# THE SWEDISH TWO-COUNTY TRIAL TWENTY YEARS LATER

## Updated Mortality Results and New Insights from Long-Term Follow-up

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The Swedish Two-County Trial is a randomized controlled trial of invitation to breast cancer screening. It was initiated in late 1977, with 133,000 women randomized between 1977 and 1979 to regular invitation to screening or to no invitation. The first mortality results were published in 1985, showing a significant 30% reduction in breast cancer mortality associated with invitation to screening.[10] On establishment of the benefit in mortality, the control group was invited to screening. On further regular follow-up, the mortality benefit has consistently remained around 30%.[6]

At around 11 years' follow-up, an update of results and a detailed investigation of the screening practice and its impact on the tumor population was published in this journal.[9] This research established the continued mortality benefit and showed that screening achieved this benefit by diagnosing high-risk tumors at an earlier stage and particularly while they are small. We now have follow-up to the end of 1998, so at approximately the twentieth anniversary of the trial it is appropriate to update the results further and establish what can be learned from long-term follow-up, notably of the tumor population diagnosed in this trial.

## DESIGN AND METHODS

The design of the Two-County study has been described repeatedly in previous publications.[6, 8–10] The trial was a cluster-randomized controlled trial taking place in two counties in Sweden, Kopparberg (W-county), now called Dalarna, and Östergötland (E-county). The trial randomized 77,080 women aged 40 to 74 years to invitation to screening (active study population [ASP]), and 55,985 to no invitation (passive study population [PSP]). Screening began in the ASP in 1977. On establishment of a significant reduction in mortality from breast cancer in the ASP in 1985, the PSP was invited to screening, on average 7 to 8 years after randomization.

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Thereafter, follow-up for subsequent mortality applied to the cancers diagnosed in both arms up to and including those diagnosed at the first screen of the PSP and at a contemporaneous final screen of the ASP.

Because of the considerable fears about radiation associated with mammography in the mid 1970s,[1] screening was by single-view screen-film mammography alone, and had a longer interscreening interval than we recommend today. In the ASP, women aged 40 to 49 at randomization were invited on average every 2 years, and women aged 50 to 74 were invited on average every 33 months. After the second round of screening, invitation of women aged 70 to 74 was discontinued because of poor response rates, but this age group was retained for intention to treat analysis of the trial mortality results. The tumor population followed-up for subsequent death from breast cancer pertains to the screening phase of the trial (on average 1978 to 1985) and includes

1. All tumors diagnosed clinically in the PSP between randomization and the first screen of the PSP;
2. all tumors diagnosed by screening at the first screen of the PSP;
3. all tumors diagnosed in the ASP aged 40 to 49 (by screening, clinically in the interval between screens, clinically in nonattendees for screening) up to and including the fifth round of screening;
4. all tumors diagnosed in the ASP aged 50 to 69 (by screening, clinically in the interval between screens, clinically in nonattendees for screening) up to and including the third round of screening;
5. all tumors diagnosed in the ASP aged 70 to 74 (by screening, clinically in the interval between screens, clinically in nonattendees for screening) up to and including the second round of screening and beyond the second round up to the time of first screen of the PSP.

A total of 2468 women were diagnosed with cancer during the trial. Tumor size, node status, histologic type, and malignancy grade were recorded. A death was classified as being from breast cancer only after a full review of the clinical or pathologic records. Details of criteria are given elsewhere.[8] In this article we present results from follow-up to the end of December 1998. We also investigate the long-term effects of screening on prognosis with particular attention to histologic type and examine the implications of mammographic findings for diagnosis, prognosis, and therapy.

The primary outcome of the trial is mortality from breast cancer. This is defined as the death rate from breast cancer per person-year in the trial (not per cancer case). Mortality was compared between the study and control arms by Poisson regression.[2] When studying prognosis of tumors diagnosed, the appropriate outcome is survival. Survival is the complement of fatality, the proportion of tumors, which prove fatal. Effects on survival were estimated using proportional hazards regression.[4]

Three indirect measures of a screening program's quality and ability to detect high-risk tumors early are (1) the potential lead time, as measured by the mean sojourn time (MST); (2) the sensitivity; and (3) the prevalent screen predictive index (PSPI). The sojourn time is defined as the period during which a tumor

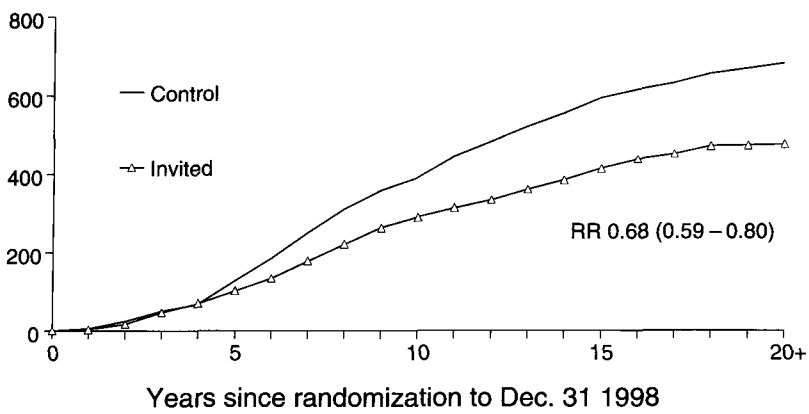


**Figure 1.** Cumulative breast cancer mortality over 20 years in the ASP and PSP.

**Table 1.** BREAST CANCERS, BREAST CANCER DEATHS, AND PERSON-YEARS BY COUNTY AND STUDY GROUP

| Study Group | W-county | | | E-county | | |
|---|---|---|---|---|---|---|
| | *Cancers* | *Deaths* | *Person-years* | *Cancers* | *Deaths* | *Person-years* |
| ASP | 694 | 152 | 672,482 | 732 | 167 | 660,242 |
| PSP | 359 | 121 | 326,091 | 683 | 213 | 643,696 |

is asymptomatic but detectable by screening. The sensitivity is the probability that a tumor that is in the asymptomatic screen-detectable phase will be diagnosed if the screening tool is applied. The PSPI (referred to by Chen et al[3] as the positive predictive value) is the proportion of tumors diagnosed at a prevalence screen that would have arisen clinically if screening had not taken place. The PSPI can be thought of as the complement of overdiagnosis, which if it occurs at all, is thought to be confined to the prevalence screen.[7] The restriction of overdiagnosis to the prevalence screen is indicated by two observations: (1) in principle a tumor that never becomes symptomatic but remains in the preclinical screen-detectable phase indefinitely only needs a single screen to diagnose it, and (2) in the Two-County study a single screen of the PSP equalized incidence in the two arms of the trial. In the 11-year update, estimates of these quantities were calculated by approximate methods. In this article we present estimates of the same quantities derived using detailed estimation of disease progression parameters by applying Markov chain models to the data.[3, 5] These have the advantage, for example, of allowing estimation of sensitivity without arbitrary assumptions of tumors being based on time since last screen.

## RESULTS: MORTALITY AND SCREENING PERFORMANCE

Figure 1 shows the breast cancer mortality in the ASP and PSP. At 20 years follow-up, there is a significant 32% reduction in mortality associated with invitation to screening (relative risk [RR] = 0.68, 95% confidence interval [CI] 0.59 to 0.80, $P<0.001$). The corresponding numbers of cancers, deaths, and person-years are given in Table 1. Figure 2 shows the cumulative mortality further stratified by age group and county. The largest effect on mortality can be seen at ages 50 to 69. Results for women aged 40 to 49 are inconsistent between the counties, with a substantial reduction in mortality observed in W-county but not in E-county, largely because of high fatality rates of cancers diagnosed in nonattendees for screening in E-county.[6]

Table 2 shows the cancers diagnosed by age and detection mode. The total number of tumors is larger than in the 11-year report by a figure of nine cancers (0.4%) whose registration was delayed in the national cancer registration system. Table 3 shows sensitivity, MST, and PSPI by age group. Sensitivity and PSPI are good overall, suggesting that few cancers were missed at screening and that there is not a serious problem of excessive

**Table 2.** CANCERS DIAGNOSED IN THE TWO-COUNTY TRIAL BY AGE AND DETECTION MODE

| Detection Mode | No. (%) in Detection Mode for Ages | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 40–49 | | 50–59 | | 60–69 | | 70–74 | |
| ASP, prescreening* | 6 | (1) | 5 | (1) | 13 | (1) | 4 | (1) |
| ASP, first screen | 39 | (9) | 103 | (15) | 184 | (20) | 101 | (25) |
| ASP, later screen | 110 | (26) | 156 | (22) | 183 | (19) | 52 | (13) |
| ASP, interval | 91 | (22) | 90 | (13) | 97 | (10) | 22 | (5) |
| ASP, nonattendee | 10 | (2) | 28 | (4) | 52 | (6) | 50 | (12) |
| ASP, postscreening† | 0 | (0) | 0 | (0) | 0 | (0) | 30 | (7) |
| PSP, before screen | 115 | (28) | 221 | (32) | 277 | (29) | 142 | (35) |
| PSP, first screen | 47 | (12) | 94 | (13) | 140 | (15) | 6 | (2) |
| Total | 418 | (100) | 697 | (100) | 946 | (100) | 407 | (100) |

*Tumors diagnosed after randomization but before first screening date.
†Tumors diagnosed after routine screening ceased in this age group.

