Screening Women Aged 40-49 Years: Where Are We Today?

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The fact that mammographic screening can reduce deaths from breast cancer is well established and is unarguably true for women aged 50-69 years (*1,2*). While the unique value of mammography in the early detection of breast cancer is also well established, it is less certain if early detection results in similar mortality reductions for women diagnosed with breast cancer between the ages of 40 and 49 years compared with women aged 50 years and older. This uncertainty is, at the outset, the result of an inadequate base of scientific data. Specifically, no trial to date, with the exception of the Canadian National Breast Screening Study (NBSS-1), was designed to have adequate statistical power to test the hypothesis of a benefit from mammography for women aged 40-49 years, and the results are not universally accepted due to concerns about study methodology. While the majority of these trials suggest a benefit for women aged 40-49 years, none of the observed mortality differences in individual studies has achieved conventional criteria for statistical significance (*3*). Periodic updates of trial data have been published, but small sample sizes in individual studies remain a limiting factor. However, there are other limiting factors that potentially influence trial results, and these factors may have been especially influential on outcomes for women aged 40-49 years. These factors include mammographic technique, one versus two views, and the interval between screenings. To address the limitations of small sample sizes and these quality-assurance elements, trial data have been combined in meta-analyses (*4-6*) and applied to simulation models (*7-9*).

In this issue of the Journal, de Koning et al. (*10*) apply the MISCAN (MIcrosimulation SCreening ANalysis) simulation model to the Swedish trial data to address three fundamental questions. 1) What proportion of the mortality reduction in the 40- to 49-year-old group is attributable to a diagnosis after age 50 years? 2) What reduction in breast cancer mortality can be expected if the Swedish trial results are applied to present and future screening programs? 3) Do differences in trial characteristics explain some of the differences in the observed mortality reductions between the trials? In all probability, the first question will receive the greatest attention, but the remaining two questions are important as well.

Applying the MISCAN model to the five Swedish trials, de Koning et al. compare observed and expected relative risks (RRs) under several different assumptions. Assuming no improvement in prognosis among screen-detected cancers diagnosed under 50 years of age and retaining the prognostic advantage for screen-detected cancers in women aged 50 years and older, the model still predicts an RR of 0.93. The 7% reduction in mortality results from the expected rate of diagnosis and survival among women who were under age 50 years at the time of entry in the trial but who were likely diagnosed with breast cancer after age 50 years. Assuming a 10% reduction in mortality on the basis of the Swedish overview analysis (*11*), de Koning et al. conjecture that up to 70% of the observed 10% benefit in the 40- to 49-year-old age group may derive from diagnosis after age 50 years.

It must be emphasized that evidence is lacking in the literature on the precise age at diagnosis for women in these trials. Just as we do not know which women in the 40- to 49-year-old cohort passed the age of 50 years before they were diagnosed with breast cancer, we likewise do not know which subset of women who entered the trial in their 50s was subsequently diagnosed in their 60s. While a majority of screens among the initially assigned group of women will be within that age group, some migration to the older age group for a subset of women is inevitable. Is this a neglected aspect of study design? In general the answer is no, since the goal of the trials was to address efficacy in a broad age range of women, generally beginning at age 40 years and continuing to age 60 years and older. Still, how compelling is the hypothesis that diagnosis after age 50 years contributes disproportionately to the observed mortality reduction in the age group 40-49 years? Because within-group aging will take place, some contribution to the observed reduction in deaths is to be expected, and in the simulation, it is certainly to be expected if the modeling exercise erases the prognostic improvement among women aged 40-49 years and retains it for those aged 50 years or older. A direct method of answering this question would be to use data on date of diagnosis. However, there are published data (*12,13*) that suggest that this estimate is high; more to the point, whatever true relative contribution exists may also be influenced by the screening protocols and the level of sensitivity estimated from the Dutch screening studies. Data from the Health Insurance Plan (HIP) of Greater New York study showed a greater contribution to the reduction in deaths in the 40- to 49-year-old group occurring in women aged 40-44 years at entry compared with women aged 45-49 years at entry (35.7% versus 15.2%), and data from the two-county trial also show similar results when comparing the mortality reduction in women aged 40-44 years with that in women aged 45-49 years (35% versus –9%) (*12,13*). On this question, the present model may be limited in other ways. By fitting the model with sensitivity derived from the Dutch screening projects, sensitivity estimates may vary from the actual sensitivity achieved in the different Swedish trials for women aged 40-49 years (*7*). de

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See "Note" section following "References."

