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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

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Background: **The efficacy of breast cancer screening in women age 40 to 49 years remains controversial.**

Objective: **To compare breast cancer mortality in 40- to 49-year-old women who received either 1) screening with annual mammography, breast physical examination, and instruction on breast self-examination on 4 or 5 occasions or 2) community care after a single breast physical examination and instruction on breast self-examination.**

Design: **Individually randomized, controlled trial.**

Setting: **15 Canadian centers.**

Participants: **50 430 volunteers age 40 to 49 years, recruited from January 1980 to March 1985, who were not pregnant, had no previous breast cancer diagnosis, and had not had mammography in the preceding 12 months.**

Interventions: **Breast physical examination and instruction on breast self-examination preceded random assignment of 25 214 women to receive mammography and annual mammography, breast physical examination, and breast self-examination and 25 216 women to receive usual community care with annual follow-up.**

Measurements: **Verified breast cancer incidence and cohort mortality through 31 December 1993 and deaths from breast cancer through 30 June 1996.**

Results: **The 105 breast cancer deaths in the mammography group and 108 breast cancer deaths in the usual care group yielded a cumulative rate ratio, adjusted for mammography done outside the study, of 1.06 (95% CI, 0.80 to 1.40). A total of 592 cases of invasive breast cancer and 71 cases of in situ breast cancer were diagnosed by 31 December 1993 in the mammography group compared with 552 and 29 cases, respectively, in the usual care group. The expected proportions of nonpalpable and small invasive tumors were detected on mammography.**

Conclusion: **After 11 to 16 years of follow-up, four or five annual screenings with mammography, breast physical examination, and breast self-examination had not reduced breast cancer mortality compared with usual community care after a single breast physical examination and instruction on breast self-examination. The study data show that true effects of 20% or greater are unlikely.**

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See editorial comment on pp 361-362.

The Canadian National Breast Screening Study-1 (CNBSS-1), an individually randomized trial in women 40 to 49 years of age at study entry, evaluated the efficacy of annual mammography, breast physical examination, and instruction on breast self-examination in reducing breast cancer mortality (1).

The 7-year (2) and preliminary 10-year (3) mortality results were previously reported. At 7 years, 38 women in the mammography group and 28 women in the usual care group had died of breast cancer, for a rate ratio of 1.36 (95% CI, 0.84 to 2.21) (2). At 10 years, there were 82 breast cancer deaths in the mammography group and 72 in the usual care group (rate ratio, 1.14 [CI, 0.83 to 1.56]) (3).

This article reports CNBSS-1 results after an average 13-year follow-up from study entry.

METHODS

Patient Selection and Recruitment

Participants were recruited through media publicity, personal invitation letters using population lists (municipal registers and provincial health insurance registers), group mailings, and physicians (4). Eligibility criteria were age 40 to 49 years, no previous diagnosis of breast cancer, not being pregnant, no mammography in the previous 12 months, and signed informed consent. The Human Experimentation Committee of the University of Toronto (Toronto, Ontario, Canada) and Human Experimentation Committees at 15 CNBSS collaborating centers approved the study. A total of 50 430 women age 40 to 49 years were enrolled from January 1980 through March 1985.

Randomization

Before randomization, all participants received an initial breast physical examination and instruction on breast self-examination. They were then immediately randomly assigned to receive mammography and, thereafter, either annual screening with mammography and breast physical examination (25 214 women in the mammography group were available for analysis) or usual care in the context of the Canadian health care system (25 216 women in the usual care group were available for analysis). Center coordinators randomly assigned participants using prepared allocation lists, independent of breast physical examination findings. This sequence ensured that the conduct and interpretation of the breast physical examination would be unbiased by knowledge of whether mammography would follow.

Context

Seven- and 10-year results of the Canadian National Breast Screening Study (CNBSS) showed no reduction in breast cancer mortality from five annual mammographies and breast examinations for 40- to 49-year-old women.

Some authors have argued that longer follow-up would reveal important benefits.