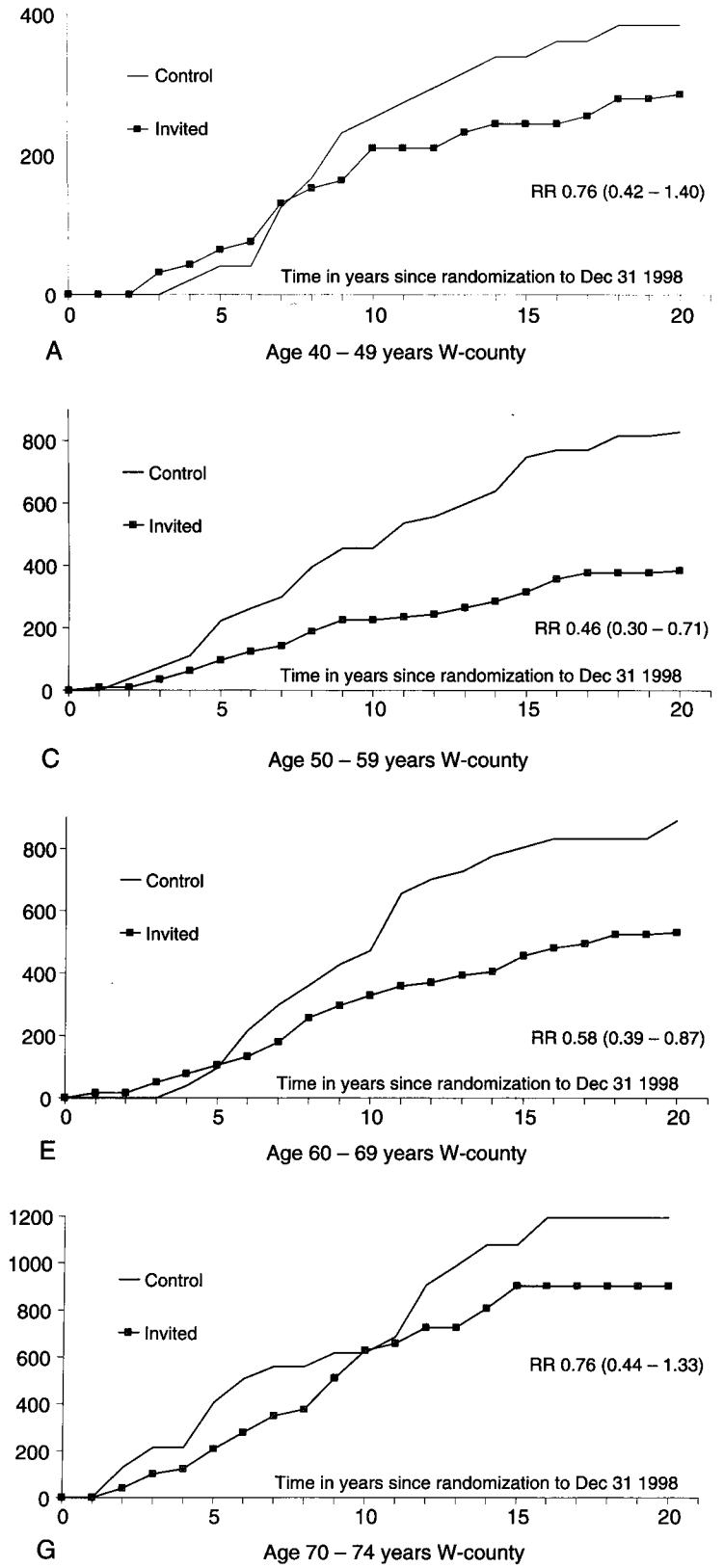


**Figure 2.** Cumulative breast cancer mortality over 20 years in the ASP and PSP by age and county.

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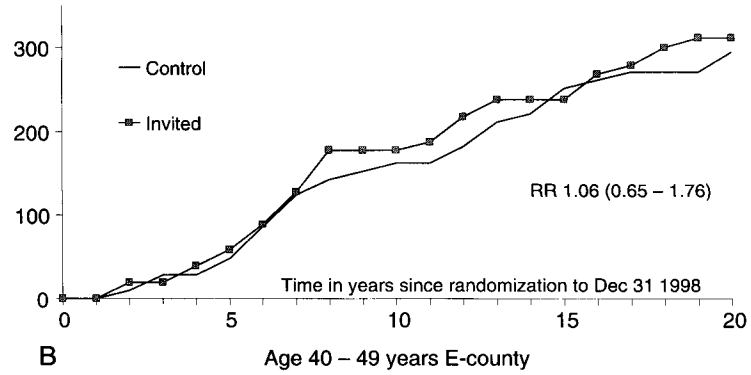


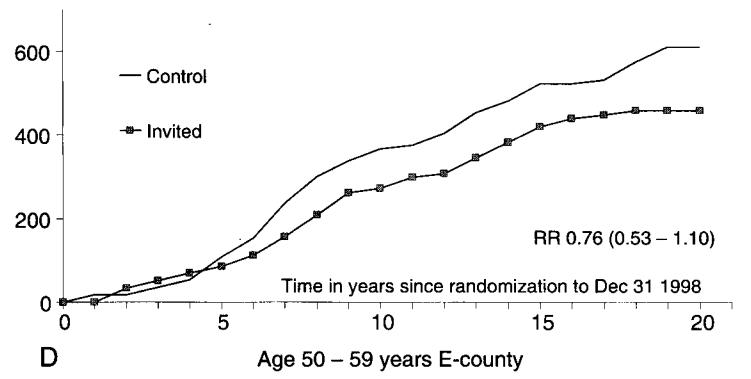


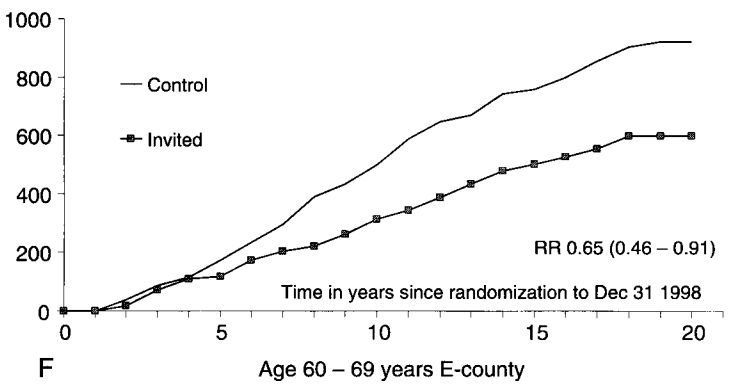


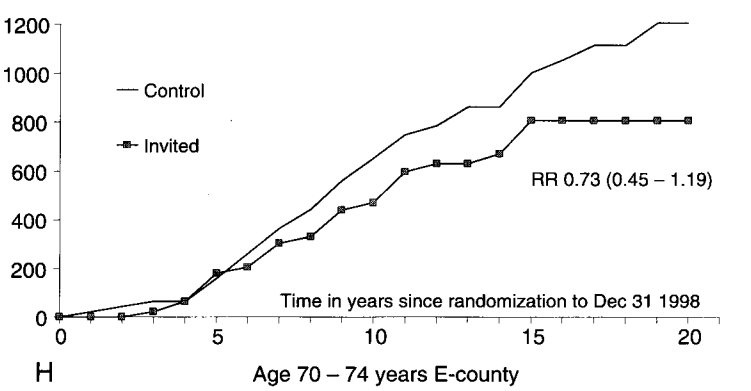


**Figure 2** *(Continued). See legend on opposite page.*

**Table 3.** SENSITIVITY, MST IN YEARS, AND PSPI BY AGE

| Age | MST (95% CI) | % Sensitivity | % PSPI |
|---|---|---|---|
| 40–49 | 2.4 (2.1–2.9) | 83 | 85 |
| 50–59 | 3.7 (3.4–4.2) | 100 | 100 |
| 60–69 | 4.2 (4–4.6) | 100 | 100 |
| 70–79 | 4 (3.6–4.4) | 91 | 87 |

diagnosis. These indirect measures are most favorable in ages 50 to 69.

## RESULTS: SCREENING, HISTOLOGY, AND PROGNOSIS

Figures 3 to 10 show survival by histologic type, size, and node status. Figure 11 shows survival by size in those of any histologic type that did not receive axillary dissection. From this, one can categorize tumors for each histologic type as having good, intermediate, and poor prognosis. These are summarized in Table 4. Figure 12 shows the survival over time by prognostic group for all histologic types combined. Clearly, the goal of screening is to shift the balance of the distribution from the poor to the intermediate or good prognosis groups, and from the intermediate to the good prognosis group. A screening program aims to diagnose as many cancers as possible while they are in the good prognosis category. Figure 13 shows the distribution of prognostic category by study group. In the ASP, 41% of cancers were in the good prognostic group, with an 18-year survival of 91%. In the PSP, only 26% were in the good prognostic group.

Figure 14 shows the distribution of prognostic group by mode of diagnosis (screening or clinical). This shows a much sharper difference and emphasizes the necessity for a screening program to have good sensitivity to maximize the number of tumors diagnosed by screening.

The distribution in the ASP in Figure 13 represents the prognostic profile of a population invited to screening, including those who decline the invitation. The profile for a screened group is given by the ASP excluding the nonattendees, and is shown in Figure 15. The prognostic profile is better in the screened group than in the ASP as a whole (all screen-detected cancers, interval cancers, and tumors in nonattendees combined). Attendance rates of 85% to 90% were observed in the Two-County study.[6] A larger nonattendance rate is expected to produce a greater dilution of the screening effect. This illustrates the importance of achieving good attendance rates in a screening program.

It is also worth considering how one might expect a more recent screening program, with more frequent screening and two-view mammography, to perform. Clearly, one expects it to have a greater effect on the prognostic distribution, but it is worth considering which tumors are more likely to benefit. Table 5 shows the distribution of prognostic group by histologic type and study group. For invasive ductal carcinoma, there is a shift both from poor to intermediate and from intermediate to good prognostic groups. Nevertheless, for ductal carcinoma of grade 2 and 3 there is still a considerable percentage of poor prognostic tumors in the ASP. For tubular carcinoma there are no tumors, and for mucinous carcinoma very few, in the poor

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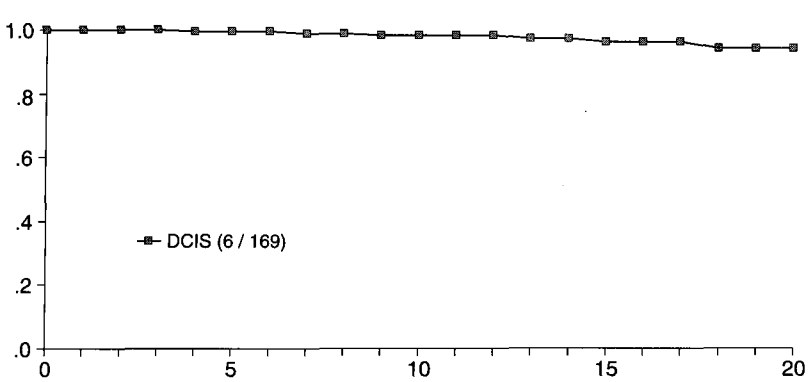
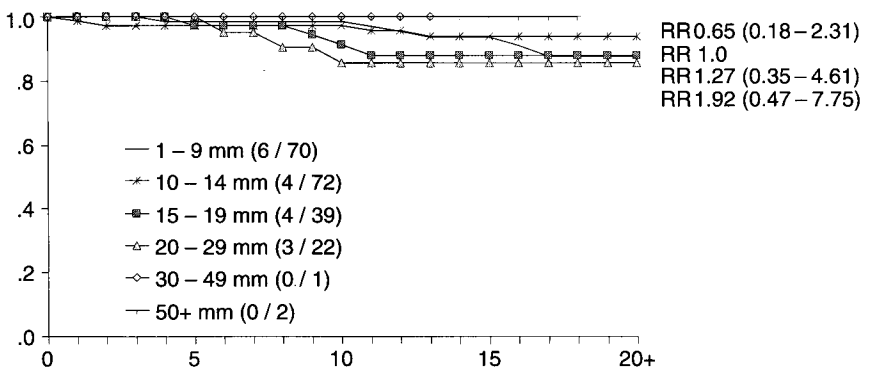



