# Recent Results From the Swedish Two-County Trial: The Effects of Age, Histologic Type, and Mode of Detection on the Efficacy of Breast Cancer Screening

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**The effect of mammographic screening in reducing mortality from breast cancer is known to be smaller and more delayed in women aged 40–49 than in women over 50. In this study, we investigated how these phenomena relate to histology-specific breast cancer incidence and mortality. The data are from 2,468 women with breast cancer who participated in the Swedish Two-County Trial. The overall relative breast cancer mortality of invited to noninvited women aged 40–49 was 0.87, and the relative mortality from poorly differentiated (grade 3) ductal carcinoma was 0.95. These results were not statistically significant. The corresponding relative risks for invited women aged 50–74 were a statistically significant 0.65 and 0.61. We conclude that in this trial, with a two-year interscreening interval, the smaller and later effect of invitation to screening on breast cancer mortality in women 40–49 years old is due to the failure of screening to reduce mortality from grade 3 ductal carcinoma in this age group. [Monogr Natl Cancer Inst 1997;22:43–47]**

Two main tumor characteristics seem to play a crucial role in controlling breast cancer: heterogeneity of the disease and its progressive nature (*1,2,3,4*). Because mammography screening can allow earlier diagnosis and treatment of breast cancer, it can significantly decrease Stage II and more advanced tumors. Since an advanced disease stage is strongly associated with death from breast cancer, the relative incidence rate of Stage II and more advanced cases among women invited to screening compared to those not invited is expected to be a sensitive measure of breast cancer mortality. The close correlation between the cumulative incidence rates of advanced breast cancers and cumulative mortality rates has been well documented in different screening trials (*5,6,7,8*).

The relationship between advanced breast cancer rates and disease-specific mortality rates has also been demonstrated in age subgroups (*9*). The relative incidence of tumors Stage II and higher is consistent with the diminished effect of screening on mortality in women aged 40–49 years, but it does not explain the reason for the delayed benefit in this age group. Also, it raises the question of why there is less reduction in advanced tumors and subsequently in breast cancer mortality in women aged 40–49 compared to older women. Investigating the heterogeneity of breast cancer, comparing the impact of mammographic screening on cancers of different histologic types, and analyzing the variability in tumor progression rates by age may give insight into the varying efficacy of screening in different age groups.

Survival analysis based on the Swedish Two-County Trial confirms that breast cancer cases can be classified into three histologic tumor types according to prognosis: Group I (consisting of ductal carcinoma *in situ* [DCIS], grade 1 invasive ductal carcinomas, tubular cancers, and mucinous cancers) has good survival, Group II (grade 2 invasive ductal, medullary, and invasive lobular cancers) has intermediate survival, while Group III (grade 3 invasive ductal cancers) has poor survival (*10*).

In previous studies, we concluded that the duration of the tumors' preclinical detectable phase (sojourn time), and therefore the rate of progression from the preclinical to the clinical phase, varies considerably not only by histologic type but also by patient age (*11*). The practical implication of this is that the impact of screening on mortality from breast cancer, and the timing of this impact, will depend largely on which histologic types will be diagnosed early in their natural history and whether screening will advance the time of diagnosis of the subgroup with poor prognosis.

The poorly differentiated invasive ductal carcinomas that make up Group III have both a rapid progression from the preclinical to the clinical phase (a short sojourn time) and a poor short-term survival. Therefore, early detection of these high-risk cases will have a demonstrable beneficial effect within a few years following diagnosis and treatment (short-term effect). On the other hand, the impact of early detection of tumors in Group I and Group II on mortality from breast cancer will not be demonstrable until many years later (long-term effect), since women with similar but undetected tumors in the control group will live much longer than those with poorly differentiated tumors.

As we have noted previously, the relative mortality invited to noninvited women in the Two-County Study was 0.87 in the 40–49 age group and 0.65 in the 50–74 group (*11*). Since the tumor progression rate from preclinical to clinical phase is more

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rapid in younger than in older women (*11,12,13*), the smaller benefit of mammography screening for women under 50 in the Two-County Trial might be due to the longer interscreening interval, which did not allow sufficiently early detection of rapidly growing and frequently fatal tumors, such as poorly differentiated grade 3 ductal carcinomas. Analysis of the cumulative incidence rate of Stage II and worse cancers by histologic type and age will test this hypothesis.

