

# Breast Cancer Detection Guidelines for Women Aged 40 to 49 Years: Rationale for the American Cancer Society Reaffirmation of Recommendations

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## Introduction

The past year has been a confusing one for women and physicians in the United States regarding recommendations for breast cancer screening. In November 1993, the Board of Directors of the American Cancer Society (ACS) approved a resolution reaffirming its guidelines for breast cancer detection including the guidelines related to screening in women aged 40 to 49 years. This action was prompted by notification by the National Cancer Institute (NCI) of plans to modify its recommendations on breast cancer screening, which formerly had been identical to those of the ACS. The ACS guidelines for early breast cancer detection are summarized in the Table. These guidelines are intended for average risk, asymptomatic women.

The NCI subsequently did alter its guidelines. The most significant change was to omit any recommendation for mammography and clinical breast examination for women aged 40 to 49 years, including instead statements that "experts do not agree on the role of routine screening mammography" for this age

group and that "randomized controlled trials had not shown a statistically significant reduction in mortality in women under age 50."<sup>1</sup> The ACS has not disputed the facts included in the NCI statement, but its own examination of the evidence has led to different conclusions about the burden of breast cancer on American women aged 40 to 49 years and the need for women and physicians to be advised of the life-saving potential of periodic examination by mammography and clinical breast examination. Herein, we review the process and some of the evidence that the ACS has relied on in reaffirming its recommended guidelines for early breast cancer detection.

## The Review Process

The topic of breast cancer screening guidelines for younger women has been scrutinized repeatedly by the ACS independently or in collaboration with other interested organizations.<sup>2</sup> When it has been deemed advisable on the basis of the scientific evidence, the ACS has modified its breast cancer detection guideline recommendations. For example, the original ACS guidelines on breast cancer screening presented in 1980 did not include a specific recommendation for mammography in women younger than 50 years, recommending instead that these women "consult their physician" about their possible need for mammographic screening. In 1983, following pub-

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lication of the first results of the Breast Cancer Detection Demonstration Project (BCDDP), the guidelines were modified to recommend that women aged 40 to 49 years have annual clinical breast examination and mammography every one to two years. In 1987, the American College of Radiology convened a consensus conference that resulted in a joint recommendation representing the views of twelve different medical organizations.

at the time for significant alteration of the ACS screening guidelines for younger women.<sup>3</sup> In October 1993, the ACS in association with the International Union against Cancer (UICC) held an international workshop on the topic of breast cancer screening in premenopausal women. The conclusion of that conference was that although other recommendations were not to be excluded, the available evidence supported the ACS guide-

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This consensus included a recommendation for routine mammography for women aged 40 to 49 years. The American College of Physicians and the United States Preventive Services Task Force independently developed guidelines that did not recommend mammographic breast cancer screening for women younger than 50 years.

Each time the ACS has reviewed or modified its recommendations, it has stated the reservation that the guidelines reflected the best available evidence and that they should be reexamined periodically as new evidence becomes available. In September 1991, then ACS President, Gerald D. Dodd, MD, convened a multidisciplinary workshop on breast cancer screening guidelines, which was attended by experts and representatives of several organizations. The consensus conclusion of that workshop was that no change in the guidelines be made for women aged 40 to 49 years although additional research was needed. In February 1993, following publication of results from a screening trial conducted in Canada, another multidisciplinary workshop was held and the summary of that conference stated a consensus that there was no basis

line recommendations for periodic breast cancer screening by mammography beginning at 40 years of age.<sup>4</sup>

### **Synopsis of the Evidence**

These recent events follow a long history of research on use of mammography for breast cancer detection that can be divided into logical phases of development. Inquiry has progressed from hypothesis development and descriptive studies to randomized screening trials, demonstration projects, and, finally, widespread implementation. Each of these phases has contributed a significant body of information concerning the efficacy of mammographic screening for breast cancer.

#### **HYPOTHESIS DEVELOPMENT AND DESCRIPTIVE STUDIES**

In 1913, Solomon, a German pathologist, reported on x-rays he took of 3,000 amputated breasts and correlated the pathologic with clinical and radiologic findings.<sup>5</sup> In 1930, Warren reported on stereoradiography as a potential aid to physicians in the diagnosis of breast cancer in symptomatic women.<sup>6</sup> In 1937, Gershon-Cohen

