Preventive health care, 2001 update: screening mammography among women aged 40–49 years at average risk of breast cancer

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Abstract

Objective: A previous review by the Canadian Task Force on the Periodic Health Examination (now the Canadian Task Force on Preventive Health Care) in 1994 indicated fair evidence to exclude mammographic breast cancer screening of women aged 40–49 from the periodic health examination. This current review considers the available new and updated evidence regarding the effect of screening mammography on breast cancer mortality among women in this age group at average risk of breast cancer.

Options: Screening mammography starting at either age 40 or age 50.

Outcome: Reduction in breast cancer mortality.

Evidence: The MEDLINE and CANCERLIT databases were searched for relevant articles published from 1966 to January 2000. Of 68 references obtained, at least 22 were published after the 1994 review. To date, the only trial designed to assess the mortality benefits of screening mammography among women aged 40–49 did not have adequate power to exclude a clinically significant benefit. Other results from randomized controlled trials (RCTs) are post-hoc subgroup analyses of larger trials.

Benefits, harms and costs: Screening mammography offers the potential for significant benefits in addition to mortality reduction, including early diagnosis, less aggressive therapy and improved cosmetic results. However, the risks of screening include increased biopsy rates and the psychological effects of false reassurance or false-positive results. Although several of the trials reviewed constitute level I evidence (RCT), at present their conflicting results, methodologic differences and, most important, uncertainty about the risk:benefit ratio of screening precludes the assignment of a “good” or “fair” rating to recommendations drawn from them.

Values: The strength of evidence was evaluated using the methods of the Canadian Task Force on Preventive Health Care. A high value was placed on changes in survival. When evidence was available, value was also placed on potential quality-of-life implications.

Recommendation: Current evidence regarding the effectiveness of screening mammography does not suggest the inclusion of the manoeuvre in, or its exclusion from, the periodic health examination of women aged 40–49 years at average risk of breast cancer (grade C recommendation). Upon reaching the age of 40, Canadian women should be informed of the potential benefits and risks of screening mammography and assisted in deciding at what age they wish to initiate the manoeuvre.

Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care.

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In 1999, there were 18 700 new cases of breast cancer and 5400 deaths from the disease.\textsuperscript{1} For women at average risk, secondary prevention (early detection) may reduce breast cancer mortality. Randomized controlled trials (RCTs) have shown that screening mammography reduces mortality among women aged 50–70. However, the Canadian National Breast Screening Study (NBSS-I)\textsuperscript{2} did not show a reduction in mortality among women aged 40–49.\textsuperscript{1} In 1994 the Canadian Task Force on the Periodic Health Examination (now the Canadian Task Force on Preventive Health Care) concluded that there was fair evidence to exclude screening with clinical examination and mammography in this age group (grade D recommendation).\textsuperscript{4}

Currently, Canadian women under 50 are not recruited for breast cancer screening, but they are accepted for screening in 7 of 11 Canadian regions (Gloria Low, Health Canada: unpublished data, December 1999).

A total of 7 RCTs have included women aged 40–49. In recent updates, 2 Swedish trials\textsuperscript{5,6} showed a statistically significant benefit of screening mammography in subgroup analyses. The most recent meta-analyses showed conflicting results. In one analysis, which included all 7 trials, a statistically significant relative risk reduction of 18% was shown,\textsuperscript{7} but a second analysis of only 2 trials that the authors considered unbiased found no effect.\textsuperscript{8}

Current guidelines for screening mammography among women aged 40–49 are conflicting. The American Association for Cancer Research\textsuperscript{9} and the National Institute of Health recommend against universal screening.\textsuperscript{10} In contrast, the American Cancer Society\textsuperscript{11} and the National Cancer Institute\textsuperscript{12} advise screening every 1–2 years.

The goal of this review was to update the 1994 task force recommendation using recent evidence, and to consider other positive and negative effects of screening mammography among women aged 40–49.

