ESMO PRECEPTORSHIP
ON BREAST CANCER

Screening

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DISCLOSURE OF INTEREST

Speaker fees from Siemens Healthineers
Aim of screening

- Detect a disease early in an asymptomatic stage
- Give early intervention and management
- Reduce the impact of a disease that has already occurred (secondary prevention)

Outcome is better because of early detection and intervention
Principles and practice of screening according to Wilson and Jungner (WHO 1968)

The disease
- Severe
- High prevalence in a preclinical stage
- The natural history of the disease known
- Long period between first sign and manifest disease

The test
- Acceptable sensitivity and specificity
- Simple and cheap
- Safe and acceptable

The treatment
- Possible treatment
- Effective, safe and acceptable
Mammography screening
Early randomized controlled trials

- New York HIP (1963)
- Malmö I and II (1976)
- Swedish Two County (1977)
- Edinburgh (1978)
- Canada I and II (1980)
- Stockholm (1981)
- Göteborg (1982)
- UK Age trial (1991)

Screening programs initiated

25/28 member states of the EU have national or regional screening programmes

Mammography screening
A global view

Countries that offer organized screening programmes

Participation rates vary

20% in Japan and Saudi Arabia
50% in Canada and France
>80% in Finland and the Netherlands

>70% is desirable
The balance of screening

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduction in mortality</td>
<td>• False positives</td>
</tr>
<tr>
<td>• Reduced suffering from metastatic disease</td>
<td>• Overdiagnosis</td>
</tr>
<tr>
<td>• Breast conserving surgery</td>
<td>• Anxiety</td>
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<tr>
<td>• Feeling of security</td>
<td>• False negatives = false sense of security</td>
</tr>
</tbody>
</table>
Reduction in breast cancer deaths

Benefit of screening

- In age group 40–49: 16% relative risk reduction
  0.049% absolute risk reduction
- 2057 women needs to be screened regularly to prevent one breast cancer death

- In age group 50–74: 23% relative risk reduction
  0.13% absolute risk reduction
- 760 women needs to be screened regularly to prevent one breast cancer death

- The effect of screening is lower in younger women:
  - Lower prevalence
  - Lower sensitivity of mammography (dense breasts)

- In Europe: 50–69 år

Gotzsche, PC, Nielsen, M. Screening for breast cancer with mammography. Cochrane database of systematic reviews (2011)
Typical mammography screening programme

- Two-view mammography
- Target age 50–69
- Biennial screening intervals
- Double reading

**Some exceptions**

From the age of 40: Sweden, Iceland

UK: Age 50–70 with 3 year interval

High-risk screening (e.g. BRCA): annual MRI + mammography (70% lower risk of being diagnosed with breast cancer stage II or higher)

Effect of screening today?

- RCTs performed in Northern European populations
- Might not be generalizable to other ethnic populations, e.g.:
  - Breast cancer incidence vary
  - Asians have denser breasts (ultrasound better)
  - Arabic women have an earlier onset of breast cancer and have more aggressive cancer subtypes

- New effective treatments and advancement in breast cancer care

Recommendations

- Regular (annual or every 2 years) mammography is recommended in women aged 50–69 years [I, A]. Regular mammography may also be done for women aged 40–49 and 70–74 years, although the evidence for benefit is less well established [II, B].
- In women with a strong familial history of breast cancer, with or without proven BRCA mutations, annual MRI and annual mammography (concomitant or alternating) are recommended [III, A].
False positives
Harm of screening

The screening exam has not been able to rule out disease in a healthy woman

- 80–90% of recalled women are false positives
- Breast cancer-specific psychological distress that may endure for up to 3 years
- Recall rates:  
  - prevalence screening <7%
  - incidence screening <5%
Overdiagnosis

Harm of screening

• The detection of a cancer that would never have been found were it not for the screening test

• Two forms of overdiagnoses:
  1. The detection of a lesion with essentially no malignant potential
  2. The detection of a lesion that is slow-growing enough that the individual will go on to die of a competing cause of death first

The consequences:

