A short history of mammography screening

- 70\textsuperscript{ies} – 90\textsuperscript{ies}: Nine Randomized Control Trials (USA, Canada, Europe)
  \rightarrow mammography decrease breast cancer mortality by 30%

- 2006 - 2011: re-analyses because:
  - **Benefits** in real life appeared to be less than in RCT (ex: no difference in mortality among screened and unscreened regions in Nordic countries or in Australia)
    - Re-estimation of reduction in mortality (original RCT) \rightarrow 15%
  - **Harms** became more and more apparent :
    - Frequence of false negatives, false positives (cost, adverse events)
    - Additional cancers due to mammography X-ray (among genetically susceptible women)
    - Over-diagnosis and over-treatment
Overdiagnosis is estimated to represent 10-30% of all breast cancers diagnosed by mammography.
"In women aged 40-49 years, more than 1900 women need to be invited for screening during 11 years of follow up, in order to prevent one death from breast cancer (BC), at the cost of more than 20,000 visits for breast imaging and approximately 2000 false positive mammograms."

“Screening of 1000 women 50 years old annually for ten years would result in one woman avoiding death from BC, with 2-10 women being over-diagnosed and treated needlessly, 10-15 women being told they have BC earlier than would have been the case with no difference in prognosis, and 100-500 women having at least one false alarm, of whom about half would undergo a biopsy.”
The Mammography debate (2006-present)

- « Anti-mammography »
  - Professors of epidemiology/public health in academia (with good competence in statistics)

- « Pro-mammography »
  - Professionnal in charge of screening (radiographers, project managers)
  - Other people making money thanks to screening (machines makers, diagnosis related industry, pharma industry)
  - Clinicians and general public (over-estimate benefit of screening)
  - Politicians

→ 2009-2014: Revision of screening recommendations in most western countries (Canada, USA, Western Europe, Australia)
≈> No systematic screening in women less than 50 or above 70
WHO recommendations

- WHO mandate is to develop Norms and Guidelines -and to promote their implementation- to improve health of the people all over the world

- **Independently** of any interest group!

- Evidence-based Guidelines
  - with particular attention to the quality of the evidence
  - Inviting and using the best experts in the world
WHO recommendations on mammography screening

Women aged 40-49:
- Mammography is not recommended (except in the context of research projects in high-income countries)

Women aged 50 to 69:
- Mammography is recommended only in countries with strong health systems and good resources
- For countries with limited resource and weak health systems: “CBE seems to be a promising approach”

Women aged 70 to 79:
- Mammography is not recommended (except in the context of research projects in high-income countries)
Harms / Benefits of Mammography

10,000 women 50-59 in Montenegro

**NO SCREENING**

After 1 year:
20 women are diagnosed with breast cancer

After 10 years:
5 die, 15 are still alive

**MAMMOGRAPHY SCREENING**

After 1 year and 1 round of screening:
23 women are diagnosed with breast cancer

2 to 5 have falsely negative mammograms, 3 are over-diagnosed

After 10 years:
4 die despite screening, 1 is still alive thanks to screening
Harms / Benefits of Mammography

As result of one round of screening:

1000 women have falsely positive mammograms

of whom 150 have to do a biopsy

Montenegro pilot program: 2500-3000 false positives and 300 biopsies
Harms / Benefits comparison

Harms:

- 2 to 6 cases over-diagnosed
- 3 false negatives (risk of delayed diagnosis)
- 1000 to 3000 false positives
  - 150 to 300 biopsies (some can result in serious adverse events)
- 19 women informed earlier that they have cancer, without any change in outcome (death/survival)
- 1 cancer induced by exposure to X-ray?