Methods

A computerized search of the MEDLINE and CANCERLIT databases for articles published from 1966 to January 2000 was conducted using the following MeSH (medical subject heading) terms: “prevention and control” + “mammography” + “breast neoplasms”; and “mammography” + “breast neoplasms” + any 1 of the following 21 terms: “controlled clinical trials,” “randomized controlled trials,” “double-blind method,” “random allocation,” “prospective studies,” “cohort studies,” “meta-analysis” or author names Nystrom, Rutqvist, Wall, Lindgren, Lindqvist, Ryden, Andersson, Bjurstam, Fagerberg, Frisell, Shapiro, Tabar, Miller, Baines. Trials meeting all of the inclusion criteria (Table 1) were reviewed. No trials were excluded by the chosen criteria.

For studies showing a reduction in mortality from screening mammography, the number needed to screen (NNS) for 10 years to prevent 1 death was calculated as the reciprocal of the absolute risk reduction attributed to screening. This terminology is analogous to the number needed to treat to prevent 1 death in therapy trials.\textsuperscript{13}

Similarly, MEDLINE and CANCERLIT were searched and reference lists manually reviewed to identify studies that measured the physical and psychological effects of mammography. Because no RCTs assessed these issues as primary outcomes, cohort, case–control and cross-sectional studies were reviewed.

The evidence was reviewed systematically using the methodology of the Canadian Task Force on Preventive Health Care.\textsuperscript{14} In brief, the principal author rated the quality of the evidence using the methodological hierarchy and circulated a preliminary draft of the manuscript to the task force members. The task force met in May 1998, at which time the final decisions on recommendations were arrived at unanimously by the group and the principal author. Feedback from 3 independent experts was incorporated into a final draft of the manuscript, which was reviewed by the task force chairman before submission for publication.

Quality and rating of the evidence

The search yielded 23 articles. Review of the reference lists provided an additional 45 papers, including a newly published RCT and 2 additional meta-analyses. A total of 7 RCTs and 6 meta-analyses were reviewed. The methodology and quality of each trial is summarized in Tables 2 and 3. The most recent meta-analyses\textsuperscript{7,8} were appraised according to the criteria described by L’Abbe and colleagues.\textsuperscript{41}

Randomized controlled trials

All 7 RCTs used intention-to-treat analyses and had breast cancer mortality as the primary outcome. Two of the trials showed benefit among women aged 40–49; the results of one (the Gothenburg trial\textsuperscript{15}) were analysed only once, and those of the other (the Malmo trial\textsuperscript{6,19,20}) were analysed by the study authors twice.

Most of the trials lacked the power to exclude a potentially clinically significant difference, such as a relative risk reduction of 20%. No sample size calculations were published for the Gothenburg Breast Screening Trial,\textsuperscript{15} the combined Malmo I and II trials,\textsuperscript{4} the Swedish Two-County Trial\textsuperscript{10} or the Stockholm Mammographic Screening Trial.\textsuperscript{40} The sample size for the Malmo I trial was chosen to detect a 25% reduction in mortality (among women aged 45–69) with an $\alpha$ of 0.05 and a $\beta$ of 0.10. In many cases the calculated power was undermined by poor compliance and cont-

### Table 1: Inclusion and exclusion criteria used to select studies for review of screening mammography among women aged 40–49

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Women aged 40–49 at average risk of breast cancer included, either as entire sample or as subgroup</td>
<td></td>
</tr>
<tr>
<td>Screening mammography used, either alone or in combination with clinical breast examination</td>
<td></td>
</tr>
<tr>
<td>Breast cancer mortality assessed as primary outcome</td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trial (RCT), or meta-analysis including all eligible RCTs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum follow-up &lt; 10 years</td>
</tr>
<tr>
<td>Outcome ascertainment &lt; 90% complete</td>
</tr>
</tbody>
</table>
amination (Table 3). The Health Insurance Plan (HIP) Trial13 planned for power to detect a 20% reduction in mortality but found a 25% reduction in relative risk that failed to reach statistical significance. The Edinburgh team calculated a sample size of 65,000 women for 80% power to detect a 35% reduction in relative risk at 7 years with a 1-sided p value of 0.05.27 All of the above trials assessed women aged 40–49 as post hoc subgroups. The NBSS-1, which included only this age group, calculated a sample size to provide 80% power to detect a 40% reduction in mortality but found a 25% reduction in relative risk that failed only this age group, calculated a sample size to provide 80% power to detect a 40% reduction in 5-year mortality with a 1-sided p value of 0.05; however, the mortality rate in the control group was less than predicted, and contamination was not considered. For the 10.5-year follow-up,16 actual power was estimated to be adequate to detect a mortality reduction of 30% or more, with a 2-sided p value of 0.05.

