Annual screening with mammography and breast examination did not reduce breast cancer mortality in women 40 to 49 years of age

Miller AB, To T, Baines CJ, Wall C. **The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow up. A randomized screening trial of mammography in women age 40 to 49 years.** Ann Intern Med. 2002;137:305-12.

QUESTION

In women 40 to 49 years of age, does annual screening with mammography, clinical breast examination (CBE), and breast self-examination (BSE) instruction reduce breast cancer mortality to a greater extent than a single CBE and BSE instruction?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessors),* controlled trial with mean 13-year follow-up.

SETTING

15 centers in Canada.

PATIENTS

50 489 women who were 40 to 49 years of age, had no previous diagnosis of breast cancer, were not pregnant, and had not had mammography in the previous 12 months. 50 430 women (99.9%) were included in the analysis.

INTERVENTION

All women received an initial CBE and instruction on BSE and were allocated to annual screening comprising mammography, CBE, and instruction and evaluation on BSE (*n* = 25 214) or to usual care (*n* = 25 216).

MAIN OUTCOME MEASURE

Breast cancer mortality.

MAIN RESULTS

Analysis was by intention to treat. During the first 5 years after study entry, the groups did not differ for breast cancer mortality rates and did not differ at each successive year of follow-up to ≥ 9 years (Table). 105 breast cancer deaths occurred in the mammography group and 108 in the usual-care group. The study had 80% power to detect a 40% difference in breast cancer mortality between groups after 5 years.

CONCLUSION

In women 40 to 49 years of age, annual mammography and breast self-examination did not reduce breast cancer mortality more than a single breast examination and usual health care.

Sources of funding: 10 Canadian funding agencies.

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*See Glossary.

Annual breast cancer screening including mammography vs usual care to prevent breast cancer mortality†

Years of follow-up	Cumulative breast cancer mortality rates/10 000 persons		Rate ratio (95% CI)
	Mammography	Usual Care	
2 to 5	2.26	2.12	1.07 (0.75 to 1.52)
6	2.55	2.51	1.01 (0.73 to 1.41)
7	3.04	2.90	1.05 (0.78 to 1.42)
8	3.29	3.15	1.04 (0.78 to 1.40)
≥ 9	3.72	3.82	0.97 (0.74 to 1.27)

†All comparisons are not significant.

COMMENTARY

At first glance, these 2 reports seem inconsistent: Miller and colleagues' study is an update of the Canadian National Breast Screening Study, continuing to show no hint of benefit in women 40 to 49 years of age; Humphrey and colleagues' review is a USPSTF meta-analysis extending a recommendation for mammography to this age group for the first time. Ironically, the Canadian study was judged to be the highest-quality study of all those evaluated by the USPSTF. Even with > 50 000 participants, the Canadian study did not have the power to detect a protective effect < 40%; the USPSTF meta-analysis found a much smaller benefit of 15% in the 40- to 49-year age group. The 95% confidence intervals/credible intervals of the reduction in breast cancer mortality in the 2 studies (0.74 to 1.27 vs 0.73 to 0.99) overlap widely. The absolute reduction in breast cancer mortality is low in all age groups. For women 40 to 49 years of age, it is estimated to be < 1/10 000 per year. For older women, the benefit is slightly greater and the confidence intervals more clearly exclude the null result.

At what price is this modest benefit obtained? Surprisingly, in the appendix the USPSTF states: "A systematic review of adverse effects was beyond the scope of our review." The evidence for adverse effects includes false-positive results, believed to occur in 6.5% of mammograms (1); radiogenic breast cancer, estimated by the USPSTF to negate < 10% of the breast mortality benefit; and diagnosis and treatment of cancer that may not become clinically important. In the Canadian study, about 14% more diagnoses of in situ or invasive breast cancer occurred in the screened group than in the usual-care group; this difference persisted to almost 10 years after the intervention ended. In 2 Swedish trials including older women, 35% more women received major surgery (mastectomy or lumpectomy) and 25% more women received radiation in the screened groups (2). These results suggest that this may be a more substantial problem than previously thought.

How can we convey these results to our patients? For women 40 to 49 years of age, the estimated benefit of mammography is small (15%, or < 1/10 000 breast cancer deaths prevented per y) and the evidence of benefit is weak, with confidence intervals nearly overlapping 1. The risk for false-positive results is higher at this age, as is the potential for radiation carcinogenesis (3). The absolute benefit might be greater in women at high risk because of a positive family history. However, mammography has been shown to be less sensitive in this group (4),

Review: Mammography reduces breast cancer mortality rates

Humphrey LL, Helfand M, Chan BK, Woolf SH. **Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force.** Ann Intern Med. 2002;137:347-60.