**Figure 3.** Long-term survival of ductal carcinoma in situ cases.




A Years since operation to Dec. 31 1998. **W-E Trial, Sweden**

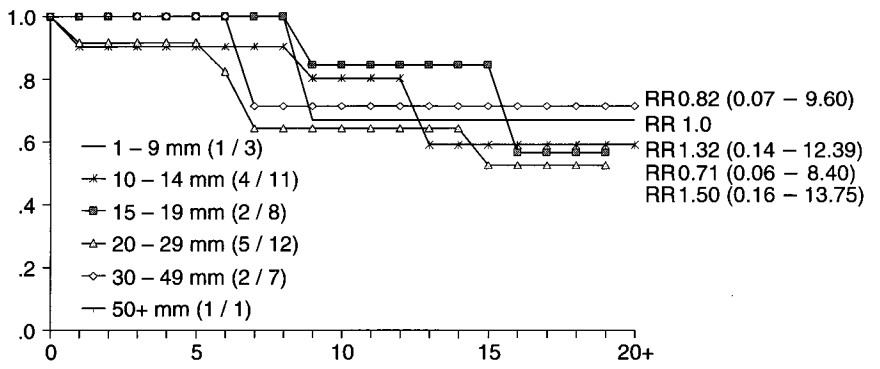



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**Figure 4.** Long-term survival by size of invasive ductal carcinoma of grade 1. *A,* Node-negative cases. *B,* Node-positive cases.

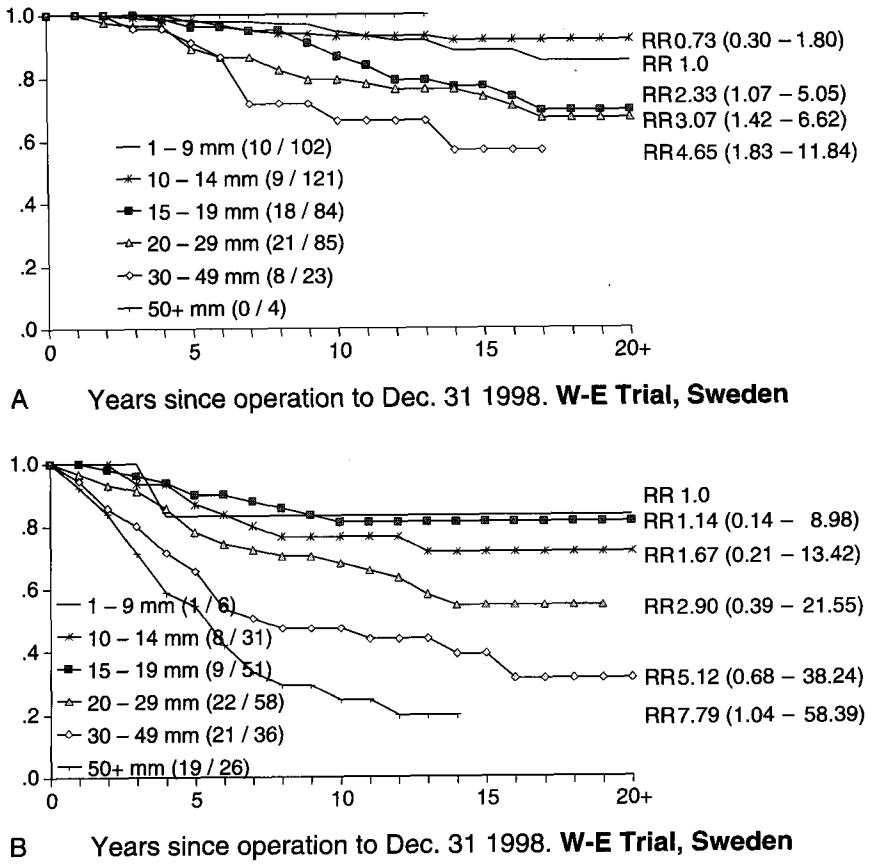
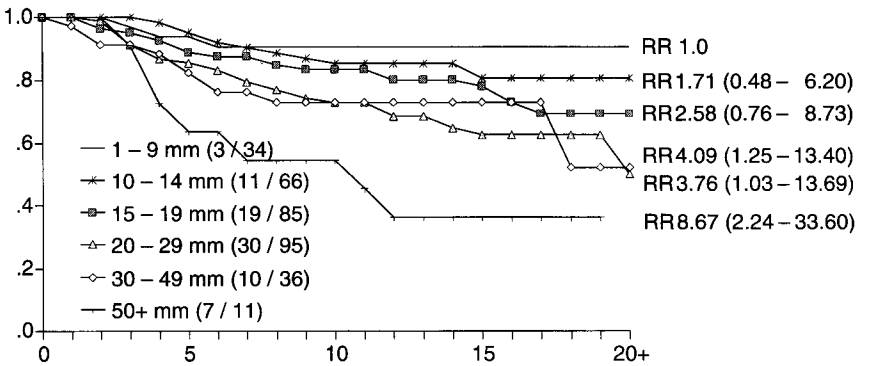
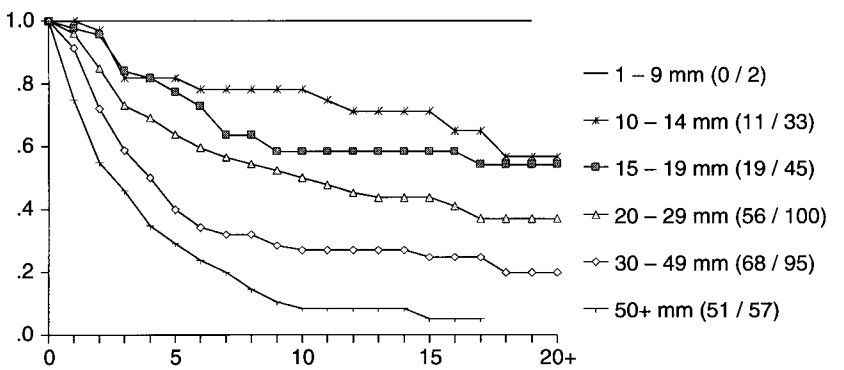



**Figure 5.** Long-term survival by size of invasive ductal carcinoma of grade 2. *A*, Node-negative cases. *B*, Node-positive cases.




A Years since operation to Dec. 31 1998. **W-E Trial, Sweden**




B Years since operation to Dec. 31 1998. **W-E Trial, Sweden**

**Figure 6.** Long-term survival by size of invasive ductal carcinoma of grade 3. *A,* Node-negative cases. *B,* Node-positive cases.

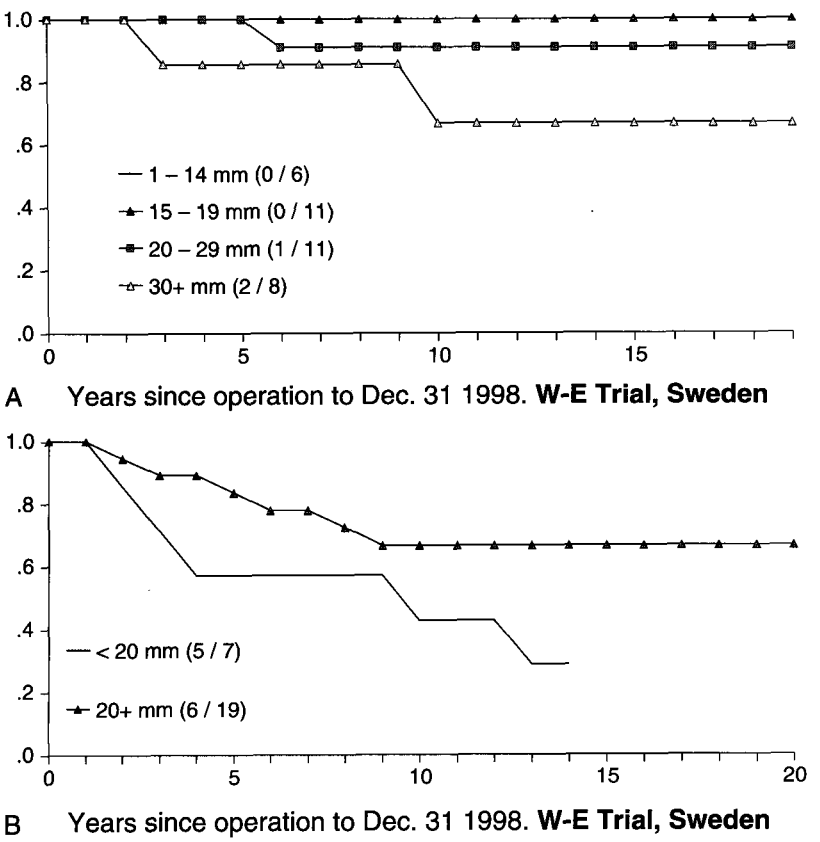
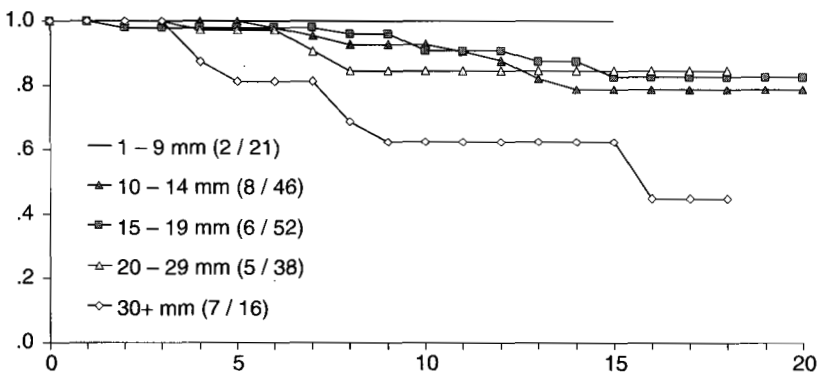



**Figure 7.** Long-term survival by size of invasive medullary carcinoma. *A*, Node-negative cases. *B*, Node-positive cases.