The following discussion focuses on recent updates of the individual trials.

HIP Trial (1963–1970): The most recent update included 18 years of follow-up and considered all deaths from breast cancer diagnosed in the 5 years following the first screening.18 Among women aged 40–49 at the first screen (14,432 invited and 14,701 control subjects), a nonsignificant reduction of 25% in mortality was found, with 50 and 66 deaths observed in the 2 groups respectively. Results of heterogeneity tests by age were negative. Only 25% of the cases were detected by mammography alone.17


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**Table 2: Relative risk of death from breast cancer reported in RCTs of screening mammography among women aged 40–49 at study entry**

<table>
<thead>
<tr>
<th>Trial*</th>
<th>Years of screening</th>
<th>Regimen (and interval)</th>
<th>Length of follow-up, yr</th>
<th>Group; no. of women</th>
<th>RR (and 95% CI)</th>
<th>NNS</th>
<th>Level of evidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP‡</td>
<td>1963–1970</td>
<td>CBE + M (12 mo)</td>
<td>18</td>
<td>Study 14 432</td>
<td>14 701</td>
<td>0.8 (0.53–1.11)</td>
<td>NA</td>
</tr>
<tr>
<td>Malmo§</td>
<td>1976–1990</td>
<td>M (18–24 mo)</td>
<td>10–15.5</td>
<td>Control 13 528</td>
<td>12 242</td>
<td>0.6 (0.45–0.89)</td>
<td>500</td>
</tr>
<tr>
<td>Two County¶</td>
<td>1977–1985</td>
<td>M (24 mo)</td>
<td>13</td>
<td>Study 19 844</td>
<td>15 604</td>
<td>0.9 (0.54–1.41)</td>
<td>NA</td>
</tr>
<tr>
<td>Edinburgh‡</td>
<td>1979–1988</td>
<td>CBE + M (24 mo)¶</td>
<td>10–14</td>
<td>Control 11 505</td>
<td>10 269</td>
<td>0.8 (0.51–1.32)</td>
<td>NA</td>
</tr>
<tr>
<td>NBSS-1‡</td>
<td>1980–1988</td>
<td>M (12 mo)</td>
<td>10.5</td>
<td>Study 25 214</td>
<td>24 216</td>
<td>1.1 (0.83–1.56)</td>
<td>NA</td>
</tr>
<tr>
<td>Stockholm¶</td>
<td>1981–1985</td>
<td>M (28 mo)</td>
<td>11.4</td>
<td>Control 14 842</td>
<td>7 108</td>
<td>1.1 (0.54–2.17)</td>
<td>NA</td>
</tr>
<tr>
<td>Gothenburg†</td>
<td>1982–1992</td>
<td>M (18 mo)</td>
<td>10</td>
<td>Study 11 724</td>
<td>14 217</td>
<td>0.6 (0.31–0.96)</td>
<td>782</td>
</tr>
</tbody>
</table>

CBE = clinical breast examination, M = mammography, RR = relative risk, CI = confidence interval, NNS = number needed to screen for 10 years to prevent 1 death from breast cancer. 

*HIP = Health Insurance Plan Trial, Malmo = Malmö I and II Mammographic Screening Trials, Two County = Swedish Two-County Trial, Edinburgh = Edinburgh Randomized Trial, NBSS-1 = Canadian National Breast Screening Study 1, Stockholm = Stockholm Breast Cancer Screening Trial, Gothenburg = Gothenburg Breast Screening Trial. 

†Post-hoc subgroup analysis in all trials except the NBSS-1. 

‡Included only women aged 45–49. 

¶CBE was annual, M was every 2 years. 

