

## Perspective

# The Canadian National Breast Screening Study: A Canadian Critique

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**The Canadian National Breast Screening Study (CNBSS) was the first study designed to determine the efficacy of screening for breast carcinoma in women 40–49 years old. Women were randomized to undergo either annual mammography and physical examination or usual care after an initial physical examination [1]. Women 50–59 years old were randomized to undergo either annual mammography and physical examination or annual physical examination only [2]. This study, published by epidemiologists on the efficacy of a radiologic examination, therefore, invites evaluation by radiologists.**

We acknowledge the efforts of CNBSS to invite an external review of technical quality [3, 4], to include an internal audit by a reference radiologist [5], and to appoint, according to protocol, pathologists and a physicist to audit the study. Nurses were specially trained to perform physical examinations of the breast and to act as local project coordinators. The positive qualities of the project design, however, are contrasted by a collection of flaws that cannot be easily inferred from the published reports of the study [1, 2]. The investigators concluded that screening with yearly mammography and physical examination of the breasts detected considerably more small tumors with no spread to the lymph nodes than did usual care or physical examination alone, but they claim that this had no impact on the rate of death from breast cancer in either age group up to 2 years following completion of the 5-year study.

### Inadequate Mammography Technique

Primary among the concerns is that publications describing the CNBSS [1, 2] failed to note that invited external

radiologic review revealed that the quality of mammography was unsatisfactory [3, 4]. Mediolateral oblique projections were not used until the study had been under way for 5 of its 8 years. Two invited external radiologic reviewers expressed concern as to sharpness, contrast, and overall quality of the mammograms. The external review demonstrated that from 1980 through 1984 (during which time 86,180 mammograms were obtained), at least half the mammograms were judged of poor quality (see Table 1 and Fig. 1 in Baines et al. [3]). Mammographic technique did not improve until after 1984. In some centers, grids were used only late in the study [3]. In 1991, one expert external reviewer expressed his concern that "because of poor mammography, the results of this trial will always be suspect" [4].

The full-time technologists who performed the mammographic studies in the centers received no special training. This is in contrast to the extensive training in clinical breast examination given to nurse examiners. This disparity in training is especially pertinent in the trial involving women 50–59 years old, for whom the incremental benefit of mammographic screening is evaluated over and above that provided by breast examination. The efficacy of mammography can be evaluated only when state-of-the-art equipment and technique have been used.

Inconsistencies appear in the investigators' assessment of the quality of mammography. Although Miller et al. [1] claimed that "facilities and equipment for modern screen film mammography were absolute prerequisites," in Vancouver, for instance, where CNBSS screening began in 1983, a 1972 mammography machine was used until 1987. This fact also corrects the statement of one of the other authors that

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"the equipment used in the study was state of the art at the time" [6]. In five of the 15 centers, no phototiming was available (see Table 1 in Baines et al. [7]).

A further critical aspect of quality relates to deficiency in mammographic interpretation [5]. None of the radiologists in the volunteer centers received special training. The overall false-negative rate for 108 interval cancers in the CNBSS was 2.5 per 1000 women, which contrasts with 1.93 per 1000 women for the Breast Cancer Detection Demonstration Project, 1.45 per 1000 for the Health Insurance Plan of Greater New York, and 0.92 per 1000 for the Screening Mammography Program of British Columbia (SMPBC). The high interval cancer rate of the CNBSS is again apparently related to the poor mammographic technique and inadequate interpretation. The British Columbia figure is low, yet it is the only program in this group in which physical examination is not part of the annual mammographic screening visit. Technologists and radiologists in the CNBSS did not enter the project with mammographic screening experience but had to learn on the job. The senior author of the CNBSS, Dr. Miller, now agrees in retrospect. In 1993, he stated that "the time taken for reduction in breast cancer mortality to appear will depend upon the initial quality of the screening modalities used" and that "the benefits anticipated from the research studies [would] not be realized unless high quality mammography and excellent diagnostic skills are available" [8].

The experience of the SMPBC suggests that the poor results of the CNBSS are in part due to delay in diagnosis. Between July 1988 and March 1992, the SMPBC detected 71 cancers solely on the basis of mammographic findings in women 40–49 years old. Nodal involvement in that group was 8.5% for both in situ and invasive cancers, whereas in the CNBSS [1], nodal involvement was as high as 25% for the screened group.

### Protocol Design and Execution

The American Cancer Society guidelines formulated in 1982 for the screening and detection of breast cancer apply to asymptomatic women [9]. The protocol of the CNBSS [10] does not cite absence of breast symptoms as an eligibility criterion. The acceptance of women into the program despite signs of breast cancer—particularly in women less than 50 years old—was the consequence of the variety of means used to attract participants. In particular, in some centers, family physicians were contacted directly by letter and encouraged to refer their patients to the program. The CNBSS handbook of operation (Section 3.4.1, p. 24) indicates that randomization was not performed at the time of entry but rather after physical examination. Although, theoretically, randomization is expected to negate any influence of the inclusion of women with poor prognoses, this did not occur in the CNBSS. This aberration is confirmed by the fact that upon entry, the number of women 40–49 years old who had cancers with four or more lymph node metastases exceeded that number in the control group by 19:5 (380%) [1]. Thus, any potential benefit of early detection in this group would simply not be available, and the huge disparity

in numbers can be expected to affect mortality in the screened group unfavorably. This flaw in the study's design and its effect—to include women with obvious cancers—will significantly affect the mortality results.