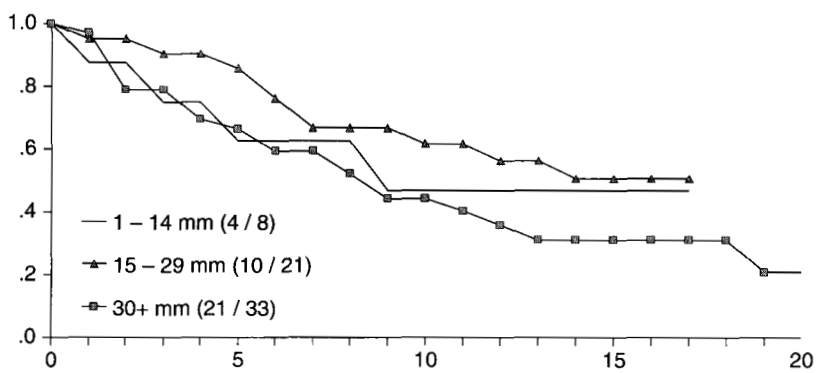
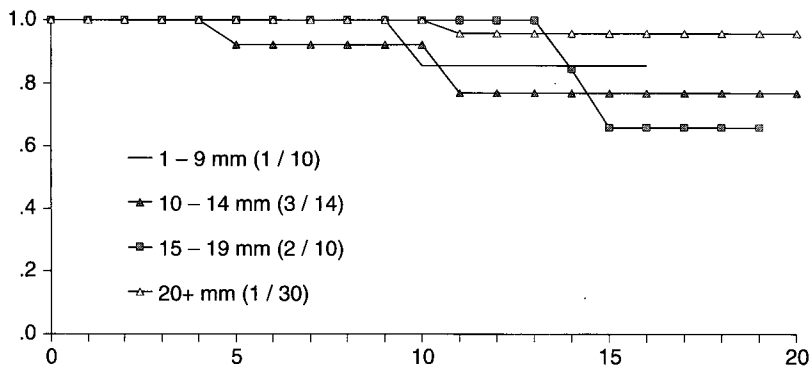
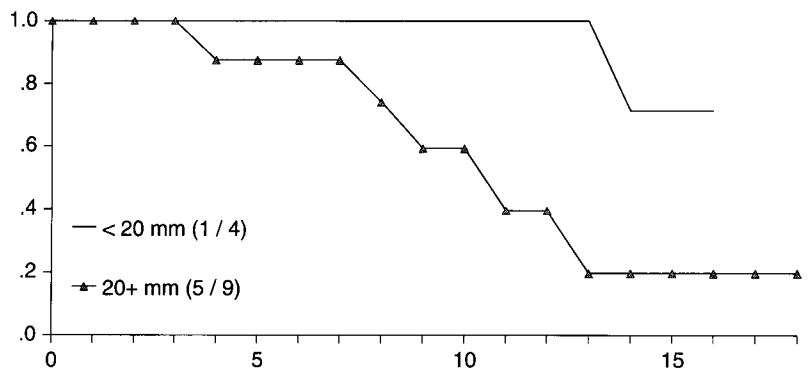




**Figure 8.** Long-term survival by size of invasive lobular carcinoma. *A,* Node-negative cases. *B,* Node-positive cases.

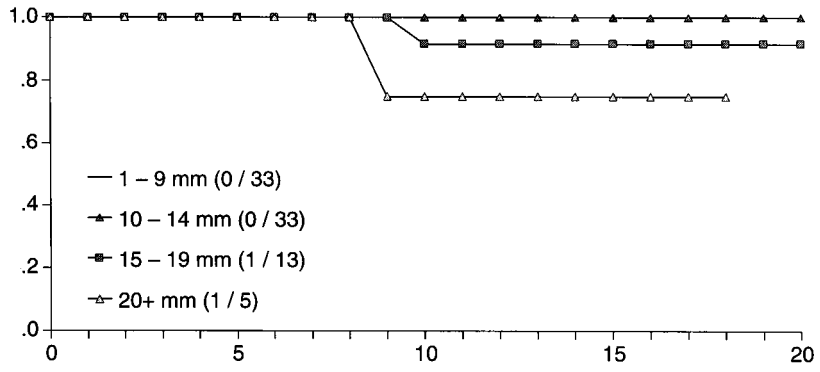



A Years since operation to Dec. 31 1998. **W-E Trial, Sweden**




B Years since operation to Dec. 31 1998. **W-E Trial, Sweden**

**Figure 9.** Long-term survival by size of invasive mucinous carcinoma. *A,* Node-negative cases. *B,* Node-positive cases.

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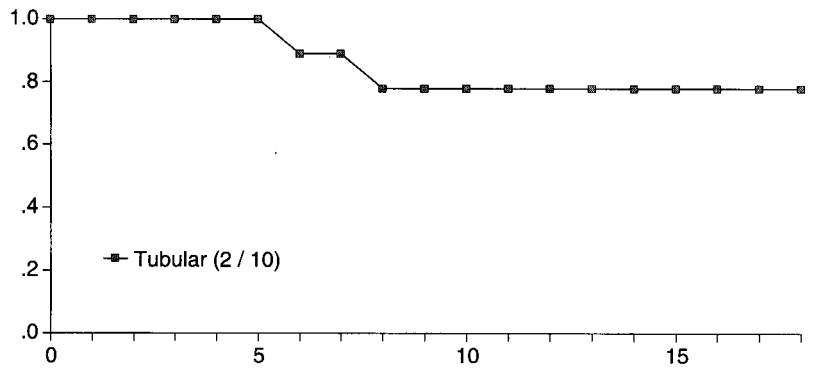
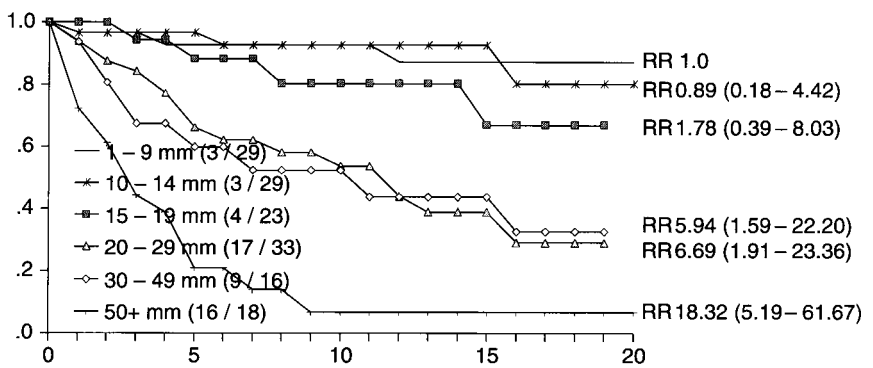



B Years since operation to Dec. 31 1998. **W-E Trial, Sweden**

**Figure 10.** Long-term survival by size of invasive tubular carcinoma. *A*, Node-negative cases. *B*, Node-positive cases.




Years since operation to Dec. 31 1998. **W-E Trial, Sweden**

**Figure 11.** Long-term survival by size of invasive carcinoma with node status unknown, all histologic types.

**Table 4.** DEFINITION OF PROGNOSTIC CATEGORY BY HISTOLOGIC TYPE

| Histologic Type | Good | Intermediate | Poor |
|---|---|---|---|
| DCIS | All | None | None |
| Ductal NOS grade 1 | N−, <20 mm | N−, 20+ mm *or* N+, <15 mm | N+, 15+ mm |
| Ductal NOS grade 2 | N−, <15 mm | N−, 15–29 mm | N−, 30+ mm *or* N+ |
| Ductal NOS grade 3 | N−, <10 mm | N−, 10+ mm *or* N+, <15 mm | N+, 15+ mm |
| Medullary | N−, <20 mm | N−, 20+ mm | N+ |
| Lobular | N−, <10 mm | N−, 10–29 mm | N−, 30+ mm *or* N+ |
| Mucinous | N−, <10 mm | N−, 10+ mm *or* N+, <20 mm | N+, 20+ mm |
| Tubular | N−, <20 mm | N−, 20+ mm *or* N+ | None |
| All types, nodes NK | <15 mm | 15–19 mm | 20+ mm |

DCIS = ductal carcinoma in situ; NOS = not otherwise specified; NK = not known.

prognostic category. For other histologic types, notably medullary carcinoma, the main difference between ASP and PSP is a shift from intermediate to good prognostic categories. The room for further improvement with more intensive or more frequent screening lies in detecting ductal carcinoma of grades 2 and 3, lobular, and medullary carcinoma before progression to the poor prognostic category.

One can see a sharper distinction between palpable and nonpalpable tumors (i.e., clinical and screen-detected). Figure 16 shows the distributions by histologic type and prognostic group for screen-detected and clinical cancers. The largest absolute reductions in poor prognostic cases in the screen-detected tumors compared with the clinically detected are observed for ductal carcinoma of grades 2 and 3, medullary, and lobular carcinoma. If with more intensive screening a larger number of such tumors are screen-detected, a substantial further benefit accrues in terms of prognosis. This is particularly important in women aged under 50 years, who have higher rates of medullary carcinoma and ductal carcinoma of malignancy grade 3.

## RESULTS: MAMMOGRAPHIC FINDINGS AND PROGNOSIS OF SMALL TUMORS

The criteria shown in Table 4 illustrate the importance of tumor size for survival. Figure 17 shows survival by tumor size in the invasive tumors in our population. The effect of size on survival is very strong, as one expects with increasingly poor survival with increasing size. From Figures 4 to 6 it can be seen that this dependence of survival on size is particularly strong for ductal carcinoma. Despite the high survival rates among small tumors, there are still some tumors of size 1 to 9 mm that result in breast cancer death. It can be seen that even malignancy grade does not distinguish the breast cancer cases that result in death among tumors of this size (Fig. 18).

