Chapter 2
The Impact of Mammography Screening on the Diagnosis and Management of Early-Phase Breast Cancer

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Introduction

Throughout history women have detected their own breast cancers and, often after a considerable delay, have brought these palpable tumors to the attention of their physicians. From the days of Hippocrates through to the mid-nineteenth century physicians considered breast cancer to be an incurable and hopeless disease [1]. During the past century there has been a gradual but steady decrease in the average delay from palpation to treatment, which has been reflected in a gradual decrease in tumor

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size and a corresponding improvement in survival. Physician- and patient-detected breast cancers still have an average size exceeding 3.0 cm [2]. The development of modern breast imaging methods has resulted in a significant improvement in the spectrum of tumor characteristics, including tumor size, node status, and histologic malignancy grade. When mammography is used as a screening tool, the balance shifts from mainly palpable to mainly impalpable breast cancers, most of which are still localized to the breast [3–5]. Half of the invasive cancers are <15 mm in modern breast centers, with only 20 % poorly differentiated and <15 % node positive [6]. This revolutionary shift in disease presentation provided the opportunity for a considerably improved control of breast cancer, which has been realized through the establishment of comprehensive breast centers specializing in the diagnosis and treatment of breast cancer as early as possible. Their diagnostic and therapeutic team members faced the challenge of maximizing the benefits and minimizing the risks by avoiding the extremes of overtreatment and undertreatment as well as the extremes of overdiagnosis and underdiagnosis. The rationale for using early diagnosis and treatment in the early phase to better control of breast cancer is based upon the continuous improvement in outcome which has followed the steady decrease in average tumor size. The implication is that most breast cancers in their non-palpable, preclinical phase are without viable metastases, and that breast cancer is a progressive disease, which is why early detection and surgical removal in the early phase can decrease the rate of advanced cancers and reduce breast cancer death. The success of the population-based randomized controlled mammography screening trials provides proof that earlier detection and treatment accomplish this goal.

Concurrently with the accumulation of evidence supporting the progressive nature of breast cancer, an opposing theory was proposed by Bernard Fisher, according to which "It is likely that a tumor (breast cancer) is a systemic disease from its inception," [7] a statement which is incompatible with the nature of an adenocarcinoma during its early stages of development. Commenting on this theory, Edwin Fisher stated: "There is no evidence that delay in diagnosis unfavorably influences the survival of patients with breast cancer" [8]. According to Bernard Fisher's theory, "… variations in the treatment of locoregional disease were unlikely to affect survival," and systemic adjuvant therapy should not be delayed [9]. The implication for the surgeon is that local disease control cannot affect survival outcomes, a long-held belief of the National Surgical Adjuvant Breast and Bowel Project (NSABP). Additionally, Fisher predicted, "it is likely that surgery for the disease will continue to diminish in importance as improved methods of detection and tumor cell eradication become more commonly used" [9].

These statements are surprising in the face of scientific data and continually accumulating evidence for the effectiveness of early detection in reducing the rate of advanced cancer and the accompanying disease-specific mortality [10]. Had all breast cancers been truly "systemic" from the time of inception, surgical removal of the primary tumor could not have affected the systematic metastases postulated by Fisher. In particular, the HIP study of Greater New York had demonstrated a significant decrease in breast cancer mortality already in 1971, [11] nearly a decade before Fisher first published his "alternative theory." The largest randomized controlled

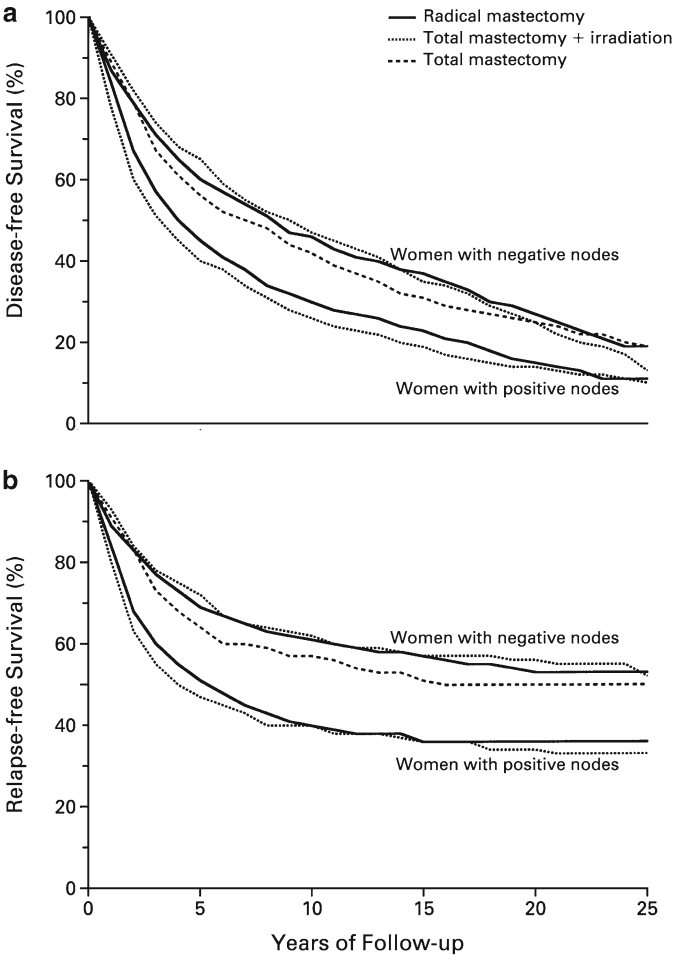
mammography screening trial used only mammography as a screening method and published in 1985 a 31 % significantly decreased mortality from breast cancer among women invited to screening compared to the control group [12]. Numerous meta-analyses of eight population-based randomized controlled trials and the evaluation of several large-scaled service screening programs have all proved that *breast cancer is a progressive disease, and is not, as advanced by Fisher*, "a systemic disease from its inception." The randomized controlled trials demonstrated a significant decrease in breast cancer death among women invited to screening, [10–17, 21] and the service screening evaluations showed a significant decrease in breast cancer death among women who attended screening regularly [18–20].

The primary results of the randomized trials of screening, with additional research on tumor progression, have demonstrated that the interruption of disease progression results in reduced mortality from breast cancer and that the time at which the progression is arrested is crucial [22]. Despite the magnitude of this evidence, it was ignored by Fisher and Anderson in 2010 when they published that "no scientific evidence has been presented to challenge the alternative hypothesis, any of its tenets, or the paradigm that currently governs the treatment of breast cancer" [23].

Comments

1. If breast cancer were "a systemic disease from its inception," then it would not be possible to cure breast cancer patients by surgery alone, no matter what the tumor size or the node status is at the time of operation, because viable metastases would already be present throughout the body. The long-term follow-up of the NSABP B-04 and B-06 trials themselves provide evidence to the contrary. Both demonstrated a significantly better outcome for women with node-negative cancers compared with node-positive cases, irrespective of the treatment methods chosen (see Figs. 2.1 and 2.2, printed with permission from NEJM) [24, 25]. Although not discussed in these publications, the better survival of the node-negative cases indicates that surgical treatment is more effective earlier in the natural history of the disease before the establishment of metastases. The three therapeutic choices in the B-04 trial were radical mastectomy, total mastectomy combined with irradiation, and total mastectomy [24]. In the B-06 trial the choices were total mastectomy, lumpectomy, or lumpectomy combined with postoperative irradiation [25]. It is noteworthy that *the outcome in each arm was equally poor (not equally good!)*, regardless of the three choices of therapy.

   Conclusion: These observations from the NSABP trials provide good evidence that the long-term outcome of the breast cancer patients will be determined by whether the treatment is given early or late in the natural history of the disease. Had the NSABP trial results been correctly interpreted, both the mammography screening trials and the NSABP trials would have arrived at the same conclusion, as follows: *The current therapeutic regimens are most effective at an earlier stage of breast cancer, when the probability of systemic metastases is lower.*



No. at Risk

Negative nodes			
Radical mastectomy	362	170	45
Total mastectomy + irradiation	352	177	39
Total mastectomy	365	159	45
Positive nodes			
Radical mastectomy	292	92	21
Total mastectomy + irradiation	294	83	23

Fig. 2.1 Disease-free survival (Panel **a**) and relapse-free survival (Panel **b**) during 25 years of follow-up after surgery among women with clinically negative axillary nodes and women with clinically positive axillary nodes. There were no significant differences among the groups of women with negative nodes or between the groups of women with positive nodes in either analysis. Printed with permission from NEJM

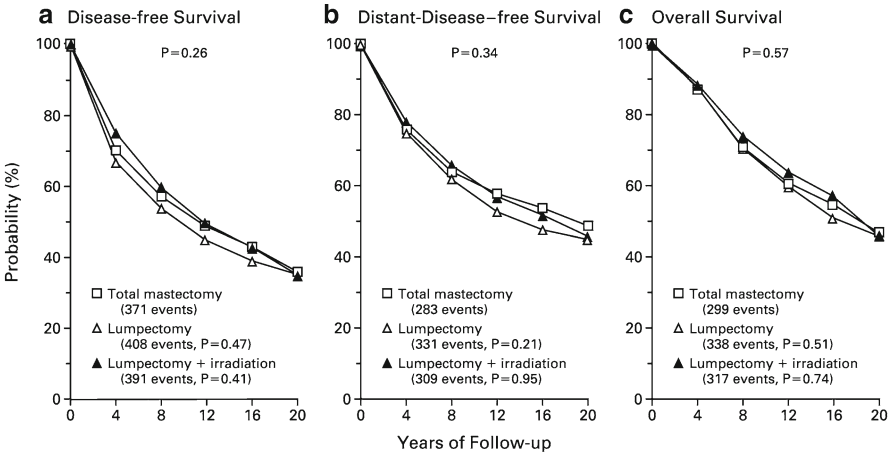


Fig. 2.2 Disease-free survival (Panel **a**), distant-disease-free survival (Panel **b**), and overall survival (Panel **c**) among 589 women treated with total mastectomy, 634 treated with lumpectomy alone, and 628 treated with lumpectomy plus irradiation. In each panel, the *P* value above the curves is for the three-way comparison among the treatment groups; the *P* values below the curves are for the two-way comparisons between lumpectomy alone or with irradiation and total mastectomy. Printed with permission from NEJM

2. Fisher's "alternative theory" also implies that finding non-palpable breast cancers at screening will not lead to a decrease in breast cancer death, but the large volume of evidence, including their own, does not support this theory.

   Results from randomized controlled trials: To date there have been ten randomized controlled mammography screening trials (eight population based) which tested the influence of early detection upon the disease-specific mortality from breast cancer. Meta-analyses of these trials have shown a highly significant, long-term mortality benefit from invitation to screening [10, 13, 14]. Very-long-term follow-up (29 years) of the largest of the mammography screening trials showed a highly significant 31 % decrease in mortality from breast cancer in the women invited to screening compared with the uninvited control group (relative risk [RR] = 0.69; 95 % confidence interval [CI]: 0.56–0.84; $P < .0001$). This long-term evaluation also demonstrated a steady increase in the absolute benefit of early detection, in terms of the number of lives saved, which continued well beyond 20 years of follow-up (71 lives saved at 10 years, 141 lives saved at 20 years, 158 lives saved at 29 years) [21]. Thus, the majority of the benefit of mammography screening occurs more than 10 years after screening begins. The more aggressive cancers would have led to breast cancer death in the first 10 years without early detection and surgical removal, while some of the more slowly growing, "indolent" cancers would have led to death after 10–20 years of follow-up in the absence of screening. Claims that mammography screening finds mostly "indolent" cancers [26–28] fail to acknowledge published evidence

documenting the propensity for a dedifferentiation of the tumor malignancy grade. The term "ultralow risk tumors" is thus unrealistic and misleading [27].

Results from evaluation of service screening: It should be noted that the randomized controlled trials use the "intention-to-treat" approach, which includes all women with breast cancer, both those who attended and those who declined the invitation to screening. Mortality from breast cancer is decreased to a greater extent in women who attended screening regularly than in the invited group as a whole. Disease-specific mortality among the women who attended screening regularly has been quantified in several ongoing service screening programs. A highly significant reduction of 43 % was observed in Sweden and 49 % in the Netherlands in women who attended mammography screening regularly [15, 19]. This emphasizes the importance of distinguishing between the effect of *invitation to* versus the effect of *regularly attending* mammography screening [20].

The issue of subgroup analysis: The population-based randomized controlled trials were all designed to have sufficient statistical power to evaluate the impact of early detection on mortality from breast cancer within the age group selected. However, when the populations were inappropriately subdivided into age cohorts of unequal size (40–49 vs. 50–69), the younger, smaller cohort with lower breast cancer incidence had insufficient statistical power. The resulting lack of a statistically significant decrease in mortality within individual age subgroups was erroneously interpreted as evidence of no impact at ages below 50 years, despite the existence of clear trends towards fewer advanced tumors and decreased mortality. Meta-analysis of trials shows a significant mortality reduction with the policy of offering screening in women aged 40–49 [10, 29]. Also, when Sweden gradually implemented nationwide screening, the option for the lower age limit was either 40 or 50 years. As it happened, the individual counties independently chose 40 years as the lower age in approximately half of the country. This gave the opportunity to evaluate the impact of screening in a population aged 40–49 which was sufficiently large for statistical significance, comprising more than 16 million women-years with 16 years of follow-up. A highly significant 29 % decrease in breast cancer mortality was documented in the women who attended screening (RR 0.71; 95 % CI, 0.62–0.80). This reduction occurred in a country where treatment guidelines are uniform and closely adhered to, so this mortality reduction was achieved in addition to the benefits of modern therapeutic advances [17].

3. All these results have convincingly demonstrated that the diagnosis and treatment of breast cancer at an earlier phase can prevent death from breast cancer, before viable metastases have been developed, confirming that breast cancer is not a systemic disease from its inception, in contradiction to the "alternative theory," developed by Fisher. The screening trial results unequivocally proved that *breast cancer is a progressive disease*, and that its progression can be arrested by early detection. As a result, the prognosis of the breast cancer patients can be substantially improved by local treatment. *Fisher's proposal that breast cancer is a "systemic disease from its inception" is either mistaken or, as the screening results convincingly show, it is not relevant to the treatment of node-negative,*

<15 mm breast cancers. "Screening has made possible the detection of a large proportion of node negative tumors less than 15 mm size (i.e. before the development of viable metastases) and there is substantial evidence that local–regional therapy is effective in these cases and that adjuvant systemic therapy has negligible scope to improve the survival of patients with these tumors; also, the notion of 'early' breast cancer for tumors up to 50 mm is clearly outmoded" [22].

Key Points

Mammography screening alters the presentation of breast cancers from mainly palpable to mainly non-palpable. Randomized controlled mammography screening trials have convincingly demonstrated the following:

- Early detection through mammography screening and surgical removal at an early phase can prevent death from breast cancer.
- Breast cancer is not a systemic disease from its inception. Therefore, when it is detected as either an in situ or a 1–14 mm invasive tumor, it is primarily a surgical disease.
- Breast cancer is a progressive disease, but this progression can be interrupted by early detection and treatment at a sufficiently early phase.
- The breast cancer patient's long-term outcome will be mostly determined by whether the treatment is given early or late, rather than by the choice of treatment offered to breast cancer patients.
- The revolution in imaging that has enabled the detection of breast cancer at these early stages awaits a similar revolution in histopathology and therapy.
- Therapeutic guidelines for screen-detected breast cancers should not be based on trial results obtained from palpable, clinically detected cancers. There is considerable risk for overtreatment when the adjuvant treatment regimens developed for palpable cancers are also used to treat mammographically detected, non-palpable cancers.
- Long-term follow up of screen-detected cases is necessary for the accurate quantification of absolute benefit of screening, because the true potential of the so-called indolent tumors to dedifferentiate cannot be accurately predicted at the time of treatment.