§Trial lacked power to exclude a potentially significant reduction of 20% in relative risk.

**Table 3: Methodology of breast cancer screening trials involving women aged 40–49**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample</th>
<th>Method of randomization</th>
<th>Contamination, %†</th>
<th>Compliance with first exam, %</th>
<th>Mammogram views</th>
<th>Radiation dose per breast</th>
<th>Blinded double reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP</td>
<td>Members of HMO</td>
<td>Age-matched random sample</td>
<td>Unlikely</td>
<td>57</td>
<td>2 (CC + ML)</td>
<td>5 cGy</td>
<td>All films</td>
</tr>
<tr>
<td>Malmo</td>
<td>Random 50% of residents</td>
<td>Cluster by birth year</td>
<td>35</td>
<td>75</td>
<td>2 initial (CC + MLO), then 1–2</td>
<td>1 mGy</td>
<td>No</td>
</tr>
<tr>
<td>Two County</td>
<td>All residents</td>
<td>Cluster by area</td>
<td>NR</td>
<td>88–93‡</td>
<td>1 (MLO)</td>
<td>1.1 mGy</td>
<td>No</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>Patients of participating GPs</td>
<td>Cluster by practice</td>
<td>NR</td>
<td>63.8‡</td>
<td>2 initial (CC + MLO), then 1–2</td>
<td>6 mGy</td>
<td>Random sample (5%) + abnormal films</td>
</tr>
<tr>
<td>NBSS-1</td>
<td>Volunteers</td>
<td>Individual</td>
<td>26.4</td>
<td>86–90</td>
<td>2 (CC + ML or MLO)</td>
<td>5 mGy</td>
<td>Random sample (10% abnormal + 1% normal)</td>
</tr>
<tr>
<td>Stockholm</td>
<td>All residents</td>
<td>Cluster by birth date</td>
<td>25–30</td>
<td>80</td>
<td>1 (MLO)</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>All residents</td>
<td>18% cluster by birth date; 82% individual</td>
<td>51</td>
<td>75–86</td>
<td>2 initial (CC + MLO), then 1–2; moving screen</td>
<td>NR</td>
<td>All films from fourth round onward</td>
</tr>
</tbody>
</table>

Note: HMO = health maintenance organization, NR = not reported, CC = craniocaudal, ML = mediolateral, MLO = mediolateral oblique, GP = general practitioner.

†% of control subjects who underwent screening mammography.

‡Values for subgroup < age 50.
and 1932 were randomly assigned to study groups between 1976 and 1978. In Malmo II, women born between 1933 and 1945 were randomly assigned between 1978 and 1990. A subgroup of 7984 women in the Malmo I cohort were aged 45–49 at entry. In Malmo II, there were 17 786 women aged 45–48 at entry; the women had a mean of 5 rounds of screening, and follow-up was 10 years on average.

The first combined analysis of Malmo I and II data was limited to women entering the studies at age 44–49. In the screening group (13 528 women, contributing 165 596 woman-years of follow-up) there were 57 deaths, and in the control group (12 242 women, contributing 144 036 woman-years of follow-up) there were 78. The point estimate of relative risk was 0.64 (95% confidence interval [CI] 0.45–0.89, \( p = 0.0009 \)). From these results, the absolute risk reduction of 0.02% per year translates to a number needed to screen for 1 year to prevent 1 death from breast cancer of 5067.91, which corresponds to the authors’ estimate of 500 for screening women aged 45–49 every 18–24 months for 12.5 years.

**Swedish Two-County Trial — Ostergotland (1977–1984) and Kopparberg (1978–1985):** The most recent mortality analysis had a follow-up of 13 years on average. The subgroup of women aged 40–49 at study entry (19 844 invited and 15 604 control subjects) had a nonsignificant relative risk of 0.87 (95% CI 0.54–1.41). Only 39 and 45 deaths occurred in the 2 groups respectively. Heterogeneity by age at randomization was not found. The point estimates of relative risk differed in the 2 counties, with a subgroup relative risk of 1.02 (95% CI 0.52–1.99) in Ostergotland and 0.73 (95% CI 0.37–1.41) in Kopparberg.