QUESTION

How effective is breast cancer screening with mammography, clinical breast examination (CBE), and breast self-examination (BSE) in preventing breast cancer mortality?

DATA SOURCES

Studies were identified by searching MEDLINE (1994 to 2001), PREMEDLINE (December 2001 to February 2002), and the Cochrane Controlled Trials Register; reviewing the reference lists of previous reviews, commentaries, and meta-analyses; and contacting experts in the field.

STUDY SELECTION

Studies were selected if they were randomized controlled trials (RCTs) of breast cancer screening and had a relevant clinical outcome (advanced breast cancer, breast cancer mortality, or all-cause mortality).

DATA EXTRACTION

Data were extracted on patient population, study design, potential flaws, missing information, analysis, and length of follow-up. U.S. Preventive Services Task Force (USPSTF) criteria were used to assess study quality (good, fair, or poor). The primary endpoint was breast cancer mortality.

MAIN RESULTS

8 RCTs (479 987 women) (154 publications) met the selection criteria: 4 evaluated mammography, and 4 evaluated mammography plus CBE. 7 trials were rated fair quality, and 1 was rated poor quality. The mean follow-up period was 14 years. Meta-analysis of the 7 fair-quality trials showed that mammography screening led to a modest reduction in breast cancer mortality across all age groups, with greater benefit conferred in older women (Table). The results were consistent with those of 5 of 7 previous meta-analyses identified in the search for trials. Mortality reductions in trials of mammography plus CBE were similar to those of trials of mammography alone. 2 RCTs of BSE met the selection criteria. Both trials showed no difference in breast cancer mortality rates in women instructed in BSE and in noninstructed women.

CONCLUSIONS

Fair-quality evidence from randomized controlled trials shows that mammography screening is effective in reducing breast cancer mortality. Biennial and annual screening are equally effective. Clinical breast examination confers no additional benefit. Instruction in breast self-examination, as a single screening method, is ineffective.

Source of funding: Agency for Healthcare Research and Quality.

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Screening with mammography vs usual care to prevent breast cancer mortality at mean 14-year follow-up*

Age groups	Number of trials†	RRR (95% CrI)	NNS (CrI)
All ages (39 to 74 y)	7	16% (9 to 23)	1224 (665 to 2564)
< 50 y	7	15% (1 to 27)	1792 (674 to 10 540)
≥ 50 y	7	22% (13 to 30)	838 (494 to 1676)

*CrI = credible interval; NNS = number needed to screen. Other abbreviations defined in Glossary.
†The meta-analysis excluded the trial rated as poor quality.

COMMENTARY   *(continued from page 38)*

and if the family history results from inherited radiation sensitivity (5), the risk for radiogenic breast cancer will be further increased.

For women ≥ 50 years, the evidence of a 20% to 25% relative benefit in breast cancer mortality is stronger and exceeds 1/10 000 per year. An important issue in this group is the discovery of cancer that might not have caused symptoms, especially in women with comorbid conditions and a limited life span.

Unfortunately, it is clear that most breast cancer deaths will not be prevented by mammography at any age. Perhaps the enormous resources devoted to the debate, promotion, and provision of mammography could be better used to study the efficacy of more sensitive detection systems (6) or to develop predictive models with greater discriminatory power (7).

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References
1. **Christiansen CL, Wang F, Barton MB, et al.** Predicting the cumulative risk of false-positive mammograms. J Natl Cancer Inst. 2000;92:1657-66.
2. **Gotzche PC, Olsen O.** Is screening for breast cancer with mammography justifiable? Lancet. 2000;355:129-34.
3. **Feig SA, Ehrlich SM.** Estimation of radiation risk from screening mammography: recent trends and comparison with expected benefits. Radiology. 1990;174:638-47.
4. **Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V.** Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA. 1996;276:33-8.
5. **Su Y, Swift M.** Mortality rates among carriers of ataxia-telangiectasia mutant alleles. Ann Intern Med. 2000;133:770-8.
6. **Stoutjesdijk MJ, Boetes C, Jager GJ, et al.** Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst. 2001;93:1095-102.
7. **Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA.** Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst. 2001;93:358-66.