Contribution

After 11 to 16 years, the cumulative rate ratios for mammography versus usual care were 0.97 (95% CI, 0.74 to 1.27) for breast cancer mortality without adjustment for nonstudy mammography and 1.06 (CI, 0.80 to 1.40) with adjustment.

Clinical Implications

The CNBSS suggests that screening 40- to 49-year-old women is unlikely to reduce breast cancer or total mortality by 20% or more.

Controversy will persist because other studies suggest that screening causes small reductions in breast cancer mortality.

–The Editors

Intervention

Screening Schedule

In the mammography group, 62% of women received five annual screenings. The remainder, recruited later, received four. Each screening examination comprised mammography, breast physical examination, and instruction and evaluation on breast self-examination. Women in the mammography group completed questionnaires at each rescreening visit.

Women in the usual care group were not recalled for rescreening but were mailed annual questionnaires. We expected that these participants would continue their normal pattern of medical care as delivered through Canada's universal health care coverage, including access to mammography for diagnosis.

Study Procedures

Two-view mammography was done on dedicated mammography units (5), and second readers reviewed mammograms deemed abnormal. Systematic audit procedures were used (6). Nurses provided breast physical examination in 12 centers and physicians in 3 centers in Québec (7). These providers taught and evaluated breast self-examination while conducting their own examination (8). If findings on breast physical examination or mammography were abnormal, participants were referred to a CNBSS review clinic. The study surgeon discussed mammography findings with the study radiologist, examined the participant, and decided whether further diagnostic procedures should be recommended to the woman's physician. The woman's physician determined whether and how to implement the study surgeon's recommendations.

Data Collection Protocol

During the screening period, the center coordinators collected surgery and pathology reports for breast-related diagnostic and therapeutic procedures. The CNBSS pathologists reviewed all slides. If the community and CNBSS pathologist disagreed, a panel of three to five CNBSS pathologists blindedly and independently reviewed the slides. Extensive quality control procedures were used during data collection.

After the screening centers closed in 1988, the central CNBSS central office annually followed all women known to have breast cancer until 30 June 1996, the cut-off for this analysis. Passive follow-up of all participants through linkage with the National Cancer Registry identified new diagnoses of breast cancer in study participants through 31 December 1993. The central office collected pathology reports for postscreening cases of breast cancer. The community diagnosis was accepted for study purposes.

Family members responding to the annual mailed questionnaire identified deaths that occurred before completion of a participant's screening schedule. Thereafter, women not known to have cancer were followed only through registry linkage; their mammography experience was not traced. However, for women known to have breast cancer, attending physicians received annual requests for updated clinical information, including death. Attending physicians, who received annual requests for information on women with breast cancer, reported deaths until 30 June 1996. Linkage with the Canadian Mortality Database at Statistics Canada (including deaths in Canadians who resided in the United States at the time of death) identified causes of death in the entire cohort until 31 December 1993.

The procedures used to verify deaths from breast cancer were described previously (2). Investigative procedures were initiated for women dying with breast cancer; those whose death certificates mentioned breast cancer; and those whose cause of death was described as unknown, unknown primary, lung cancer, colon cancer, or liver cancer. The reviewers were blinded to study group allocation. All other causes of death were accepted as certified. For the most recent record linkage, more stringent confidentiality requirements exercised by many hospitals hindered verification. Thus, of the breast cancer deaths reported in this paper, a panel reviewed 67% in the mammography group and 77% in the usual care group. The remaining deaths are as reported on death certificates.

Study Outcomes

Death due to or probably due to breast cancer was the major study outcome.

A previous report of the CNBBS-1 noted axillary node status, as assessed by community pathologists, through 7 years of follow-up (2). Subsequently (1993 to 1997), to

achieve consistent reporting of tumor size, all available material for screening-detected cancer and cancer detected between screenings was re-collected from originating institutions and reviewed by one of the CNBSS pathologists or a colleague. Slides were obtained for review for nearly 80% of requested cases. For the current analysis, pathologists measured the size of small tumors as observed on the slide or the size of the invasive component for mixed invasive and in situ tumors.