Koning et al. correctly note that differences in the observed and expected RRs may be due to important differences in the quality of screening that are yet unquantified. It may be that sensitivity is actually higher for ductal carcinoma in situ (DCIS) compared with a T1a lesion, insofar as DCIS is often associated with calcifications that may be more apparent in the denser breast than a subtle architectural density. In another analysis of Nijmegen data, calcifications were associated with fewer screening errors than were densities (*14*). The assumption of linear variability by age of the patient and disease stage is also questionable. Other factors that may have served to seemingly depress sensitivity in the Dutch screening program are single-view mammography, screening every 2 years, and the desire to maximize specificity (*14,15*). In a recent analysis of two-county data, Tabar et al. (*7*) estimated that a 19% reduction in deaths could have been achieved if the screening interval had been 1 year rather than 2 years. Furthermore, in a recent comparison of Dutch data with data from a U.S. screening program in California, results were remarkably similar for women aged 50 years and older and remarkably dissimilar for women under age 50 years. Among women aged 40-49 years in the California data, the rate of screen-detected cancers under 10 mm was 41% versus 19% in the Nijmegen data. The rate of lymph node-positive cancers in the age group 40-49 years was more than three times higher in the Nijmegen program (39%) than in the California program (12%). Finally, it has been clear that a mortality reduction does not appear as early for women aged 40-49 years as it does for women aged 50 years and older. In this particular analysis, taking advantage of more recent trial data would have offered the benefit of a longer period of follow-up and, in several instances, a greater observed reduction in mortality (*6*).

The question of screening efficacy in the 40-49 age group has been an issue for debate since the publication of early results of the HIP of Greater New York study (*1,16*). However, the debate gained additional momentum after publication of initial results from the NBSS-1 that not only showed no reduction in deaths, but also showed a nonsignificant 36% excess in the death rate among women invited to participate in screening compared with those who received usual care (*17*). Since that publication, several international meetings have addressed the specific question of the value of screening women aged 40-49 years. In February 1993, the National Cancer Institute (*18*) and the American Cancer Society (ACS) (*19*) each convened meetings in which experts were asked to review new data, and in September 1993, the International Union Against Cancer (UICC) (*20*) convened a meeting to further address the issue with an emphasis on policy recommendations. The conclusions of two work groups at the UICC meeting are worth noting. Work group 1 concluded that analysis of existing trial data should continue but that there was little long-range potential with these data to resolve the ultimate question of efficacy for women aged 40-49. Since the question was worth answering, a new trial was proposed and a study is currently under way to determine the feasibility of such a trial in Europe. Work group 2 likewise acknowledged the uncertainty of the existing data and noted that the available data were sufficient to support guidelines and policy to begin screening at either age 40 years or age 50 years.

While we do not have the same quality of evidence about the efficacy of mammography in women aged 40-49 years compared with women aged 50 years and older, there are compelling data that mammography is beneficial to the 40-49 age group. First, a recent meta-analysis, excluding the NBSS-1, estimated a statistically significant 24% benefit reduction in breast cancer mortality among the group invited to participate in screening (*6*). Other analyses have demonstrated equivalent long-term survival times for women aged 40-49 years compared with women aged 50 years and older when tumors were grouped by tumor size, lymph node status, and histologic grade (*21*). Reports from screening centers have demonstrated comparatively favorable distribution of tumor characteristics in women aged 40-49 years compared with women aged 50 years and older (*15*). Taken together, data from the most recent trial updates, modeling that addresses prior screening protocol limitations, and emerging data from clinical centers add to the body of evidence that suggests a possible benefit for women in their 40s. Results are consistent with trial data that show improved prognosis with tumors detected early with mammography. These analyses also suggest that the screening regimens evaluated in some trials, i.e., screening every 2 years, single-view mammography, etc., were less sensitive for women aged 40-49 compared with women aged 50 years and older. Rather than evaluate these results and conclude that mammography is simply less beneficial to women aged 40-49, a very practical use of trial data has been to demonstrate that improved sensitivity would likely be achieved with annual, two-view screening. It is also likely that improvements in the technical quality of mammography have contributed to improved sensitivity as well.