The purpose of this study, then, is to:

(1) consider whether the effect of invitation to mammography screening on mortality from breast cancer is uniform for all tumor types, or if the reduction in mortality is more pronounced for some histologic types;
(2) examine whether the impact of screening on mortality from different histologic tumor types varies with age;
(3) compare the cumulative incidence rate of Stage II and more advanced (Stage II+) tumors with the corresponding observed mortality in each histologic group; and
(4) make suggestions for mammography screening of women aged 40–49 years, based on (1), (2) and (3).

## Methods

### Data Source

Data used in this study are from 2,468 women diagnosed with breast cancer who participated in the Swedish Two-County Trial: 1,053 and 1,415 were from the W and E counties respectively. Average follow-up was 14 years through December 31, 1994. Screening intervals for the invited groups were 24 and 33 months, respectively, for women aged 40–49 and those over 50. (Note that although we refer to the younger age group as the ''40–49'' group, 30% of follow-up screens in this age group actually took place after the women had reached age 50.) The prospectively determined histologic tumor types include ductal carcinoma *in situ* (DCIS), invasive ductal carcinomas not otherwise specified (NOS) of malignancy grades 1, 2 and 3, and medullary, invasive lobular, tubular, and mucinous carcinomas. Details of the study design have been described fully elsewhere (*6*). Note that in this paper, we follow the convention, employed whenever reporting results of the Two-County Trial, of referring to the group invited to screening as the Active Study Population (ASP) and the uninvited control group as the Passive Study Population (PSP).

### Statistical Methods

Cumulative mortality rates were calculated by dividing deaths from breast cancer of various histologic types by person-years.

Calculation of relative risk of cumulative incidence of Stage II+ or cumulative mortality since time at entry is by Poisson regression analysis (*14*).

## Results

Table 1 shows the cumulative mortality by tumor type for the ASP and PSP. Statistically significant reductions of 37% and 39%, respectively, can be seen in deaths from grade 2 and grade 3 invasive ductal carcinomas in invited women aged 50–74 at randomization. In the 40–49 group, most of the mortality reduction is confined to Group II tumors (grade 2 invasive ductal cancers, medullary cancers, and invasive lobular carcinomas), and a 5% reduction in death from grade 3 invasive ductal carcinoma was observed. The absolute risk of dying from breast cancer in Group I (DCIS and grade 1 ductal, tubular, and mucinous carcinomas) is negligible in comparison to deaths from breast cancers in Groups II and III, although the relative risk is high due to the large number of Group I cancers detected at screening.

As noted above, detecting tumors of various histologic types at an earlier stage will be expected to have varying effects on the short-term and long-term mortality results. Early detection of high-risk (Group III) breast cancer cases will reduce mortality a few years after randomization, since poorly differentiated clinically diagnosed cancers are often associated with poor short-term survival (within five years). The beneficial effect of early detection of intermediate risk (Group II) cancers will not be

**Table 1.** Cumulative mortality (number of deaths) per 100,000 from breast cancers by histological tumor type and age in women invited to screen (ASP) and not invited to screen (PSP), with relative risk (RR) of breast cancer death, Swedish Two-County Trial

| | 40–49 | | | 50–74 | | |
|---|---|---|---|---|---|---|
| Age group histology | PSP (PY* = 226,526) | ASP (PY = 278,703) | RR (95% CI) | PSP (PY = 543,939) | ASP (PY = 772,979) | RR (95%) CI |
| Grade 3 ductal | 10.59 | 10.05 | 0.95 | 23.90 | 14.23 | 0.61 |
| (Group III) | (24) | (28) | (0.55–1.64) | (130) | (110) | (0.47–0.78) |
| Grade 2 ductal | 3.09 | 2.15 | 0.70 | 12.31 | 7.76 | 0.63 |
| (Group II) | (7) | (6) | (0.23–2.07) | (67) | (60) | (0.44–0.89) |
| Lobular | 1.77 | 1.43 | 0.81 | 4.60 | 2.85 | 0.62 |
| (Group II) | (4) | (4) | (0.20–3.25) | (25) | (22) | (0.35–1.10) |
| Medullary | 1.32 | 0.36 | 0.27 | 0.92 | 0.52 | 0.56 |
| (Group II) | (3) | (1) | (0.03–2.60) | (5) | (4) | (0.15–2.10) |
| Grade 1 ductal | 0 | 1.43 | — | 1.84 | 1.55 | 0.84 |
| (Group I) | | (4) | | (10) | (12) | (0.36–1.95) |
| Mucinous | 0 | 0 | — | 0.55 | 1.29 | 2.34 |
| (Group I) | | | | (3) | (10) | (0.65–8.52) |
| Tubular | 0 | 0 | — | 0 | 0.39 | — |
| (Group I) | | | | | (3) | |
| DCIS | 0 | 1 | | 0.18 | 0.26 | 1.41 |
| (Group I) | | | | (1) | (2) | (0.13–15.52) |