Statistical Analysis

Sample Size

The CNBSS-1 was planned to evaluate whether breast cancer mortality would decrease by 40% in the mammography group compared with the usual care group after 5 years of follow-up, with a required sample size of 50 000 women ($\alpha = 0.05$; power, 80%) (1). At 5 years, however, too few women had died of breast cancer for the study to achieve the planned power. Thus, for the first report on breast cancer mortality, we extended follow-up to 7 years (2).

CNBSS Database

The database includes records for 50 430 women, including demographic and risk factor variables and results of screening examinations, diagnostic and therapeutic procedures, pathology results, and causes of death.

CNBSS Terminology

The terms "screen 1," "screen 2," through "screen 5" denote events associated with screening examinations in the mammography group. The initial breast physical examination received by the usual care group is called screen 1. Screening-detected cancers are those diagnosed after a recommendation made by the study surgeon at the CNBSS review clinic. "Interval cancers" are cases of cancer that occurred less than 12 months after a screening examination at which no recommendation for diagnostic procedures was made. "Incident cancers" are cases of cancer that occurred more than 12 months after the previous CNBSS screening examination.

Statistical Tests

The statistical significance of differences in proportions was determined by using the chi-square test (two-sided $\alpha = 0.05$). For all observed-to-expected ratios, 95% CIs were computed.

Death rates were computed by using person-years based on stratification by quinquennium of age; we assumed that all women not known to be dead are alive. Age was defined as age at entry. Because all eligible participants were included in the analysis and follow-up, this is an intention-to-treat analysis.

Cox proportional hazards regression was done to examine variables with the most significant independent influence on survival (9), using the PHREG program in SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina). Because the variable "allocation to screening" was our primary interest, it was forced to stay in the regression model regardless of statistical significance. In addition, a stepwise selection procedure based on the partial likelihood ratio was applied to select all other factors of prognostic importance in the multivariable Cox regression model. All variables listed in **Appendix Table 1** (available at www.annals.org) were included for selection. Limits for inclusion and exclusion of variables were *P* values of 0.05 or less and greater than 0.10, respectively. The overall goodness of fit of the Cox regression model was assessed by the −2-log likelihood ratio.

Role of the Funding Source

The scientific conduct of the trial was guided by the Policy Advisory Group, appointed by the principal funding agencies (2). The Policy Advisory Group was disbanded after our first mortality report (2). The decision to publish was the authors'.

RESULTS

Participants

Of the 50 489 women who entered the study, 59 were excluded from analysis for reasons shown in **Figure 1**. The mean duration of follow-up from study entry is 13 years (range, 11.3 to 16.5 years).

