Benefit of Screening Mammography in Women Aged 40–49: A New Meta-Analysis of Randomized Controlled Trials

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Eight randomized controlled trials (RCTs) of screening mammography have been conducted involving women aged 40–49 at entry. Current data are now available from these trials at 10.5 to 18 years of follow-up (average follow-up time: 12.7 years). Meta-analysis has been performed using a Mantel-Haenszel estimator method to combine current follow-up data from the eight RCTs of mammography that included women aged 40–49 at entry, including new follow-up data presented at the NIH Consensus Development Conference held January 21–23, 1997. Combining the most recent follow-up data on women aged 40–49 at entry into all eight RCTs yields a statistically significant 18% mortality reduction among women invited to screening mammography (relative risk: 0.82; 95% confidence interval: 0.71–0.95). Combining all current follow-up data on women aged 40–49 at entry into the five Swedish RCTs yields a statistically significant 29% mortality reduction among women invited to screening (relative risk: 0.71; 95% confidence interval: 0.57–0.89). Meta-analysis including the most recent follow-up data from all eight RCTs involving women aged 40–49 at entry demonstrates for the first time a statistically significant mortality reduction due to regular screening mammography in women of this age group. [Monogr Natl Cancer Inst 1997;22:87–92]

At the National Institutes of Health (NIH) Consensus Development Conference on Breast Cancer Screening for Women Ages 40–49, new longer-term follow-up data were presented from seven of the eight randomized controlled trials (RCTs) involving screening mammography in women aged 40–49 years at entry (*1–7*). These data updated previous results presented at the Falun Meeting in Sweden in March 1996 (*8*). All trials presented additional years of follow-up on women aged 40–49 except the Health Insurance Plan of New York (HIP) trial, which had previously published 18-year follow-up data on women 40–49 at entry (*9,10*). All trials now have follow-up data on women aged 40–49 with at least 10.5 years average follow-up since randomization.

Table 1 lists the updated subgroup data from each RCT relevant to screening mammography in women aged 40–49, the screening regimen, the number of women in the 40–49 subgroup who were entered into each arm of the trial, and the most recently presented relative risks and 95% confidence intervals from each trial. Two Swedish trials, Gothenburg and Malmö, demonstrate for the first time a statistically significant benefit from screening mammography for women under age 50 at entry. The Gothenburg trial demonstrates a statistically significant 44% mortality reduction among women 39–49 invited to screening mammography (*1*). The Malmö trial shows a statistically significant 36% mortality reduction among women aged 45–49 invited to screening mammography (*2*). Of these eight RCTs, only the Canadian National Breast Screening Study (CNBSS-1) was specifically designed to study women 40–49 at entry (*11*), and that trial now shows a slight mortality increase among women 40–49 invited to screening mammography plus clinical breast exam (*7,8*).

A previous meta-analysis of RCTs involving women 40–49, published in 1995 (*12,13*), included follow-up data ranging from 7 to 18 years since randomization (weighted average follow-up time: 10.4 years). That meta-analysis yielded a 16% mortality reduction, statistically nonsignificant at the 95% confidence level, among women 40–49 invited to screening when all eight RCTs were combined. A 24% mortality reduction, statistically significant at the 95% confidence level, was found among women aged 40–49 when all seven population-based trials were combined.

Just as the statistical power of an individual RCT increases with more participants and longer-term follow-up, the statistical power of a meta-analysis combining different trials also increases due to longer-term follow-up of individual trials. This point was noted in the Fletcher report (*14*), which acknowledged the limitations of available studies and summary analyses, stating:

> A second meta-analysis of the data from all available trials of screening in women aged 40–49 may be useful, especially when longer follow-up is available and when the effect of reclassification is clarified in the combined Swedish studies. Such a meta-analysis should use the raw data from each of the trials.

This paper presents a new meta-analysis that includes the latest follow-up data from each RCT of screening mammography in-

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See ''Note'' following ''References.''