If a screening program places emphasis on high quality, i.e., regular attendance and high-quality imaging and interpretation, there is reason to believe that similar performance should be attainable for women aged 40-49 years compared with women aged 50 years and older. It is likely that the adherence to high quality is especially important in premenopausal women, given shorter lead times and a greater prevalance of women with denser breasts in this age group. The value of the MISCAN model is that it can apply sensitivity analysis to these different parameters. It can demonstrate the sobering reality that poor screening quality, measured by varying estimates of screening parameters, such as participation rates and sensitivity, may mean that results will be disappointing. However, modeling also creates the opportunity to project the outcome of a screening program that adhered strictly to quality-assurance guidelines and performance monitoring. Applied this way, these models serve not only to demonstrate the costs and benefits of varying levels of performance, but by demonstrating the potentially greater reduction in mortality that is attainable from achieving a high level of performance, to motivate as well.

References

(*1*) Shapiro S. Evidence on screening for breast cancer from a randomized trial. Cancer (Suppl) 1977;39:2772-82.

(*2*) Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1985;1:829-32.

(3) Hurley SF, Kaldor JM. The benefits and risks of mammographic screening for breast cancer. Epidemiol Rev 1992;14:101-30.
(4) Elwood JM, Cox B, Richardson AK. The effectiveness of breast cancer screening by mammography in younger women [*see* comment citations in Medline]. Online J Curr Clin Trials 1993; Doc. 32.
(5) Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. JAMA 1995;273:149-54.
(6) Smart CR, Hendrick RE, Rutledge JH, Smith RA. Benefit of mammography screening in women aged 40-49: current evidence from randomized controlled trials. Cancer 1995;75:1619-26.
(7) 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.
(8) Feig SA. Estimation of currently attainable benefit from mammographic screening of women aged 40-49 years. Cancer 1995;75:2412-9.
(9) van Oortmarssen GJ, Habbema JD, van der Maas PJ, de Koning HJ, Collette HJ, Verbeek AL, et al. A model for breast cancer screening. Cancer 1990;66:1601-12.
(10) de Koning HJ, Boer R, Warmerdam PG, Beemsterboer PM, van der Maas PJ. Quantitative interpretation of age-specific mortality reductions from the Swedish Breast Cancer-Screening Trials. J Natl Cancer Inst 1995;87:1217-23.
(11) Nystrom L, Rutqvist LE, Wall S, Lindgren A, Lindqvist M, Ryden S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials [*see* comment citation in Medline]. Lancet 1993;341:973-8.
(12) Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer: the Health Insurance Plan Project and its sequelae, 1963-1986. Baltimore: Johns Hopkins Press, 1988.
(13) Tabar L, et al. Screening for breast cancer in women aged under 50. J Med Screening. In press.
(14) van Dijck JA, Verbeek AL, Hendriks JH, Holland R. The current detectability of breast cancer in a mammographic screening program. A review of the previous mammograms of interval and screen-detected cancers [*see* comment citation in Medline]. Cancer 1993;72:1933-8.
(15) Curpen BN, Sickles EA, Sollitto RA, Ominsky SH, Galvin HB, Frankel SD. The comparative value of mammographic screening for women 40-49 years old versus women 50-64 years old [*see* comment citation in Medline]. AJR Am J Roentgenol 1995;164:1099-103.
(16) Shapiro S, Venet W, Strax P, Venet L, Roeser R. Ten- to fourteen-year effect of screening on breast cancer mortality. J Natl Cancer Inst 1982;69:349-55.
(17) Miller A, Baines C, To T, Wall C. Canadian National Breast Screening Study: 1. breast cancer detection and death rates among women aged 40 to 49 years [published erratum appears in Can Med Assoc J 1993;148:718] [*see* comment citations in Medline]. Can Med Assoc J 1992;147:1459-76.
(18) Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the International Workshop on Screening for Breast Cancer. J Natl Cancer Inst 1993;85:1644-56.
(19) Lawrence W, Smith RA. Conference summary: American Cancer Society Workshop on Breast Cancer Detection in Younger Women. A current assessment. Cancer 1993 (Suppl);72:1491-97.
(20) Eckhardt S, Badellino F, Murphy GP. UICC meeting on breast-cancer screening in premenopausal women in developed countries. Geneva, 29 September-1 October 1993. Int J Cancer 1994;56:1-5.
(21) Tabar L, Duffy SW, Burhenne LW. New Swedish breast cancer detection results for women aged 40-49. Cancer 1993 (Suppl);72:1437-48.

Note

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