### American Cancer Society Recommendations for Breast Cancer Detection in Asymptomatic Women

Age Group	Examination	Frequency
20-40	Breast self-examination	Every month
	Clinical breast examination	Every three years
40-49	Breast self-examination	Every month
	Mammography	Every 1 to 2 years
	Clinical breast examination	Every year
50 and older	Breast self-examination	Every month
	Mammography	Every year
	Clinical breast examination	Every year

et al pointed out the value of mammography in diagnosis and in screening asymptomatic women for the detection of nonpalpable cancer.<sup>7,8</sup> In 1960, Egan reported on mammograms of the opposite breast in 634 mastectomy patients being followed at the M.D. Anderson Hospital.<sup>9</sup> He improved the technique of soft tissue radiography (dosage, film, filtration, coning) and demonstrated its value in detecting a large number of nonpalpable breast cancers. This experience was then verified in a 15-hospital study.<sup>10</sup>

#### RANDOMIZED TRIALS

In 1963, Sam Shapiro and Dr. Philip Strax conducted the first randomized screening trial that used mortality as the primary endpoint. In this randomized trial of 62,000 women aged 40 to 64 years, screening mammograms and clinical breast examinations were offered to the study group and usual medical care to the control group of women enrolled in the Health Insurance Plan of Greater New York (HIP).<sup>11,12</sup> In 1969, a statistically significant decrease in mortality from breast

cancer of 30 percent was demonstrated. Subgroup analysis showed the benefit to be largely among women older than 50 years. In 1986, the 18-year follow-up of the HIP study showed a decrease in mortality of 24 percent for women who entered the study at ages 40 to 49 years. This reduction in mortality did not start to appear until the eighth to ninth year of follow-up.<sup>13</sup> There was a reduction of 23 percent for women who were 50 to 59 years of age at entry. In 1988, after further analysis, the decrease in mortality in women aged 40 to 49 years at entry was found to be statistically significant, but this conclusion remains controversial.<sup>14,15</sup>

The HIP study is the only randomized trial of mammography to be conducted in the United States, but several other randomized trials of mammography alone or combined with clinical examination provided at differing frequencies have been conducted in other countries. Few of these studies have included large numbers of younger women, and all have limited statistical power to address questions specific to age subgroups. To compensate for these statisti-

cal limitations, investigators have combined the results of several trials in meta-analyses to determine whether a pattern of effect not possible to assess in an individual study can be observed. The results of one meta-analysis of randomized trials that focus on results for women aged 40 to 49 years at entry to the trial is shown in the Figure.<sup>16</sup> These data, presented at the ACS-UICC meeting, show that breast cancer mortality reductions in women aged 40 to 49 years, albeit not individually significant, have been observed in randomized trials from the United States, the United Kingdom, and Sweden.<sup>4</sup>

The National Breast Screening Study, known as the Canadian trial, was designed specifically to study women aged 40 to 49 years, and its results, although not statistically significant, suggest increased risk of breast cancer death associated with mammographic screening.<sup>17</sup> The early results of the Canadian trial, however, are affected by an unexplained significant excess of women with positive physical-examination findings who ultimately proved to have breast cancer with four or more positive nodes. Among these women with positive physical findings, 17 were assigned to the mammography screening arm and only five to the control group. The trials conducted prior to the Canadian study suggested a reduction of 15 percent in mortality in women aged 40 to 49 years at entry (relative risk [RR]=.85; 95% confidence interval [CI], .68 to 1.08). When the Canadian trial results are included, the level of mortality reduction suggested drops to seven percent (RR=.93; 95% CI, .76 to 1.15).

#### DEMONSTRATION PHASE

In 1973, the BCDDP was started by the ACS and later joined and supported by the NCI in screening 280,000 women in 28 centers. Half of these women were younger than 50 years, with 93,471 women aged 40 to 49 years.<sup>18</sup> In 1976, as concerns developed over possible harm

due to radiation exposure, routine mammographic screening of asymptomatic normal risk women younger than 50 years was discontinued in the BCDP.<sup>19,20</sup> Radiation exposure was strictly monitored, and with time new low-dose films were developed that further improved radiographic images while reducing radiation risks to a negligible level.<sup>21</sup>

Mammography was shown in the BCDDP to be greatly improved in the 1970s from that of the 1960s. In the HIP study, only 38 percent of the breast cancers in women aged 40 to 49 years were detectable by mammography, whereas in the BCDDP it was 90 percent. In women aged 50 to 59 years, mammography detected 60 percent of the breast cancers in