*PY: Person-years

demonstrable until around eight years after randomization, when those tumors with intermediate survival will result in breast cancer death in the control group.

Our results support this varying effect, as shown in Figures 1–4. The reduction in mortality from grade 3 ductal carcinoma begins to appear four to five years after randomization in the 50–74 age group (Figure 1b) and is hardly apparent in the 40–49 age group (Figure 1a). The diminished impact of grade 3 ductal cancers on mortality in the 40–49 age group explains both the reduced effect of screening on breast cancer death in younger women and the lack of short-term benefit. The deaths prevented in this age group were from the Group II cancers (grade 2 invasive ductal, medullary, and invasive lobular), showing a demonstrable benefit only after six to eight years in both age groups (Figures 4a and 4b).

We also compared the cumulative mortality by histologic type and age (as shown in Figures 1 and 2) with the cumulative incidence rates of Stage II+ cancers by histologic type and age. The reductions in mortality from Group III cancers were 5% and 39% for 40–49 and 50–74 age groups respectively (Figure 1). The corresponding reductions in Group III cancers of Stage II or worse were 0% and 37%. The mortality reductions from Group II tumors were 36% in both age groups (Figure 2). The reduction in Stage II+ tumors were 28% and 35%. These findings suggest that two-year screening in the 40–49 age group failed to detect grade 3 tumors at an early stage, which in turn resulted in similar incidence of Stage II+ cancers in both the invited and control groups. This indicates that poorly differentiated ductal cancers have a more rapid progression during their preclinical phase in women aged under 50 compared to women 50 years of age and older.

## Discussion

Our analysis of mortality and incidence of Stage II+ breast cancer cases according to histologic tumor type has demonstrated a considerable reduction in mortality from poorly differentiated ductal breast carcinomas in women aged 50–74 years at randomization, in spite of the long 33-month interscreening interval, while only a 5% reduction was achieved with the 24-month interval in women aged 40–49 years. These findings imply that the aggressive tumors are more amenable to early detection when they occur at a later age in the host's life.

The more rapid progression of grade 3 ductal cancers in younger women makes early detection more difficult. This is reflected in steady incidence of Stage II+ grade 3 ductal cancers in the younger age group. The lesser and later mortality reduction in women aged 40–49 years can be explained by the fact that the mortality reduction is limited to the histologic types with intermediate survival—that is, to grade 2 ductal, medullary, and invasive lobular cancers.

Our results may also explain the difference in results observed between the two counties. We have published a 27% reduction in mortality from breast cancer in the 40–49 age group in W-county as opposed to a 0% reduction in E-county (*2*). When plotting the cumulative mortality curves by histologic type and age in W-county, we observed a mortality reduction from grade 3 ductal cancers both under and over age 50, although there was a lesser reduction in the younger age group (Figure 3). The reduction in E-county was confined to the age group 50–74 (Figure 4). It should be kept in mind, however, that in the invited group in E-county, age 40–49 at randomization, five breast cancer deaths occurred among nonattenders with grade 3 cancer (*10*).