• Women become cancer patients with psychological and treatment side effects

• A breast cancer diagnosis is associated with comorbidity: increased risk of dying of various causes (pulmonary circulation, suicide, heart failure, and gastrointestinal disease)
Estimates of overdiagnosis

- <5\% (Paci et al., J Med Screen 2004; Duffy et al., Breast Cancer Res 2005)
- 10\% (invited), 20\% (attending) (Zackrisson et al., BMJ 2006)
- 11\% (Kalager et al., Ann Intern Med 2012)
- 50\% (Peeters et al., Int J Epidemiol 1989)

The screening controversy
- The rate of overdiagnosis?!
- The effect on breast cancer mortality?!
The benefits and harms of breast cancer screening: an independent review

Review of the early mammography RCTs

Reduction of breast cancer mortality about 20% (invited)

Overdiagnosis rate: 11% (invited), 19% (attending)

If 10,000 women aged 50 are invited to screening for 20 years:

- 43 breast cancer deaths prevented
- 129 women overdiagnosed and overtreated

1 breast cancer death prevented
3 women overdiagnosed and overtreated
Can we reduce overdiagnosis and overtreatment?

- Potentially overdiagnosed cancer: low-grade DCIS and invasive tubular cancer

- Detection of DCIS has increased with screening (10–20%), 90% of DCIS do probably not evolve into invasive cancer

- Watchful waiting of low-grade DCIS vs. treatment (ongoing RCTs, The LORIS trial, the LORD trial mfl.)

Evans A and Vinnivombe S. Breast (2017)
• An early detection and treatment does not affect the outcome

• Screening tends to pick up slow growing cancers

• Rise of DCIS incidence after screening introduction
Interval cancers
A challenge in screening

- Symptomatic cancers diagnosed in the interval between two screening examinations
- True interval cancers (fast growing, not visible retrospectively)
- False negative interval cancers (missed, 20–25%)
- More aggressive with poorer prognosis
- Strong indicator on how successful your screening program is
- Reported interval cancer rates range from 8.4 to 21.1 per 10,000 screens (based on biennial screening)
3 months later lump in the breast

PAD: 12 mm TNBC
Typical outcome of screening

1000 screened women

- 30 recalls: 5 true positives, 25 false positives, 4 clinically relevant cancers
- 970 no recalls: 969 true negatives, 1 false negatives, 1 overdiagnosed cancer

1/3 of all cancers are missed in screening partly due to the limitation of the mammographic technique

Birdwell et al. Radiology (2001)
Overlapping tissue obscures the tumour
Next generation screening modality

Breast tomosynthesis

Pivot
Detector
Compression paddle
Breast
X-ray source

Pseudo-3D
Synthetic-2D
Breast tomosynthesis reduces the effect of overlapping tissues

The use of tomosynthesis in screening has recently been evaluated in several large prospective screening trials

30% more cancers in screening (+2/1000 screens)

Marinovich ML et al. JNCI 2018
Breast cancer screening in transition

Tomosynthesis

- Improve screening performance and efficiency
- Artificial intelligence
- Liquid biopsy?
- Novel screening methods
- Supplement modality in dense breasts
- Individualized screening
- High risk screening already established
  - MyPebbs
  - Wisdome trial
- Abbreviated MRI
  - Contrast enhanced mammography
  - ABUS

Screening

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Artificial intelligence in breast imaging and screening

A rapid development

- Since 1990s CAD software have been available for screening mammography interpretation, e.g. as a second reader
- No improvement in accuracy (false positives)
- Recent improvements in AI, due to deep-learning algorithms, is closing the gap between humans and computers


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Performance of AI

- 101 radiologist vs. AI in mammography reading

AI is as good as an average breast radiologist

1/5 of normal mammograms can be excluded from screen reading performed by radiologists

Rodriguez-Ruiz A et al. JNCI (2019)

Lång K et al. ECR (2019)
Breast cancer screening

Summary

• Implemented in most countries in Europe

• Screening interval: age 50–69, mammography with 2 year interval

• RCTs: Reduction in breast cancer mortality by 20%

• Overdiagnosis rate 11%

• False positives is a drawback of screening

• The screening policy will most likely be modified in the future with new imaging techniques, individualized screening and with the implementation of AI
Thank you for your attention