The Mechanism by Which Screening Affects the Natural History of the Disease

The randomized controlled mammography screening trials have provided the opportunity to study the mechanism by which earlier diagnosis and treatment affect the outcome of breast cancer. In these trials one group was randomized to receive an invitation to screening, but the other, randomly selected group of women (control

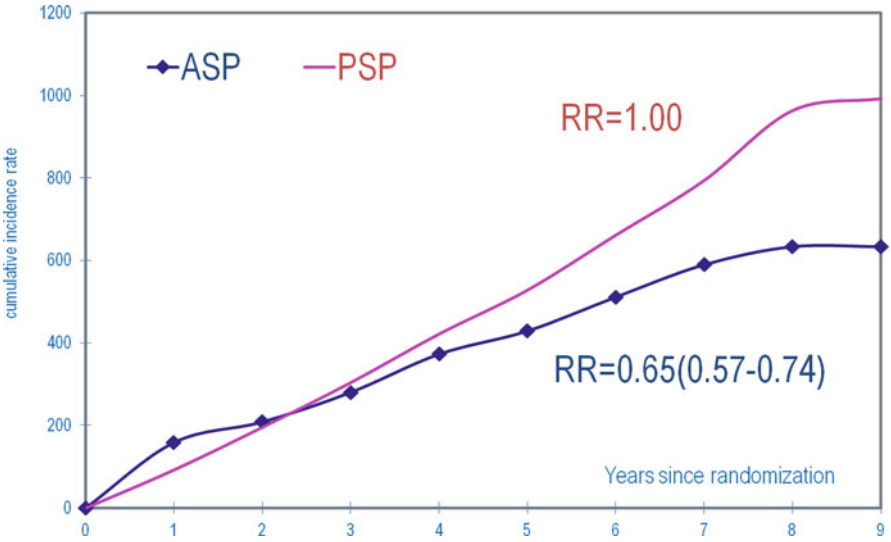


Fig. 2.3 Cumulative incidence rates of advanced breast cancers (Stage II or more advanced) in women invited versus not invited to the Swedish Two-County mammography screening trial. The first screening brought to light both occult and clinically advanced cancers, resulting in the initial slight excess of Stage II+cancers in the invited group. After the first round of screening the advanced cancer rate in women invited to screening fell significantly below that of the control group, because many small invasive cancers were detected at screening and surgically removed before they could grow to a more advanced stage

group) was not invited. The breast cancers in women invited to screening were diagnosed on average at an earlier phase than the self-detected tumors in the control group. Screening has a significant impact on all three first-generation prognostic factors: tumor size, axillary node status, and histologic malignancy grade. In a high-quality service screening program 15–20 % of the cancers will be in situ and more than 50 % of the invasive carcinomas will be <15 mm in diameter. Early detection also results in significantly fewer cases with axillary lymph node metastases and also prevents worsening of the malignancy grade in a certain percentage of the tumors. Since two components of the TNM classification, tumor size and node status, will improve significantly in women invited to screening, the incidence of Stage II and more advanced cancers will decrease in this same group of women (see Fig. 2.3).

There is parallelism between the incidence of advanced cancers and the breast cancer-specific mortality rate in any given population, since most breast cancer deaths occur in women whose tumor was at an advanced stage at the time of detection [10, 12, 30–32]. Thus decreasing the incidence rate of advanced tumors through screening will result in a corresponding decrease in breast cancer mortality in this same group of women. In the Swedish Two-County Trial the advanced cancer rate began to fall starting from year four and onwards in women invited to screening, as did the breast cancer death rate. Both of these declines were a consequence of early detection and treatment in an earlier phase (see Fig. 2.4).

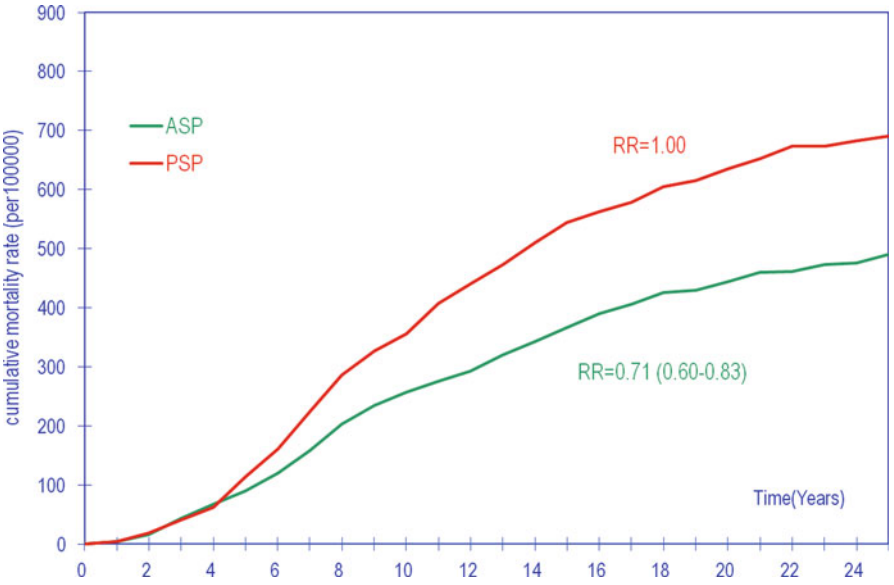


Fig. 2.4 Cumulative breast cancer mortality in women invited to mammography screening (*ASP*) compared to women not invited (control group, *PSP*) at 25-year follow-up after randomization

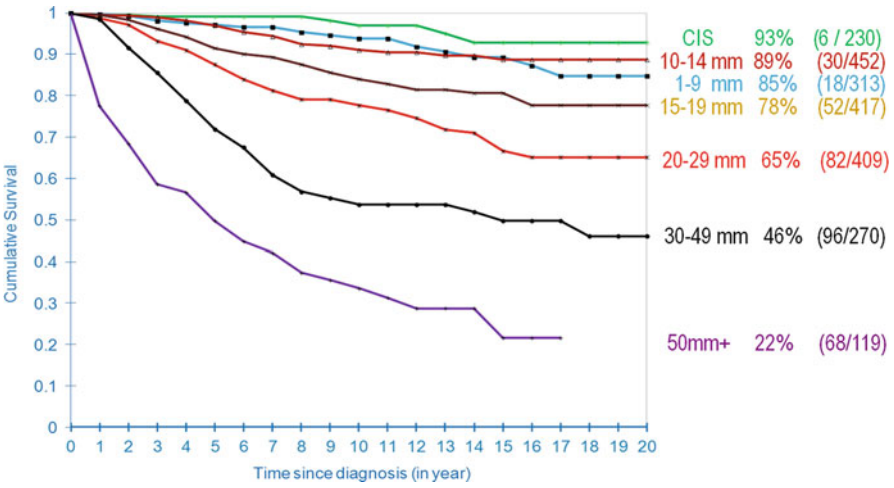


Fig. 2.5 20-year disease-specific survival of women according to tumor size in Dalarna County, Sweden

The effect of tumor size on long-term survival (28 years) in the Swedish Two-County Trial is presented in Fig. 2.5. The beneficial impact of screening is reflected in the excellent long-term survival of women with in situ and 1–14 mm invasive

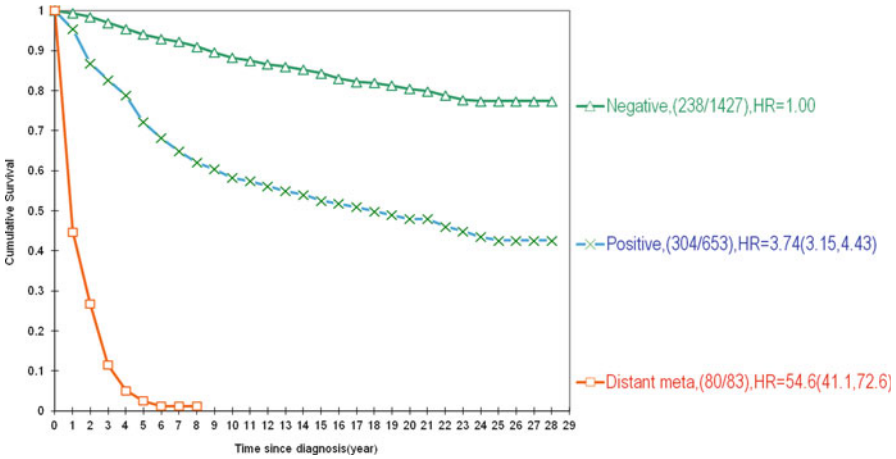


Fig. 2.6 28-year disease-specific survival of women according to axillary node status and the presence of distant metastases in the Swedish Two-County Trial, for all tumor sizes

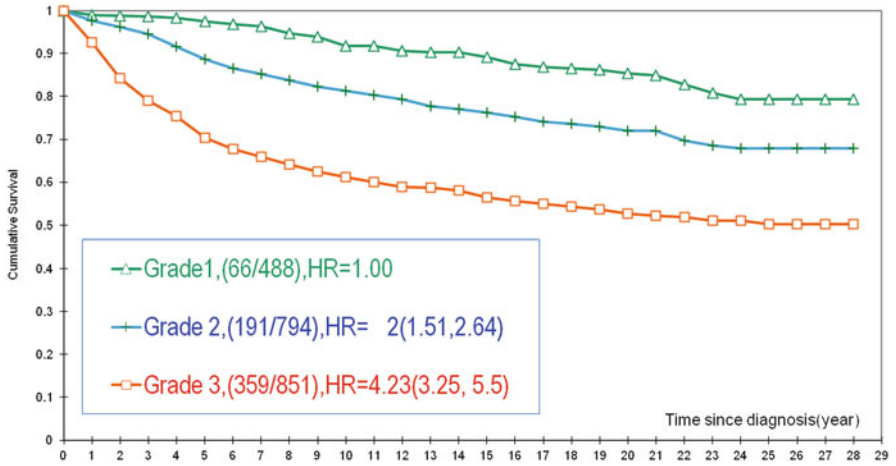


Fig. 2.7 Cumulative survival of women aged 40–69 years according to the histologic grade of invasive breast cancers from the Swedish Two-County Trial, for all tumor sizes

breast cancer. The 28-year survival according to axillary node status and distant metastases for all tumor sizes demonstrates the profound prognostic impact of these parameters (see Fig. 2.6). These survival rates are from the era prior to the widespread use of chemotherapy for primary breast carcinoma; none of the women with <20 mm node-negative tumors received chemotherapy in the Swedish Two-County Trial (1977–1985). Women with lymph node metastases had significantly poorer survival than those without lymph node metastases. The cumulative survival of women aged 40–69 years according to the histologic grade of the invasive cancers is shown in Fig. 2.7.

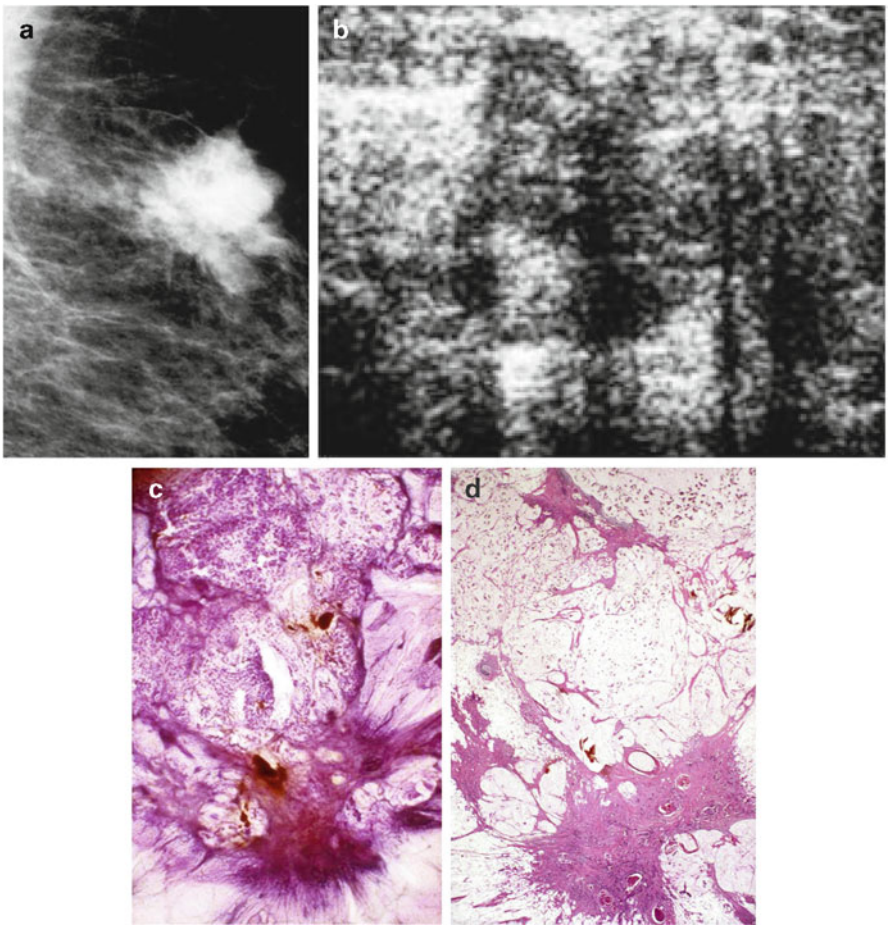


Fig. 2.8 Details of the mammographic (**a**) and ultrasound (**b**) images of a tumor containing both a circular/lobulated and stellate components. Subgross, 3D (**c**) and large thin-section (**d**) histology images show that the stellate component corresponds to a moderately differentiated invasive ductal carcinoma and the lobulated component is a well-differentiated mucinous cancer

Many breast tumors display intratumor heterogeneity, containing two or more histologic types and phenotypes (see Fig. 2.8a–d) [33–35]. Early detection through screening prevents many small, well- or moderately differentiated tumors from developing into more poorly differentiated, larger tumors. The evidence that the histologic malignancy grade worsens as the breast cancer progresses comes from the analysis of both clinical [36] and screening data [37]. The clinical research of Tubiana et al. demonstrated that "during their growth tumors progress towards higher grades" [36]. Duffy et al. used data from a randomized controlled mammography screening trial to perform a more precise measurement of progression by comparing the tumor characteristics in the control group, where the tumors were allowed to grow until clinically detectable, with the tumor characteristics in the

group of women invited to mammography screening, where screening aimed at arresting tumor growth [37]. This comparison required the removal of the prevalence screen tumors from both groups in order to eliminate length bias. These two sets of tumors were then equivalent in all aspects except that the tumors in the group invited to screening were diagnosed, on average, earlier. Comparison of tumor size, node status, histologic malignancy grade, and detection mode showed that the proportion of cancers with positive nodes and a higher malignancy grade increased with increasing tumor size [3, 37]. There were also significantly fewer node-positive and poorly differentiated cancers among women invited to screening. There could be two competing explanations for these results: (1) The malignancy grade remains unchanged as the tumor grows, and screening has mostly detected well- and moderately differentiated tumors (length bias sampling). (2) The malignancy grade tends to worsen as the tumor grows, and tumor progression does indeed occur. If this were to happen, one would see a deficit of poorly differentiated tumors in the incident cancers of a group of women invited to screening compared with an uninvited group. When Duffy et al. eliminated the length bias cases from both groups, i.e., the prevalent screen, and could thus compare the incident cancers in those invited and those not invited to screening, they observed that the tumors were significantly smaller and there was a significant deficit of poorly differentiated tumors in the invited group. This demonstrated that screening prevented the deterioration of the malignancy grade of some of the tumors. In summary, tumor progression (worsening of the malignancy potential through the process of dedifferentiation) has been shown to occur in both clinical and screening studies [36, 37].