**Edinburgh Randomized Trial (1979–1988):** Women aged 45–64 entered the trial between 1979 and 1981, with others entering if they turned 45 before 1985. No statistically significant differences in mortality were observed between the study and control groups. Subgroup analysis of women aged 45–49 at enrolment (with 14 years of follow-up in the 11 391-person subgroup from the original cohort and 10–12 years of follow-up in the 10 383-person group entering from 1982 to 1985) showed a relative risk of 0.82 (95% CI 0.51–1.32); no heterogeneity was observed relative to all trial participants. In all, there were 46 deaths from breast cancer among the 11 505 women in the study group and 52 among the 10 269 control subjects. Socioeconomic status was a confounding factor in the study. Correction for this factor eliminated the difference in mortality from causes other than breast cancer and gave a relative risk of 0.75 (95% CI 0.48–1.18) in the subgroup aged 40–49 at enrolment.

**Canadian National Breast Screening Study 1 (1980–1988):** The NBSS-1 is the only study limited to women aged 40–49. Concerns about subversion of randomization have not been supported by internal and external reviews or by examination of an alternative data source. Participants had a higher socioeconomic status, more risk factors for breast cancer and smoked less heavily than the Canadian population. An imbalance in the number of women with more than 3 lymph nodes involved was seen in the study and control groups: 17 versus 5 at randomization (\( p = 0.017 \)) and 47 versus 23 at 7 years (\( p = 0.006 \)). Fewer lymph node dissections in the control group and more deaths among women with node-negative disease suggest that the difference could have been due to more aggressive surgery among women undergoing screening. No difference in mortality was observed between the study and control groups. Follow-up to the end of 1993 (8.75–13 years) revealed 82 deaths from breast cancer among the 25 214 women screened, and 72 among the 25 216 control subjects. The relative risk was 1.14 (95% CI 0.83–1.56).

**Stockholm Breast Cancer Screening Trial (1981–1985):** The subgroup of women aged 40–49 at entry included 14 842 invited to undergo screening and 7108 control subjects. In the 173 866 woman-years of follow-up for the screened women, 24 deaths from breast cancer were observed, as compared with 12 deaths in the 87 826 woman-years of follow-up for the control subjects. With a mean follow-up of 11.4 years the relative risk was 1.08 (95% CI 0.54–2.17). No statistically significant differences in mortality were observed between the 2 groups.

**Gothenburg Breast Screening Trial (1982–1992):** The long-awaited results of this trial were published in 1997. All female residents of Gothenburg, Sweden, born between 1923 and 1944 were randomly assigned to mammography every 18 months for 5 rounds or to control status with a single mammogram at trial completion. Cluster randomization was used for the 1923–1936 cohort and individual randomization for the 1936–1944 cohort. Data were analyzed for a subgroup of 25 941 women aged 39–49 at study entry (82% individually randomized) with at least 10 years of follow-up. A ratio of 1:1.2 was used to apportion the women, giving 11 724 women in the study group and 14 217 in the control group.

The study group had 18 deaths over 138 402 woman-years of follow-up, and the control group had 40 deaths over 168 025 woman-years of follow-up. The relative risk was 0.55 (95% CI 0.31–0.96, \( p = 0.046 \)). The absolute risk reduction of 1.28 per 1000 (mortality rates of 2.8 per 1000 in the control group v. 1.5 per 1000 in the study group) translated into a number needed to screen of 782 for the 5 screens at 18-month intervals.

**Meta-analyses**

Table 4 summarizes the 6 meta-analyses reviewed. The most recent meta-analysis of all the trials had a mean follow-up of 12.7 years (minimum 10.5 years), included an additional 17 000 participants in the Malmo II trial and used updated results for all the trials except the HIP trial. It also showed a statistically significant benefit (relative risk 0.82, 95% CI 0.71–0.95). This meta-analysis was the first to include all participants aged 40–49 in RCTs measuring breast cancer mortality. No attempt was made to assess the rela-
tive quality of the trials. Homogeneity testing indicated no significant heterogeneity \( (p = 0.2) \).

