



Benefits and Harms of Detecting Clinically Occult Breast Cancer

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Abstract and Introduction

Abstract

Over the last few decades there has been an increase in the use of strategies to detect clinically occult breast cancer with the aim of achieving diagnosis at an earlier stage when prognosis may be improved. Such strategies include screening mammography in healthy women, diagnostic imaging and axillary staging in those diagnosed with breast cancer, and the use of follow-up imaging for the early detection of recurrent or metastatic disease. Some of these strategies are established, whereas for others there are inconsistent supportive data. Although the potential benefit of early detection of clinically occult breast cancer seems intuitive, use of such strategies can also be associated with harm. In this commentary, we provide an extended discussion on the potential benefits and harms of the routine and frequent use of screening interventions to detect clinically occult breast cancer and question whether we may be causing more harm than good.

Introduction

Early stage breast cancer can be cured, whereas metastatic disease is generally incurable. It is therefore intuitive to assume that detection of early stage breast cancer will lead to improved outcomes. Advances in imaging allow clinicians to detect primary breast cancer, loco-regional involvement, and recurrent disease before it becomes symptomatic. Some of these interventions, such as screening mammography and axillary surgery, have become standards of care; however, their optimal use remains unclear. For other interventions, such as follow-up imaging, there remain questions regarding the balance between absolute benefits and risks. Here we provide a discussion on the use of strategies aimed at detecting clinically occult breast cancer.

Screening Mammography

Despite an increase in breast cancer diagnoses, mortality rates have fallen. In the United States, data from the Surveillance, Epidemiology, and End Results database show a greater than 40% reduction in the rate of death from breast cancer in the last 30 years.^[1] Although this finding has been attributed to the combined effects of increased use of screening mammography, better patient awareness, and improved adjuvant therapy, the differential effects of these factors is not known.^[2] Results of both randomized clinical trials and health outcomes analyses of the benefit of screening mammography have shown inconsistent results. Systematic reviews and meta-analyses have been conducted to define the true benefit of screening mammography. The United States Preventive Services Taskforce (USPSTF) concluded that in average-risk women mammography was associated with a statistically significant relative reduction in breast cancer-specific mortality in women between the ages of 39 and 69 years.^[3] Similar data were presented by the Canadian Task Force on Preventive Health Care and the Cochrane Collaborative, both of which concluded that mammography reduced the relative risk of

breast cancer mortality in average risk women aged 50 years or older. ^[4,5] The authors of the Cochrane review suggested that some trials included in their analysis suffered methodological limitations such as inclusion of women with prior breast cancer, selection bias such as postrandomization exclusion, nonconcealed randomization, or suspected contamination. When these studies were excluded, the benefit from screening mammography was no longer statistically significant.

In absolute terms, the benefit of mammography appears less impressive. Based on data from randomized trials, to prevent one death from breast cancer in women aged 50–69 years, more than 700 women would need to be screened for about 10 years. ^[4] Therefore, in a hypothetical cohort of 10000 women aged 50 years undergoing mammographic screening for 10 years, it would be expected that around 40 breast cancer deaths would occur. If these women were not screened, between 50 and 55 breast cancer deaths would occur. ^[6]

One of the criticisms of data reporting the benefit from screening mammography is that the data are based on randomized studies that were carried out in an era before the routine use of adjuvant therapy. It has been argued that in the setting of modern adjuvant treatment, benefits are even smaller. ^[2] Randomized screening trials are also susceptible to participation bias, a type of selection bias that can enrich trials with motivated and health-seeking individuals. Data from such studies may, therefore, not be representative of the intended target of population-based screening programs. The importance of validation of randomized data with population-based assessments is, therefore, important.

Although initial observational studies suggested mammography is associated with an independent reduction in breast cancer mortality, ^[7,8] more recent population-based analyses have questioned the benefit from screening mammography after adjustment for important confounders. An analysis from Western countries with population-based screening programs showed that following establishment of such programs there were stable or increasing rates of advanced disease. ^[9] The authors concluded that screening could not account for reduced mortality from breast cancer because there was no evidence that the introduction of such programs led to a shift from advanced presentation to more early stage disease ("stage shift"). Improvements in breast cancer outcome may have instead resulted from improvements in patient awareness and advances in systemic and loco-regional therapy. A Norwegian study showed statistically nonsignificant reductions in breast cancer-specific mortality associated with mammography in women aged 50–69 years. ^[10] In this study, authors attempted to isolate the benefit of mammographic screening from other factors that may have changed over time, including increased breast cancer awareness and improvements in treatment. Results showed that approximately two-thirds of the apparent improvement in mortality was likely related to improvements in the multidisciplinary management of breast cancer. Similar results were reported in a study of the World Health Organization database. ^[11] Investigators showed reductions in breast cancer mortality of up to 29% between 1989 and 2006. However, after adjustment for time differences in implementation of mammographic screening, the reductions in mortality between three independent country pairs suggested that screening did not play a direct part in the reductions in breast cancer mortality. The absolute benefit of screening mammography in isolation was, therefore, questioned. A possible explanation for these findings is that screen-detected tumors appear to have less aggressive biology as determined by both standard pathology ^[12] and gene expression profiling. ^[13] In tumors with such good outcomes, it would be more difficult to detect statistically significant improvements in mortality resulting from screening.