Detailed analysis of the breast cancer cases from women invited and not invited to a randomized controlled trial demonstrated that the rate of poorly differentiated breast cancer increases in all age subgroups with increasing tumor size, but in premenopausal women this process of dedifferentiation occurs more rapidly, earlier in the preclinical detectable phase, and to a greater extent than in postmenopausal women. All these factors in combination make it necessary that women are invited to screening at a frequency which takes into account the varying tumor growth rates according to different histologic tumor types and women's age [29, 38]. Reversion to less frequent screening, as recommended by the US Public Services Task Force (USPSTF), would tend to increase the number of advanced (more frequently poorly differentiated and node positive) cancers at the time of treatment and increase fatality from breast cancer [39].

The recent publications by Esserman et al. maintain that screening does not decrease the incidence of advanced breast cancers [27, 28]. This is contrary to the published evidence [10, 12, 30–32, 40]. The claim of Esserman et al. that “tumor biology does not change over time” [27] reflects unfamiliarity with appropriate statistical analysis of clinical [36] and screening trial data [37] and fails to account for certain fundamental observations in breast tumor biology, including the consequences of intratumor heterogeneity [35].

Key Points

- Breast cancer screening has a favorable impact on all three first-generation prognostic factors: tumor size, node status, and histologic malignancy grade.
- The favorable prognosis of women with screen-detected breast cancers can be accounted for by smaller tumor size, less node positivity, and lower malignancy grade at the time of treatment.
- The frequency of poorly differentiated breast cancers increases with increasing tumor size.
- The frequency of node positivity increases with increasing tumor size.
- More frequent screening will reduce the number of interval cancers, and also improve the prognostic characteristics of screen-detected cancers.

Multifocal and Diffusely Invasive Breast Cancers: High Fatality Rate and High Recurrence Rate

Our primary goal is to reduce mortality from breast cancer. Mammography screening and the associated improvements in diagnosis and therapy have enabled us to reduce the breast cancer mortality in women attending screening regularly by 40–50 % [19]. Despite this accomplishment, women are still dying from breast cancer. Investigation into the characteristics of the cancers that are still causing breast cancer death requires assessing the *extent* of the disease as a measure of the tumor burden. Two comprehensive whole-breast histologic studies examined the unifocal, multifocal, and diffusely infiltrating nature of breast cancer [41, 42]. The term multifocality includes (a) multiple in situ cancer foci without invasion, (b) a solitary invasive carcinoma associated with multiple in situ foci, and (c) multiple invasive breast cancer foci with or without associated in situ cancer. The invasive cancers with or without an associated in situ component are responsible for breast cancer death; the relative frequency of unifocal/multifocal/diffusely infiltrating invasive breast cancers is approximately 68/27/5 % [109]. In which of these groups is breast cancer most fatal? The fatality ratio of unifocal breast cancers (with or without associated in situ foci) is 9.1 % and most (74 %) of these fatal cancers were >2.0 cm in size. In the era of mammography screening enhanced by the use of multimodality breast imaging, unifocal tumors can be detected and successfully removed before they reach the size of 2.0 cm. The fatality ratio in multifocal and diffusely infiltrating invasive breast cancers is 20 and 26 %, respectively, considering all sizes of tumors [43]. Multifocality is an important, independent negative prognostic factor (see Fig. 2.9) and its harmful effect becomes more significant with increasing tumor size. Weisenbacher and coworkers have arrived at the same conclusion [44].

The highly significant size-related survival difference also applies to multifocal breast cancers, suggesting that a combination of imaging methods that enables detection of multifocal cancers with a lower tumor burden (when the largest tumor

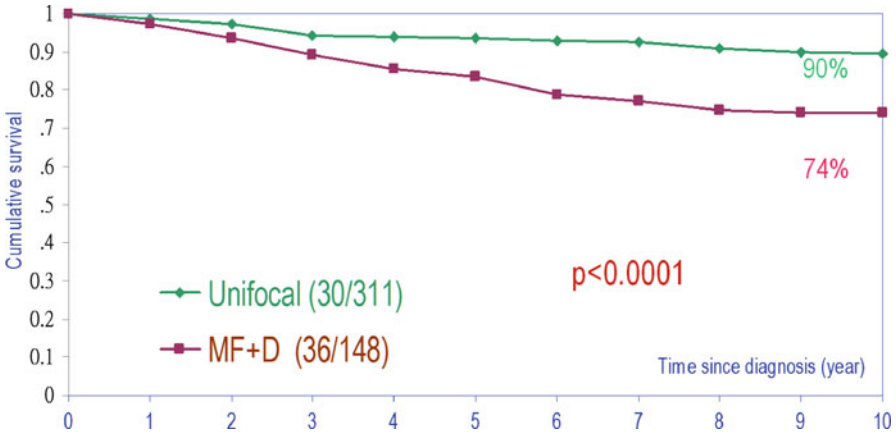


Fig. 2.9 Cumulative survival of women with unifocal invasive versus combined multifocal and diffusely infiltrating breast cancer

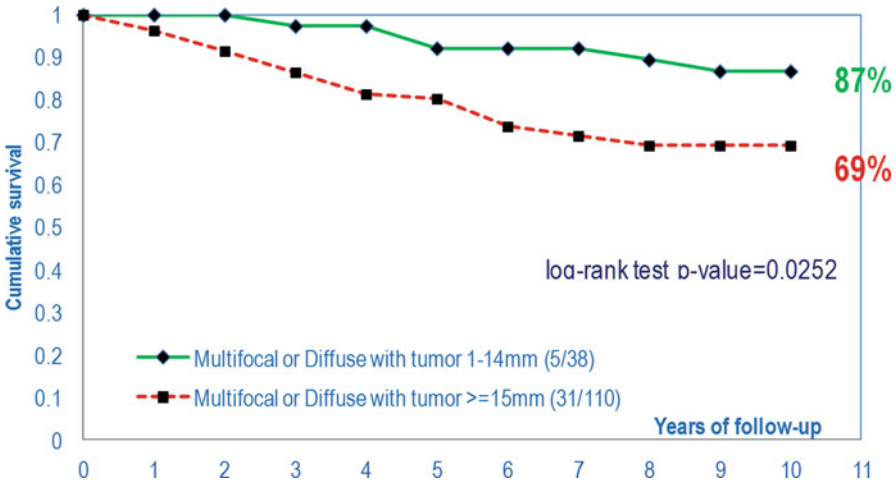


Fig. 2.10 Cumulative survival of women with 1–14 mm multifocal invasive versus >15 mm multifocal invasive breast cancer

focus is <15 mm) will result in a lower fatality rate (see Fig. 2.10). The multimodality approach (mammography, automated breast ultrasound, and especially breast MRI) will detect multifocal cancers having a lower tumor burden, and will correspondingly lower the fatality rate. This emphasizes the importance of using breast MRI to determine the presence and extent of multifocal disease. The use of breast MRI in multifocal and diffusely infiltrating invasive breast cancers is invaluable in

describing the true extent of the disease. This is an important part of treatment planning to prevent incomplete resection of breast cancer at primary surgery. Incomplete resection of invasive cancer foci is associated with a poor outcome: "For patients who underwent second surgery, the finding of a residual invasive carcinoma was associated with increased risk for distant recurrence (22.8 vs. 6.6 %; HR 3.5; 95 % confidence interval, 1.8–7.4; $P < .0001$)." These same authors concluded, "there is a need to improve techniques for the presurgical and/or intraoperative determination of margins" [45].

Modern, high-resolution breast MRI has the capability of describing the true extent of the disease in the vast majority of cases, far exceeding that of earlier MRI technology, on which most currently available reviews are based. The COMICE trial, which used 2.4/4.0 mm slice thickness (as opposed to the current practice of 0.7–1.0 mm), was a multicenter trial in which 45 centers supplied an average of only 18 cases each during the 5-year accrual period starting in 2002. This study's failure to detect an impact of preoperative MRI upon reoperation rate may reflect the outdated technology and the extremely low average rate of patient accrual per site, reflecting limited experience in breast MRI interpretation. High-resolution breast MRI was practically nonexistent prior to 2007. For these reasons the COMICE trial results [46], the meta-analysis by Houssami et al. [47], and other earlier studies may have lost their relevance to current breast MRI practice.

The reliance upon local recurrence as a measure of success or failure of breast cancer treatment is subject to serious limitations. Fatality often occurs without local recurrence and the term "local recurrence" as used in the literature does not discriminate among recurrences in unifocal, multifocal, and diffusely infiltrating breast cancers. One classification system uses a cutoff point of 4.0 cm to separate "extensive" from "non-extensive" breast cancer [42]. Using this arbitrary cutoff point, "A disease extent ≥4 cm was shown to be an independent marker for local recurrence; the cumulative 10-year local relapse rate for the group with a disease extent ≥4 cm was 20.5 %, and for the rest 6.7 % (p value = 0.003)" [48].

The seriousness of multifocal and diffusely infiltrating breast cancers has not been generally appreciated for two main reasons. First, the current TNM classification system does not account for multifocality, using only the size of the largest invasive focus as the major descriptive factor. This seriously underestimates the actual tumor burden of multifocal tumors. We have proposed a quantitative evaluation of tumor burden in terms of total tumor volume and surface area [43].

Second, the current practice of histopathology of breast specimens has serious limitations; "conventional techniques may not reflect the extent of neoplasia when the neoplasia is impalpable or grossly indistinct as in the case of dense breast tissue." Additionally, "complete specimen examination is rarely performed in clinical practice." "In a typical 8-cm diameter lumpectomy specimen, assuming four conventional pathology margin sections are removed in a single plane, only 16 % of the circumference is examined microscopically" [49] (see Fig. 2.11). "People blame MRI instead of the limitations of conventional pathology *and* a failure of small section pathology to correlate with MRI and mammography." (Lee Tucker, M.D., F.A.P.C., personal communication 2012).

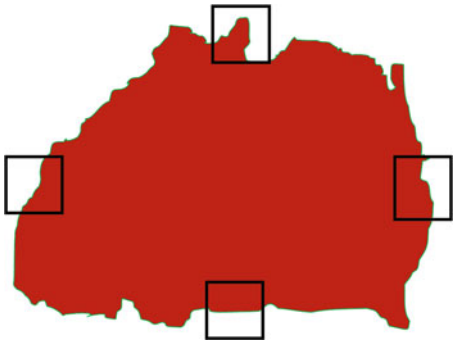


Fig. 2.11 Conventional pathology samples only 16 % of the circumference in a typical 8 cm lumpectomy specimen (courtesy of Lee Tucker M.D., F.C.A.P.)

We recommend that *large-section histopathology should be standard* for all breast cancer surgical specimens, as it also provides better correlation with breast imaging (see Fig. 2.12a–m).

Key Points

Despite the remarkable improvements in the diagnosis and therapy of breast cancer that resulted in a significantly decreased mortality from the disease, it is unfortunate that women are still dying from breast cancer.

- The fatality rate is highest for multifocal and diffusely infiltrating breast cancer cases and lowest for unifocal tumors.
- Multifocality is an important, independent negative prognostic factor whose harmful influence increases with increasing tumor size.
- Even multifocal invasive breast cancers can be detected in a relatively early phase with a lower tumor burden and a correspondingly lower fatality rate, provided that the most sensitive imaging methods are used preoperatively. The combination of currently available imaging methods, especially breast MRI, has this capability.
- The use of preoperative MRI helps to prevent incomplete resection of breast cancer at primary surgery because it provides more accurate determination of tumor size and extent than either mammography or breast ultrasound.
- The failure to remove invasive breast cancer foci is associated with a poorer outcome.
- The current TNM classification system should be upgraded to provide a better quantitative evaluation of the tumor burden by categorizing unifocal, multifocal, and diffusely infiltrating breast cancers separately.
- Large-section histopathology of all breast cancer surgical specimens should be the standard of care.

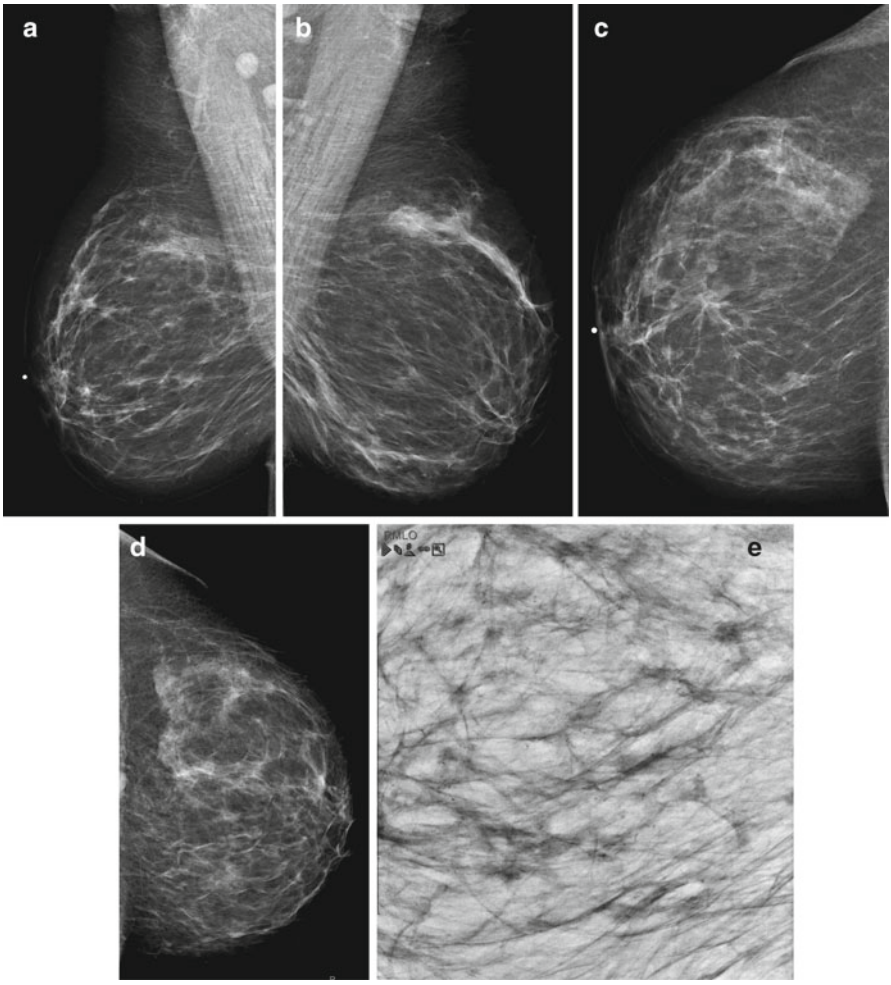


Fig. 2.12 (**a**–**e**) This 49-year-old woman felt a lump under her right areola. A slight degree of skin retraction could be provoked over the tumor. Physical examination confirmed the presence of a hard tumor, but also revealed a "thickening" in the upper and central portions of the right breast. The mammograms show a retroareolar asymmetric density corresponding to the palpatory finding. In addition, there are a large number of small stellate lesions spread throughout the upper-medial portion of the right breast, pathologic lymph nodes in the right axilla, and an oval tumor mass in the upper portion of the left breast. (**f**–**i**) Breast MRI of the right breast shows at least 30 independent tumor foci in the upper-medial portion of the breast with washout pattern (histologically proven invasive breast cancer foci) and a solitary, oval lesion with benign features in the left breast (histologic examination of the core biopsy specimen: fibroadenoma). (**j**–**m**) Correlation of the right mastectomy specimen slices with large-section histology. Multifocal cancer: at least 25 invasive tumor foci (well and moderately differentiated), the largest measuring 33 mm × 15 mm, and the smallest focus being 8 mm. The second and third largest foci measure 20 mm × 12 mm and 10 mm × 8 mm. In addition LCIS and Grade 1 and 2 in situ carcinoma are found over a 45 mm × 11 mm area. Six out of 17 surgically removed axillary lymph nodes showed metastases at histologic examination