Several factors have contributed to the decrease in mortality from breast cancer in the Two-County Trial. One of the most important is reducing the tumor size and frequency of axillary lymph node metastases of grade 3 invasive ductal carcinomas. Also, there is a 15% reduction in the incidence of poorly differentiated ductal cancers in the ASP compared to the PSP in age group 50–74 years, suggesting that some of the tumors may dedifferentiate during growth and that early detection may stop progression of the malignancy grade. This is consistent with our earlier findings, according to which approximately 50% of grade 1 and 2 ductal cancers have the potential to dedifferentiate during growth in women aged 50–69 years (*11*). We have not found a reduction in the incidence of grade 3 ductal cancers in women aged 40–49 years. This suggests that dedifferentiation of grade 1 and 2 cancers occurs rapidly in this age group, during the short preclinical phase (*12*), and can only be prevented by shortening the interscreening interval.

The length of the interscreening interval for women aged

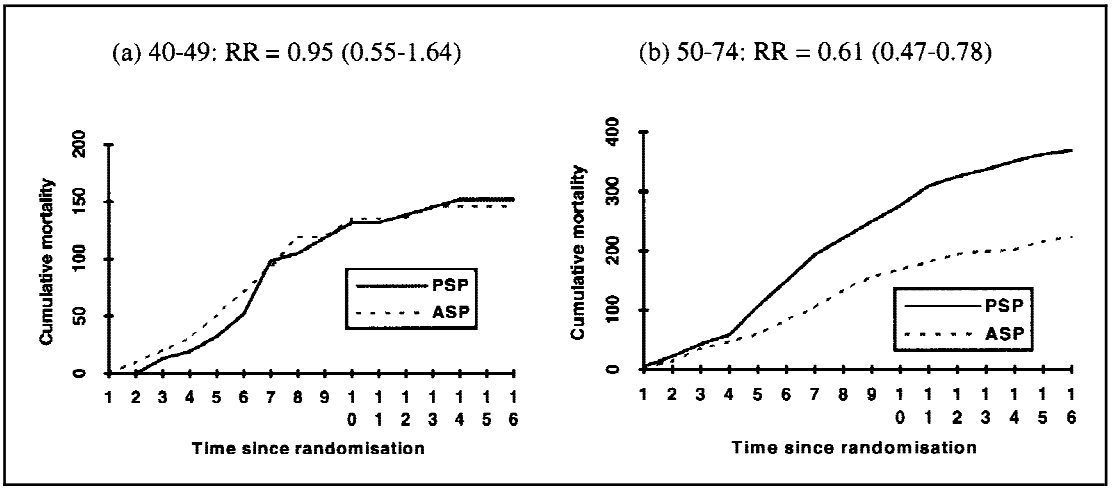


**Fig. 1.** Cumulative mortality from breast cancer for ductal-grade 3 carcinoma by age, Swedish Two-County Trial.

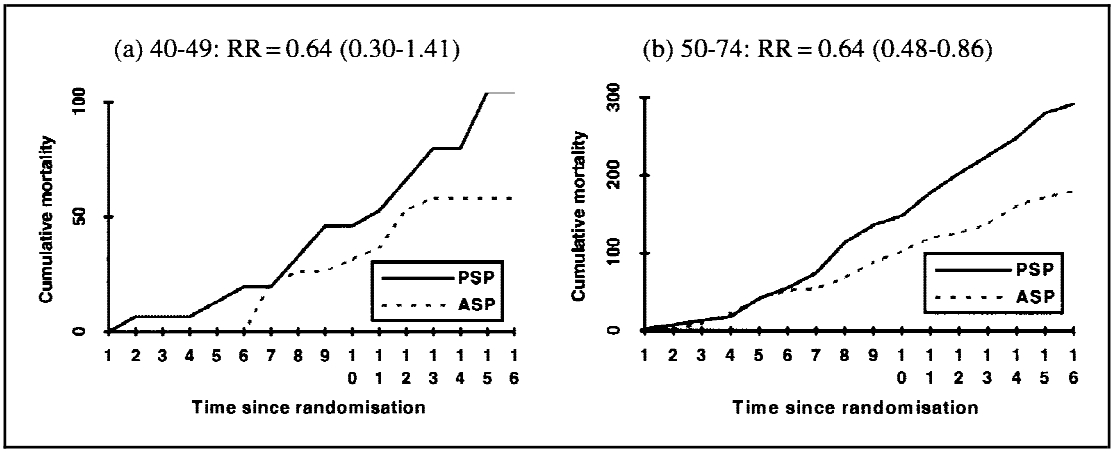


**Fig. 2.** Cumulative mortality from breast cancer for ductal-grade 2, lobular and medullary carcinoma by age, Swedish Two-County Trial.