Table 1. Summary of RCT results for women 40–49

Study (Dates)	Screening Regimen	Frequency No. Rounds	Yrs F/U	Number of women		RR 95% CI
				Invited	Control	
HIP Study[9] (1963–69)	2 V MM + CBE	Annually 4 rounds	18	14,432	14,701	0.77 0.53–1.11
Edinburgh[6] (1979–88)	1 or 2 V MM	24 mos 4 rounds	12.6	11,755*	10,641*	0.81* 0.54–1.20
Kopparberg[5] (1977–85)	1 V MM	24 mos 4 rounds	15.2	9,650	5,009	0.67 0.37–1.22
Östergötland[5] (1977–85)	1 V MM	24 mos 4 rounds	14.2	10,240	10,411	1.02 0.59–1.77
Malmö[2] (1976–90)	1 or 2 V MM	18–24 mos 5 rounds	12.7	13,528**	12,242**	0.64** 0.45–0.89
Stockholm[4] (1981–85)	1 V MM	28 mos 2 rounds	11.4	14,185	7,985	1.01 0.51–2.02
Gothenburg[1] (1982–88)	2 V MM	18 mos 5 rounds	12	11,724†	14,217†	0.56† 0.32–0.98
CNBSS-1[7] (1980–87)	2 V MM + CBE	12 mos 4–5 rounds	10.5	25,214	25,216	1.14 0.83–1.56

1 V MM = one-view mammography of each breast; 2 V MM = two-view mammography of each breast; CBE = clinical breast exam.

*The Edinburgh trial included three separate groups of women 45–49 at entry: the first had 5,949 women in the invited group and 5,818 in the control group (with 14 years' follow-up); the next had 2,545 in the invited group and 2,482 in the control group (12 years' follow-up); and the third had 3,261 in the invited group and 2,341 in the control group (10 years' follow-up) (*6*). Only the first group's results had been reported previously (*8*).

**The Malmö trial included two groups of women aged 45–49 at entry: one group (MMST-I) received first-round screening in 1977–8 and had 3,954 women in the invited group, 4,030 women in the control group; the second group (MMST-II) received first-round screening from 1978–90 and had 9,574 women in the invited group, 8,212 women in the control group (*2*). Only the first group's results had been reported previously (*5,8*).

†The Gothenburg trial includes women aged 39–49 at entry (*1*).

volving women aged 40–49 to assess the benefit of screening mammography in women of this age group.

Methods

A new meta-analysis of current RCT data for women aged 40–49 at entry has been performed using a Mantel-Haenszel estimator method to combine data from different trials (*15*). The Mantel-Haenszel estimator method approximates the maximum likelihood method of data pooling, with the added advantage of computational ease (*16*). The input data used for this meta-analysis are the numbers of deaths from breast cancer in both invited and control groups in each trial and the numbers of women-years of follow-up in each arm of each trial. Table 2 lists input data to the RCT meta-analysis and the references from which the most recent follow-up data were taken. The Mantel-Haenszel method weighs each trial according to the number of deaths occurring in both the invited and control groups in that trial; the greater the number of deaths, the greater weight a trial has relative to other trials included in the meta-analysis. Determinations of relative risks and confidence intervals using the Mantel-Haenszel estimator method have been based on the formalism of Breslow and Day (*17*).

Table 2. Data used in the current meta-analysis of women 40–49

Screening study	Number of Women-Years (in 1,000s)		Number of Breast Cancer Deaths	
	Invited	Control	Invited	Control
HIP study[9]	248	253	49	65
Edinburgh[6]	146*	135*	46*	52*
Kopparberg[5]	144	75	23	18
Östergötland[5]	143	147	27	27
Malmö[2]	166*	144*	57*	78*
Stockholm[4]	174	88	24	12
Gothenburg[1]	138†	168†	18†	39†
CNBSS-1[7]	283	283	82	72

*Included only women aged 45–49 at entry.

†Included women aged 39–49 at entry.