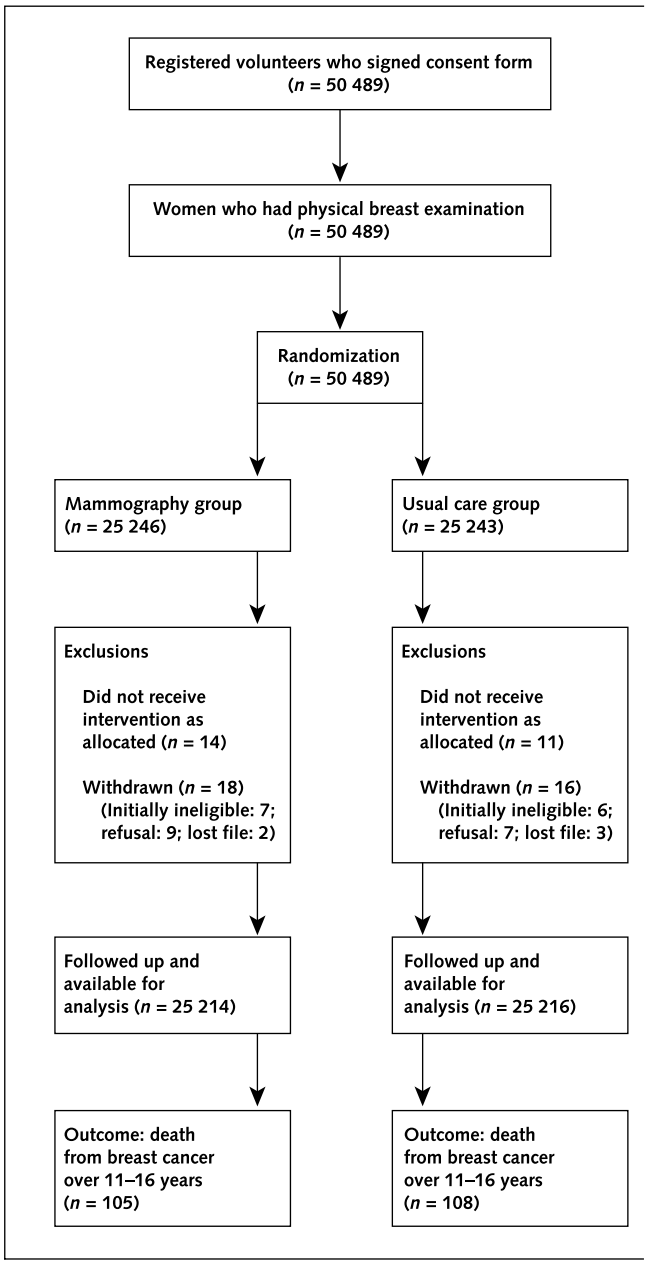
Mortality

Table 1 provides the underlying causes of death through 31 December 1993. Total numbers of deaths are equal in the two groups, and distributions by specific causes of deaths are similar. The 84 breast cancer deaths in the mammography group and 75 breast cancer deaths in the usual care group yielded a cumulative rate ratio of 1.12 (CI, 0.82 to 1.53). **Figure 2** presents cumulative numbers of breast cancer deaths by time from enrollment. In the 3- to 10-year follow-up period, the numbers were larger in the mammography group than in the usual care group.

Table 2 presents breast cancer deaths through 30 June 1996 by allocation and time of breast cancer detection during years 2 to 5 and then yearly to 9 or more years after entry. The follow-up period is longer for the data in **Table 2** than the data in **Table 1** because we only had data on non–breast cancer causes of death through 1993. No data from the usual care group are given for screens 2 to 5 and intervals 2 to 5 because this group was ineligible for rescreening. When we included only breast cancer deaths in women with cancer diagnosed in the first 5 years after entry, the rate ratio was 1.07 (CI, 0.75 to 1.52). Rate ratios close to 1.0 were found as each successive year of breast cancer ascertainment was added. Including deaths from all cases of breast cancer diagnosed yielded a rate ratio of 0.97 (CI, 0.74 to 1.27).

Table 3 summarizes the results of a Cox proportional hazards regression analysis whose end point was breast can-

Figure 1. **Random assignment and follow-up of volunteers who signed the informed consent form in the Canadian National Breast Screening Study-1.**



There was no defined list of potential participants from which the numbers not randomly assigned can be determined.

cer deaths among all cases of breast cancers diagnosed. Of the covariates listed in **Appendix Table 1** (available at www.annals.org), only family history of breast cancer in the participant's mother and the report of a lump to the examiner at initial breast physical examination were significantly associated with risk for death. Neither factor affected the effect estimate of allocation to mammography versus usual care. However, among the 1799 participants in the mammography group and 6655 participants in the usual care group who reported having mammography outside the CNBSS, 13 and 36 women, respectively, died of breast cancer, compared with 92 and 72 women in the 23 415 mammography group participants and 18 561 usual care group participants who did not report having "outside" mammography. These numbers yielded crude ratios of 1.30 and 1.02, respectively, and an adjusted Mantel–Haenszel odds ratio of 1.07. Including "outside mammography" as a variable in the Cox regression resulted in an odds ratio for the effect of allocation to the mammography group of 1.06 (CI, 0.80 to 1.40).