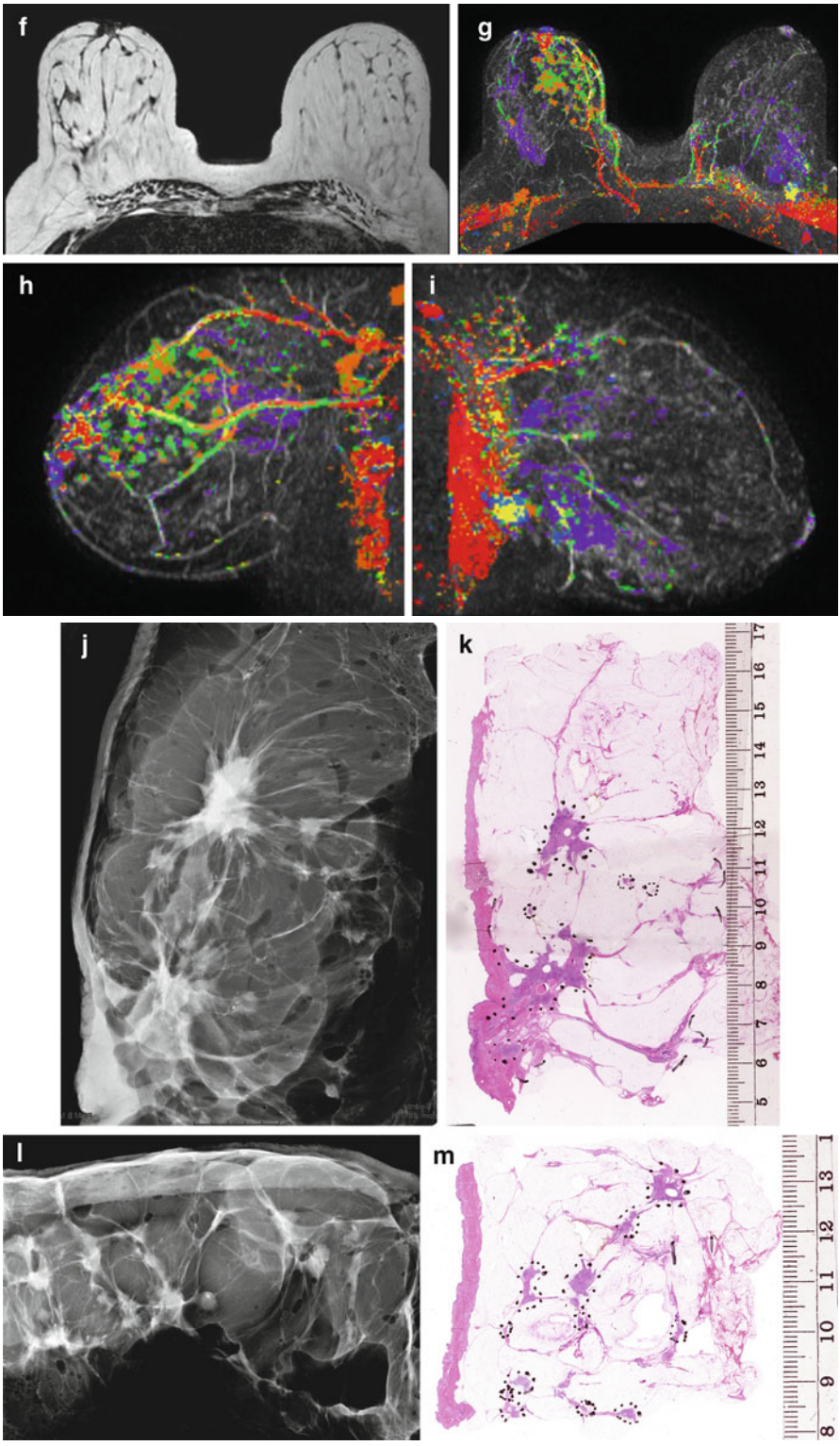


Fig. 2.12 (continued)

The Need for Improved Terminology Reflecting the Site of Origin of Breast Cancer

Breast cancer originates either from the epithelial cells lining the acini within the terminal ductal lobular unit (TDLU) or from the cells lining the milk ducts (see Fig. 2.13). The majority of breast cancers originate from the TDLUs, not from the ducts. Figure 2.14 shows the relative distribution of the crushed stone-like and powdery microcalcifications on the mammogram, both of which are the mammographic presentations of in situ tumor growth which arise from and are localized within the TDLUs. Despite the fact that these in situ tumors arise within the lobules and not from the ducts, they are paradoxically termed "ductal" carcinoma in situ. When this population of cancer cells invades the surrounding breast tissue, forming a stellate or circular/oval-shaped tumor mass, the invasive tumor is also erroneously called "ductal."

In situ breast cancers are usually detected at mammography. There are more than ten distinctly different mammographic presentations of in situ cancer subtypes (see Figs. 2.15a–c and 2.16a–x), but current terminology bundles them all under the same name: DCIS. This simplification unfortunately leads to misunderstanding and confusion. Additionally, the term DCIS is a misnomer, since the vast majority of in situ carcinomas do not arise from the milk ducts and are not situated within these ducts.

Breast cancers actually arising within the major milk ducts have a histopathologic appearance (see Fig. 2.17a, b) very similar to that of metastatic prostate cancer (Fig. 2.17c–e) and metastases of breast cancer to the axillary lymph node(s) (Fig. 2.18a, b). Although the histopathologic appearance shown in Figs. 2.17c–e and 2.18a, b will be termed by pathologists as invasive cancer, i.e., when found in the prostate or in the axillary lymph node(s), the similar histopathologic appearance is termed "DCIS" when found in the breast. The unpredictable clinical course and

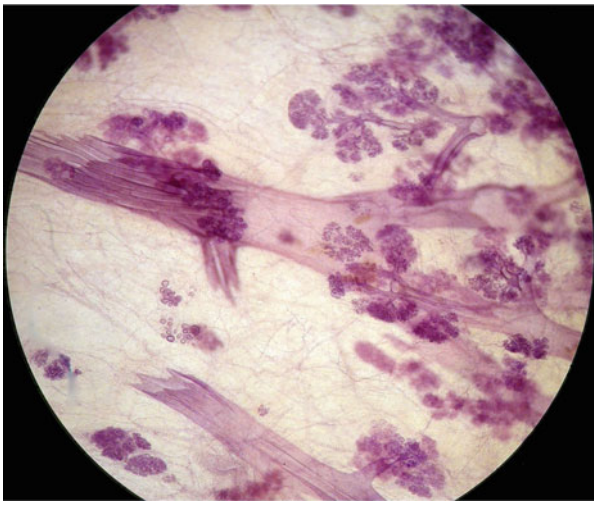


Fig. 2.13 3-Dimensional histology image of major milk ducts and several terminal ductal lobular units (TDLUs). The majority of breast cancers originate from the TDLUs

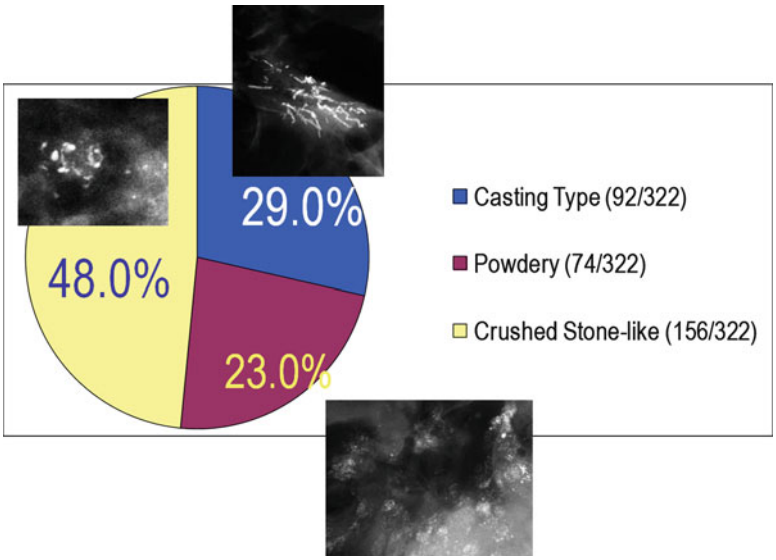


Fig. 2.14 Relative distribution of histologically proven calcified in situ carcinoma cases according to their presentation on the mammogram. The crushed stone-like and powdery microcalcifications constitute the majority of in situ cases. Both of them are the mammographic presentations of in situ tumor growth arising from and localized within the TDLUs

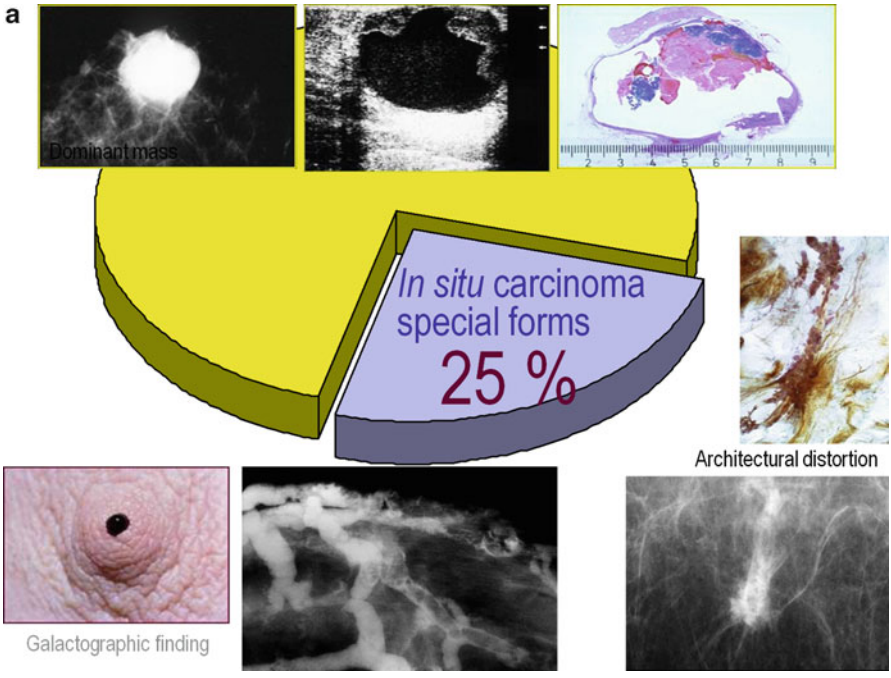


Fig. 2.15 (**a**) About 25 % of the mammographically demonstrable in situ carcinomas lack calcifications on the mammogram. In these cases the mammogram shows either a dominant mass or a architectural distortion; the third option is a galactographic finding. (**b**) In 75 % of the

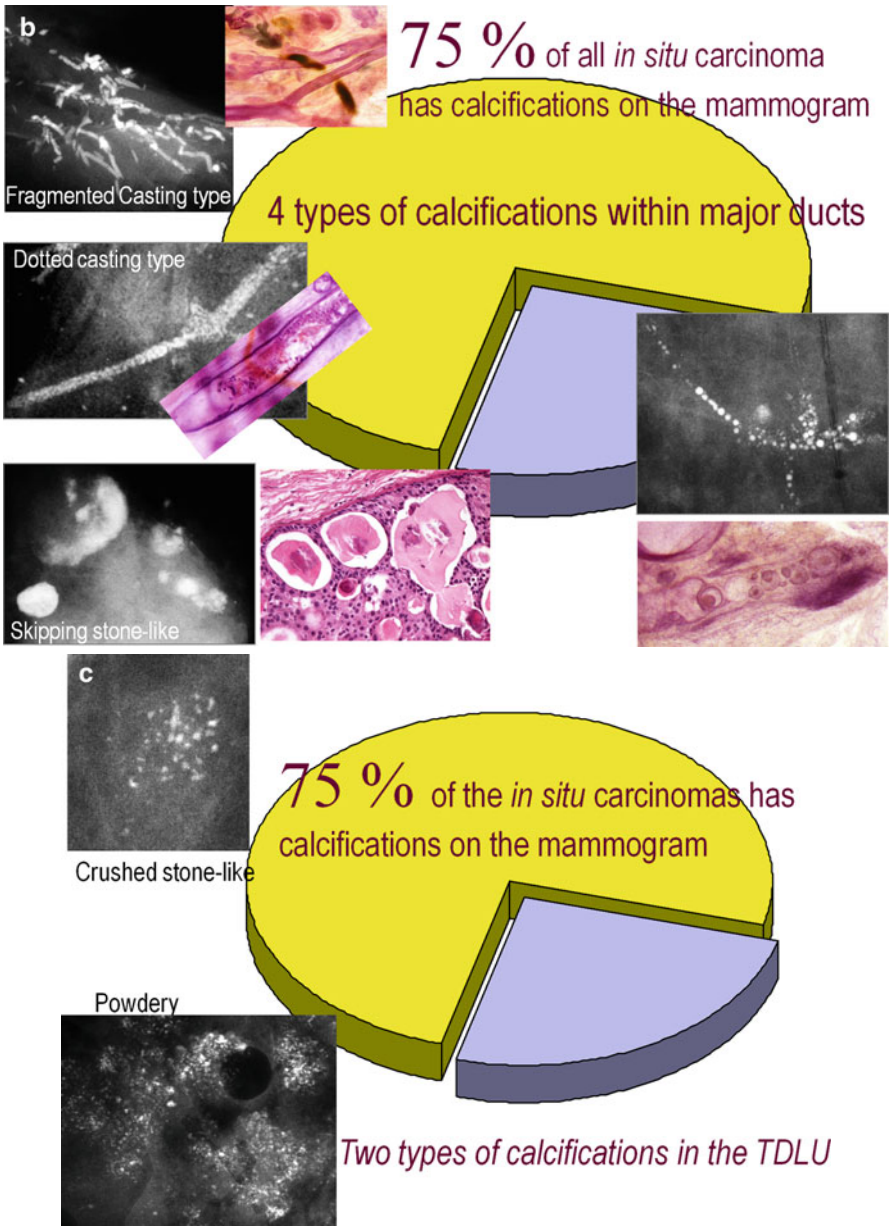


Fig. 2.15 (continued) mammographically demonstrable in situ breast cancer cases calcifications are seen on the mammograms. There are four different mammographic appearances of the calcifications associated with the malignant processes localized within the major ducts. (**c**) In 75 % of the mammographically demonstrable in situ breast cancer cases calcifications are seen on the mammograms. There are two different mammographic appearances of the calcifications associated with the malignant process localized within the terminal ductal lobular units (TDLUs)

