produce 843 death from cardiovascular disease within the next 30 years. [27]

Another study provided attributable risk of new primary tumors attributable to radiotherapy.[25] The number of such tumors for sites other than breast would amount to 214 during the 10.5 years following overtreatment by radiotherapy in 2010, that is up to 2020.
Sure, such result were unacceptable or unconscionable. However, the hypotheses were very limited:

Same age-specific incidence of progressive cancer in 2010 as in 1980

Incidence of progressive cancer was between the rate of breast-cancer mortality, and the incidence rate of breast cancer diagnosis before mammography screening

• Question raised by the result:

How to improve criteria for defining breast cancer?

Discussion

• Assumptions:
  – Same age-specific incidence of progressive cancer 2010 as in 1980
  – Incidence of progressive cancer was between the rate of breast-cancer mortality, and the incidence rate of breast cancer diagnosis before mammography screening

Sure, such result were unacceptable or unconscionable. However, the hypotheses were very limited:


When looking for progress in cancer management, the question raised by the result is How to improve criteria for defining breast cancer?
Here is a proposed answer: why should we not investigate Broca’s recommendation in 1850? Let us observe the dynamic of the suspected tumor before deciding to biopsy or not. A workshop will start at 11 am in room L6 to build an evaluation of active surveillance within screening programs.[28]

Thank you for your attention!

| Conclusion:  |
| Focus on the natural history of cancer |
| If discordance when rating mammograms: |
| **Randomized controlled trial** |
| **Design:** comparison of immediate biopsy with active surveillance before deciding to biopsy or not. |
| **Outcome:** Occurrence of breast-cancer diagnosis (including overdiagnosis), breast-cancer mortality, and overall mortality. |
Any question welcomed

Three well-tried attitudes towards overdiagnosis

Evading  fading  facing
References 1 to 10: see notes

3. Hippocrates translated by Francis Adams. The Law. eBooks@Adelaide; The University of Adelaide Library; University of Adelaide; South Australia 5005. p1.
5. http://www.formindep.org/La-loi-sur-la-transparence-de-l.html