Cancer Detection

Seventy-one cases of in situ breast cancer were detected in the mammography group compared with 29 in the usual care group, for cumulative rates to 31 December 1993 of 2.92 per 1000 women and 1.19 per 1000 women, respectively. By the end of year 5, 290 and 237 cases of invasive breast cancer had been ascertained in the mammography and usual care groups, increasing to 592 and 552, respectively, by 31 December 1993 (**Figure 2**).

Readers should refer to our 7-year results (2) for descriptions of adherence to rescreening, biopsy rates, and rates of screening and interval detection.

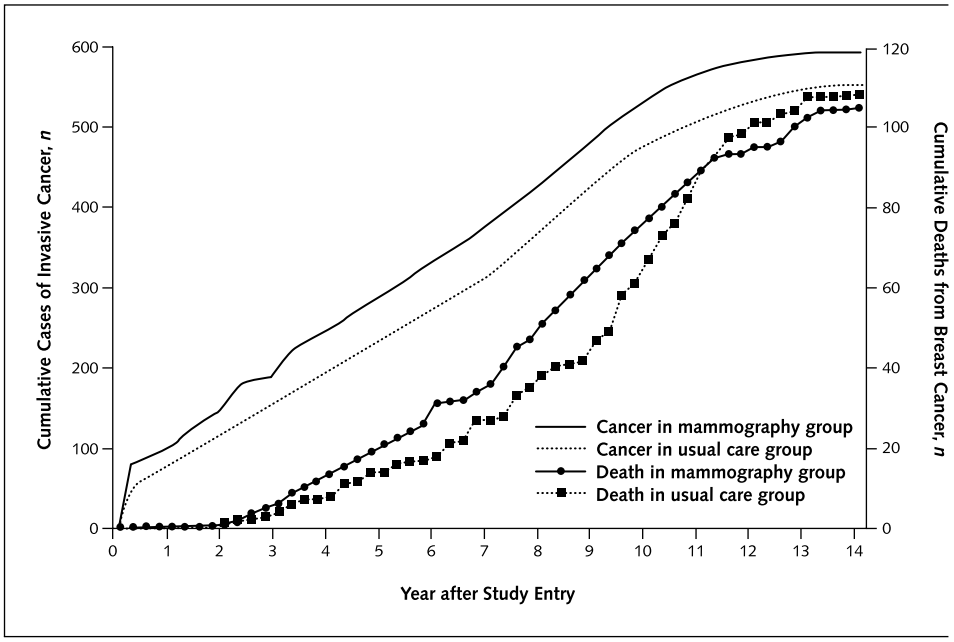
Appendix Table 2 (available at www.annals.org) presents tumor size for all cases of invasive cancer ascertained up to 31 December 1993. Size distribution was more favorable for cancer detected by mammography alone than for cancer found by breast physical examination. At screen 1 in the mammography group, 19% of tumors found by mammography alone were 20 mm or more in diameter compared with 42% of tumors found by breast physical examination (only or with mammography) and 50% of tumors in the usual care group.

Appendix Table 3 (available at www.annals.org) summarizes size and nodal status for all cases of invasive cancer. As of 31 December 1993, 19% of the cases of invasive

Table 1. **Causes of Death through the End of 1993**

Cause of Death	Mammography Group	Usual Care Group
	n (%)	
Breast cancer	84 (20.3)	75 (18.2)
Lung cancer	44 (10.6)	41 (9.9)
Colorectal cancer	24 (5.8)	32 (7.7)
Stomach cancer	5 (1.2)	11 (2.7)
Pancreatic cancer	17 (4.1)	14 (3.4)
All uterine cancer	5 (1.2)	7 (1.7)
Ovarian cancer	22 (5.3)	21 (5.1)
Hematopoietic neoplasms	28 (6.8)	24 (5.8)
Other neoplasms	51 (12.3)	60 (14.5)
Infectious/parasitic diseases	7 (1.7)	3 (0.7)
Endocrine/metabolic cause	3 (0.7)	4 (1.0)
Central nervous system (nonvascular) cause	13 (3.1)	8 (1.9)
Circulatory disease	54 (13.1)	43 (10.4)
Respiratory disease	9 (2.2)	13 (3.1)
External cause	34 (8.2)	35 (8.5)
Other cause	13 (3.1)	22 (5.3)
Total	413	413

