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**Minireview**

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## European Breast Cancer Service Screening Outcomes: A First Balance Sheet of the Benefits and Harms

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### Abstract

A recent comprehensive review has been carried out to quantify the benefits and harms of the European population-based mammographic screening programs. Five literature reviews were conducted on the basis of the observational published studies evaluating breast cancer mortality reduction, breast cancer overdiagnosis, and false-positive results. On the basis of the studies reviewed, the authors present a first estimate of the benefit and harm balance sheet. For every 1,000 women screened biennially from ages 50 to 51 years until ages 68 to 69 years and followed up until age 79 years, an estimated seven to nine breast cancer deaths are avoided, four cases are overdiagnosed, 170 women have at least one recall followed by noninvasive assessment with a negative result, and 30 women have at least one recall followed by invasive procedures yielding a negative result. The chance of a breast cancer death being avoided by population-based mammography screening of appropriate quality is more than that of overdiagnosis by screening. These outcomes should be communicated to women offered service screening in Europe. *Cancer Epidemiol Biomarkers Prev*; 23(7); 1159–63. ©2014 AACR.

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### Background

Decades ago, randomized controlled trials showed that mammographic screening was effective in reducing breast cancer mortality (1). With cost-effectiveness of screening having been shown in several studies in the early 1990s, service screening programs were implemented nationally and regionally in many parts of Europe, although with minor differences in their protocols. Service screening implementation across the different countries was documented in the European Cancer Screening Report (2), which has been recently updated in a collaborative paper with the EUNICE Working group (3). Most programs are population-based, meaning that in each round of screening the women in the target population in the area served by a program are individually identified and personally invited to attend a screening center. The majority of countries have followed the European Guidelines (4)

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limiting screening invitations to women aged 50 years and more, but with varying upper-age limit.

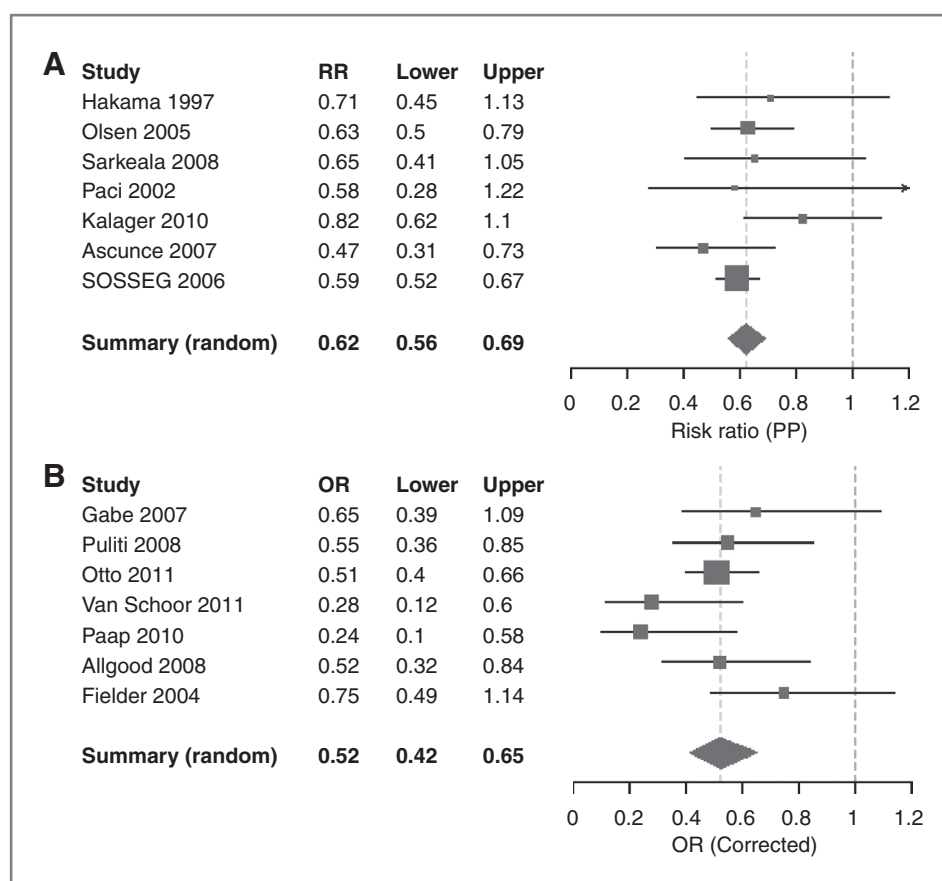
### Materials and Methods

A recent comprehensive review has been carried out to quantify the benefits and harms of European population-based mammographic screening programs. Outcomes of service screening were assessed with breast cancer mortality reduction as the principal benefit and overdiagnosis and false-positive test results as principal harms. The review and the balance sheet estimate methodology are reported in full in a Supplement of the Journal of Medical Screening (<http://jms.rsmjournals.com/>). The evidence on breast cancer mortality reduction from observational studies was reviewed in three articles (5–7) of the Supplement. Broeders and colleagues (7) summarized results from all European observational studies according to the study design, i.e., mortality trend studies (5), incidence-based mortality studies (6), and case-control studies (8). The evidence from observational studies on the main harms of service screening, breast cancer overdiagnosis and false-positive results, were reviewed in two specific articles (9, 10). In this short communication, the major results of these reviews are summarized.

### Results

#### Breast cancer mortality overview

The use of mortality trends to evaluate organized mammographic screening (5) is an approach with strong



**Figure 1.** Forest plots of estimates for breast cancer mortality reduction in women screened versus not screened excluding overlapping data from incidence-based mortality studies (A) and from case-control studies (B; corrected for self-selection bias). Reproduced with permission from JMS 2012; 19 (Suppl 1): 21.

methodologic limitations. First, this type of study included breast cancer deaths in women diagnosed before they could have been invited for screening. Second, the analyses could be misleading as they do not acknowledge that only a minority of women after screening introduction are actually screened (according to the time needed for the implementation phase and the compliance). For this reason, this approach is not considered adequate for evaluating the impact of screening. The incidence-based mortality (IBM) approach (6) is based only on breast cancer deaths occurring in women diagnosed with breast cancer after their first invitation. The estimated mortality reduction from European IBM studies was 25% [pooled response rate (RR) = 0.75; 95% confidence interval (CI), 0.69–0.81] with invitation to screening and 38% (pooled RR = 0.62; 95%CI, 0.56–0.69) in women screened (ref. 7; Fig. 1A). Finally, the results of European case-control studies, a well-established approach in the evaluation of screening mortality outcomes and recently reviewed by Paap and colleagues (8), found that mortality was reduced by 31% (pooled OR = 0.69; 95%CI, 0.57–0.83) among invited women and, after adjustment for self-selection bias, that is, taking into account the background mortality rate of nonresponders, by 48% (pooled OR = 0.52, 95%CI, 0.42–0.65) among screened women (Fig. 1B). All the studies considered

include at least some of the age groups between 50 and 69 years.

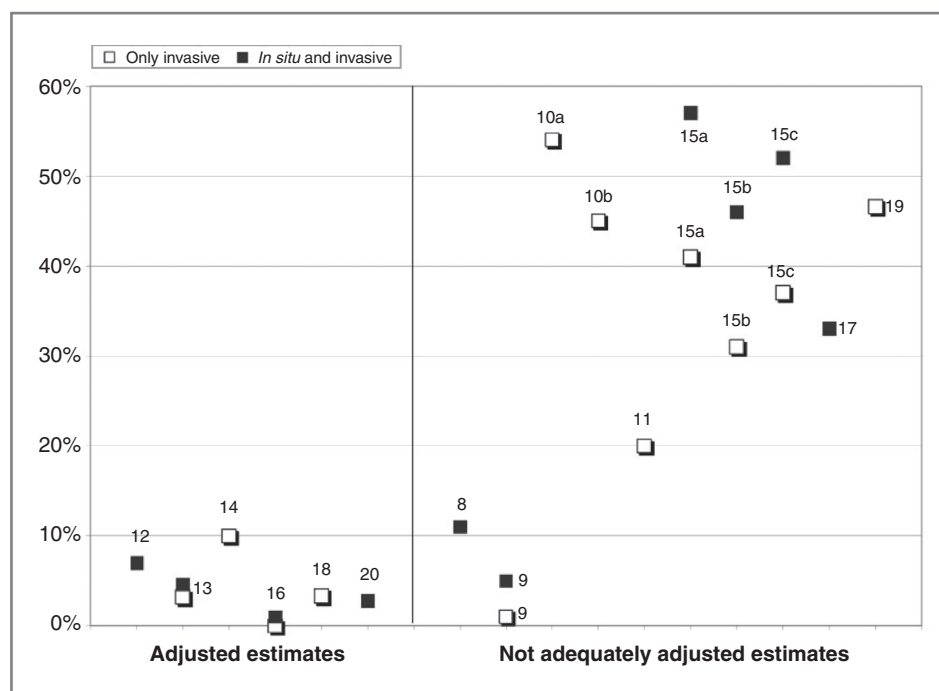
### Overdiagnosis risk overview

Overdiagnosis in a breast cancer screening program is the diagnosis, as a result of screening, of cancer that would not have been made in the woman's lifetime had she not been screened (11). Disentangling the excess of incidence arising as a result of lead-time from that of overdiagnosis is a major methodologic difficulty in the estimation of overdiagnosis. The methodologic approaches that have been applied vary between studies and so far there is no agreement on the optimal analytical method (9). Studies were classified by adjustment for trends in breast cancer risk occurring independently of screening and for lead time; the most plausible estimates of overdiagnosis ranged from 1% to 10% (Fig. 2), where overdiagnosis is expressed as a percentage of the expected incidence in the absence of screening. Taking into account the major sources of variability among these estimates, the average estimate of overdiagnosis in screened women between 50 and 79 years, including carcinoma *in situ*, is 6.5%.

### False-positive result overview

The European Guidelines stress the importance of a controlled rate of recalls in breast cancer service screening.

**Figure 2.** Overdiagnosis estimates classified according to the presence/absence of adjustment for breast cancer risk and for lead-time. Reproduced with permission from JMS 2012; 19 (Suppl 1): 52.



The cumulative risk of a false-positive result in women undergoing 10 biennial screening tests varied between 8% and 21%, with a pooled estimate of 17% without invasive assessment and 3% with invasive assessment (the assessment was defined as invasive when a needle biopsy and/or a surgical biopsy were conducted; ref. 11).

### The balance sheet

The balance sheet is a decision-making tool which may help policy makers, stakeholders, and especially potential participants in the target population to weigh up the benefits and harms which accrue with participation in a screening program (12). The decision-making process of a woman invited to participate is supported by the quantified outcomes, in terms of benefits and harms, based on the experience of 1,000 women participating, compared with 1,000 nonparticipants. The cumulative risks of breast cancer and breast cancer-related death from 50 to 79 years in the absence of screening were 6.7% and 3.0%, respectively. To obtain these risks, we used the age-specific breast cancer incidence and mortality in the period 1985 to 1986 (i.e., before the start of screening programs) in the United Kingdom, the Nordic countries (Denmark, Finland, Norway, and Sweden), and area covered by the Italian Association of Cancer Registries. To calculate the absolute number of lives saved, the estimate of breast cancer mortality reduction (38%–48%) was applied to the expected number of breast cancer deaths in the absence of screening among women diagnosed in the 50 to 69 years age group. We estimated that 19 of the 30 expected breast cancer-related deaths occurring in the 50 to 79 years age group were diagnosed at ages 50 to 69 years. Similarly, we calculated the number of overdiagnosed cases applying

the corrected average estimate of overdiagnosis (6.5%) to the expected number of breast cancer cases in the absence of screening. On average, for every 1,000 screened women aged 50 years at the outset, participating biennially until 69 years in accordance with the European guidelines and followed up until 79 years, 7 to 9 breast cancer deaths were avoided (out of 19 expected deaths in the absence of screening), 4 women were overdiagnosed (in addition to the 67 cancers expected in the absence of screening), 170 women had at least one recall with no invasive assessment giving a negative result, and 30 women had at least one recall with invasive procedures yielding a negative result, as a result of their 10 screens (Table 1).

### Discussion

The impact of a screening program was evaluated in terms of its benefits and harms (12), providing a first estimate of a balance sheet related to participation in European service screening. In summary, the evidence shows that service screening in Europe achieves a mortality benefit at least as great as observed in the randomized controlled trials (13). The chance of a woman's life being saved by population-based mammography screening of appropriate quality is more than that of overdiagnosis by screening. These outcomes should be communicated to women offered service screening in Europe.

A lot of time is needed for the implementation of breast cancer service screening and, due to the very good survival rate of the disease, even if it is not diagnosed early, final outcomes can only be evaluated after a long follow-up period. For this reason, the research evidence for outcomes is still initial and refers to selected areas and

**Table 1.** European mammography service screening balance sheet

	<b>Benefits</b>	<b>Harms</b>
Estimates from the reviews	Pooled estimates of mortality reduction among screened women range from 38% (IBM studies) to 48% (case-control studies)	Estimates of overdiagnosis adjusted for lead-time and breast cancer risk range from 1% to 10%, with a corrected average estimate of 6.5%. Estimates of cumulative risk of false-positive results range from 8% to 21%, with a pooled estimate of 17% without invasive assessment and 3% with invasive assessment.
<b>Balance sheet</b>		
For every 1,000 women ages 50 years screened biennially until 69 years and followed until 79 years:	Seven to 9 women's lives are saved (out of 30 deaths expected in the absence of screening <sup>a</sup> )	Four women are overdiagnosed (67 cancers expected in the absence of screening). One hundred and seventy women have at least one recall with noninvasive assessment giving a negative result. Thirty women have at least one recall with invasive assessment giving a negative result.
<sup>a</sup> Nineteen of the 30 expected breast cancer-related deaths were diagnosed in ages 50–69.		

countries where screening was implemented a number of years ago. Nevertheless, the reviewed results are a good representation of most of the experience of breast cancer service screening in Europe in the last 20 years.

Longer follow-up of service-screening outcomes and coverage of the population experience with well-designed, possibly coordinated, studies of larger areas is certainly needed for definitive conclusions. However, the evidence provided by research on screening outcomes available in Europe today is sufficient to inform a woman who needs to consider the implications of screening for her personally and to choose between nonparticipation and participation. At the same time, these results are informative for health professionals, policy makers, and stakeholders, and supportive of their demands for continuing service screening and for further research in the technologic innovation of breast imaging and biomarkers of aggressiveness in tumors to reduce the risks of mammographic screening.

Communication methods should certainly be improved to raise women's awareness of benefits and harms, to change practices, and to make information more accessible, relevant, and comprehensible (14).

The Independent UK Panel (15) evaluated that estimates from observational studies could be biased and best evidence on both breast cancer mortality reduction and overdiagnosis come from randomized controlled trials (RCT). Considering only results from RCTs, they concluded that breast screening programs confer significant benefit and should continue. The results from the EUROSCREEN Working Group, based on observational studies, confirmed

that the impact of service screening on breast cancer mortality is consistent with the effect expected on the basis of RCTs, whereas the overdiagnosis estimates disagree and supported the continuation of the screening programs as they are organized in Europe. Research is needed to minimize the negative side effects of screening (such as overdiagnosis, false-positive rates, and others not dealt with in this review such as radiation dose), most likely including tailored approaches and a better knowledge of the natural history of the disease. Further evaluation of service-screening outcomes in the near future would benefit from the implementation of European coordinated action.

#### Disclosure of Potential Conflicts of Interest

H. de Koning is employed in Rijksinstituut voor de Volksgezondheid (RIVM), the Netherlands, as project leader of National Evaluation Team Breast cancer screening (NETB), as a researcher in CISNET Breast Cancer Screening (NCI/NIH), and has a commercial research grant from SCOR Global Life SE. E. Lynge participates in a project together with the company Biomediq and has no income from or shares in the company. J. Patnick is employed as a visiting professor in cancer screening at Oxford University. No potential conflicts of interest were disclosed by the other authors.

#### Disclaimer

The views expressed in this report are those of the authors and do not necessarily reflect the official position of the European Commission. The National Monitoring Italian Centre (ONS) hosted the EUROSCREEN meetings in Florence in November 2010 and in March 2011 and funded the supplement publication. The National Expert and Training Centre for Breast Cancer Screening, Nijmegen, the Netherlands hosted a meeting of the EUROSCREEN mortality working group in July 2011.

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# Cancer Epidemiology, Biomarkers & Prevention

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