A further area of concern is that most trials of screening mammography have predominantly assessed breast cancer-specific mortality. Data describing disease-specific outcomes should be interpreted with

caution because there can be inconsistencies in determination of cause of death in screening trials—even in those with prospective randomized designs.^[14] All-cause mortality is more robust in this setting, but observing differences in this endpoint requires high statistical power. Among trials reporting all-cause mortality, approximately 1000 of the 23000 deaths were attributed to breast cancer. This sample compares favorably with many studies of adjuvant therapy in breast cancer in which differences in all-cause outcome were evident. Failure to detect any differences in all-cause mortality despite improvements in breast cancer-specific survival^[5] is, therefore, surprising.

In women aged less than 50 years, a lower incidence of breast cancer combined with increased breast density make mammographic detection more difficult.^[15] Consequently, the number of patients that would need to be screened to reduce the incidence of breast cancer deaths by one is substantially higher.^[4] Mammography for unselected (ie, average-risk) women aged less than 50 years has, therefore, not been consistently recommended in all jurisdictions with population-based screening programs.

Screening mammography can be associated with harm. Over a 10-year period, between 30% and 50% of women screened every 1–2 years can expect a false-positive result,^[16,17] and between 7% and 20% receive a false-positive biopsy recommendation.^[16,18] Furthermore, compared with unselected patients not undergoing mammography, screened patients are more likely to undergo surgery, chemotherapy, and/or radiation therapy.^[5] This finding appears counterintuitive because it would be expected that mammographic screening would reduce presentation with regional or advanced stage disease and therefore require less aggressive loco-regional or systemic therapy.

Another potential source of harm is over-diagnosis, a scenario which refers to the detection of cancer that would have otherwise not been identified in a patient's lifetime. Over-diagnosis is an inevitable outcome of all screening tests because some patients will die of causes other than cancer before their screen-detected tumors would have appeared clinically.^[19] Autopsy data has shown that in women not known to have had breast cancer during their lives, the median prevalences of invasive and in-situ breast cancer were 1.3% and 8.9%, respectively.^[20] Furthermore, recent data from the Swedish mammography screening program showed that some invasive breast cancers detected by repeated mammography screening do not persist to be detected by imaging in later years, suggesting that the natural course of a proportion of screen-detected invasive breast cancers is spontaneous regression.^[21] Early detection of occult indolent breast cancer may, therefore, lead to an apparent increase in the incidence of breast cancer as well as potentially leading to an erroneous association with improved outcome. Analysis of randomized trials suggests that approximately 10% of invasive cancers are over-diagnosed.^[22] In population-based cohorts, estimates of over-diagnosis are much higher, with suggestions that between 15% and 50% of cancers may be over-diagnosed.^[23,24] All these analyses are limited by relatively short follow-up. With longer follow-up, it would be expected that the differences in incident cancers between screened and unscreened groups would diminish as more tumors in the unscreened group would become clinically apparent. Because of these and other methodologic and epidemiologic limitations,^[25] accurate estimates of over-diagnosis are difficult to determine. Nevertheless, over-diagnosis is a limitation of screening mammography and results in unnecessary treatment with its attendant morbidity.

The balance between absolute benefits and harms of annual mammography is therefore uncertain.^[26] Based on the evidence described above as well as computer modeling, the USPSTF has recommended biennial mammography for women aged 50–74 years.^[27] The Canadian Task Force on Preventive Health Care suggested screening every 2–3 years in the same age group of patients.^[4]

The rationale for extending the screening intervals was based on statistical modeling with this interval showing the best balance between benefit and harm.^[4,28] These recommendations have been criticized for not being inclusive of all evidence supporting mammography, especially for women aged 40–49 years.^[29,30]