Figure 2. **Cumulative numbers of invasive breast cancers and deaths in the mammography and usual care groups according to year from study entry.**



breast cancer in the mammography group and 17% of cases in the usual care group had one to three positive nodes, and 12% and 9%, respectively, had four or more nodes involved. Lymph node status was unknown for 23% of breast cancer cases in the mammography group and 24% of cases in the usual care group. Tumors detected by mammography alone were less likely to be node positive than those detected by breast physical examination. Small tumors were less likely to be node positive, but, even so, almost half of the tumors detected in the first screening of the mammography group with four or more positive nodes were less than 20 mm in diameter.

Appendix Table 4 (available at www.annals.org) describes nodal status for 3682 women reporting a lump at screen 1; the major difference arose from an excess of 9 usual care group participants with unknown status balanced by an excess of 7 mammography group participants with four or more positive nodes.

DISCUSSION

In CNBSS-1, combined screening of women age 40 to 49 years with annual mammography and breast physical examination for up to 5 years did not reduce breast cancer mortality compared with women who had a single breast physical examination and subsequent care from Canada's universal health care system. We would not expect this null result to be explained by the instruction of both groups in breast self-examination (10), although such instruction may benefit younger women (11).

CNBSS-1 was planned to evaluate whether breast cancer mortality would decrease by 40% in the mammography group compared with the usual care group after 5 years of follow-up (1). In the late 1970s, expectations for breast screening efficacy in this age group were high despite early negative findings in the Health Insurance Plan trial (12). Our null result is consistent with findings from the Östergötland and Stockholm trials (13). Furthermore, the initial nonsignificant excess in breast cancer mortality in screened women that we previously reported (2) was also observed in the Swedish Two County trial (14). However, the lower 95% CI for reduction in breast cancer mortality in CNBSS-1 does not exclude the 18% reduction derived from the most recent meta-analysis of screening trials (15). Nevertheless, this meta-analysis included trials that only randomly assigned women 45 to 49 years of age, and much of the benefit could be due to the screening of women older than 50 years of age (16). Thus, the true effect of mammography screening of women in their forties is likely to be small.

Because of lead time from mammography, corresponding cancers in the usual care group will present later. The period until the cumulative curves for breast cancer incidence come together theoretically encompasses the cancer cases influenced by screening (17). In CNBSS-1, this did not happen (**Figure 2**). However, with inclusion of successive sets of cancer diagnosed (**Table 2**), potential effects of screening will be masked; this explains the approximation of the rate ratios to 1.0 with successive reports of the trial.

We do not have information on the extent of screening in either group after the CNBSS screening centers closed. However, it is unlikely that much screening oc-

Table 2. **Cumulative Number of Deaths from Breast Cancer through 30 June 1996, according to Allocation and Time of Breast Cancer Detection**