Numerous questions have been raised about the statistical power of the CNBSS. Dr. Yaffee, the CNBSS reference physicist, states that "the only responsible conclusion that can be drawn from the CNBSS at this time is that there is not yet sufficient power to test whether the mortality reduction for which the study was designed actually exists" [11].

New cases of breast cancer and deaths from breast cancer were ascertained through linkage of the CNBSS data base with the national data base (Canadian Mortality Database), which was in effect until December 31, 1988. The investigators stated that "all women with breast cancer [were] followed annually." However, although some linkages with provincial cancer registries had end points varying from 1988 to 1990, any accounting of new breast cancer diagnoses or of deaths after 1988 has not been described. Thus, completion of follow-up after 1988 has not been documented. This is very relevant, since for women enrolled up to 1985, mean follow-up is cited as 8.5 years. Dr. Tom Fajak, from the statistics division of the American College of Radiology, has estimated that approximately one third of the participants have been followed up for less than 5 years (10 screening centers did not begin operation until 1983) [12].

Previous to the study, the senior author of the CNBSS publications, Dr. Miller, had difficulty accepting the benefits of screening. When experts in British Columbia published a report on cervical cytology in the control of cancer of the cervix in 1970, 21 years after screening began in British Columbia, they stated that the British Columbia mortality rates (refined as well as crude rates) "show a drop that is now becoming significant" and "the present generally accepted methods of detection and treatment of preclinical carcinoma of the cervix are capable of almost eliminating death from this disease" [13]. Even 3 years later, Miller wrote, "There is no indication of a change in the rate of fall (in mortality) that could be attributable to screening. Indeed, it is probable that factors other than screening must be invoked" [14]. It was not until several years later, and at a time when international experts had acknowledged the mortality decrease from cervical screening, that Miller followed suit.

### Contradictions and Inconsistencies

Contradictions and inconsistencies appear in the reports published by Miller et al. [15, 16] since the conclusion of the CNBSS. Although it is known that the inclusion of symptomatic women in a screening trial will dilute the results with cancers that are already beyond benefit from screening, page 38 of the CNBSS handbook for center staff reads, "Women presenting with clinically evident breast cancer which has not been diagnosed are treated and accepted as participants." Yet, in 1993, Miller et al. stated that "in the CNBSS, recruitment was directed to asymptomatic women. During recruitment, if a woman indicated that she had symptoms, she was advised to see her physician" [15]. In a recent inter-

view, a former staff member of the British Columbia CNBSS center has revealed that no written or verbal instructions were given to inquire about breast symptoms (Sally Haugen, personal communication).

Drs. Feig and Logan-Young served as advisers to the program for 3 years then resigned because their concerns over the poor quality of mammography went unheeded. Miller et al. stated that the center radiologists did not accept the advisers' recommendations for quality improvement, but they neglected to comment that this reflects on the protocol, leadership, and execution of the program [15].

Even though radiologic program consultants recommended pretrial training of radiologists, and Drs. Tabar and Logan-Young are on record as having offered to train CNBSS radiologists in mammographic screening, Miller now states that "to be criticized for failing to produce in 1980 what took a decade to come about is illogical" [15].

Miller—in answer to a letter stating that in British Columbia an 11-year-old mammography machine was used—responds that "it had little impact on the quality in view of the way the quality control procedure was run" [15]. Yet, the reference physicist in charge of quality control in the CNBSS writes that "quality was far below the state of the art. Problems in the quality of mammography resulted not only from inadequate equipment" [11].

Miller argues that "it is conceivable that the lower proportion (of node positive cancers detected by mammography alone in B.C.) involves an element of over-diagnosis of cancer in screened women" [15], yet all cancers in British Columbia were histologically proved and double-read by an internationally recognized pathologist. The sizes of the breast cancers found in the CNBSS study were not published because the pathologic examinations were performed by local pathologists.

No mortality benefit for women, either among those less than 50 years old or those more than 50 years old, could be demonstrated [1, 2]. Miller would like part 1 of the CNBSS to be accepted but part 2 to be disregarded, because he advises against screening women less than 50 years old; however, he states that "we would not like the findings of our study, particularly with regard to women age 50 to 59, to be made a reason for family physicians not to include these women in the ongoing provincial programs" [15].

In 1992, when referring to the number of mammograms obtained in the first 2 years of the CNBSS, Miller stated that this amounted to 2% of the total number of mammograms [16]. Yet in 1993, he used different mathematics and said "only 5.1% of all CNBSS mammograms were produced in the first 2 years of screening" [15]. If we look at the number of women who had mammography in 1980 and 1981 [3], we find we are dealing with 10,920 studies, which in relation to the total of 187,485 in fact amounts not to 2% or 5.1% but to 5.8%, a figure that is more relevant to an analysis because it represents the initial prevalence group. And further corrections to the original figures cited by the CNBSS were recently published [17].

## Conclusion

Many Canadian physicians believe that the CNBSS has yielded no new findings and has served no new scientific purpose. It was already well known that mammography is more sensitive than physical examination for detecting breast cancer. Miller [8] recently credited five international, randomized studies of women more than 50 years old with producing a reduction in breast cancer mortality, yet the CNBSS was not able to show even a benefit in this age group, and it is likely that further follow-up will be just as unreliable. The yield of mammography cannot be evaluated when mammographic technique and interpretation are unsatisfactory. If the more than \$17 million spent on the CNBSS had been used in British Columbia, we would have obtained 340,000 screening mammograms (at a rate of \$50 for production and interpretation) and detected (at a rate of 4/1000) 1360 breast cancers in asymptomatic women, yielding a decrease in breast cancer mortality and a better quality of life in younger women, a benefit that was not even discussed in the CNBSS.

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