Benefits:

- 1 life significantly prolonged
How to limit harms? Quality is the key

Quality assurance scheme for the screening program
- Performances of radiographers / radiotechnicians (training, use of Birad classification, double reading, minimum of 500-1000 reading per year, etc.)
- Quality of the machines (X-ray < 2mgy per breast)

The sensitivity/specificity trade-off
- Less false positives → **high specificity** → more false negatives
- Less false negatives → **high sensitivity** → more false positives

*Lure of high-tech: last-generation digital mammo, tomography, MRI, etc. do not increase sensitivity very significantly, and always by decreasing specificity*

Type of screening program
- “Population-based” (individual invitation for all women in a certain age group)
- “Opportunistic” (women offered screened when visiting for other reasons)
  - Women over-screened, women never screened
  - Do not achieve good coverage, create inequalities, is less cost-effective
Each country is unique

- Genetic background and risk factor profiles differ from one population to the other, so different populations will have a different spectrums of cancers (the fast, slow and very slow)
  - Lower incidence is associated to younger, more aggressive breast cancer

- Effectiveness of treatment, notably early for stages, differ between countries (access, compliance, drugs availability, etc)

- Sensitivity, specificity, quality of screening will differ between countries

→ Each screening program is unique: harms and benefits can vary a lot
→ Careful monitoring and evaluation of pilot programs strongly needed prior to scaling up
Adequate Monitoring & Evaluation

- False positive rate $\rightarrow$ easy to measure
  - % of women screened positive who are not diagnosed with cancer

- False negative rate $\rightarrow$ not so easy to measure
  - Need linked databases, takes time

- Over-diagnosis rate $\rightarrow$ not easy to measure
  - Need population-based cancer registry, takes a lot of time

- Problems following biopsies $\rightarrow$ not easy to measure
  - Need linked databases or dedicated study with large samples

- Survival differences among screened / un-screened groups
Quality of treatment impacts benefit of screening

As Treatment Gets More Effective

Screening Becomes Less Effective
What is the future of screening?

Improvement of treatment

High public awareness

Efficient health systems
- High “sensitivity” of 1st line health professionals
- Rapid and accurate diagnosis

Early detection based on symptoms

Mammography screening less and less beneficial

New approaches required
Screening of high risk women only?
Montenegro situation

Quality of treatment?

Public awareness?

Efficiency of the health systems?
- “sensitivity” of 1st line health professionals?
- Rapid and accurate diagnosis?

→ Interesting asset: a strong culture of screening by Clinical Breast Exam (CBE)
Clinical Breast Exam (≠ Breast Self Exam):

- Breast exam performed with **hand and eyes** by a trained clinician/nurse/health worker

*Survival by stage (Sweden 1980 – 2001)*

![Graph showing survival rates by stage and time since diagnosis](image)
Evidence on CBE

Trial “Mammo+CBE compared to CBE alone”

1. **USA**: 70% mortality reduction attributable to CBE and 30% left to mammography  
   *(Shapiro et al. JHU press. 1988)*

2. **Canada**: same mortality in both groups  

Trial “CBE alone compared to Education”

3. **Mumbai - not finished**: Major improvement in stage at diagnosis, no effect on mortality yet.  
   *(Mittra et al. Int J Cancer. 2010)*

Modelisation studies

- Annual CBE can save as many lives as biennial mammography  
  *(Okwonko et al. JNCI 2008)*
CBE compared to Mammography

Advantage of CBE over mammography

- Less false-positive (good specificity), less over-diagnosis
- Cheaper, no machines to purchase and maintain
- Less demanding in human resources (radiographer, radio-technicians)

- Sensitivity ? Up to 95% (mammography: 98%)
- If treatment is efficient, the difference between mammography and CBE may not be important

Quality assurance is as important as for mammography
(but quality assurance schemes not as developed as for mammography)
1. Generally benefits of mammography screening are overestimated, while harms are largely underestimated.

2. Quality assurance is a “must” in any screening program to limit harms and ensure minimal benefit.

3. Monitoring & evaluation is very important, despite it is not easy.

4. New models of breast cancer screening are to be found for the 21st century.
   → Montenegro could be among the countries providing high quality evidence about CBE.
Thank you for your attention