In cases where multiple follow-up data were available from the same trial, the data with the longest follow-up were selected for inclusion in this meta-analysis. This was determined by selecting the follow-up data that had the greatest number of breast cancer deaths among women in the invited and control groups combined.

Meta-analysis of current RCT data on mammography in women aged 40–49 were conducted under two different conditions:

1) inclusion of the most current follow-up data from all eight RCTs of mammography in women aged 40–49 at entry, and
2) inclusion of the most current follow-up data from the five Swedish RCTs of mammography in women aged 40–49 at entry.

The second meta-analysis included the five Swedish trials, each of which excluded clinical breast exam as part of its trial design (*1–5*). The HIP, Edinburgh, and CNBSS-1 trials included clinical breast exam as part of their study interventions (*9,10,6,7*), and the CNBSS-1 trial provided a clinical breast exam to all trial participants prior to their randomization into study or control groups (*11*). The five Swedish trials studied the effect of mammography alone, without the confounding influence of clinical breast examinations.

Results of our meta-analysis are stated in terms of summary relative risks (the mortality rate among women in the invited group divided by the mortality rate among women in the control group) and 95% confidence intervals (a range capturing the point estimate of relative risk 95 times if the trial or collective set of trials were repeated 100 times) determined from the combined data; 99% confidence intervals are also determined. Two-sided confidence intervals are used in each case.

Heterogeneity tests were used to assess the statistical signifi-

cance of differences among individual RCT results. The null hypothesis was that data included in the meta-analysis are homogeneous and therefore can be combined by meta-analysis without correction. A correction to the Mantel-Haenszel estimate of confidence interval is necessary if there is statistically significant evidence to reject the null hypothesis (that is, if the data are significantly heterogeneous). A chi-square test was used to assess the statistical significance of heterogeneity of individual RCT results. Breslow's random effects model was used to study the effects of possible differences among studies (*18*). The model allows for variation among studies over and above Poisson sampling errors, but without attribution to any particular factor (such as cluster randomization, screening interval, inclusion of clinical breast examination, etc.).

Results

Average follow-up time among all eight RCTs, weighted by the number of women aged 40–49 at entry in each trial, is 12.7 years. Combining the most recent follow-up data from all eight RCTs for women 40–49 years of age at entry yields the following relative risk (RR) and 95% confidence interval (95% CI):

$$\text{RR (95\% CI)} = 0.82\ (0.71\text{–}0.95).$$

This overall 18% mortality reduction among women invited to screening mammography is statistically significant at the 95% confidence level and just achieves statistical significance at the 99% confidence level (99% CI: 0.673–0.999).

Combining the most recent follow-up data from the five Swedish RCTs of women aged 40–49 at entry yields the following RR and 95% CI:

$$\text{RR (95\% CI)} = 0.71\ (0.57\text{–}0.89).$$

This 29% mortality reduction among women invited to screening mammography without clinical breast exam is also statistically significant at both the 95% and 99% confidence levels (99% CI: 0.53–0.96).

Figure 1 summarizes individual RCT results and our meta-analysis results. Bars about each relative risk point estimate in the figure represent 95% confidence intervals for individual trials and, about the two bottom points, 95% confidence intervals for the RCTs combined by meta-analysis.

Tests for statistical significance of heterogeneity of the combined RCT data demonstrate that heterogeneity is not significant among either all RCTs or the five Swedish RCTs. Chi-square tests for the heterogeneity of all eight RCTs gave $P = 0.20$; tests for the heterogeneity of the five Swedish RCTs gave $P = 0.40$. These nonsignificant results support the combination of individual RCT data by meta-analysis using the Mantel-Haenszel estimator method without correction (widening) of the 95% confidence intervals. Differences in study designs and protocols have raised the question of the effect of heterogeneity, despite the absence of statistically significant differences among RCT results. Breslow's random effects model including all eight RCTs combined yielded a relative risk of 0.81 and a 95% CI of 0.68–0.98, a slightly wider 95% CI than was given by the fixed effects model reported above. Breslow's random effects model yielded exactly the same results as the fixed effects model when the five Swedish trials were combined. These results indicate that study heterogeneity and design differences do not alter the finding of a statistically significant benefit when combining all eight RCTs involving women aged 40–49 at entry.