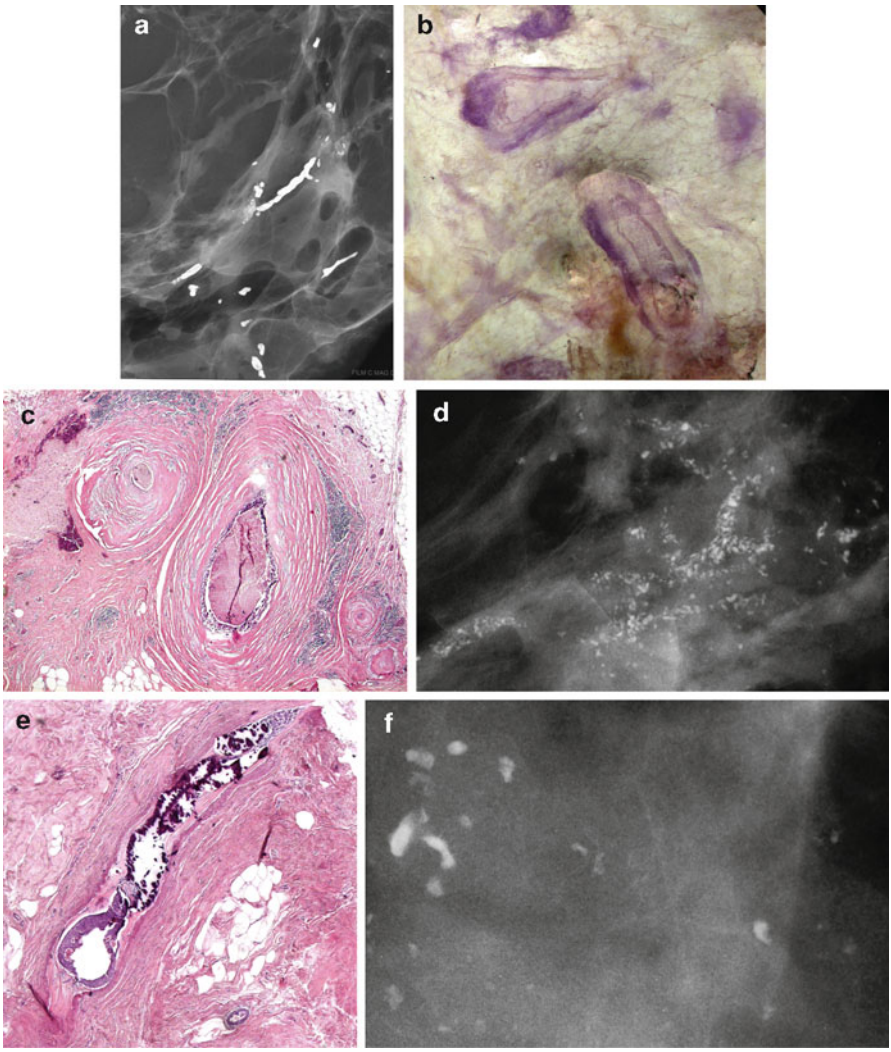


Fig. 2.16 A collage demonstrating the mammographic and histologic heterogeneity of *in situ* carcinoma of the breast. Regrettably, there is still only one term in current use to describe all these different diseases, and that term is "DCIS." (**a**–**c**) Fragmented casting-type calcifications in Grade 3 in situ carcinoma with solid cell proliferation. (**d**, **e**) Dotted casting-type calcifications seen in high-grade carcinoma in situ with micropapillary cell proliferations and necrosis within the major ducts. (**f**, **g**) Skipping stone-like calcifications seen in high-grade carcinoma in situ with micropapillary cell proliferations without necrosis, but with fluid production in the major ducts. (**h**–**j**) A mixture of crushed stone-like and skipping stone-like calcifications spread over two-thirds of the right breast. The Grade 2 and 3 in situ carcinoma contiguously fills the major ducts and branches as well as a large number of TDLUs. (**k**, **l**) Pearl necklace-like calcifications: Grade 1 in situ carcinoma with cribriform cell architecture and large psammoma body-like calcifications in the major ducts. (**m**, **n**) Multiple clusters of crushed stone-like calcifications localized within TDLUs: Grade 2 in situ carcinoma with solid cell proliferation, central necrosis, and amorphous calcifications in

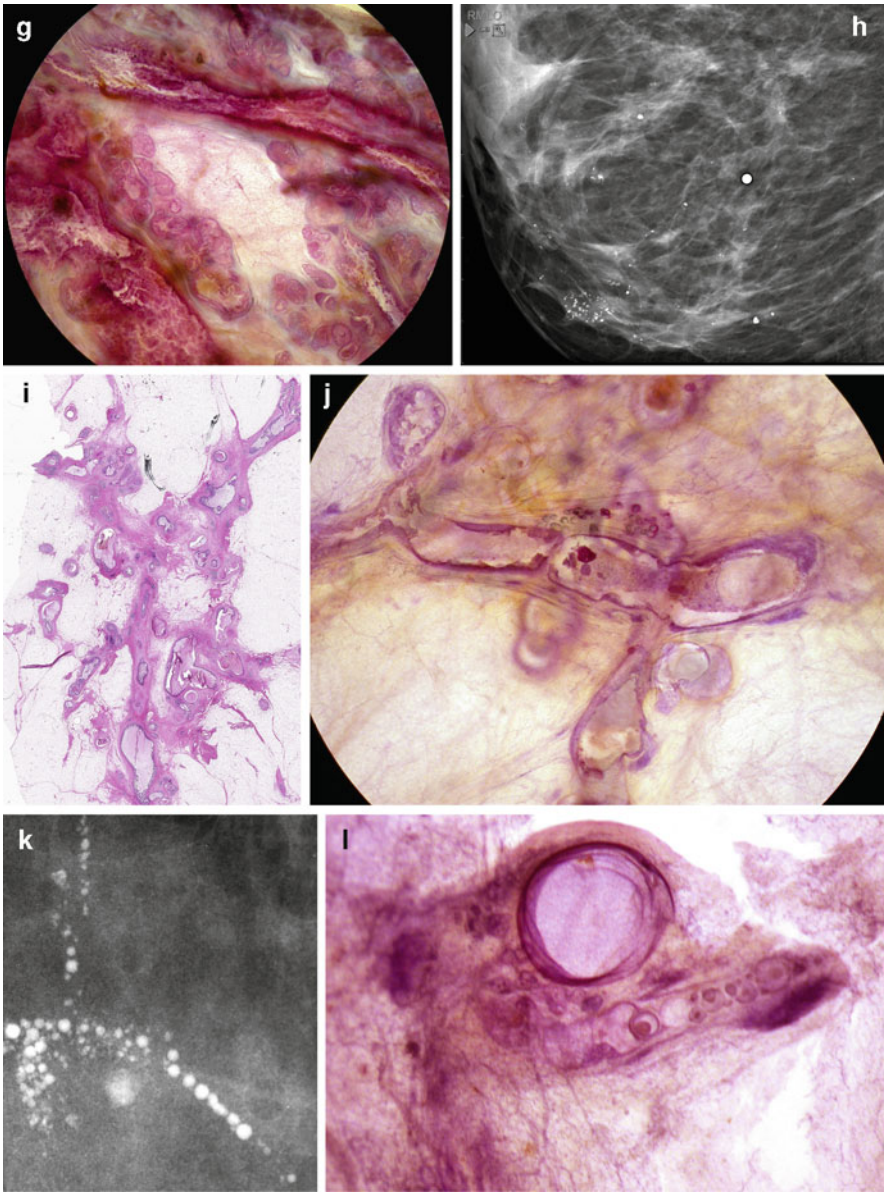
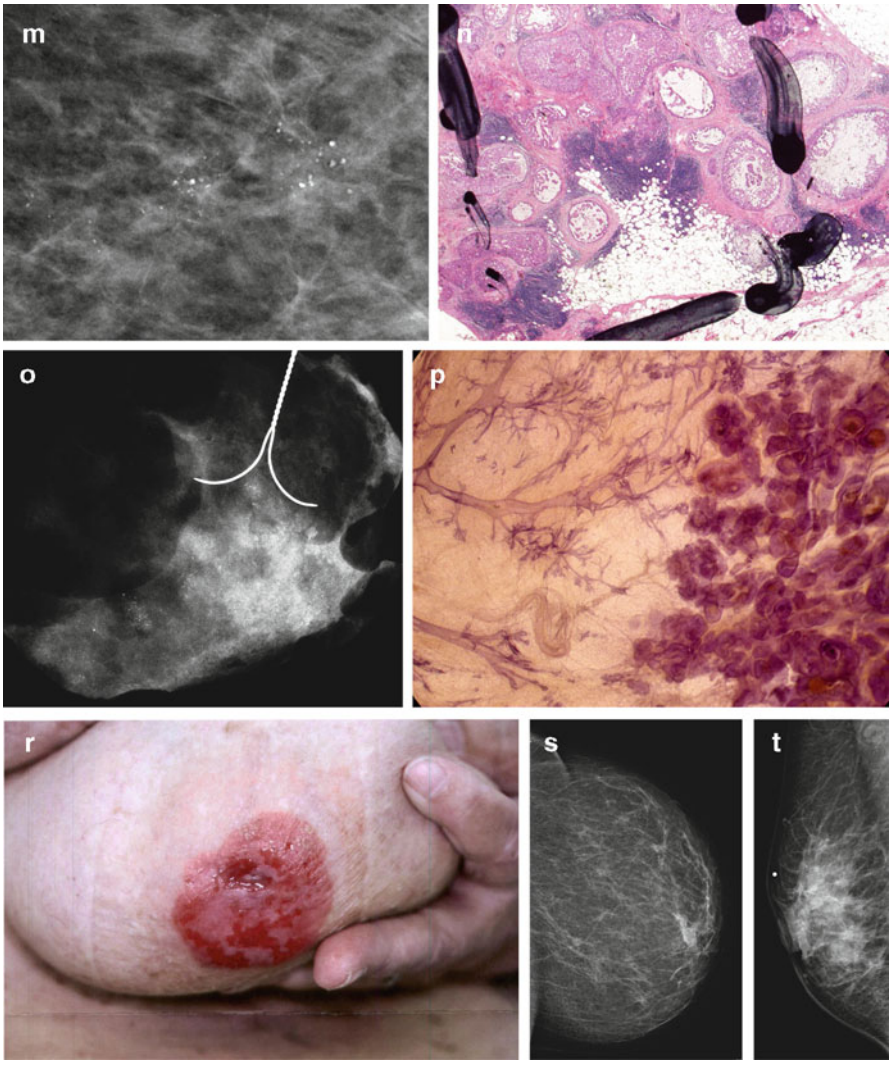


Fig. 2.16 (continued) the extremely distended acini. (**o**, **p**) Multiple clusters of powdery calcifications: Grade 1 in situ carcinoma associated with psammoma body-like calcifications in the TDLUs. (**r**, **s**) Paget's disease. In this case the mammogram is normal, and the high-grade in situ carcinoma was occult for mammography. In most of the Paget's disease cases the mammograms show malignant-type calcifications within the major ducts. (**t**–**v**) Palpable tumor and architectural distortion with no associated calcifications on the mammogram. The histology shows a large number of cancer-filled, tortuous ducts with high-grade micropapillary cancer in situ, no necrosis, and extreme fluid production. (**w**, **x**, **z**) Architectural distortion associated with calcifications within the cancer-filled, distended, tortuous ducts



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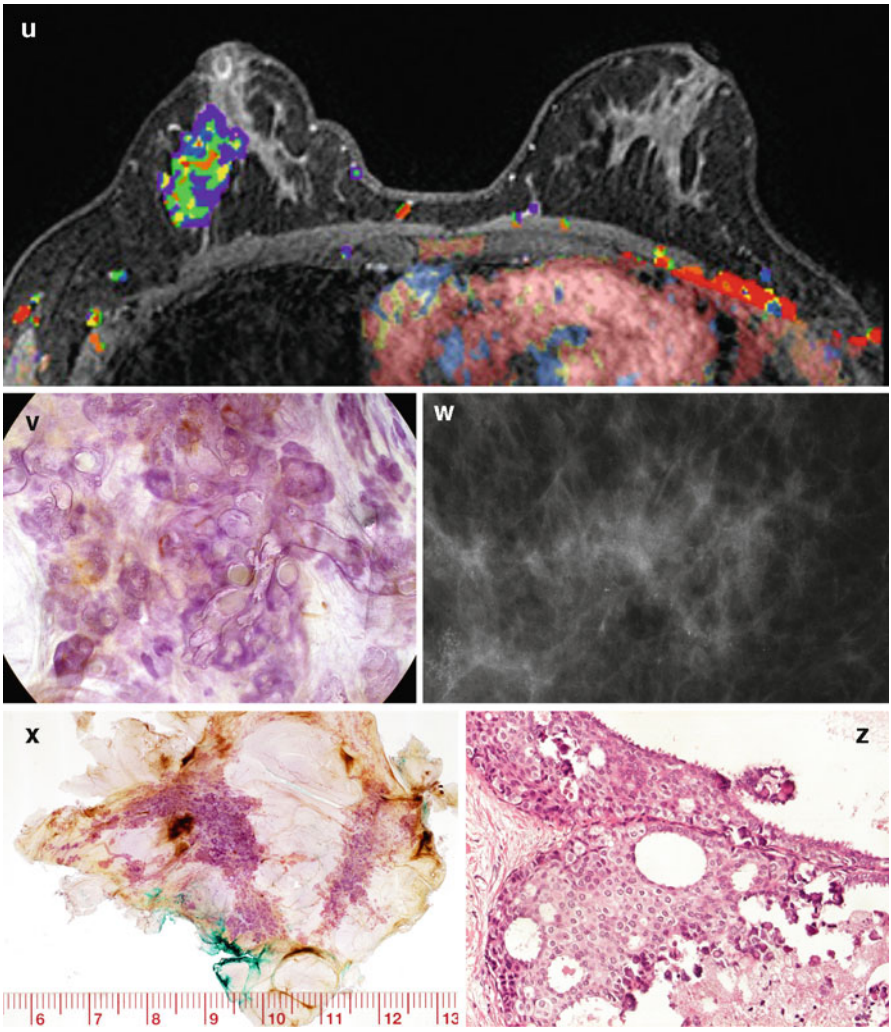