A controversial new meta-analysis from the Nordic centre of the Cochrane Collaboration\(^5\) included only the NBSS and the Malmo I studies. The authors reviewed published reports and concluded, on the basis largely of the mean age in the intervention and control groups, that randomization in the HIP, Malmo II, Swedish Two-County, Edinburgh, Stockholm and Gothenburg trials had been inadequate. Not surprisingly, the analysis was dominated by the negative findings of the NBSS and showed no benefit of screening mammmography (relative risk 1.04, 95% CI 0.84–1.27). This analysis has been criticized\(^{10,11}\) and will no doubt continue to be debated. It is difficult, however, to imagine that selecting 1.5 of 7 trials does not introduce bias.

**Effects of screening mammography**

Any benefit of reduced mortality is offset at least in part by the potential adverse effects of screening mammography. Positive and negative effects of screening not related to mortality are shown in Table 5. Additional benefits of screening women aged 40–49 include the diagnosis of tumours of a smaller size and at an earlier stage than might be detected later.\(^{26}\) Advanced tumour size and stage are predictive of worse outcome.\(^{58,60}\)

The estimated risk of death from radiation-induced cancer is 8 per 100 000 women screened annually for 10 years beginning at age 40.\(^{48}\) This rate is much lower than the 65,\(^7\) 128\(^5\) or 200\(^6\) deaths per 100 000 women that might be prevented by screening over the same 10 years.

Over a decade of screening, 12.6% of younger women in the Malmo trial required additional mammograms and 0.56% had biopsies that showed benign lesions.\(^4\) In the Gothenburg trial 2.5% of the women were called back, 0.9% had fine-needle aspiration biopsies, and 0.1% had surgery that revealed benign disease.\(^5\) About 2–3 operations were done for every death prevented (number needed to treat \(= 3\)). In the United States a retrospective study of breast cancer screening and diagnostic evaluations in a community-based cohort revealed a biopsy rate of 5333 per 100 000 women screened 4 times on average in 10 years.\(^{21}\) By extrapolation (which overestimates false-positive results\(^{12}\)) to annual screening, the authors estimated a false-positive biopsy rate of 18.6% (95% CI 9.8%–41.2%) and a risk of 56% (95% CI 39%–76%) of any additional investigation. A similar extrapolation using British Columbia data suggested a 38% cumulative 10-year risk of any false-positive result.\(^{14}\) Specialized screening centres such as those used in the Swedish trials may minimize the impact of false-positive screening results.

The psychological effects of screening have been investigated in 12 studies, most included in a recent review.\(^{77}\) On the day of screening, women had less anxiety and depression than at baseline.\(^{64}\) Lower age was associated with increased anxiety.\(^{68}\) Increased emotional and physical dysfunction\(^{20}\) was seen only in women recalled for additional testing\(^70\) and resolved 8 months later.\(^{71}\) With time, psychological distress decreased in women with normal or false-positive mammograms or negative biopsy results,\(^7\) but it increased in those found to have cancer.\(^7\) In a US study\(^{42,43}\) 17% of women with mammograms arousing a suspicion of cancer reported anxiety, as compared with 3% of those with normal mammogram results. Anxiety levels did not predict compliance with future screening. In a retrospective survey of NBSS participants,\(^9\) 72% of women felt “reassured” by screening. Less information is available on the effects of false-negative screening.

**Table 5: Effects of screening mammography not related to mortality**

<table>
<thead>
<tr>
<th>Positive effects</th>
<th>Negative effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of tumour at earlier stage(^{24}) (possibly predictive of less toxic treatment)</td>
<td>Radiation-induced carcinoma(^{48})</td>
</tr>
<tr>
<td>Improved cosmesis(^{20,60})</td>
<td>Unnecessary biopsies (0.6%–0.9% of cases in Sweden,(^{14}) 5%–9% of cases in US(^{25}))</td>
</tr>
<tr>
<td>Reassurance (72% of cases)(^9)</td>
<td>Psychological stress of call-back (40% of cases)(^{65})</td>
</tr>
<tr>
<td>Reduced anxiety about cancer at time of screening(^{48})</td>
<td>Additional x-ray films (3%–13% of cases in Sweden,(^{14}) 56% of cases in US(^{25}))</td>
</tr>
<tr>
<td></td>
<td>Possible false reassurance</td>
</tr>
</tbody>
</table>