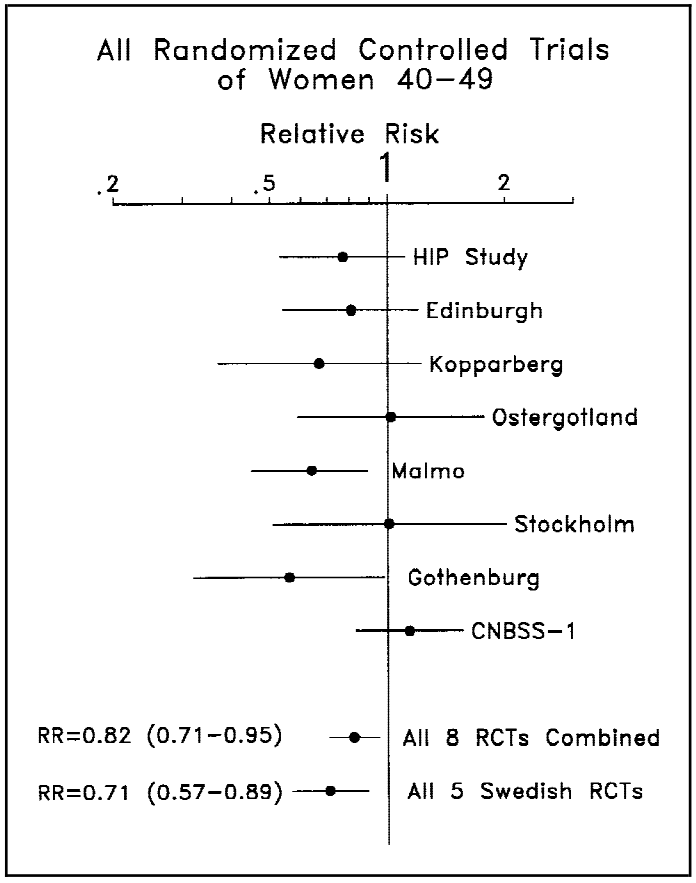

Fig. 1. Relative risks and 95% confidence intervals of all RCTs of screening mammography that included women ages 40–49 at entry. The last two data points show relative risk and 95% confidence interval results of the current meta-analysis for women ages 40–49 at entry from all eight RCTs and from the five Swedish RCTs of screening mammography.

Discussion

Current follow-up data from the eight RCTs that included women aged 40–49 at entry demonstrate delayed but increasing benefit from mammography screening. Figure 1 illustrates that two individual RCTs, the Gothenburg and Malmö trials, each have demonstrated a statistically significant mortality reduction from mammography screening among women under age 50 at entry. The Gothenburg trial included women ages 39–49 at entry (*1*), and the Malmö trial included women ages 45–49 at entry (*2*). Three other trials (HIP, Edinburgh, and Kopparberg) suggest mortality benefit to women of this age group, but the findings are not statistically significant at the 95% confidence level (*3,5,6,9,10*), and three trials (Östergötland, Stockholm, and CNBSS-1) show no benefit from screening mammography among women 40–49 (*3–5,7,8*).

It is worth examining what the entire current world's RCT data, taken collectively, say about the benefit of the invitation to screening mammography in women aged 40–49 at entry. This meta-analysis answers that question, demonstrating that all eight RCTs collectively yield a statistically significant 18% mortality

reduction among women aged 40–49 invited to screening mammography.