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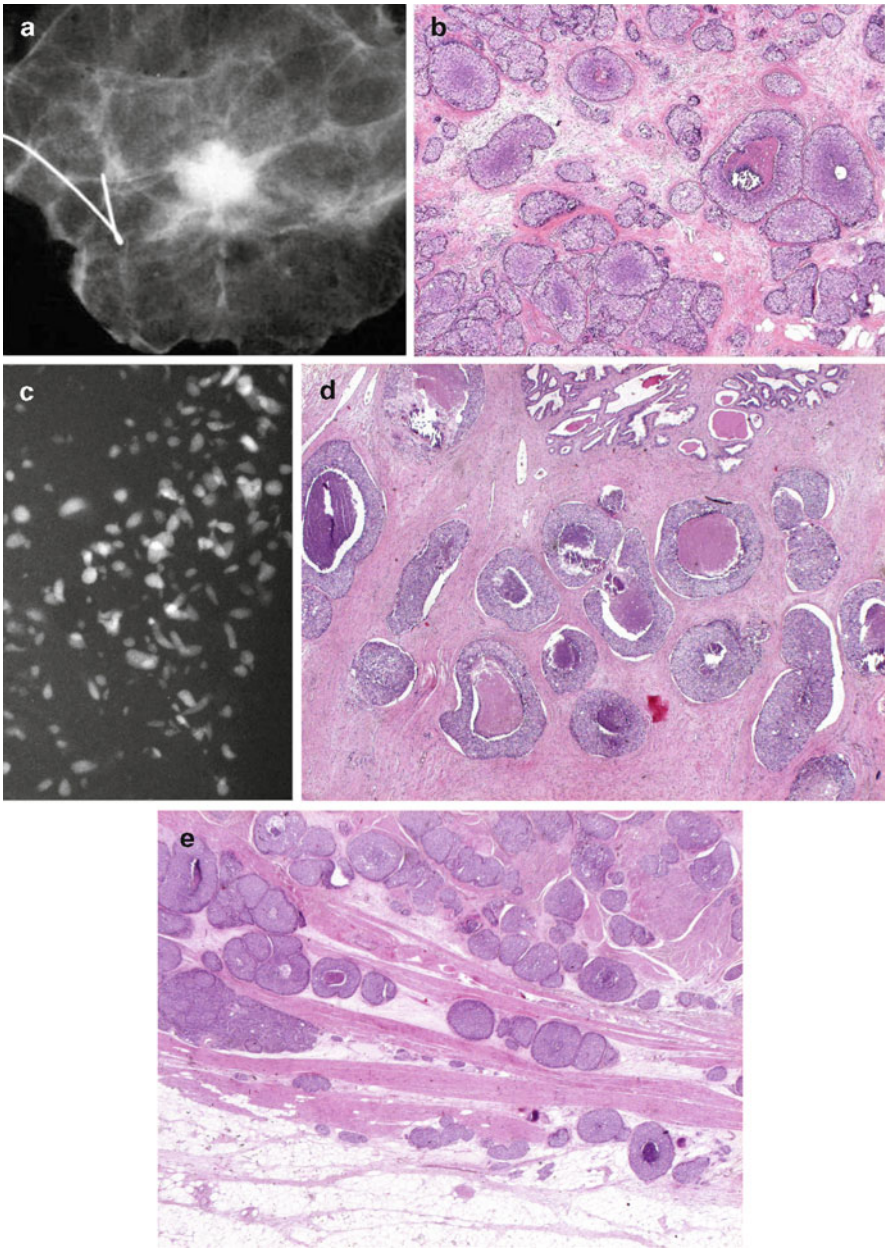

Fig. 2.17 (**a**, **b**) Segmentectomy specimen radiograph containing breast cancer. The histology image (**b**) is very similar to the histology of the prostate cancer shown in (**d**). (**c**) Specimen radiograph of a prostate cancer (ductal adenocarcinoma of the prostate *DAP*). (**d**) Intermediate power histology image of this prostate cancer. (**e**) This DAP infiltrates the surrounding organs in the lesser pelvis; the cancer-filled ducts can be seen among the muscle fibers of the urinary bladder

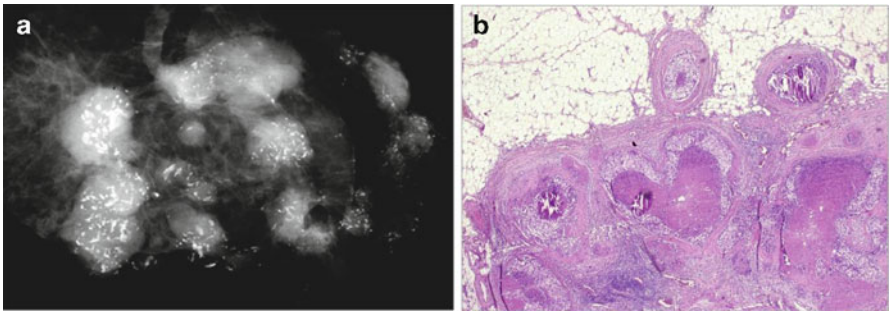

Fig. 2.18 (**a**, **b**) Radiograph of an axillary specimen containing 12 pathologic lymph nodes with malignant-type calcifications. The histology of one of the axillary lymph nodes contains "duct-like structures," mimicking the histologic image of prostate cancer (DAP) shown in Fig. 2.17d and the so-called in situ breast cancer shown in Fig. 2.17b

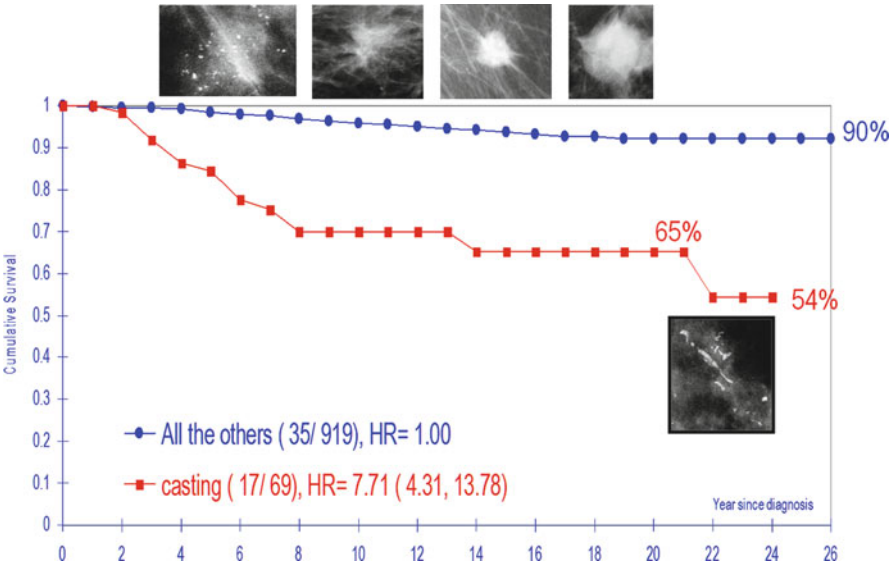

Fig. 2.19 26-year cumulative survival of women aged 40–69 years with 1–14 mm invasive breast cancers by mammographic tumor features. Dalarna County, Sweden. 1–14 mm invasive breast cancers originating from the TDLU (AAB) have excellent (90 %) long-term survival, compared to the subtype of ductal origin (DAB), presented on the mammogram as casting-type calcifications (65 % long-term survival)

also the occasional fatal outcome of these cases indicate that, contrary to its name "ductal carcinoma in situ" of the breast, the special breast cancer subtype originating from the major ducts may behave as an invasive cancer and can prove fatal (see Figs. 2.19, 2.20, and 2.21) [50].

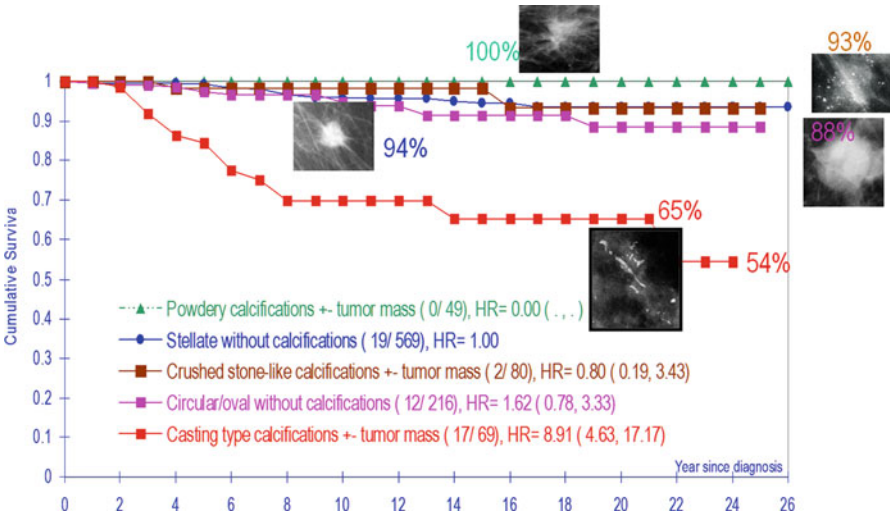

Fig. 2.20 Cumulative survival of women aged 40–69 years with 1–14 mm invasive breast cancers as a function of the five mammographic tumor features

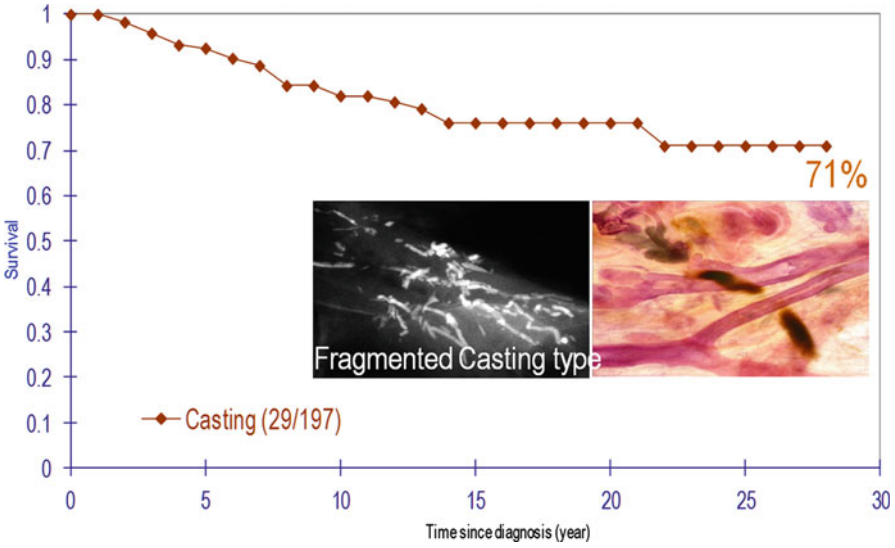

Fig. 2.21 Cumulative survival of breast cancer cases with casting-type calcifications on the mammogram. Women 40–69 years old, diagnosed in Dalarna county, Sweden, between 1977 and 2006

Taking the logical and consistent nomenclature that is used to describe prostate cancer and using it to describe breast cancer as well can resolve these terminological inconsistencies and the resulting confusion. Our proposed terminology emphasizes the site of origin of the cancer: *a*cinar *a*denocarcinoma of the *p*rostate (AAP)

would correspond to *a*cinar *a*denocarcinoma of the *b*reast (AAB), in which the cancer originates from the TDLU. Similarly, *d*uctal *a*denocarcinoma of the *p*rostate (DAP) would correspond to *d*uctal *a*denocarcinoma of the *b*reast (DAB), in which the breast cancer originates from the major milk ducts. The striking difference between the long-term outcome of breast cancers of similar size originating from the TDLUs (AAB) and the cancers originating from the major ducts (DAB) justifies the radical change in terminology (Figs.2.19 and 2.20).

The Mammographic Appearance of 1–14 mm Invasive Breast Cancers Has Important Prognostic Significance

The mammogram can be viewed as a low-resolution, grayscale image of the underlying histopathology of the breast. The mammographic presentations of breast cancers originating from the TDLUs (AAB) are as follows: crushed stone-like clustered calcifications (most often Grade 2 in situ carcinoma) [51], clustered powdery microcalcifications (characteristic of Grade 1 in situ carcinoma), and stellate or circular/oval tumor masses representing invasive carcinoma. The in situ and 1–14 mm breast cancers of acinar origin (i.e., from the TDLU) have excellent long-term prognosis. In the minority of cases when the cancer originates from the cells lining the milk ducts (DAB), the mammographic presentation and the patient's long-term prognosis are considerably different [50] (see Figs. 2.19 and 2.21). The myriad of prognostic features (histologic types and first-generation prognostic factors/biomarkers/gene profiling) should be correlated with the "mammographic prognostic features" described above (Figs. 2.22, 2.23, and 2.24).

Patient management planning routinely utilizes specific prognostic factors including tumor size, histologic malignancy grade, lymph node status, and a series of second-generation tumor characteristics (receptor status, HER2/neu status, gene expression profiling, etc.). The predictive value of these prognostic factors is, however, less successful in distinguishing screen-detected 1–14 mm invasive breast cancers, which have an excellent prognosis, from those with a potentially poor long-term outcome, when classified according to the current TNM criteria. This deficiency can be remedied by *adding the mammographic tumor features* to the treatment planning of these small, early-stage tumors, because four out of the five mammographic appearances are characteristic of tumors originating from the TDLU (AAB) and have a good/excellent long-term outcome. Within the AAB subgroup, multifocal cases have a poorer prognosis than the unifocal AAB cancers.

The fifth mammographic feature, the eminently characteristic "casting-type" calcifications on the mammogram (see Fig. 2.16a–d), represents cancer originating from the major ducts (DAB) and indicates a breast cancer subtype having a high fatality rate (71 % long-term survival) (see Fig. 2.21) despite its histologic description as a node-negative 1–14 mm invasive cancer associated with Grade 3 in situ carcinoma [50–55].

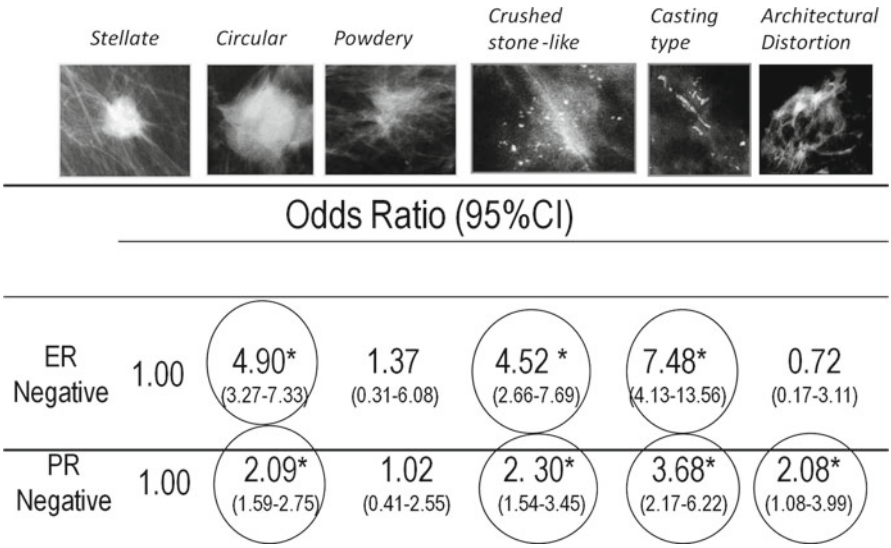

Fig. 2.22 Comparison of the mammographic prognostic features with the tumor biomarkers estrogen and progesterone receptors. There is a significant correlation between receptor negativity and the circular/oval shape of the tumor on the mammogram, and also with the presence of crushed stone-like and casting-type calcifications on the mammogram

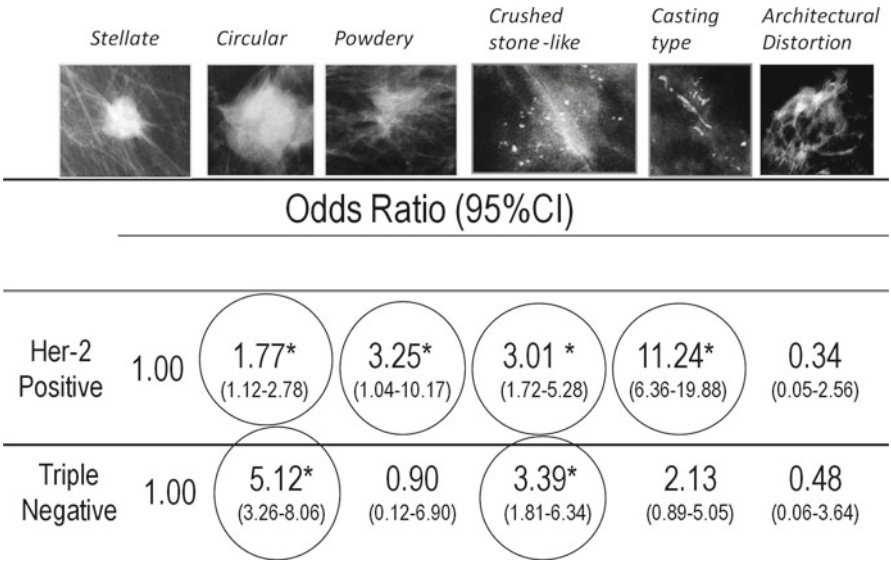

Fig. 2.23 Comparison of the mammographic prognostic features with the tumor biomarkers Her-2 and triple negativity. Her-2-positive and triple-negative tumors correlate significantly with the circular/oval shape of the tumor on the mammogram, and also with the presence of crushed stone-like calcifications on the mammogram

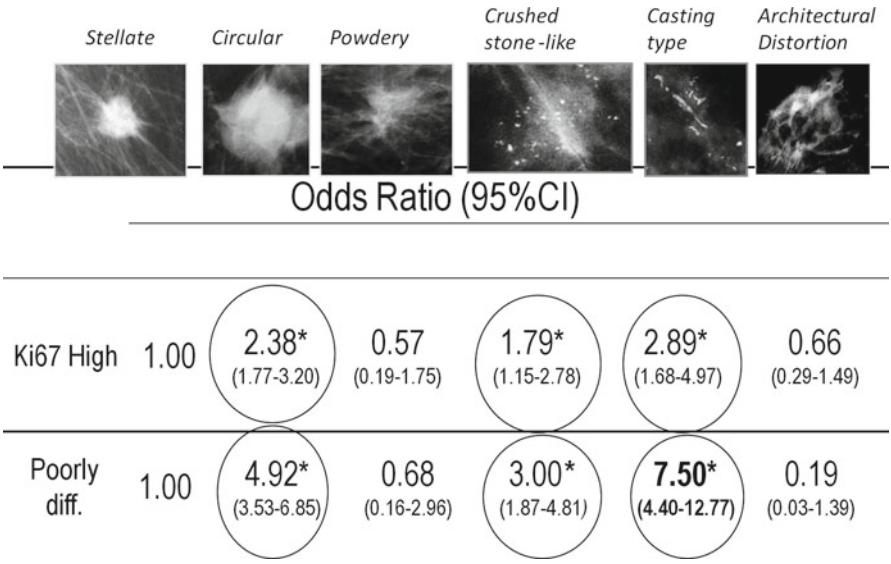

Fig. 2.24 Comparison of the mammographic prognostic features with high Ki67 value (proliferation index) and poorly differentiated malignancy grade. Tumors with high proliferation index and poorly differentiated tumors correlate significantly with the circular/oval shape of the tumor on the mammogram, and with the presence of crushed stone-like and casting-type calcifications on the mammogram

The efficacy and reproducibility of the mammographic tumor features for predicting patient outcome in consecutive, in situ, and 1–14 mm invasive breast cancer cases have been demonstrated in Europe and in the USA. There was poor prognosis for the cases with casting-type calcifications on the mammogram, and excellent prognosis for the remaining mammographic categories, providing further evidence that the current practice of predicting the long-term outcome of breast cancers in their earliest detectable phases can be significantly improved by including the mammographic tumor features in treatment planning [54]. The poor long-term survival of T1a and T1b breast cancers having casting-type calcifications on the mammogram (RR = 6.50, 95 % CI: 3.61–11.72) indicates that we are dealing with a much larger tumor burden than would be expected from 1–14 mm tumors. This large tumor burden with its poor prognosis can be explained by the theory of neoductgenesis, according to which the "Grade 3 in situ carcinoma" is a mixture of both in situ and a poorly differentiated duct-forming invasive cancer, which accounts for its high fatality rate [50, 55]. Including the mammographic tumor features to evaluate the small, 1–14 mm invasive breast cancers will enable planning targeted therapy for the 10 % of breast cancers which have the greatest potential fatality, i.e., those associated with casting-type calcifications on the mammogram. In the remaining 90 % of small breast cancers, distinction has to be made between unifocal and multifocal cases. In unifocal cases the necessity for using adjuvant treatment following surgery needs to be seriously reconsidered, since the long-term survival of these patients has been excellent with local therapy alone.

The integration of imaging morphology into the TNM classification in the 1–14 mm tumor size range has great potential for more accurate outcome prediction, facilitation of specifically targeted therapy, and curtailment of needless therapy.

Key Points

Despite the excellent prognosis of most patients with small breast cancers, a small number of women still die from tumors of <15 mm in size a few years after diagnosis.

- The first- and second-generation prognostic tumor features in current use do not discriminate between fatal and nonfatal invasive breast cancers <15 mm.
- The inclusion of mammographic tumor features provides significantly improved outcome prediction for these patients.
- Invasive breast cancers originating from the acini of the TDLU (i.e., cancers with good/excellent outcome) have a characteristically different mammographic appearance from those originating within the major ducts (i.e., cancers with poor outcome).
- The integration of imaging morphology into the TNM classification of the in situ and 1–14 mm invasive tumor size range would facilitate more accurate outcome prediction, specifically targeted treatment and curtailment of unnecessary therapy.

The Mortality Benefit in Relative and Absolute Terms and Related Issues

1. *The relative mortality benefit*. Evaluation of randomized mammography screening trials and service screening has shown a significant 25–30 % relative decrease in breast cancer mortality in women invited to screening and 43–49 % among women who attended screening at regular intervals [10–21, 29, 40, 56, 57]. These results have been available for decades and have not changed with time. The accuracy of these results is based upon *comprehensive individual patient data* detailing both diagnosis and treatment. These data include precise knowledge of each tumor's detection mode (detected at screening, in the interscreening interval, among invited but not attending women or among non-invited women), time of detection (whether the breast cancer case was diagnosed prior to the beginning of screening or during the screening period), and the ability to isolate breast cancer deaths attributable to cancers that were diagnosed before screening was offered to the population. *None of the publications questioning the benefit of early detection on mortality from breast cancer have had access to individualized patient data, making their claims that modern mammography screening plays*

little or no role in reducing breast cancer death simply a biased guess. The harsh critics of screening mammography, Jørgensen, Zahl, and Gøtzsche, "were unable to find an effect of the Danish screening programme on breast cancer mortality," using only registry data and admitted that "we compared open cohorts because our data did not allow identification of individual women" [58]. Their methodological shortcomings caused them to inflate the number of breast cancer deaths in the screening period by including cases diagnosed before screening began. The same severe biases affect other critics who rely upon registry data [59–62].

The lack of precision in Jørgensen, Zahl, and Gøtzsche's analysis is reflected in their use of "hedging" text: [58] i.e., "is unlikely," "It may be reasonable," "suggest," "may have," "would be expected," and "could be." Welch et al. state, "We were forced to make an assumption to capture the downstream benefit of screening" [61] while Haukka et al. admit, "Without individual data it is impossible to completely separate the effects of improved treatment and health service organization from that of screening … There will also be some contamination of post-screening mortality from breast cancer diagnosed prior to screening" [62]. Indeed, there is more than "some" contamination. We demonstrated in a 10-year period that more than half of all breast cancer deaths are attributable to diagnoses before the beginning of that 10-year period [32]. Yet, despite inadequate data and unjustified assumptions, all these authors still consider their estimates on breast cancer mortality worthy of publication and freely allow themselves to speculate on the impact of treatment versus screening. These comments are made without accurate data and should not have been published in peer-reviewed journals.

Access to individual patient data is crucial for an accurate evaluation of the true impact of screening, because more than 50 % of the breast cancer deaths occurring in a 10-year screening period are from cases diagnosed before the start of that period (see Fig. 2.25a, b) [18, 63]. One cannot expect mammography to have an impact on patients who were treated before mammography was used, yet these patients were included in the biased calculations of Jørgensen, Zahl, and Gøtzsche [58].

2. *The absolute mortality benefit*. Following the evaluation of the randomized controlled trials, case–control studies and large population-based service screening programs have also demonstrated a statistically significant decrease in breast cancer mortality as a result of diagnosis and treatment at an earlier phase of the disease. Attention has subsequently turned to estimating the absolute benefit in terms of deaths prevented. Several estimations have been made of the number of women needed to undergo repeated mammography screening examinations over a 10-year period in order to prevent one breast cancer death. Differences among the results are due to several factors:

   (a) *Calculations based on meta-analysis* of screening results always use the number of women invited, not the number actually screened. This considerably underestimates the benefit [26, 60, 64, 65]. If a woman does not attend mammography screening, she should not be included in a group that ostensibly measures the value of screening, yet this error has been repeated over and over.

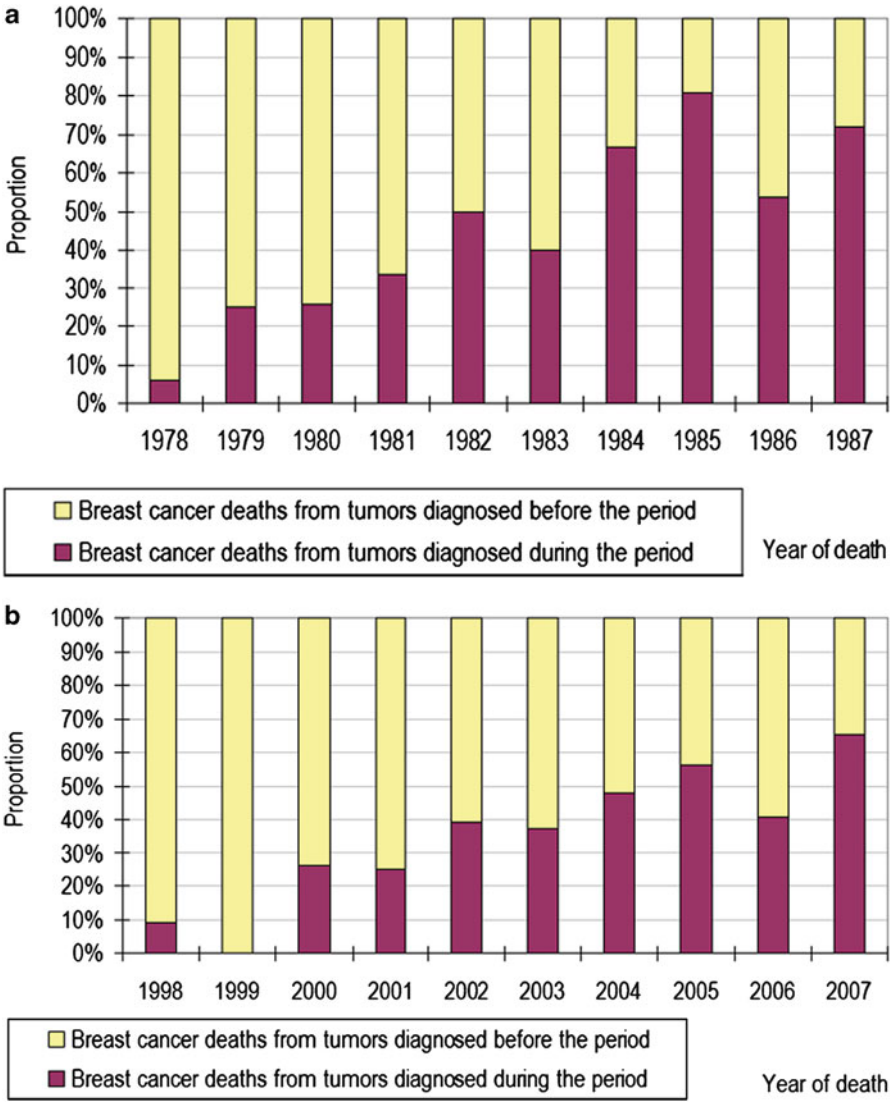

Fig. 2.25 (**a**, **b**) Proportion of breast carcinoma deaths between 1978–1987 and 1998–2007, Dalarna, Sweden, according to the date of diagnosis occurring before (*yellow columns*) or during (*red columns*) these periods. Irrespective of the starting date of mammography screening, a majority of the breast cancer deaths occurring within the decade in question were from breast cancers detected prior to that decade (*yellow columns*)

(b) *Short-term follow-up*. Mammography screening prevents breast cancer death which would otherwise have occurred over the next 2–3 decades if screening had not taken place. Although some benefit may be seen as soon as 4–6 years after screening has started, the majority of the benefit occurs

after the first decade of follow-up [21]. Thus, an evaluation with a follow-up limited to only 10 years will seriously underestimate the absolute mortality benefit of screening. Combination of the above two errors magnifies the underestimation of the true benefit, particularly if the relative benefit of screening has already been erroneously underestimated [66]. The resulting miscalculation can produce a tenfold error as pointed out by Wald et al. and Duffy [41, 67, 68].

It is perhaps illuminating to consider one of the most high-profile publications claiming that the absolute benefit of screening is small, the Nordic Cochrane review [26]. The authors claim that 2,000 women need to be screened for 10 years to prevent one breast cancer death. Although screening 2,000 women five times at 2-year intervals is a small price to pay to save one woman's life, this estimate is inaccurate for the following reasons:

- Their estimate is based on invitation to screening rather than on the screening examination itself. Gøtzsche et al. thus biased their calculations by including many women who did not actually receive any screening at all. Their estimate was calculated from an arbitrary assumption of a 15 % reduction in breast cancer mortality which was never observed, not even by the same authors [66]. They simply assume that 15 % is "reasonable" in the absence of supporting data.
- Their estimate is derived from a follow-up time which is far too short to observe the full benefit of screening, as described above.
- The authors then apply their unrealistic 15 % mortality reduction estimate to a population dominated by 40–49-year-old women, mainly from the UK Age Trial. These women will have a much smaller absolute mortality from breast cancer than the 50–70-year age groups usually targeted for screening. These errors and biases, in combination, cause Gøtzsche and Nielsen to seriously underestimate the absolute benefit of mammography screening.

Several recent studies avoided the above errors by calculating the benefit based on women actually undergoing regular screening and having a sufficiently long-term follow-up [17, 21, 69–71]. The benefit of mammography screening can be expressed in terms of one breast cancer death prevented by regular mammography screening examinations of 300 women aged 40–74 years over a period of 10 years, with follow-up for 20 or more years [70, 71]. These results demonstrate how important long-term follow-up is for determining the full absolute mortality benefit from screening. There is a steady increase of the number of lives saved at ever-longer follow-up [21].

3. *The issue of overdiagnosis*. Overdiagnosis of breast cancer can be defined as cases detected at screening which would never have been detected if screening had not taken place. This topic has attracted considerable attention in recent years. The opponents of screening have estimated rates of overdiagnosis of 15–54 % and some have used these estimates as a reason to advocate cessation of mammography screening programs [28, 72–75]. However, studies with adequate statistical evaluation (such as adjusting for lead time and correcting for

changes in background incidence) of individualized patient data have found rates of overdiagnosis less than 10 % [69, 70, 76–85].