**Table 4: Relative risk of death from breast cancer reported in meta-analyses of screening mammography among women aged 40–49 at study entry**

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Year</th>
<th>Mean length of follow-up, yr</th>
<th>RR (and 95% CI)</th>
<th>NNS</th>
<th>Method of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smart et al(^4)</td>
<td>1995</td>
<td>10.4</td>
<td>0.84 (0.69–1.02)</td>
<td>NA</td>
<td>Mantel–Haenszel fixed effects</td>
</tr>
<tr>
<td>Kerlikowske et al(^4)</td>
<td>1995</td>
<td>7–9</td>
<td>0.92 (0.75–1.13)</td>
<td>NA</td>
<td>Greenland fixed effects</td>
</tr>
<tr>
<td>Glazsiou et al(^6)</td>
<td>1995</td>
<td>7–9</td>
<td>0.95 (0.77–1.18)</td>
<td>NA</td>
<td>Mantel–Haenszel random effects</td>
</tr>
<tr>
<td>Tabar(^7)</td>
<td>1996</td>
<td>NR</td>
<td>0.85 (0.71–1.01)</td>
<td>NA</td>
<td>Mantel–Haenszel fixed effects</td>
</tr>
<tr>
<td>Kerlikowske (update)(^6)</td>
<td>1997</td>
<td>&gt; 10–12</td>
<td>0.84 (0.71–0.99)</td>
<td>NRS</td>
<td>Greenland fixed effects</td>
</tr>
<tr>
<td>Glazsiou et al (update)(^6)</td>
<td>1997</td>
<td>&gt; 10–12</td>
<td>0.85 (0.71–1.01)</td>
<td>NA</td>
<td>Mantel–Haenszel random effects</td>
</tr>
<tr>
<td>Hendrick et al(^7)</td>
<td>1997</td>
<td>12.7</td>
<td>0.82 (0.71–0.95)</td>
<td>1540*</td>
<td>Mantel–Haenszel random effects</td>
</tr>
<tr>
<td>Gotzsche et al(^8)</td>
<td>2000</td>
<td>NR</td>
<td>1.04 (0.84–1.27)†</td>
<td>NA</td>
<td>Fixed effects</td>
</tr>
</tbody>
</table>

Note: NA = not applicable, NR = not reported.
*Absolute risk reduction = 0.00005166 for 1 year; NNS = 19 356 per year or 1540 for the mean of 12.7 years of follow-up.
†Authors excluded 5 of 7 completed trials from analysis because of an assessment of bias.
results. False reassurance did not, however, lead to reduced compliance with screening in one US study.6,34,47

The full implications of population screening for Canadian women have not yet been quantified, and some of the effects may vary from one woman to another. Sensitivity to the preferences of individual women is appropriate in applying any guideline on this issue.

Interpretation

The only RCT designed to test screening mammography among women aged 40–49 did not have adequate power to exclude a clinically significant benefit. Other RCT results were from post hoc subgroup analyses. Although these trials constitute level I evidence, at present their conflicting results, methodologic differences and, most important, uncertainty about the risk:benefit ratio of screening mammography preclude the assignment of a “good” or “fair” rating to recommendations drawn from them.

Recent updates of the trials point to a smaller mortality benefit for women aged 40–49 than for older women and suggest that a screening interval shorter than 2 years may be required. A recent meta-analysis suggested a relative risk reduction of 18%, driven by 2 Swedish trials showing a larger mortality benefit. Estimates of the number needed to screen range from 500 to 1540 in the trials showing a positive benefit, as compared with 526 at age 50 and 169 at age 60.43 However, the financial and personal costs of screening in Canada must be quantified, and the negative psychological consequences of screening have not yet been adequately evaluated.