The major changes in individual RCT data that led to this collective demonstration of a statistically significant benefit are changes in the Gothenburg and Malmö trial results. Among women under 50, the Gothenburg trial showed a nonsignificant 27% mortality reduction at seven years' follow-up (*19,20*), a nearly significant 38% mortality reduction at 10 years' follow-up (*8*), and a statistically significant 44% mortality reduction at 12 years' follow-up (*1*). The most recent data reported by Malmö investigators have included results from the so-called MMST-II group, an additional 17,000 women randomized at ages 45–48 and entered into the study between 1978 and 1990 (*2*). These additional 17,000 women, added to the approximately 7,000 women ages 45–49 randomized and reported on previously (the MMST-I group) (*5*), have significantly boosted the statistical power of the Malmö trial results (*2*), producing a statistically significant 36% mortality reduction from the combined Malmö (MMST-I and MMST-II) trial results.

Results for the subgroup of women aged 40–49 at entry from the HIP trial (*9,10*), the Edinburgh trial (*6*), and the combined Swedish trials (*20,21*) indicate that as more years of follow-up are included, benefit eventually emerges and there is a steady progression toward greater benefit from screening mammography. Meta-analyses of the eight RCTs show this same trend. Cox's meta-analysis of RCT data on women 40–49 at approximately seven years of follow-up showed no benefit, yielding a relative risk of 1.04 (95% CI: 0.81–1.33) when all eight RCTs were combined (*22*). At seven to nine years of follow-up, Kerlikowske's meta-analysis of RCT data on women 40–49 gave a similar relative risk of 1.02 (95% CI: 0.82–1.27) (*23*). Our previous meta-analysis of RCT data on women 40–49, at an average of 10.4 years follow-up, gave a 16% mortality reduction from the invitation to screening to women 40–49 in all eight RCTs (*12,13*). The current meta-analysis, at an average of 12.7 years of follow-up, gives an 18% mortality reduction from invitation to screening to women 40–49 from all eight RCTs, statistically significant at the 95% confidence level for the first time.

It has been pointed out previously that the potential benefit of screening mammography takes longer to manifest in women aged 40–49 than in older women (*12,20*). A delayed demonstration of benefit is to be expected in women 40–49 years of age compared to older women due to fewer breast cancer deaths for the following reasons:

1) breast cancer incidence and mortality rates are lower in women 40–49 than in women 50 and over;
2) the number of women 40–49 included in the eight RCTs is approximately one-third the total number of women included in the eight trials;
3) the higher rates of ductal carcinoma *in situ* (DCIS) in women 40–49 than in older women and the slow progression of DCIS to invasive carcinoma require a longer time to manifest a mortality difference between screen-detected DCIS in the study group and undetected DCIS in the control group.

A delayed demonstration of benefit in women 40–49 is also to be expected due to somewhat less favorable cancer stage distributions resulting from use of a wide screening interval in some RCTs:

4) on average, the lead time of mammography is shorter in women 40–49 than in women 50 and over;
5) the sensitivity of mammography in the RCTs is known to be lower in women 40–49 than in women 50 and over (*14*);
6) a longer period of follow-up will be needed if the benefit from screening mammography in the trials among women 40–49 was limited to cancers detected with good to intermediate prognosis. Recent analyses of the Swedish two-county data have shown that the two-year screening interval used in these two trials (Kopparberg and Östergötland) was not effective in detecting more aggressive tumors with poor prognosis (*8*). These findings, in conjunction with previous analyses estimating age-specific mean sojourn times, support the conclusion that annual screening is necessary to achieve mortality reductions in women 40–49 similar to those obtained in women 50 and over with wider screening intervals (*24*).

These factors influence the outcomes of trials for women 40–49 and make it more difficult to demonstrate a statistically significant mortality reduction in them as compared with women 50 and older. Hence, longer follow-up is needed to manifest a statistically significant mortality reduction in women aged 40–49.