Time of Detection	Deaths from Breast Cancer, *n*		
	Mammography Group		Usual Care Group
Including only breast cancers identified up to 5 years from entry			
Screen 1	17		12
Screens 2–5	21		–
Interval cancer year 1	6		7
Interval cancer years 2–5	13		–
Incident cancer years 2–5	7		41
Total	64		60
Cumulative breast cancer death rates per 10 000*	2.26		2.12
Rate ratio (95% CI)		1.07 (0.75–1.52)	
Including breast cancer identified up to 6 years from entry			
Among breast cancers detected up to year 5	64		60
Incident cancer year 6	8		11
Total	72		71
Cumulative breast cancer death rate per 10 000*	2.55		2.51
Rate ratio (CI)		1.01 (0.73–1.41)	
Including breast cancers identified up to 7 years from entry			
Among breast cancers detected up to year 6	72		71
Incident cancer year 7	14		11
Total	86		82
Cumulative breast cancer death rate per 10 000*	3.04		2.90
Rate ratio (CI)		1.05 (0.78–1.42)	
Including breast cancers identified up to 8 years from entry			
Among breast cancers detected up to year 7	86		82
Incident cancer year 8	7		7
Total	93		89
Cumulative breast cancer death rate per 10 000*	3.29		3.15
Rate ratio (CI)		1.04 (0.78–1.40)	
Including breast cancers identified up to 9 years from entry			
Among breast cancers detected up to year 8	93		89
Incident cancer year 9	6		8
Total	99		97
Cumulative breast cancer death rates per 10 000*	3.50		3.43
Rate ratio (CI)		1.02 (0.77–1.35)	
Including breast cancers identified 9 or more years from entry			
Among breast cancers detected up to year 9	99		97
Incident cancer years 9 or more	6		11
Total	105		108
Cumulative breast cancer death rate per 10 000*	3.72		3.82
Rate ratio (CI)		0.97 (0.74–1.27)	

* Based on 282 606 person-years of observation in the mammography group and 282 575 person-years of follow-up in the usual care group.

curred until women reached 50 years of age because the Canadian programs that emerged after 1988 (except for those in British Columbia) actively recruited only women 50 years of age or older (18). The partial "catch up" in numbers of breast cancer cases diagnosed in the usual care group after year 7 (**Figure 2**) may represent an effect of mammography screening. The crossover of numbers of breast cancer deaths at year 11 appears to occur among women in whom breast cancer was diagnosed in their early fifties. However, it seems unlikely that post-CNBSS screening masked a benefit from CNBSS screening.

Critics have suggested that limitations of CNBSS-1 include its randomization, the quality of mammography, greater nodal positivity in cases of cancer detected during screen 1 in the mammography group, mammography in the usual care group, and our analytic methods. Good evidence suggests that randomization was successful (2, 19–21), but the age distribution has been questioned (22). **Table 4** shows the age distribution in CNBSS-1. Also equally distributed were women reporting self-detected breast lumps at screen 1 (**Appendix Table 1**; available at www.annals.org) and the numbers of women referred for review (2).

As measured by sensitivity, specificity, and cancer detection rates, the performance of mammography during CNBSS was adequate (2, 13, 23, 24). The greater numbers of node-positive cancer detected at screen 1 in the mammography group are probably due to a failure to identify node involvement in cancer cases in the usual care group (24). This explanation is supported by the fact that 47% of women with node-negative cancer in the usual care group died of breast cancer compared with 28% in the mammography group (3).

Concerns were raised about contamination because 14.5% of the usual care group had one mammography outside the CNBSS, 7.8% had two, and 4% had three or

more (24). Even if all mammographies had been done for screening, they affected only 26% of the usual care group compared with the nearly 90% of women in the mammography group who had annual mammography screening. Thus, masking of a true mortality benefit from screening is unlikely. Women in the usual care group who had mammography were at higher risk for breast cancer death than those who did not; **Table 3** shows that the use of mammography in such women did not mask a beneficial effect of screening in the mammography group.

As for our analysis, Tarone (25) suggested that women with cancer detected at screen 1 by breast physical examination should be excluded from both groups. Although the validity of excluding subgroups identified after the intervention as a result of mortality analyses is uncertain (26), Cox regression analysis performed after such exclusions results in an odds ratio of 0.93 (CI, 0.70 to 1.24). A similar analysis excluding women who reported a lump to the examiner at screen 1 yields an odds ratio of 0.88 (CI, 0.66 to 1.18).

Important questions on mammography screening of women 40 to 49 years of age still need to be answered. First, why did the Swedish Two-County trial show mortality reduction even though screening detection rates in that study were marginally lower than those in CNBSS-1? The answer probably lies in the control groups: Tumor sizes in the Swedish control group exceeded those in the Canadian control group, leaving more opportunity to observe a benefit (27). The superior breast cancer survival rate in the CNBSS usual care group compared with the rate in the Swedish Two-County trial (28) was already seen at 7 years (2).