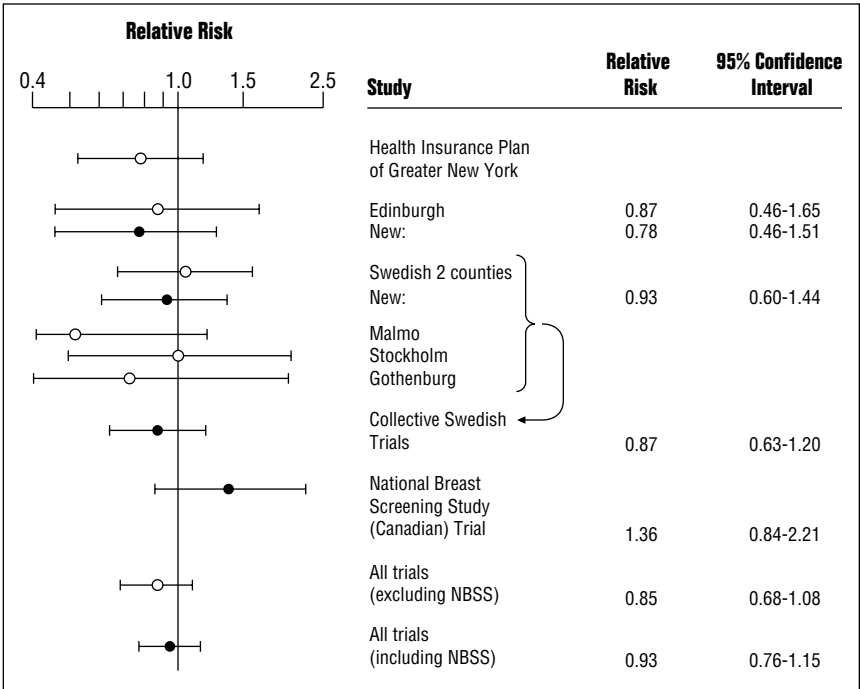
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*The substantial increase in the use of mammography in the 1980s will not affect mortality rates until the 1990s*

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the HIP study, but 92 percent in the BCDDP. This improved mammographic capability resulted in the detection of many smaller cancers than were previously possible. The results of the first five years of screening in the BCDDP were reported in 1982.<sup>18</sup> Minimal cancer (non-invasive and invasive cancers under 1 cm) made up 32.4 percent of cancers. More than 80 percent of all cancers detected showed no evidence of nodal involvement.

In a 1987 report, the BCDDP survival, even accounting for lead time, was much higher than reported in the Surveillance, Epidemiology, and End Results (SEER) program. This was because of the more favorable stage distribution in the BCDDP. Survival by subcategories of tumor size and nodal status were similar to those in the SEER program.<sup>22</sup> It was



Meta-analysis results for randomized controlled trials of screening mammography in women aged 40 to 49 years (adapted with permission from Eckhardt et al<sup>4</sup>).

estimated that if the stage distribution seen in the BCDDP could be duplicated in the general US population, it would equate to a reduction of 46 percent in breast cancer deaths.

Morrison applied a method for estimating reductions in the breast cancer mortality in the BCDDP due to screening to control for the bias of lead time.<sup>23</sup> In that study, the nine-year cumulative mortality from breast cancer from entry into the BCDDP was compared with the expected mortality based on SEER experience. The results showed a gradient of benefit. The estimated reduction was 11 percent for ages 35 to 49 years, 24 percent for ages 50 to 59 years, and 26 percent for

ages 60 to 74 years. For all ages combined, the estimated reduction in mortality was 20 percent.

In 1993, the 14-year follow-up of the BCDDP cancer cohort was reported.<sup>24</sup> The 14-year adjusted survival and case fatality rates were not statistically different for the 1,004 women aged 40 to 49 years as compared to the 1,560 women aged 50 to 59 years and the 1,001 women aged 60 to 69 years. The 14-year adjusted survival rates were also similar across age groups by cancer sizes, lymph node status, and stages of disease with the following exceptions: survival was slightly increased in women with positive lymph nodes aged 40 to 49 years and slightly decreased in

women with positive lymph nodes aged 60 to 69 years. These differences appeared to be related to the number of positive lymph nodes per patient, with less in the younger group and more in the older group.

#### IMPLEMENTATION

Use of mammography and clinical breast examination has increased significantly from the time of the first ACS recommendations in 1980. The number of women older than 40 years who have ever had a mammogram increased 200 percent during the 1980s.<sup>25</sup> Other events have influenced this trend as well. The diagnosis of breast cancer in the wives of the President and Vice President of the

greatest in women older than 50 years, in women aged 40 to 49 years at diagnosis, ductal carcinoma in situ increased 216 percent, and for invasive cancers smaller than 1.0 cm with no axillary node involvement, the increase was over 80 percent. In contrast, invasive metastasized cancers 1.0 to 1.9 cm or larger than 2.0 cm decreased 38 percent and 23 percent, respectively. These data were interpreted by the investigators as suggesting consistent benefit of breast screening across all age groups, including women aged 40 to 49 years. Another study of SEER data showed that the increase of 32 percent in breast cancer incidence between 1980 and 1987 was mainly for cancer classified as localized or less than 2.0 cm at diagnosis.<sup>28</sup>

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### *Breast cancer mortality reductions in women aged 40 to 49 years have been observed in randomized trials from the United States, United Kingdom, and Sweden.*

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United States in 1973 caused much increased publicity and public awareness of the disease. Over the following five years, there was an increase of 27 percent in breast cancer incidence. Between 1985 and 1990, 44 states passed legislation requiring health insurance companies to cover mammographic examination. In 1991, Medicare began reimbursement for screening mammograms every other year in women aged 65 years or older.

There now have been sufficient levels of use and passage of time to observe some of the population impact of mammography in younger women. Investigators from the SEER program recently reported on analyses of 104,351 breast cancer cases diagnosed between 1983 and 1989.<sup>26,27</sup> Those data suggest that the types of breast cancer most likely to be diagnosed following detection by mammography have increased in incidence. Although some of the increases were

Lowered breast cancer mortality rates would be the most convincing sign of progress in breast cancer control, but changes in breast cancer screening have an impact on mortality rates only years later. The substantial increase in use of mammography in the 1980s will not affect mortality rates until the 1990s, and there is some evidence that this is occurring. Early reports on national breast cancer mortality rates for 1991 showed a decrease of three to five percent.<sup>29</sup>

#### Discussion

Breast cancer in women younger than 50 years is an important public health problem. Breast cancer is the leading cause of death in women aged 40 to 44 years. One third of all years of life lost from breast cancer are in women diagnosed between 40 to 49 years of age compared with 38 percent for women diagnosed between 50


to 64 years of age.<sup>12</sup> Twenty-three percent of all breast cancer deaths occur in women who had their breast cancer diagnosed when they were younger than 50 years.

This limited review of epidemiologic and other data on the effectiveness of mammographic screening in women aged 40 to 49 years may demonstrate that there is information to support the guidelines recommended by the ACS. Certainly, there is no intervention for women aged 40 to 49 years who are at risk of breast cancer with as much supporting evidence and clinical experience as there is for mammography and clinical breast examination.

In light of the significance of the problem, the extent of supporting data, and the lack of alternative interventions of documented effectiveness, it is reasonable to ask how different organizations examining the same issue can present different recommendations. Social, political, and economic influences aside, one explanation may relate to differences in types of evidence relied upon in reaching conclusions. The NCI places emphasis in its recommendation only on evidence of mortality reduction derived from randomized clinical trials. The ACS recommendation, in contrast, considers benefits in addition to mortality reduction, such as opportunity for more conservative therapies as well as evidence from descriptive studies, trends in breast cancer incidence and mortality, and large nonrandomized studies such as the BCDDP. Data from randomized clinical trials are possibly the best evidence that can be used, but only one such study, the Canadian trial, has been designed to address the issue of screening effectiveness in women aged 40 to 49 years. While the early reports of that trial do not suggest benefit, working groups from the NCI and ACS that have reviewed the methodology of that trial have stated reservations, particularly con-

cerning randomization and the initial balance of risk of the screened and unscreened groups.<sup>30,31</sup> Additional data from new trials in women aged 40 to 49 years would be very valuable to validate or correct the results suggested by the recent Canadian trial.

Although the meta-analysis of trials that include women younger than 50 years suggests as much as a 15 percent reduction in mortality associated with mammographic screening in younger women, the absence of statistical significance in any single trial or for all trials combined is a reason for caution in interpreting the results. Statistical significance, however, can be informative only when trials are large enough for statistical significance to be achievable. No trial has yet included a sufficient number of women aged 40 to 49 years for a reduction in mortality that could reasonably be expected to be statistically significant. Thus, while the presence of statistical significance in a randomized clinical trial in women aged 40 to 49 years is important, it cannot be the sole criterion by which results are judged.

The controversy concerning guideline recommendations for early breast cancer detection in younger women should not distract from the more general consensus on the benefits of mammography and clinical breast examination in women older than 50 years. Risk is greater in this age group, and mortality reductions from annual screening have been of greater magnitude and more uniformly observed across different studies. The emphasis for cancer control efforts in women aged 50 years or older should be on increasing access to and use of these proven technologies. For women aged 40 to 49 years, continued adherence to the ACS guidelines is recommended while strategies to reduce the burden of breast cancer in young women are monitored and improved. 

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