Because of the delayed benefit of screening mammography in women 40–49, some have argued that the observed benefit of mammography among women 40–49 at randomization may be due to ''age migration'': the effect that women 40–49 at entry may benefit in terms of mortality reduction only from screening mammography performed at or after the age of 50 (*25,26*). Age migration is an inevitable consequence of randomizing a wider age range of women, screening them over a number of years, and then attempting to perform subgroup analyses of trial results based on age at entry. While it may be interesting to examine trial data in terms of age at diagnosis rather than age at entry, it is methodologically unsound to do so. As Prorok *et al.* point out, age at diagnosis is a pseudovariable, since it is influenced by the study intervention (screening) during the trial, reducing the comparability of the study and control groups (*27*). Thus, however intriguing, it is not clear that any results from subgroup analyses based on age at diagnosis are credible. Moreover, such analyses only further subdivide original data sets that have already been subdivided by age at entry, completely eliminating any possible statistical power of the data. Nevertheless, data in the published literature and presented at the NIH Consensus Conference do not support the age migration hypothesis that benefit among women 40–49 at entry is due to the subset of women diagnosed after age 50. Tabar *et al.* compared invited and control groups from the Swedish two-county trial based on age at diagnosis and showed a 15% mortality benefit among women both randomized and diagnosed before age 50, compared with only a 5% benefit among women randomized in their forties and diagnosed in their fifties (*28*). The mortality difference is actually higher among women diagnosed in their forties than among women diagnosed in their fifties in the Swedish two-county trial.

The suggestion that much of the benefit to women invited to screening within RCTs results from clinical breast exams that were included along with screening mammography is also spe-

cious. None of the five Swedish trials included clinical breast exams, yet previously combined results of those five trials demonstrated a 23% mortality reduction from screening, just barely lacking statistical significance at the 95% confidence level: RR (95% CI) = 0.77 (0.59–1.01) (*5,8*). Including all new follow-up data presented at the NIH Consensus Conference, combined data from the five Swedish trials yields a 29% mortality reduction for women under 50 at entry, statistically significant at the 95% confidence level: RR (95% CI) = 0.71 (0.57–0.89). These results indicate that clinical breast exams play an insignificant role in the mortality reductions observed in RCTs.

The true benefit of mammography today is likely to exceed the benefit demonstrated in RCTs for at least two reasons:

1) RCTs test the efficacy of the invitation to screening mammography in a predefined study group compared to no invitation in a predefined control group. In population-based RCTs that measured compliance among women offered screening, compliance rates for the first screening mammogram ranged from 61% to 89%, with lower compliance rates in each subsequent screen. Since a statistically significant benefit from mammography in women 40–49 has been shown to exist, the true benefit to women receiving regular screening mammography will be greater than the benefit demonstrated among women in the RCTs invited to screening mammography, since a reasonable fraction of women invited to screening did not comply. Likewise, women who were assigned to the control group but who went outside the trial to obtain regular screening mammography diluted the observed benefit of screening in the RCTs, providing a second reason why the true benefit of regular screening mammography will be greater than the demonstrated benefit (*29*).

2) The technology of mammography has improved markedly since the time of even the most recent RCTs. Women receiving regular, high-quality mammography today are more likely to have their cancers detected at smaller sizes and at earlier stages than women who participated in the eight RCTs, as illustrated by comparing the surrogate prognostic indicators of mammography as practiced today in the United States to those same indicators in any of the eight RCTs. Sickles (*30*) and Linver (*31*) have presented prognostic indicators of modern mammography in clinical practice in women 40–49, comparing them to the results of RCTs, suggesting that modern mammography in the United States should do a better job of detecting cancers and saving lives in women 40–49 than did the RCTs.

Conclusions

With the latest follow-up data from RCTs involving women 40–49, there is now convincing evidence of benefit from screening mammography to women of this age group. A statistically significant mortality reduction is shown at the 95% confidence level for women 40–49 at entry from two of the eight individual RCTs (Gothenburg and Malmö), from the combined data on women 40–49 from all eight RCTs, and from the combined data on women 40–49 from the five Swedish trials. These results indicate that screening mammography was effective in reducing breast cancer deaths among women 40–49 at entry with or without clinical breast exams, even with noncompliance of some women in the invited groups and mammography outside the trials among some women in the control groups. Even greater benefits should accrue today from regular screening mammography in women ages 40–49 than has been demonstrated by the collective results of the eight randomized controlled trials.

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Note

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