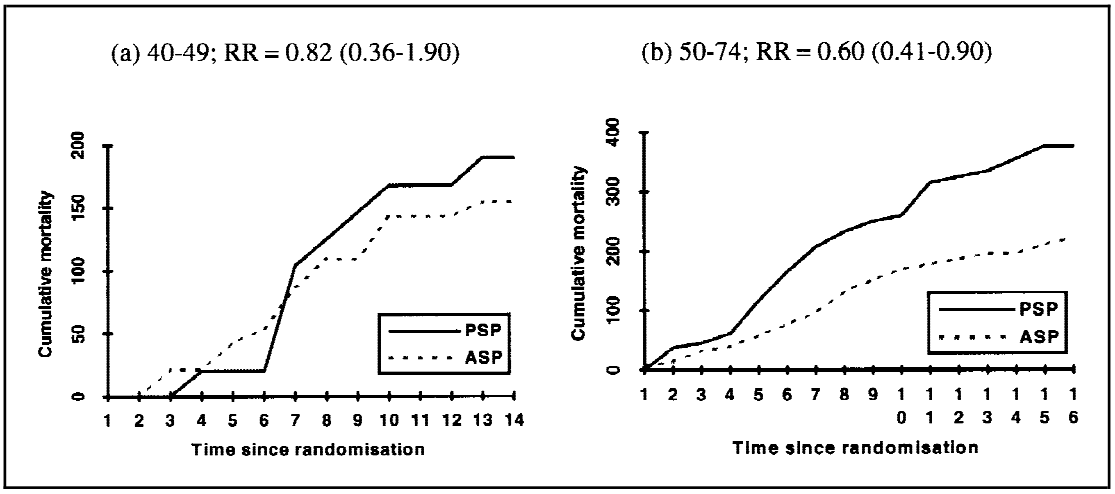


**Fig. 3.** Cumulative mortality from breast cancer for ductal-grade 3 carcinoma by age, W-county.

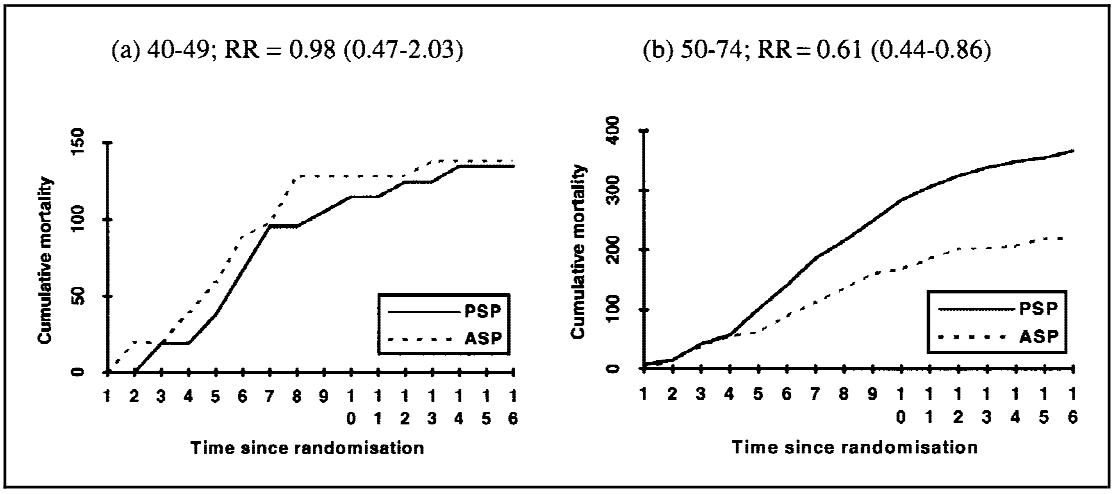


**Fig. 4.** Cumulative mortality from breast cancer for ductal-grade 3 carcinoma by age, E-county.

40–49 is likely to be more crucial than for women aged 50 and over (*15*). Using Markov-chain models based on tumor size, node status, and malignancy grade, we have recently demonstrated that when changing the screening interval from three years to one year, the proportion of tumors which are already advanced in their development (tumors of size 2 cm or more, node positive, and grade 3) may be reduced from 17% to 5% in women aged 40–49 but only from 9% to 4% and from 6% to 3% in women aged 50–59 and 60–69 respectively (*12*).

The good correlation between relative mortality (ASP versus PSP) and relative incidence of Stage II and worse tumors, as shown in Figs. 1 and 2, suggests that the relative incidence of tumors of Stage II+ is a good predictor of the subsequent effect on mortality. This is in accordance with previous findings (*5*,*6*,*7*,*8*). The relative mortality predicted from tumor size, node status, and malignancy grade has also been shown to agree well with observed relative mortality (*13*).

Our results point out the particular value of malignancy grade

in predicting how soon after initiating screening one can expect to see a mortality benefit. If indeed the screening program reduces the incidence of grade 3 ductal cancers and/or reduces the tumor size and frequency of nodal spread of the poorly differentiated ductal cancers, one could be confident that breast cancer mortality will be decreased and that an early benefit will be demonstrable. At the other extreme, early detection of DCIS cases and tubular, mucinous, and grade 1 ductal cancers will have little demonstrable effect on mortality within 10–15 years.

In conclusion, the results here suggest that the smaller and delayed benefit of two-year breast cancer screening in women aged under 50 years is mostly due to a small reduction in mortality from grade 3 ductal cancers. Progression of grade 3 carcinomas seems to be more rapid and dedifferentiation of low-grade cancers more frequent in younger women. This makes early detection more difficult, especially with a two-year screening interval. Accordingly, a shorter interscreening interval is required to detect these rapidly growing cancers at an earlier stage in their natural history.

## References


(*1*) Tabar L, Dean PB. Breast cancer: a progressive, heterogeneous disease requiring multidisciplinary diagnosis and treatment. J Oncol Management 1994;Nov/Dec:12–3.

(*2*) Hellman S. Natural history of small breast cancers: Karnofsky Memorial Lecture. J Clin Oncol 1994;12:2229–34.

(*3*) Tubiana M, Koscielny S. Natural history of breast cancer: recent data and clinical implications. Breast Cancer Res Treat 1991;18:125–40.

(*4*) Tabar L, Fagerberg G, Day NE, Duffy SW, Kitchin RM. Breast cancer treatment and natural history: new insights from the results of screening. Lancet 1992;339:412–4.

(*5*) Shapiro S, Venet W, Strax P, et al. Ten- to fourteen-year effect of screening on breast cancer mortality. J Natl Cancer Inst 1982;69:349–55.

(*6*) Tabar L, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography. Lancet 1985;I: 829–32.

(*7*) Andersson I, Aspegren K, Janzon L, et al. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. Br Med J 1988;297:943–8.

(*8*) Frisell J, Eklund G, Hellstrom L, et al. Randomized study of mammography screening—preliminary report on mortality in the Stockholm trial. Breast Cancer Res Treat 1991;18:49–56.

(*9*) Tabar L, Fagerberg G, Chen HH, Duffy SW, Gad A. Screening for breast cancer in women aged under 50: mode of detection, incidence and histology. J Med Screening 1995;2:94–8.

(*10*) Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age: new results from the Swedish Two-County Trial. Cancer 1995;75:2507–17.

(*11*) Tabar L, Fagerberg G, Chen HH, Duffy SW, Gad A. Tumor development, histology and grade of breast cancers: prognosis and progression. Int J Cancer 1996;66:413–9.

(*12*) Chen HH, Duffy SW, Tabar L, Day NE. Markov chain models for progression of breast cancer: I. Tumor attributes and the preclinical screen-detectable phase. Submitted to Amer J Epidemiol.

(*13*) Committee and Collaborators, Falun meeting. Report of the meeting on mammographic screening for breast cancer in women aged 40–49, Falun, Sweden, March 1996. Int J Cancer. In press.

(*14*) Breslow NE, Day NE. Statistical Methods in Cancer Research. Vol II. The Design and Analysis of Cohort Studies. Lyon: International Agency for Research on Cancer, 1987.

(*15*) Tabar L, Fagerberg G, Day NE, Holmberg L. What is the optimum interval between mammographic screening examinations? An analysis based on the latest results of the Swedish Two-County breast cancer screening trial. Br J Cancer 1987;55:547–51.