None of the publications claiming high rates of overdiagnosis have had access to individualized patient data, seriously limiting the reliability of the results of such analyses. Jørgensen and Gøtzsche [75] did not even base their estimation on registry data, but resorted to estimating trends by "eyeballing" previously published graphs of breast cancer incidence. Such crude methodology introduces a wide margin of error. Furthermore, these authors failed to adjust for lead time, and assumed that the excess number of breast cancers detected in the early years of screening was entirely due to overdiagnosis, and refuse to acknowledge that screening detects cancers in their early phase that would have surfaced clinically in future years. Additionally, the ongoing, gradually increasing breast cancer incidence is one of the essential factors requiring statistical adjustment in overdiagnosis calculations [70]. However, this adjustment was also inadequately performed, as can be seen from the excess incidence observed in unscreened as well as screened age groups [75]. All of these errors in combination can lead to highly unrealistic estimates, as indeed has happened [70, 84, 85]. Welch and Black, when seeking evidence to support their claim that early detection leads to overdiagnosis, stated: "A persistent excess in the screening group years after the trial is completed constitutes the best evidence that overdiagnosis has occurred" [74]. No such evidence for considerable "overdiagnosis" has been found in studies that have avoided the above-mentioned errors [69, 80].

A sufficiently long follow-up time is also necessary to adequately assess the magnitude of potential overdiagnosis. A randomized controlled trial that was followed for 29 years [82] had equal cumulative breast cancer incidence in the invitation and control arms of the study (RR = 1.00, 95 % CI 0.92–1.08). This complete lack of excess breast cancer incidence at 29 years of follow-up in the population invited to mammography applied to every age group, and was unaffected by the inclusion or the exclusion of in situ cases. Although there was an overall excess of in situ carcinomas in the group of women invited to screening, this excess was balanced by the deficit in invasive cancers, because some of the surgically removed in situ cancers would have progressed to the invasive stage. The substantial excess of node-negative cancers <20 mm in the invited population was balanced by a corresponding excess of advanced cancers in the control population. The significant deficit in advanced cancers in the invited group explains the long-term and highly significant decrease in breast cancer mortality in the trial [82].

The issue of overdiagnosis in the age group 40–49 was recently studied from individualized data of the nationwide service screening program in Sweden, and concluded: "We found no significant overdiagnosis for women aged 40–49 in the Swedish service screening programme with mammography" (RR = 1.01, 95 % CI: 0.94–1.08) [83].

4. *All-cause mortality*. There is a broad consensus that mammography screening accomplishes its main objective, a significant reduction in breast cancer-specific mortality [14]. Some opponents of screening have insisted that, rather than breast cancer mortality, all-cause mortality should define the true measure of the success of screening, even though the screening examination is restricted to the

organ in question (in this case the breast) [86–89]. In fact, all-cause mortality is an inappropriate endpoint, since it depends on the unrealistic expectation that "deaths from road-traffic accidents or hip fractures were in some way indicative of the effect of breast-cancer screening" [90]. Since screening for breast cancer is unlikely to affect mortality in women who do not develop the disease, the cause of death investigation should be restricted to those women diagnosed with breast cancer [91].

Rather than all-cause mortality, mortality analysis should therefore be focused upon the following: (1) evaluation of the impact of *invitation to* and *attendance at* screening on breast cancer death, which has been discussed in detail above and (2) investigation of death from other causes in *women with breast cancer*, in order to ascertain (a) whether there was any misclassification of cause of death in breast cancer cases and (b) whether or not treatment of breast cancers detected at screening might increase the risk of death from other causes (e.g., cardiovascular death from radiotherapy, death from chemotoxicity).

We have already established that a considerable body of evidence accumulated over the past three decades demonstrated that invitation to and exposure to screening substantially reduces breast cancer mortality. With respect to misclassification of death, or collateral death associated with therapy, no significant evidence of an increased rate of death from other causes was found in women invited to screening in the Swedish Two-County Trial, and thus there was no evidence of bias in cause of death classification [91]. The first overview of all Swedish randomized mammography trials agreed, concluding: "The cause of death pattern in the invited group was, except for breast cancer, very similar to that in the control group, showing that the groups were comparable" [92].

5. *Investigation of all causes of death in women diagnosed with breast cancer*. There was a significant 19 % reduction in death from all causes *in breast cancer cases* in the invited group (RR 0.81, CI 0.72–0.90, $p < 0.001$) [91]. Indeed, a difference in disease-specific mortality and all-cause mortality associated with screening is expected since death from breast cancer is a leading cause of premature death in women among all causes of death.

Key Points

- Invitation to mammography screening substantially reduces mortality from the disease (intention-to-treat approach).
- The number of breast cancer deaths prevented is greater for women who attend screening at regular intervals compared to those who do not attend.
- No significant evidence of an increased rate of death from other causes was found *in women with breast cancer* in the group invited to screening; thus there was no evidence of bias in the cause of death classification.
- There was a significant reduction in death from all causes *in the breast cancer cases* in women invited to screening.

Is There Really a Controversy About Breast Cancer Screening?

Evidence-based medicine requires careful collection of reliable individual patient data and adherence to well-established evaluation methods. The eight population-based randomized mammography screening trials, carried out in several countries with different health care systems, provide an excellent example of careful data collection and competent evaluation. In stark contrast, the criticism emerging from the Nordic Cochrane Center (Director: Peter C. Gøtzsche) lacks access to individual patient data and fails to adhere to well-established evaluation methods. These elementary limitations were immediately apparent to competent investigators, some of whom published rather harsh criticism.

1. Nicholas Day, Professor of Public Health, University of Cambridge, UK, wrote the following: "the Lancet paper by Gøtzsche and Olsen … is not simply controversial, it contains a number of serious statistical mistakes which invalidate its conclusions, and uses a selective approach to the studies and data it assesses. It is a worthless piece of work which if it had been produced by one of our masters students, would have been sent back with demands for a complete rewrite" [93].
2. David Freedman, Professor of Statistics, University of California at Berkeley concluded after an extensive overview of all the trials: "The basis for the Gøtzsche–Olsen critique turns out to be simple. Studies that found a benefit from mammography were discounted as being of poor quality; remaining negative studies were combined by meta-analysis. The critique therefore rests on judgments of study quality, but these judgments are based on misreading of the data and the literature." "There is good evidence from clinical trials that mammographic screening reduces the death rate from breast cancer. The critique by Gøtzsche and Olsen has little merit and has generated much confusion" [94].
3. Nicholas Wald, Professor of Epidemiology and Institute Director, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, wrote the following about the first paper on breast cancer screening emerging from the Nordic Cochrane Centre: "Gøtzsche and Olsen's paper lacks scientific merit." "The Lancet should not have published this paper" [95].
4. The trialists of the Two-County Swedish study, having been subjected to a considerable amount of unjustified criticism, were obliged to respond frequently in peer-reviewed journals. The Swedish Cancer Society initiated comprehensive overviews of this influential trial [13, 96], confirming the accuracy and transparency of the published data and disproving the unjustified accusations of the opponents of screening. The following citation summarizes the viewpoint of the trialists concerning the accusations of Olsen and Gøtzsche (OG) and colleagues: "Because of serious flaws such as those noted above, we conclude that OG's review provides no grounds for the medical community to alter the conclusion that has been based on millions of person-years of experimental evidence, i.e., that breast cancer screening leads to a substantial reduction in mortality from the

disease. Health care professionals should have confidence that more meticulous and credible reviews have been carried out by numerous independent expert panels in Europe and the United States and consistently reached the same conclusion: early breast cancer detection and treatment results in decreased breast cancer mortality. Clinicians should have confidence in the current recommendations issued by leading organizations, and they should impart that confidence to their patients. We should remain vigilant to avoid any setbacks to the progress we've made in encouraging women to get regular mammograms. Women who have developed confidence in breast cancer screening should not be intimidated, and overworked staff who go to great lengths to make screening work should not have their morale damaged by poor quality reviews such as that of OG. It would be wrong to use this error-prone analysis to discourage an early detection procedure that has been shown in trial after trial to reduce breast cancer mortality" [97].

5. Daniel Kopans, Professor of Radiology, Harvard Medical School, summarized his view with the following title: "*The most recent breast cancer screening controversy about whether mammographic screening benefits women at any age*: *nonsense and nonscience*" [98].
6. A group of 41 screening experts, exasperated by the steady flow of nonscientific criticism, published a letter in The Lancet [99]. "Although the wider scientific community has long embraced the benefits of population-based breast screening, there seems to be an active anti-screening campaign orchestrated in part by members of the Nordic Cochrane Centre. These contrary views are based on erroneous interpretation of data from cancer registries and peer reviewed articles. Their specific aim seems to be to support a pre-existing opposition to all forms of screening" [100]. "We consider the interpretation by Jørgensen, Keen, and Gøtzsche [101] of the balance of benefits and harms to be scientifically unsound. Women would be better served by focusing efforts on how best, and not whether, to provide breast screening" [99]. Gøtzsche and Jørgensen responded with the following suggestion: "stopping the mammography screening programme would reduce the breast cancer incidence in the screened age group" [102]. In response three of the Lancet letter's authors stated: "We regard the proposal to reduce the apparent incidence of breast cancer by failure of detection as unethical" [103].
7. Peter Gøtzsche has recently published a book summarizing his personal view of breast cancer screening, entitled "*Mammography Screening*. *Truth*, *Lies and Controversy*," in which he declares: "The most effective way to decrease women's risk of becoming a breast cancer patient is to avoid attending screening" [104]. Jack Cuzick, Professor of Epidemiology at the Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, in a review of this book made the following comment: "Gøtzsche's desire to abandon screening altogether … has detracted from efforts to improve breast cancer screening, so that it can make its maximal contribution to controlling this devastating disease" [105].

In summary, the term "controversy" hardly seems to apply to mammography screening. The scientific establishment and health care professionals who care for breast cancer patients support the detection and treatment of breast cancer in its early phases. What ought to be regarded as controversial is the regular opportunity provided by scientific journals and mass media for a group of pseudo-skeptics to repeat over and over again the same flawed science and logic to question the value of screening.

The Alleged Harm of Attending Versus the Actual Harm of Not Attending Mammography Screening

The balance between the benefits and risks of mammography screening has been under continuous evaluation for the past four decades, ever since the publication of the first successful randomized controlled trial in 1971 [11]. During these decades the evidence has been steadily accumulating for the multiple benefits of attending mammography screening. These benefits include considerably and significantly decreased breast cancer mortality, less need for radical treatment (mastectomy, axillary dissection, systemic treatment), and assuring most women that, at a given point in time, they have no detectable breast cancer [106]. Additionally, the vast majority of those whose impalpable breast cancer is detected will have a normal life expectancy without the disease having a major impact on their life quality. Despite this accumulating evidence there has been much recent discussion about the alleged harms of mammography screening [73, 107–117]. These include radiation exposure, discomfort from breast compression, anxiety from screening or from assessment procedures and their outcome, overdiagnosis, and the detrimental effects of treatment. The magnitude of these potential harms has been exaggerated in many reports, where the benefits of screening are either discounted or seriously underestimated [72–75, 86, 104, 114, 116].

Feig and Duffy have carefully reviewed these arguments and have concluded: "Adverse consequences of screening such as callbacks for additional imaging, false positive biopsies, potential over-diagnosis, and any hypothetical radiation risk do not outweigh the benefits from early detection" [106]. Although anxiety from screening, callback for further assessment of the finding at screening, and waiting for the results are important issues, they do not appear to have a negative effect upon subsequent attendance of women who are not diagnosed with breast cancer [107]. The subject of "overdiagnosis," which is currently touted as the most important "harm" of screening, has been discussed in detail in the previous section. The influence of the introduction of mammography screening upon breast surgery has been extensively studied, particularly upon mastectomy rates. There is a claim that screening is associated with an increase in mastectomy rates [117]. Objective studies have repeatedly demonstrated a decline in mastectomy rates corresponding to the decline in advanced cancer rate as a direct consequence of screening [118, 119]. "Women with screen-detected breast cancer in the UK have half the mastectomy rate of women with symptomatic cancers i.e., 27 versus 53 %" [99].

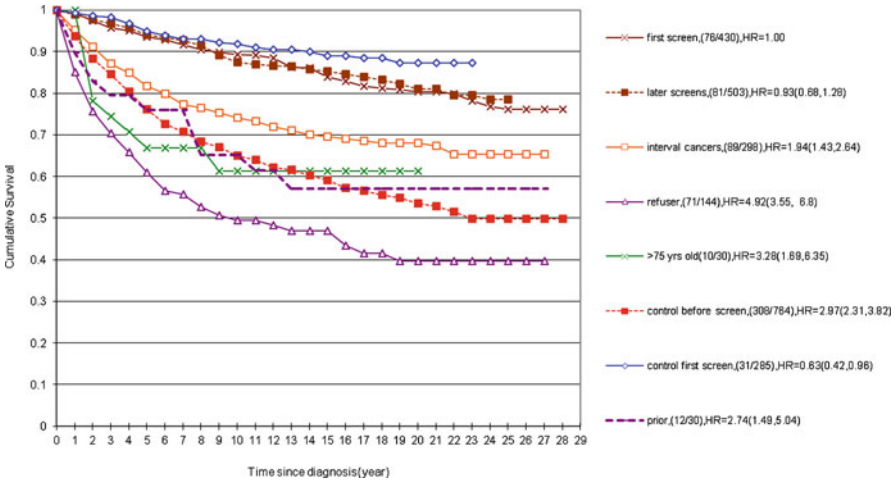

Fig. 2.26 28-year disease-specific survival of women according to the mode of detection in the Swedish Two-County Trial

The harm of *not* attending mammography screening has seldom been discussed in the medical literature. A recent review of prospectively collected data provides insight into the consequences of delaying the diagnosis of breast cancer until it becomes symptomatic. This study on 1977 women aged 40–49 diagnosed with breast cancer compared the tumor characteristics, treatment regimens used, and long-term outcome of women with symptomatic versus women with mammographically detected breast cancer [2]. Women whose cancers were self-detected or physician-detected had significantly more mastectomies (47 vs. 25 %), larger average tumor size (3.02 vs. 1.63 cm), significantly worse disease-specific survival (log-rank test = 22.04 $p < .001$), and overall survival (log-rank test = 20.67 $p < .001$) than did women whose asymptomatic cancers were detected mammographically. In the randomized controlled trials, the women in the control groups did not have access to mammography screening, presented with palpable tumors, and had significantly higher breast cancer mortality. Delay in diagnosis will occur in some women attending mammography whose cancer is not detected at the time of screening, resulting in interval cancers. Women who chose not to attend mammography screening had even worse outcomes (see Fig. 2.26) [19].

In the light of these serious harms associated with detection of breast cancer at a later stage it is astonishing and disconcerting that opponents of mammography now are calling for mammography screening to be abolished [72, 104, 120] and recommend that women not perform breast self-examination. The Director of the Nordic Cochrane Center, Peter Gøtzsche, M.D., stated the following in a BBC Radio 4 interview: "What women should do is, as they have always done, if they find something unusual, go and see a doctor, but don't examine yourself regularly. It has no effect … there is general agreement now that women should not be advised to examine themselves every month. Our advice is that you should not examine your breasts regularly" [121].

Key Points

Of all the harms associated with breast cancer screening, *the greatest harm comes from nonattendance*. Earlier detection of breast cancer through mammography screening results in:

- Significant decrease in advanced breast cancers.
- Significantly better disease-specific survival, relapse-free survival, and overall survival.
- Fewer breast cancer deaths.
- Fewer mastectomies and more lumpectomies (higher frequency of breast-conserving surgery).
- Fewer patients needing advanced forms or more severe forms of adjuvant therapy.

Our efforts should be directed at further improving the efficacy of screening.

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