Diagnostic Imaging

The use of breast magnetic resonance imaging (MRI) for assessment of breast lesions has become widespread. In women with biopsy-proven breast cancer, breast MRI increases the detection of further loco-regional disease by 16%.^[31] Breast MRI may also influence surgical planning, resulting in a change from the original planned surgery in up to one-third of women.^[32] Because of the higher prevalence of multifocal, multicentric (multiple quadrant), and bilateral disease, MRI appears particularly useful for invasive lobular carcinoma^[33] and for those with germline mutations in *BRCA1* and *BRCA2* genes.^[34] However, two prospective randomized trials conducted in unselected women with breast cancer demonstrated no influence of breast MRI on reoperation rate, including both margin re-excision and conversion to mastectomy.^[35,36] Observational data confirm these findings^[37] and also show that preoperative MRI does not lead to a reduction in local recurrence or a reduction in mortality.^[38,39] Breast MRI is also associated with undesired effects. A substantial rate of false-positive results^[31] and high inter-observer variability have been reported.^[40] Breast MRI also leads to avoidable mastectomy in 1%–2% of patients^[31,35,37] and increased rates of contralateral mastectomy.^[41]

The optimal patient selection for preoperative breast MRI remains unknown, but the balance between benefit and risks of preoperative breast MRI in unselected cases appears detrimental.^[42] Preoperative MRI may be useful to identify the primary tumors in patients who present with axillary nodal metastases and no detectable breast tumor or assessment of the extent of residual tumor after neoadjuvant chemotherapy, although there are currently few data to inform its optimal use in these settings.

Surgical Staging

Completion axillary dissection to remove occult metastatic disease has generally been recommended in the presence of positive lymph nodes after sentinel lymph node biopsy. Retrospective analyses showed a substantial rate of detection of further axillary nodal involvement.^[43] More recently, two randomized trials of completion axillary dissection or observation in patients with positive nodes on sentinel node biopsy have reported results. The American College of Surgeons Oncology Group (ACOSOG) Z0011 clinical trial randomized patients with early-stage breast cancer and positive sentinel lymph nodes (detected by hematoxylin and eosin staining) to completion axillary dissection or observation. Eligible patients completed breast conserving surgery for T1–2 tumors with no more than two positive sentinel nodes. Further involved axillary lymph nodes were detected in more than 27% of those who underwent completion axillary node dissection. After more than 6 years of follow-up, there was no significant difference in either disease-free or overall survival between the study arms, with lower event rates seen in the observation group.^[44] Similar data were presented by the International Breast Cancer Study Group (IBCSG). In protocol 23–01, patients with evidence of micrometastasis in sentinel lymph nodes were randomized to completion axillary dissection or observation. Similarly to the ACOSOG Z0011 trial, preliminary data showed that after a median follow-up of 57 months, there were no differences in either disease-free or overall survival, with numerically lower number of events in the observation group.^[45] Both these trials closed early because of low accrual but remain the most comprehensive assessments of the benefit of completion axillary dissection for patients with limited nodal metastatic disease. The rate of local recurrence in both trials was low [$<5\%$ of trial populations],

^[45,46] and this likely explains why the addition of further local intervention did not influence outcome. All women in the ACOSOG trial and 90% of those in the IBCSG trial received adjuvant breast radiation, and many received adjuvant systemic therapy. With low rates of loco-regional recurrence and overall and disease-free survival numerically favoring the observation arms in both studies, it is unlikely that a difference between the two intervention arms would have become evident even with higher accrual and longer follow-up. It is possible that the administered adjuvant therapies were sufficient to control any occult residual axillary disease.

Axillary dissection does have substantial excess morbidity compared with sentinel node biopsy. Randomized data show that there is reduced arm morbidity and better quality of life for those treated with sentinel node biopsy alone. ^[47] Axillary dissection is also associated with increased risk of lymphedema as well as both motor and sensory neuropathy. ^[45]

Follow-up Imaging

Health outcome data indicate that surveillance mammography can detect early-stage in-breast recurrences. ^[48] However, when compared with the use of mammography in healthy women, follow-up mammography was associated with a higher frequency of interval cancers. ^[48] The positive predictive value for mammography was less than 30%, suggesting a high frequency of false-positive screens. The benefit of surveillance mammography has also been questioned. There are currently no data supporting the routine use of MRI as follow-up for patients with prior breast cancer. ^[42] Randomized clinical trials have also assessed the benefit of the addition of chest radiography, liver sonography, and bone scintigraphy to clinical examination and mammography in early breast cancer patients. Although intensive radiographic surveillance led to the earlier detection of recurrent disease, this did not improve overall survival. ^[49,50] Furthermore, the provision of intensified surveillance did not enhance emotional well-being or quality of life. ^[49] Such investigations are therefore not recommended in practice guidelines. ^[51,52] Despite this, use of surveillance imaging in the adjuvant setting remains prevalent. Linked data from the Surveillance, Epidemiology, and End Results and Medicare databases show that 30% of women with breast cancer received at least one computerized tomography scan and 19% received at least one bone scan in the first 4 years after diagnosis. ^[53]

It is unclear whether more sensitive diagnostic methods will be beneficial. At present, there is no evidence that earlier and more aggressive treatment of asymptomatic occult metastatic disease is associated with improved outcome. Furthermore, there is little data to support the benefit of aggressive local therapy for oligometastatic disease. Because such patients represent a very small minority of all patients with recurrent breast cancer, the ability to study this population is limited, and the absolute impact of any improvements in therapy are likely going to be small.