Part of the mortality benefit for women screened in their 40s is certainly due to mammograms performed after the age of 50. Analyses based on the date of diagnosis are their 40s is certainly due to mammograms performed after the age of 50. Analyses based on the date of diagnosis are subject to lead-time bias. An ongoing British trial75 is randomly assigning 195 000 women aged 40 or 41 to annual mammography or usual care; the study has been designed with an 80% power to detect a 20% reduction in mortality. Results will not be available until 2003. This should help to settle the question, since 10 years of follow-up will be possible before women enter their fifties. The International Union Against Cancer has expressed interest in using a similar design elsewhere in Europe.76

Should the clinically significant 18% relative risk reduction suggested by meta-analysis be confirmed, decision analysis incorporating health utilities and cost-effectiveness techniques should be used to assess the trade-offs. Efforts must therefore be made to acquire more objective data on the physical and psychological effects of screening mammography.

Recommendations

Current evidence regarding the effectiveness of screening mammography does not suggest the inclusion of the manoeuvre in, or its exclusion from, the periodic health examination of women aged 40–49 at average risk of breast cancer (grade C recommendation) (Table 6). Upon reaching the age of 40 Canadian women should be informed of the potential benefits and risks of screening mammography and assisted in deciding at what age they wish to initiate the manoeuvre. These guidelines are not intended to apply to women at increased risk of breast cancer, symptomatic women undergoing diagnostic mammography or women with a history of breast cancer receiving follow-up mammograms.

Research priorities

A meta-analysis of raw data should be done for women aged 40–49 enrolled in existing trials. The sample size for the ongoing British RCT75 should be confirmed to ensure that compliance and contamination do not undermine the study’s power; consistency of mammographic quality should be maintained if International Union Against Cancer centres are added. The psychological effects of breast cancer screening should be studied prospectively in a randomly selected sample of participants in the ongoing British trial, with the use of both a validated scale and health utilities. Research should continue on potential new strategies for the prevention of breast cancer, including the use of genetic markers, nuclear medicine imaging, MRI and chemoprophylaxis.

Table 6: Summary table of recommendation for screening mammography among women aged 40–49 years

<table>
<thead>
<tr>
<th>manoeuvre</th>
<th>Effectiveness</th>
<th>Level of evidence*</th>
<th>Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography every 12–18 months†</td>
<td>Relative risk reduction of 18%–45% for breast cancer mortality at 10 years was shown in 2 trials and 1 meta-analysis; no benefit was shown in 6 other trials‡</td>
<td>RCTs3,4,15,47 (I)§</td>
<td>Current evidence does not support the recommendation that screening mammography be included in or excluded from the periodic health examination of women aged 40–49 at average risk of breast cancer (grade C¶)</td>
</tr>
</tbody>
</table>

Note: RCT = randomized controlled trial.

*See Appendix 1 for definitions of the levels of evidence and grades of recommendations.
†Comparison of RCT results suggests that, if done, frequent screening may be required. The value of adding clinical breast examination to mammography is unclear.
‡The only trial that enrolled Canadian women failed to show an effect of screening mammography, possibly because of low power.
§55% of the 7 RCTs assessed mammography for this age group as a subgroup analysis.
¶This represents a change from the 1994 grade D recommendation. Level I evidence is available, but some results conflict and not all relevant issues are resolved. Upon reaching the age of 40, Canadian women should be informed of the potential benefits and risks of screening mammography and assisted in deciding at what age they wish to initiate it.


9. AACC comments on mammography screening for women age 40 to 49. Oncology (Huntingt) 1997;11(3):368.


Levels of evidence

I Evidence from at least one well-designed randomized controlled trial
II-1 Evidence from well-designed controlled trials without randomization
II-2 Evidence from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here

Grades of recommendations

A Good evidence to support the recommendation that the condition or manoeuvre be specifically considered in a periodic health examination (PHE)
B Fair evidence to support the recommendation that the condition or manoeuvre be specifically considered in a PHE
C Insufficient evidence regarding inclusion of the condition or manoeuvre in, or its exclusion from, a PHE, but recommendations may be made on other grounds
D Fair evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE
E Good evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE