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# The impact of mammography screening on breast cancer incidence

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**Evaluation of: Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N. Engl. J. Med.* 377, 1998–2005 (2012). Mammography screening must advance the time of diagnosis of breast cancer to be able to reduce the rate of death from breast cancer. This article examined the temporal effects of mammography on the stage-specific incidence of breast cancer in the USA from 1976 through to 2008. Despite substantial increases in the number of cases of early-stage breast cancer, only a marginal reduction was observed in the number of cases presenting with late-stage breast cancer. These results provide convincing evidence that mammography screening entails a substantial risk of detecting tumors that would not have become symptomatic during a woman's lifetime if no screening had taken place. To improve the effectiveness of screening mammography, more knowledge is needed on the natural history of breast cancer, especially the risk of progression from *in situ* to invasive breast cancer.**

**KEYWORDS:** breast neoplasm ▪ diagnosis ▪ early detection of cancer ▪ incidence ▪ mammography ▪ mass screening

The effectiveness of mammography screening has been demonstrated in several randomized trials, largely published in the 1980s [1]. The publication of their favorable results has been followed by widespread use of mammography as a screening tool. In many countries, breast cancer screening programs were started, most of them aimed at women aged 50 years or older, but in the USA, programs were also directed at many women still in their 40s. If applied in a sufficiently organized fashion, the first (or prevalent) round of mammography screening is expected to result in a sharp but temporary increase in breast cancer incidence in a population not yet exposed on a wide scale to mammography [2]. This is explained by the detection of a relatively large number of generally slow growing tumors with long lead times. After the initial increase of the incidence, one would expect the age-specific incidence to drop during the subsequent (incident) screening rounds and return to the level before the start of the screening, but with fewer cancers presenting at a late stage. If the incidence rate does not return to the prescreening level but remains high or continues to increase, this could point to a rise in the underlying or background incidence, or the diagnoses of tumors that would not have become symptomatic during a woman's lifetime if no screening had taken place, so-called overdiagnosis. These were also the assumptions underlying the study by Bleyer and Welch [3].

## Methods & results

Bleyer and Welch used Surveillance, Epidemiology and End Results (SEER) data to examine trends in the incidence of breast cancer from 1976 through to 2008. Separate trend analyses were made for early- and late-stage breast cancer. Early-stage breast cancer was defined as ductal carcinoma *in situ* (DCIS) or invasive disease confined to the breast, and late-stage cancer as regional or distant disease.

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The baseline incidence before screening was estimated by using the incidence figures in the period 1976–1978, and the current incidence was based on the incidence observed in the period 2006–2008. The effect of hormone replacement therapy, which is known to have played an important role in the rising incidence of breast cancer from 1990 to 2005, was eliminated by truncating the incidence rates in these years if they were higher than in the period 2006–2008. Since women younger than 40 years of age generally did not have exposure to screening, the change in breast cancer incidence in this age group was examined to make an inference about the change in the background incidence in the population who were 40 years of age or older. Among the younger women, the observed annual percent change was 0.25% in the period 1979–2008. To account for this growth, analyses were repeated to allow the baseline incidence among women 40 years of age or older to increase by 0.25%. Two additional analyses were performed to provide more conservative estimates of the effect of screening on breast cancer incidence. In the first analysis, it was assumed that the annual percentage change of the underlying incidence was 0.5%. This scenario was called the 'extreme' assumption. In the second analysis, in addition to the annual increase of 0.5%, the baseline incidence of late-stage breast cancer was adjusted by using the highest incidence observed in the period 1976–2008, thereby maximizing the potential reduction of the incidence of late-stage cancer through screening. This scenario was called the 'very extreme' assumption.

Information from the National Health Interview Survey showed that the percentage of women reporting to have undergone mammography screening within the past 2 years had increased from 29% in 1986 to 70% in 1999 and remained stable thereafter. From 1976 to 2008 the incidence of early-stage breast cancer increased from 112 (seven *in situ* and 105 invasive cancers) to 134 (56 *in situ* and 178 invasive cancers) per 100,000 women aged 40 years or older. During the same period, hardly any increase was visible in the incidence of early-stage breast cancer among women younger than 40 years of age, who generally did not have exposure to screening mammography. The incidence of late-stage cancer among women 40 years of age or older decreased from 102 per 100,000 women in 1976 to 94 per 100,000 in 2008.

Assuming that the underlying incidence of breast cancer had increased at a rate of 0.25%, this would mean that 31% of the cancers were overdiagnosed. Expressed as absolute numbers, this would mean an excess detection associated with three decades of mammography screening of 1.3 million women with breast cancer in the USA alone. Under the extreme assumption, the proportion of cancers that were overdiagnosed was estimated to be 26% and under the very extreme assumption, the estimate was 22%.

## Discussion

Bleyer and Welch are not the first to demonstrate a clear effect of mammography screening on the incidence of early-stage breast cancer [4–6]. The most dramatic increase was observed in the incidence of DCIS, which was only rarely seen before mammography became available. It is very unlikely that the observed excess risk of breast cancer represents lesions that would have all become symptomatic invasive breast cancers if they had not been detected by screening. This assumption is supported by the results of a 25-year-old study based on consecutive medicolegal autopsies of 110 women aged between 20 and 55 years old [6]. Extensive hisptopathological evaluation of the breasts of these women showed that two (2%) had invasive breast cancer, 15 (14%) had DCIS and four (3%) had lobular carcinoma *in situ*. These findings indicate that clinically occult *in situ* breast cancer is frequent in young and middle-aged women and that many of these cancers will never become symptomatic, but are likely to regress spontaneously. Recently, findings from a large cohort study suggest that not only *in situ*, but also many of the invasive breast cancers detected at mammography, seem to have the potential to undergo spontaneous regression [7].

Further studies, using genetic profiling or specific tumor markers, are required to gain more insight into the biology of DCIS and to be able to predict which lesions will progress to invasive breast cancer if left untreated. A better discrimination between high- and low-risk carcinomas will help to minimize the risk of overtreatment of screen-detected lesions.

Confronted with the growing numbers of patients with screen-detected DCIS, many clinicians now believe that a randomized clinical trial is urgently needed for patients with low-risk DCIS, in which active monitoring and surgical intervention are compared regarding the risk of

invasive breast cancer and psychological sequelae of diagnosis and treatment [8].

The lack of a substantial decline in the incidence of advanced breast cancer found in the study by Bleyer and Welch is in agreement with the results of several other studies [8–10]. Monitoring of advanced breast cancer seems to be an attractive method to determine the impact of screening on breast cancer mortality in the general population [11]. However, one has to be aware that the definitions of late-stage breast cancer and the quality of the data with respect to tumor stage vary widely between studies. The definition of late-stage breast cancer used by Bleyer and Welch was rather crude. No detailed information was available in the SEER database with respect to the extent of tumor involvement of the regional lymph nodes. This raised the question of whether patients diagnosed with late-stage disease in 1976 are comparable with those diagnosed in 2008. For example, the number of positive lymph nodes may be lower among patients with (often smaller) screen-detected tumors with positive axillary lymph nodes than among those with symptomatic breast cancer extending to the regional lymph nodes. Moreover, in the 1990s the detection of lymph node metastases improved with the introduction of the sentinel node procedure. The use of immunohistochemistry to examine the removed sentinel nodes has been shown to cause an increase in the proportion of patients with micrometastatic disease [12]. As a result, the true decrease in the proportion of late-stage disease may have been much larger than the reported 8%.

Another potential pitfall in the study by Bleyer and Welch is their estimates of the change in background incidence. It is questionable whether trends in background incidence in women younger than 40 years of age can be extrapolated to those older than 40 years old. Risk factors for breast cancer are known to differ between younger and older women. For example, women who get the disease at an early age are much more likely to be carrying a genetic mutation that has predisposed them to developing breast cancer, most notably the *BRCA1* or *BRCA2* genes, or have a strong family history of early-onset breast cancer [13]. The rising trends in BMI over the last decades may have reduced the breast cancer risk among premenopausal women, but will have increased the risk among postmenopausal women [14]. This could mean that even the extreme assumption of a rise in the background incidence of 0.5% may still have been too cautious. It is difficult, if not impossible, to judge how the trends in incidence would have developed in the absence of breast cancer screening. This difficulty is thought to be an important explanation for the large discrepancy in the reported estimates of overdiagnosis, which vary between less than 5% and more than 50% between studies [15,16].

## Future perspective

There is no doubt that mammography screening entails a substantial risk of overdiagnosis. This is most clearly demonstrated by the dramatic increase in the incidence of DCIS. The recent introduction of digital mammography and the development of other highly sensitive breast imaging techniques carries the risk of a further increase in the incidence of *in situ* and early invasive breast cancer. Currently, there is no consensus about the amount of overdiagnosis resulting from screening and the estimates vary largely between studies. What the discussion on overdiagnosis is clearly demonstrating is that much more knowledge is needed about the natural history of breast cancer, especially the risk of progression from *in situ* to invasive breast cancer, to improve the effectiveness of mammography screening and to be able to help all patients with screen-detected breast cancer to make informed decisions about their treatment.

**Financial & competing interests disclosure**

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## Executive summary

- Mammography screening entails a substantial risk of overdiagnosis. This is most clearly demonstrated by the dramatic increase in the incidence of ductal carcinoma *in situ* during the last three decades.
- Consensus is lacking about the exact amount of overdiagnosis resulting from screening and estimates vary largely between studies.
- More knowledge is needed about the natural history of breast cancer, especially the risk of progression from *in situ* to invasive breast cancer, to improve the effectiveness of current screening programs.

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