Discussion

Data from randomized clinical trials and well-conducted health outcomes studies show that the detection of clinically occult primary breast cancer, loco-regional disease, and recurrent disease may not be associated with a consistent improvement in either breast cancer-specific or all-cause mortality. With the exception of screening mammography, other strategies for detecting clinically occult breast cancer in asymptomatic women have not shown benefit in randomized trials. Even for screening mammography, the true benefit is difficult to isolate from other improvements in treatment over time.

There are a number of possible explanations for these findings. First, because of their long, asymptomatic phase, slow-growing tumors are over-represented in tests designed to detect clinically occult disease. This length-time bias can lead to over-diagnosis and unnecessary treatment if slow-

growing tumors, which may never produce symptoms, are detected and treated. Second, early detection of breast cancer may not have a large impact on outcome, and such lead-time bias may overestimate the benefit of detection of clinically occult disease. The impact of tumor size on prognosis has recently been questioned. Data from patients with node-positive, triple-negative breast cancer suggest that tumor size does not substantially influence prognosis.^[54,55] Finally, improvements in breast cancer outcomes are strongly influenced by advances in modern therapy.^[10] Such treatment may improve the ability to cure patients presenting with early breast cancer and may prevent or delay progressive disease in advanced breast cancer. In an era of highly effective adjuvant breast cancer therapy, it is increasingly recognized that biological factors that affect response to treatment may influence prognosis more than the anatomic extent of disease.

Screening mammography has benefit in healthy women aged 50–74 years, but the balance between benefit and harm means that screening every 2–3 years is likely the optimal frequency. More frequent screening of these women or screening of women younger than 50 years or older than 75 years remains contentious and likely only benefits subgroups at higher risk. Evidence suggests that imaging to detect occult loco-regional disease or recurrent and/or metastatic disease and surgical staging of residual axillary disease may have limited or no benefit. Oncologists should be dissuaded from overuse of screening investigations that may have reduced benefit and that are associated with harm (see). It is also imperative that women are made aware of uncertainties in the balance between benefit and harm for many investigations designed to detect clinically occult breast cancer.

Table 1. Absolute benefits and harms of detecting clinically occult breast cancer

Intervention	Comparison	Disease-specific outcome		All-cause outcome		Harms	
		Outcome	Magnitude	Outcome	Magnitude	Outcome	Magnitude
Primary breast cancer							
Mammography	No mammography	Breast cancer mortality	<1% lower [†]	All-cause mortality	No effect	False-positive result; Need for biopsy; Overdiagnosis	20%–30% of patients [†] 2%–5% of patients [†] 15%–50% of all invasive cancers [†]
Loco-regional disease							
Breast MRI in addition to mammography and clinical examination	Mammography and clinical examination	Detection of further loco-regional disease; Disease-free survival	~15% of patients No effect	Overall survival	No effect	False-positive result; Avoidable mastectomy	10%–15% of patients 1%–2% of patients
Completion axillary dissection	Observation after sentinel	Detection of further axillary	~25% of patients No effect	Overall survival	No effect	Arm lymphedema	3%–12% of patients [†]

after sentinel node biopsy	node biopsy	disease; Disease-free survival					
Recurrent or metastatic disease							
Surveillance mammography	No mammography	Detection of in-breast recurrence	~65% of recurrences [§]	Overall survival	Not reported	False-positive result	~70% of patients [§]
Intensified radiological screening [*]	Mammography and clinical examination	Relapse-free survival	~8% lower at 5 years	Overall survival	No effect	Increased anxiety	<1% increase from baseline

* Chest x-ray, abdominal sonography, and bone scintigraphy conducted every 6 months.

† After 10 years of regular screening.

‡ Dependent on whether axillary radiation therapy also provided.

§ After 5 years of regular screening.

For strategies for which benefit has been established, such as screening mammography, it is likely that a more favorable balance between benefit and risk will be derived from ongoing but less-frequent screening. For strategies for which the balance between benefit and risk has not yet been fully established, such as preoperative breast MRI and completion axillary staging, clinicians should carefully consider the use of these methods only in settings where there are supportive data. For other strategies for which evidence of benefit is uncertain, such as follow-up imaging, clinicians should be discouraged from requesting such tests. As physicians, we should ask ourselves, "Could we be causing more harm than good?"

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