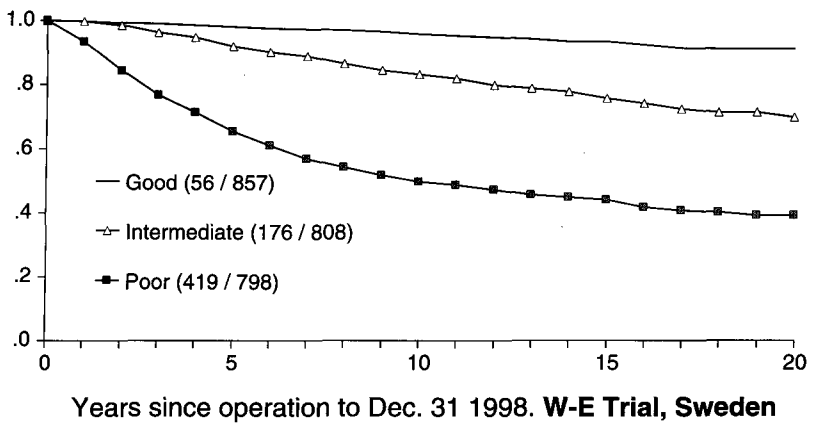



**Figure 12.** Long-term survival by prognostic category for all histologic types.

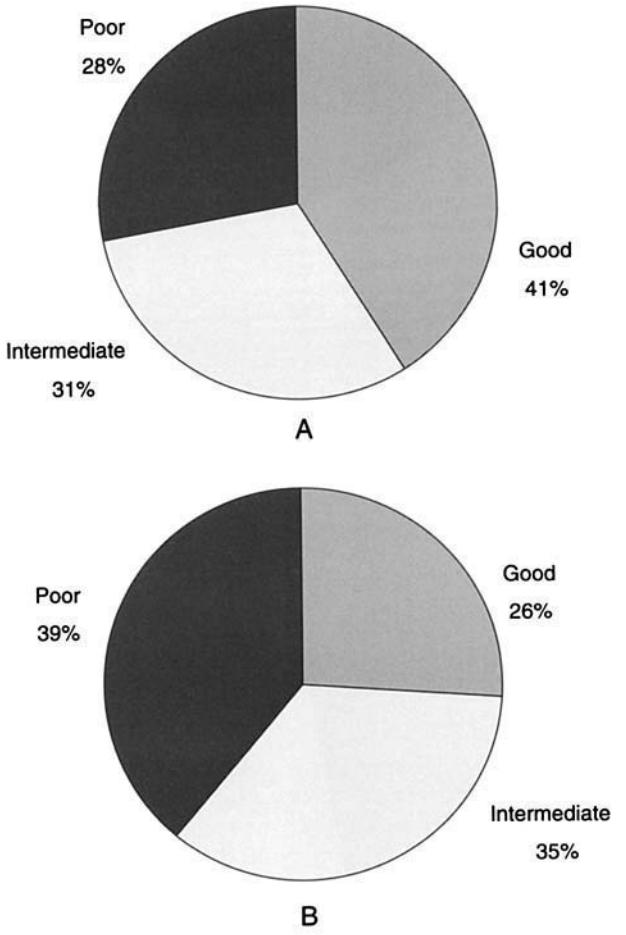



**Figure 13.** Distribution of prognostic category in the ASP (*A*) and PSP (*B*).

We now consider whether mammographic appearance can distinguish these high-risk cases.

There were 140 invasive tumors of size 1 to 9 mm in W-county. Mammograms of 138 of these patients were available and were reviewed. Figure 19 shows survival of these by mammographic findings. Of the 138 tumors, 19 showed casting-type calcifications with or without an associated tumor mass, and of these 8 resulted in breast cancer death. In the remaining 119 tumors without casting-type calcifications there were only 3 deaths. Table 6 shows the results of proportional hazards regression of survival on mammographic findings. Within tumors of size 1 to 9 mm, the relative risk of breast cancer death where casting-type calcifications are present is 42.61 compared with a lesion with calcifications of a different pattern (95% CI 5.30 to 342.05, $P<0.001$). The 14% (19 of 139) of cancers with such casting type calcifications account for 73% (8 of 11) of the deaths. Considered another way, within this group of nominally small invasive tumors with excellent prognosis, the mammographic findings can distinguish a subgroup with 42% (8 of 19) long-term fatality. Mammography gives an opportunity to identify a very important poor prognostic subgroup in a population of tumors that overall has good survival.

This result also enables us to identify another subgroup with excellent prognosis, the small stellate lesions without associated calcifications. Of the 54 stellate lesions of size 1 to 9 mm and without associated calcifications, none caused breast cancer death. The converse of identification of the group who might benefit from additional therapy also identifies the complementary low-risk group. Consider-

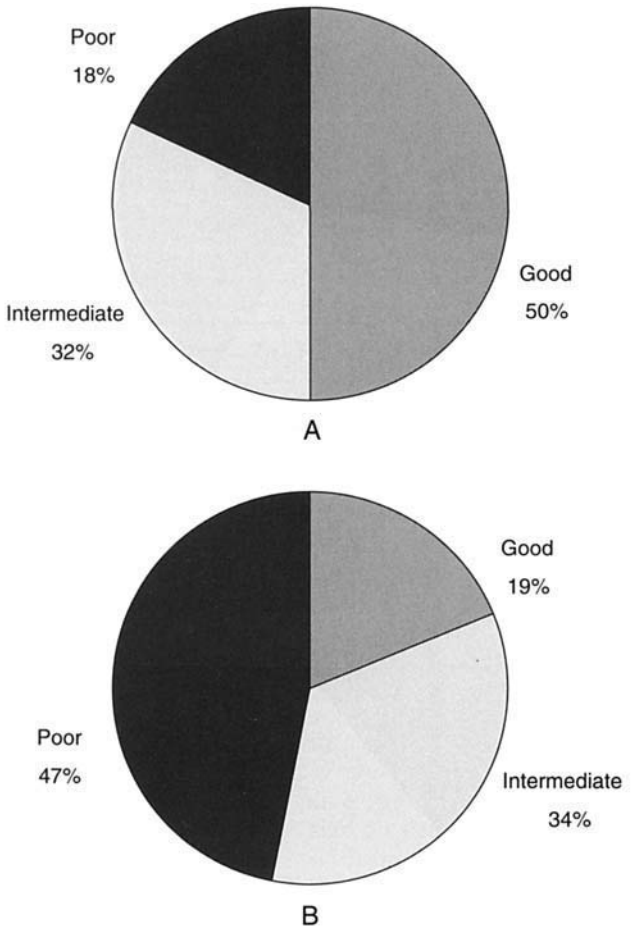



**Figure 14.** Distribution of prognostic category for screen detected *(A)* and clinically detected *(B)* cancers.

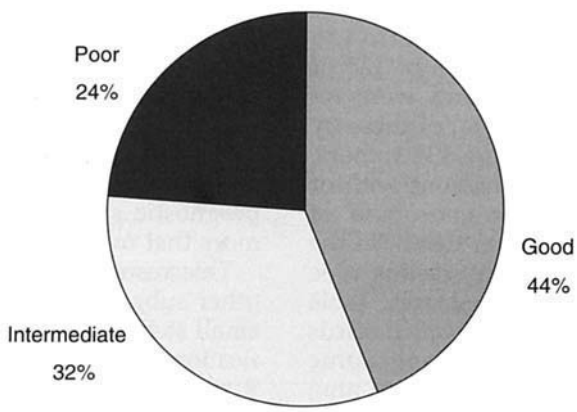



**Figure 15.** Distribution of prognostic category in the population actually attending for screening in the ASP.

**Table 5.** PROGNOSTIC GROUP BY HISTOLOGIC TYPE AND STUDY GROUP

| Histologic Type | Study Group | No. (%) in Prognostic Group | | | | | |
|---|---|---|---|---|---|---|---|
| | | *Good* | | *Intermediate* | | *Poor* | |
| DCIS | ASP | 123 | (100) | 0 | (0) | 0 | (0) |
| | PSP | 46 | (100) | 0 | (0) | 0 | (0) |
| Ductal NOS grade 1 | ASP | 125 | (79) | 17 | (11) | 16 | (10) |
| | PSP | 64 | (60) | 25 | (24) | 17 | (16) |
| Ductal NOS grade 2 | ASP | 152 | (42) | 86 | (24) | 126 | (34) |
| | PSP | 86 | (28) | 91 | (30) | 126 | (42) |
| Ductal NOS grade 3 | ASP | 35 | (9) | 204 | (52) | 155 | (39) |
| | PSP | 12 | (4) | 129 | (41) | 171 | (55) |
| Medullary | ASP | 12 | (32) | 10 | (26) | 16 | (42) |
| | PSP | 5 | (19) | 1025 | (38) | 11 | (42) |
| Lobular | ASP | 14 | (12) | 69 | (57) | 38 | (31) |
| | PSP | 10 | (8) | 72 | (57) | 45 | (35) |
| Mucinous | ASP | 9 | (19) | 32 | (65) | 8 | (16) |
| | PSP | 3 | (9) | 26 | (82) | 3 | (9) |
| Tubular | ASP | 60 | (87) | 9 | (13) | 0 | (0) |
| | PSP | 24 | (80) | 6 | (20) | 0 | (0) |

DCIS = ductal carcinoma in situ; NOS = not otherwise specified.

able overtreatment can be avoided by taking the mammographic appearance into account. It should be noted that these cancers presented in the epoch before chemotherapy was widely used, and so their long-term survival is not attributable to adjuvant chemotherapy.

## RESULTS: DIAGNOSIS AND DISCRIMINATION OF SMALL BUT HIGH-RISK TUMORS

Mammography is clearly a very useful tool, not only for early detection of cancers but also for successful discrimination between the highly fatal and nonfatal cancers. The four mammographic prognostic features are (Figs. 20 to 23):

1. Spiculated tumor mass with no associated calcifications.
2. Circular- or oval-shaped tumor mass with no associated calcifications.
3. Spiculated or circular- or oval-shaped tumor mass, associated with either pleomorphic-heterogeneous-granular–type or amorphous-indistinct–type calcifications (BI-RADS).
4. Casting-type calcifications are present on the mammogram (BI-RADS: fine linear branching or casting). Associated tumor mass is not necessarily demonstrated on the mammogram or at breast ultrasound, but histologic examination reveals invasive tumor focus or foci within the size range 1 to 14 mm.

## DISCUSSION

### Updated Mortality Results and Screening Measures

Our results show a 32% reduction in breast cancer mortality that is maintained 20 years after randomization and around 13 years after the end of the screening phase of the trial. That is, the ASP continues to have lower mortality from breast cancer than the PSP despite the fact that for the last 13 years there has been no difference in intervention applied to the two groups. Considered another way, screening in 1977 to 1985 was continuing to save lives in 1998. The absolute costs have remained the same (between 7 and 8 years' screening costs) for the past 13 years, but the absolute benefits continue to rise.

This has implications for any assessment of cost-effectiveness or cost-benefit of a screening program. To establish the benefits fully, long-term follow-up is essential. For example, in our 11-year report[9] we found a 30% reduction in breast cancer mortality in the ASP compared with the PSP. There were 232 breast cancer deaths in the ASP. The absolute number of deaths prevented at 11 years' follow-up was $232 \times 0.3/(1 \text{ to } 0.3)$, (i.e., 99 deaths prevented). Now, with follow-up to the end of 1998, there is a similar percentage reduction in breast cancer mortality (32%), but the number of breast cancer deaths in the ASP is now 319 and the absolute number of deaths prevented is $319 \times 0.32(1 \text{ to } 0.32)$ (i.e., 150 deaths prevented).

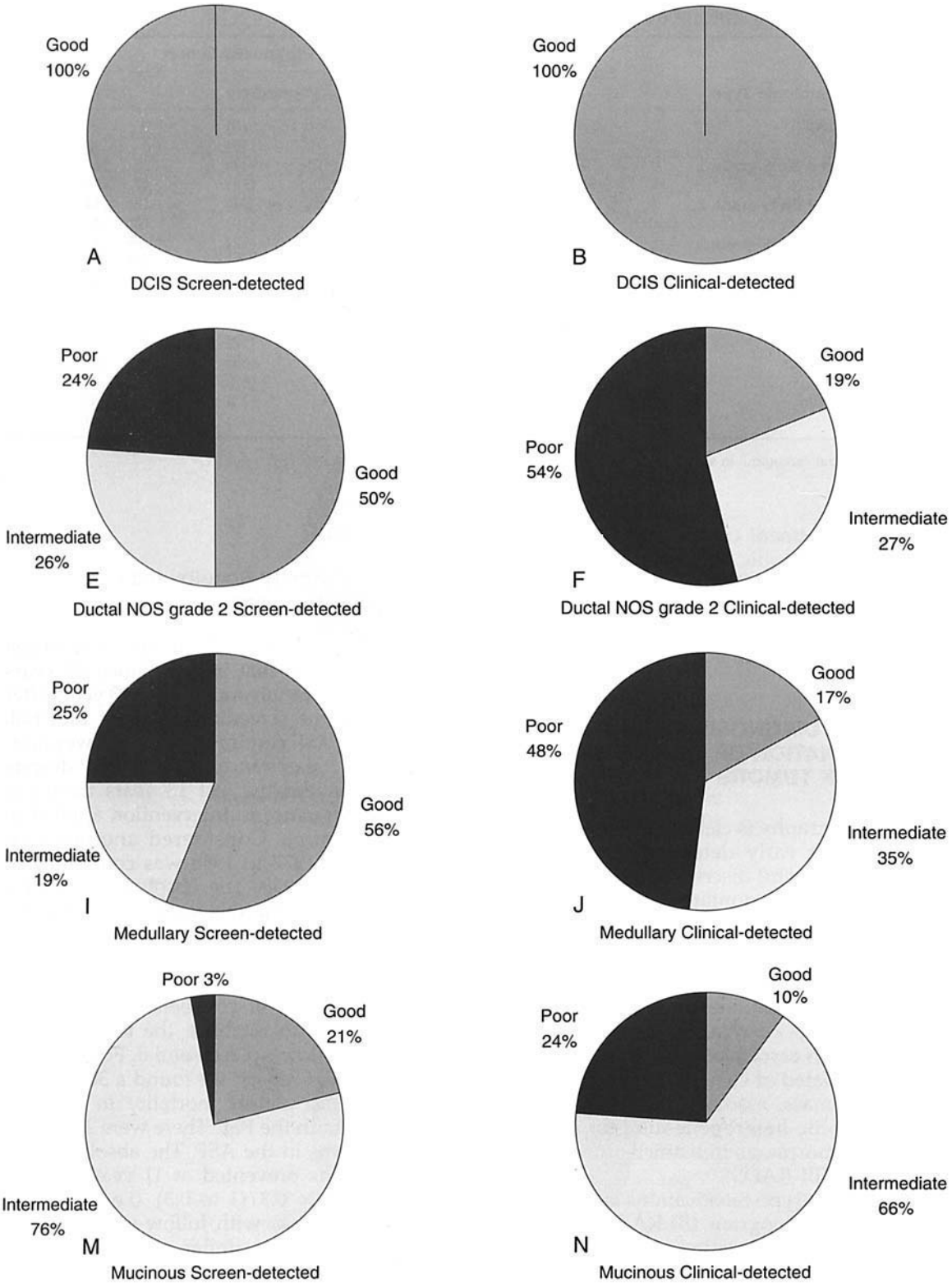



**Figure 16.** Distribution of prognostic category and histologic type in screen-detected and clinically detected cancers.

*Illustration continued on opposite page*

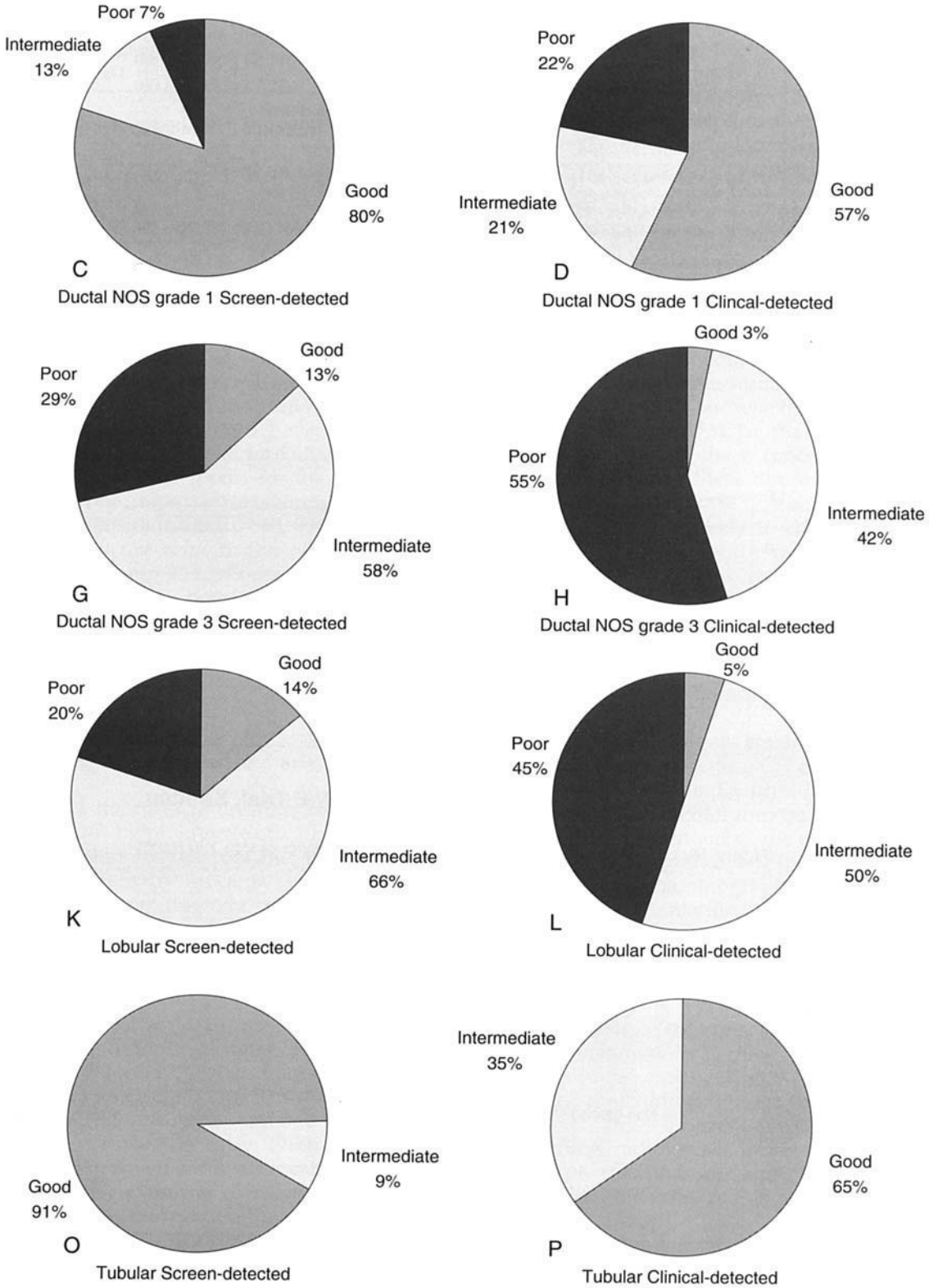



**Figure 16** *(Continued). See legend on opposite page.*

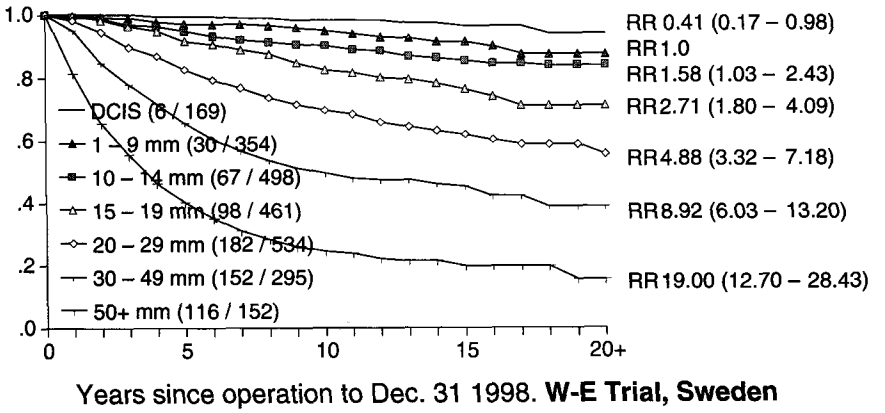



**Figure 17.** Long-term survival by tumor size.

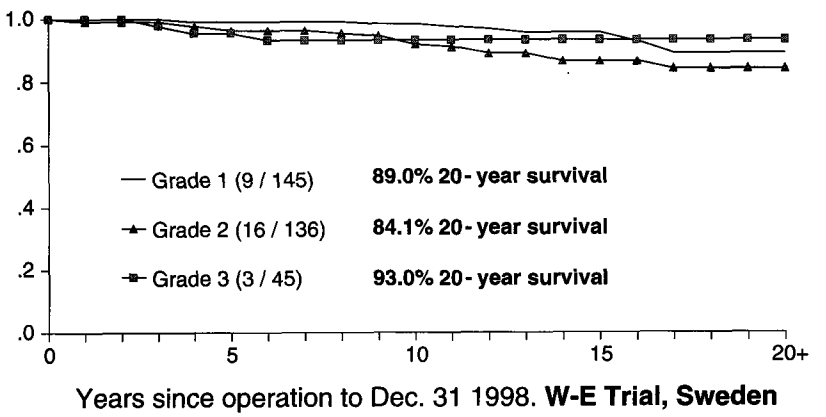



**Figure 18.** Long-term survival by malignancy grade in tumors of size 1 to 9 mm.

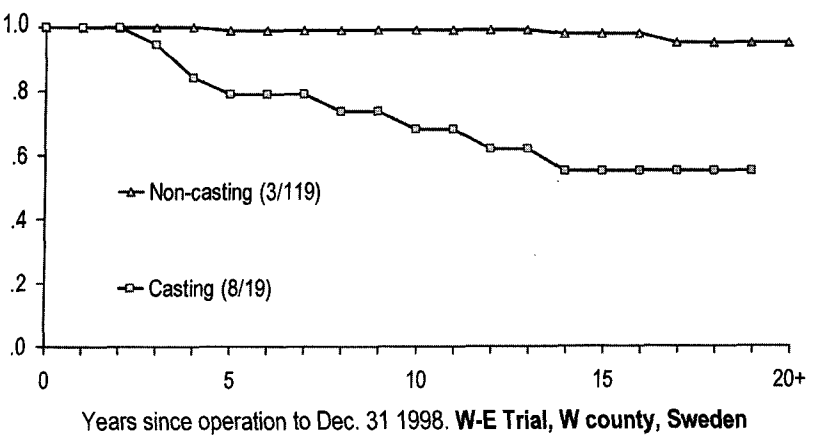



**Figure 19.** Long-term survival by mammographic findings in tumors of size 1 to 9 mm.

**Table 6.** RELATIVE HAZARDS BY MAMMOGRAPHIC FINDINGS OF DEATH FROM BREAST CANCER FOR 140 TUMORS OF SIZE 1 TO 9 mm, ESTIMATED BY PROPORTIONAL HAZARDS REGRESSION

| Mammographic Findings | Relative Hazard | 95% CI |
|---|---|---|
| Spiculated or circular- or oval-shaped tumor mass with non–casting-type calcifications | 1 | — |
| Stellate mass, no calcifications | 0 | — |
| Casting-type calcification | 42.61 | 5.30–342.05 |
| Circular mass, no calcifications | 5.67 | 0.51–62.81 |

It is also worth mentioning that our use of more exact statistical methods to estimate MST, sensitivity, and PSPI have resulted in similar estimates to the approximate methods used in the 11-year report for the most part, but with one important exception. The estimates of sensitivity and PSPI (referred to as *positive predictive value* in the 11-year report) for the age group 40 to 49 are more favorable and more credible, both being between 80% and 90%, suggesting that problems of sensitivity and specificity in this age group are considerably smaller than previously thought.

## Screening and Prognosis

Perhaps the most interesting aspect of the distributions by prognostic category is not the achieved shift in this trial but the potential further benefit by modern screening programs with more frequent or more intensive screening. Table 5 indicates that there is a potential for considerable improvement to the prognosis of ductal carcinoma of grade 2 and 3, lobular, and medullary carcinoma, in addition to that achieved in our ASP. Figure 16 shows that if more of these tumors could be screen-detected by more frequent or more comprehensive screening, including further views, use of grid, and updated diagnostic technology since the early 1980s, then this potential improvement is achievable.

Taking the example of medullary carcinoma, among those attending for incidence screening in the ASP, 62% were interval cancers and 38% incidence screen detected. Because around 50% of interval cancers were diagnosed in the third year after screening,[9] one expects a 2-yearly regime to have 69% of medullary carcinoma screen detected and 31% to be interval cancers. Applying these figures to the percentages in prognostic groups by detection mode in Figure 16 and to the survival rates in Figure 12, one expects a 2-year regime to confer a further 38% reduction in deaths from medullary carcinoma over the 33-month regime in women aged 50 or more in the Two-County trial.

A related point is that the shift in the prognostic group might be used as a quality measure in future screening programs. Of particular interest is the effect of the program on the ductal carcinomas of grade 2 and 3, lobular, and medullary carcinoma. These tumors are of significance in the context of quality because they include large numbers of the potentially fatal cancers; because there is further room for improvement in the prognostic group distribution of these cancers, even in the ASP, and because these tumors have relatively short sojourn times.[7] This last implies that length bias is unlikely to complicate interpretation, which is not the case for evaluation using such measures as detection rates and proportion of ductal carcinoma in situ and other non–high-risk breast cancers.

## Small but High-Risk Tumors

The result that among small tumors the mammographic appearance of casting-type calcification is associated with a high risk of fatality is of fundamental importance. It pertains to a small percentage of the tumor population but a growing and very important one. In the epoch of mammography, the typical tumor size at presentation is small. The aim of mammographic screening is to detect potentially fatal tumors at a stage when there is still an opportunity for effective control. The finding that among very small tumors one can distinguish a subgroup from mammographic screening with a strong fatal potential has two crucial implications: (1) it is important for screening programs to aim to diagnose such cases as early as possible, and for screening radiologists to be vigilant for casting-type calcifications; and (2) these tumors should be considered as candidates for more radical therapy.

The second point is of particular interest. In oncology, it is often the practice to apply a given therapy to large numbers of patients in the knowledge that it has the potential to benefit only a small subgroup of patients, but the subgroup for which the treatment is

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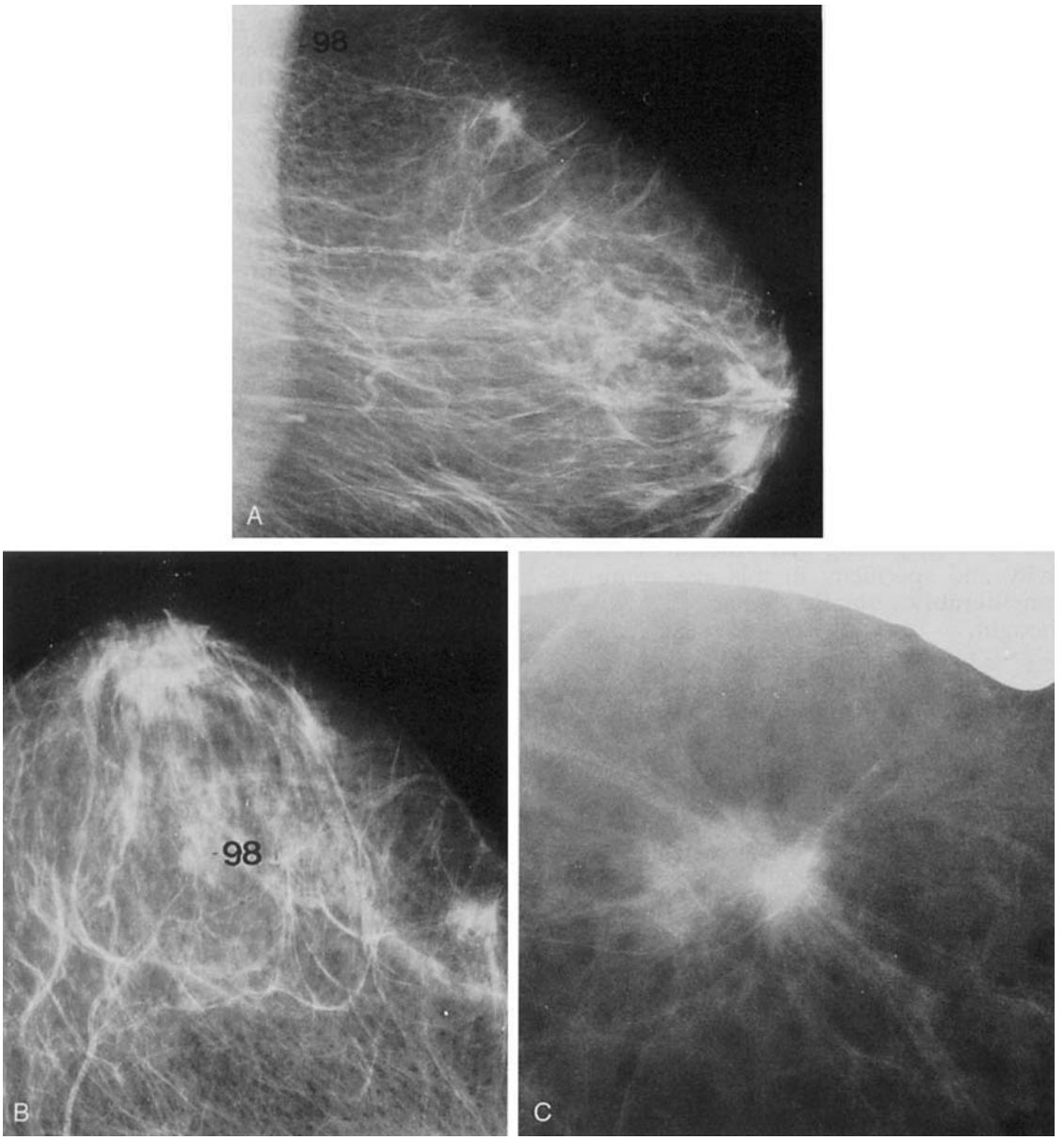


**Figure 20.** *A–C,* Left breast mediolateral oblique and craniocaudal projections and microfocus magnification image. A less than 10-mm solitary spiculated, mammographically malignant tumor mass with no associated calcifications is seen in the upper-outer quadrant. *D,* See page 649.

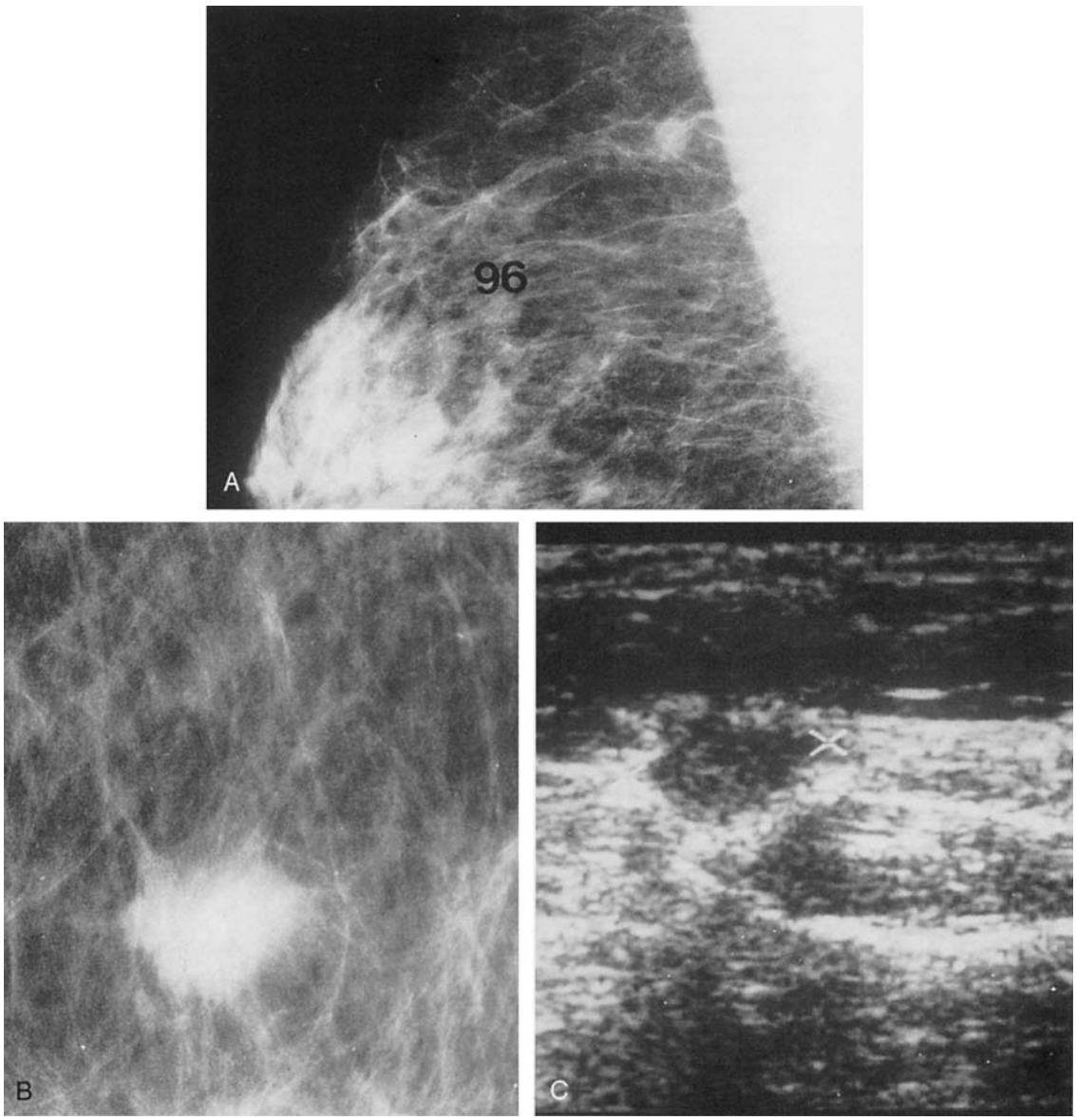


**Figure 21.** *A* and *B,* Right breast mediolateral oblique projection and microfocus magnification image. A solitary, ill-defined mammographically malignant tumor mass is seen with no associated calcifications. *C,* Ultrasound image of the tumor. *D,* See page 649.

**Figure 20.** *A–C,* See page 646. *D,* Histology image of the 9-mm, well-differentiated, invasive ductal carcinoma.

**Figure 21.** *A–C,* See page 647. *D,* Large section histology image of the 9-mm, moderately differentiated invasive ductal carcinoma.

**Figure 22.** *A,* See page 650. *B,* Histology shows a tubular carcinoma of less than 10 mm.

**Figure 23.** *A,* See page 650. *B,* Histology of the casting type calcification and grade 3 in situ component. *C,* Histology of the invasive component (< 10 mm).

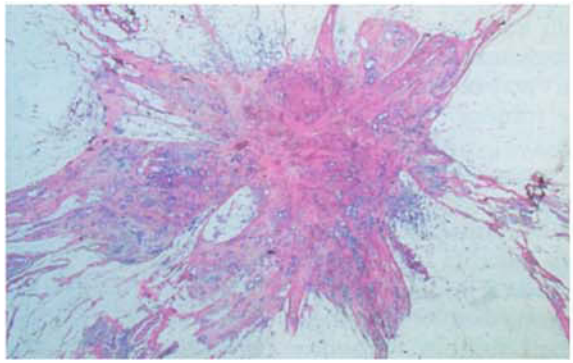

**Figure 20D.**

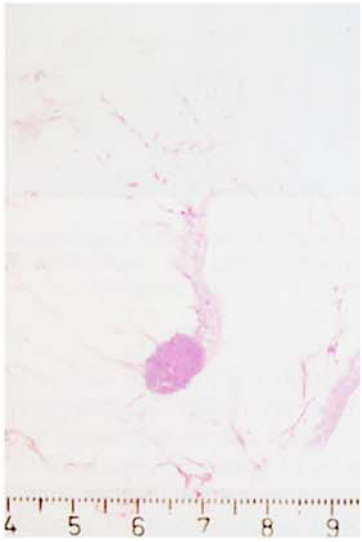


**Figure 21D.**

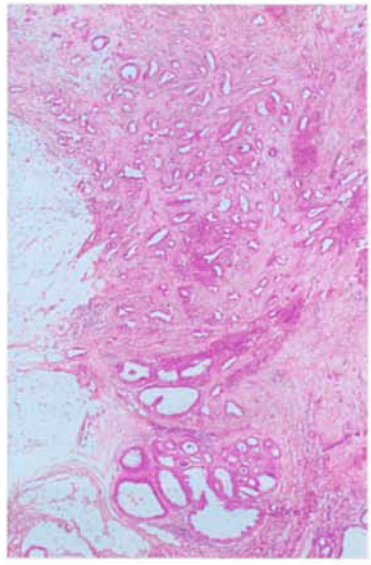

**Figure 22B.**

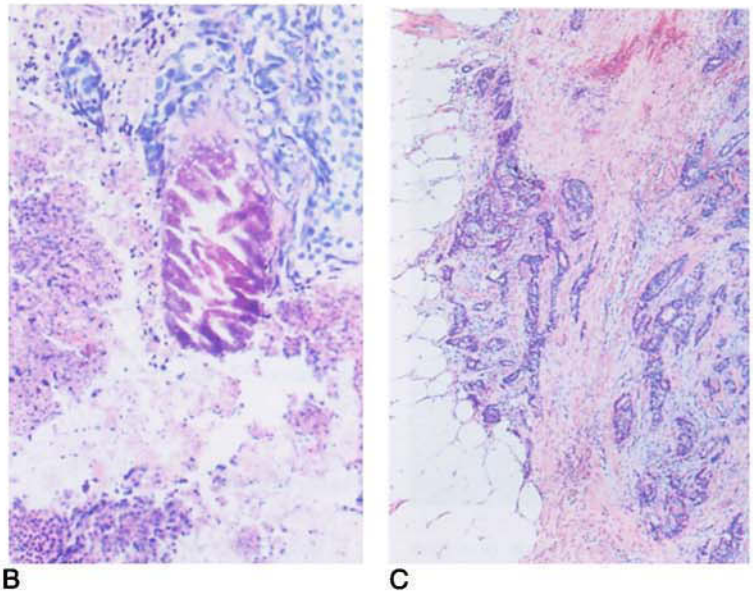


**Figure 23.**

beneficial is not known in advance. Here we are able to identify a subgroup of tumors of size 1 to 9 mm whose survival resembles that of grade 3 node-positive tumors of size less than 20 mm or grade 2 node-positive tumors of size 20 to 29 mm. It is reasonable to postulate that tumors with the mammographic feature of casting-type calcifications should be treated like grade 3 node-positive tumors of size less than 20 mm or grade 2 node-positive tumors of size 20 to 29 mm. Conversely, the excellent survival of small tumors without this mammographic feature indicates that such tumors are most unlikely to derive any benefit from radical or adjuvant therapy. In particular, there were no breast cancer deaths at all in the 54 stellate lesions without calcifications, indicating that any adjuvant therapy applied to such lesions of this size constitutes considerable overtreatment. The implications of this are important both for everyday patient care and from the health economic point of view.

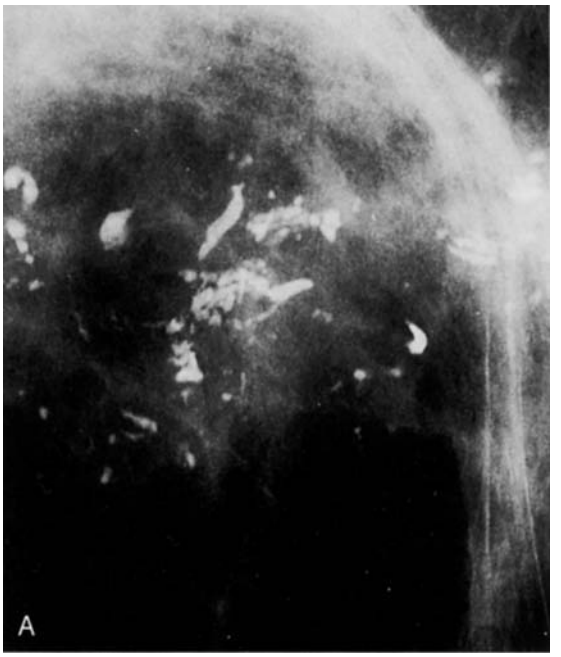


**Figure 23.** *A*, Microfocus magnification image of a large area with casting type calcifications. No tumor mass is seen. *B* and *C*, See page 649.

## SUMMARY

The benefit of invitation to mammographic screening observed in this trial is maintained as a highly significant 32% reduction in breast cancer mortality. Mammographic screening for breast cancer continues to save lives after up to 20 years. Screening derives this benefit by improving the distribution of tumors diagnosed with respect to prognostic categories based on node status, size, and histology of tumors. There is potential for modern screening programs with shorter interscreening intervals to achieve even greater improvements in prognostic category and greater reductions in breast cancer mortality. Mammography can discriminate a subpopulation of high-risk cases, those displaying casting-type calcifications on the mammogram, among very small tumors, with fundamental implications for diagnosis and treatment.

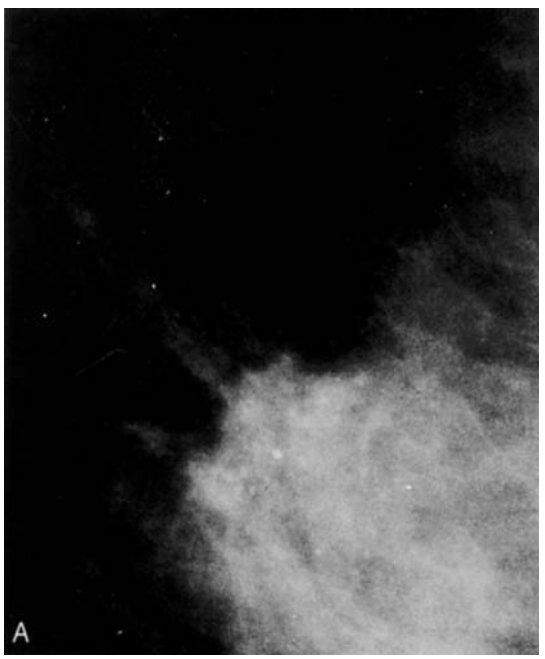


**Figure 22.** *A*, Microfocus magnification image of a less than 10-mm spiculated tumor mass with amorphous/indistinct microcalcifications. *B*, See page 649.

ACKNOWLEDGMENTS

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