Second, why have trials consistently shown increased breast cancer mortality in screened women 40 to 49 years of age soon after screening begins? This may relate to premenopausal status, tumor status at time of diagnosis, and tumor growth factors (29). Third, why does the reduction in breast cancer mortality diminish with progressive follow-up of the trials? The answer may reside in improving treatment regimens or the masking of an effect by the inclusion of cases not influenced by screening.

Table 3. **Summary of Results from Cox Proportional Hazards Regression Model**

Variable*	Odds Ratio (95% CI)	*P* Value
Mammography group	0.97 (0.74–1.27)	>0.2
Mammography group	0.97 (0.74–1.27)	>0.2
Lump reported	2.10 (1.44–3.08)	0.00
Mammography group	0.97 (0.74–1.27)	>0.2
Lump reported	2.11 (1.44–3.08)	0.00
Breast cancer in mother	1.71 (1.15–2.54)	0.01
Mammography group	1.06 (0.80–1.40)	>0.2
Lump reported	2.04 (1.39–2.99)	0.00
Breast cancer in mother	1.67 (1.12–2.48)	0.01
Outside mammography	1.48 (1.06–2.08)	0.02

* Lump reported = patient reported lump to nurse at initial examination; Outside mammography = one or more mammographies done outside the Canadian National Breast Screening Study.

Table 4. **Distribution of Participants by Single Year of Age**

Age	Mammography Group (*n* = 25 214)	Usual Care Group (*n* = 25 216)
y	*n* (%)	
40	3334 (13.2)	3342 (13.3)
41	2741 (10.9)	2748 (10.9)
42	2505 (9.9)	2500 (9.9)
43	2414 (9.6)	2387 (9.5)
44	2315 (9.2)	2341 (9.3)
45	2445 (9.7)	2462 (9.8)
46	2461 (9.8)	2507 (9.9)
47	2379 (9.4)	2361 (9.4)
48	2329 (9.2)	2336 (9.3)
49	2291 (9.1)	2232 (8.9)

Another important issue is whether mammography screening leads to "overdiagnosis" of breast cancer—that is, the detection of a tumor that would not have become clinically detectable in the patient's lifetime. Lobular carcinoma in situ is usually considered a marker of breast cancer risk, and ductal carcinoma in situ should probably be regarded similarly (30). Overdiagnosis of in situ breast cancer has been documented previously (31). CNBSS-1 provides evidence that overdiagnosis of nonpalpable invasive breast tumors may also occur. **Figure 2** shows that unless the lead time gained by mammography exceeds 10 years, an excess 40 cases of invasive breast cancer detected by mammography persist. This represents 58% of the 69 cases of nonpalpable invasive breast cancer in the mammography group and 70% of the nonpalpable (69 nonpalpable and 42 in situ) tumors in the mammography group. This proportion is greater than the 50% of cases of in situ plus invasive cancer detected by screening in the mammography group that meet the definition of minimal breast cancer (in situ plus invasive tumors $<$ 10 mm in diameter). Detection of minimal breast cancer was a main objective for early breast screening programs and was expected to provide the main benefit of mammography screening (32). The null results for CNBSS-1 and CNBSS-2 (33) place substantial doubt on such claims. More breast cancers were detected in the mammography group than in the usual care group, but breast cancer mortality did not differ between the groups.

CNBSS-1 is the only trial designed to assess screening in women 40 to 49 years of age, and its merits were recognized in a recent review (34). Until the ongoing United Kingdom trial of women recruited at ages 40 to 41 years reaches fruition, it will be uncertain whether women in their forties benefit from mammography (35). Women younger than 50 years of age should understand that in the setting of physician breast examination, breast self-examination, diagnostic mammography, and effective cancer therapy, the benefits of screening mammography are uncertain. Women must also consider the adverse consequences of false-positive mammograms.

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Appendix Table 1. **Baseline Characteristics of Participants Who Did and Did Not Report a Self-Detected Breast Lump at Screen 1**

Characteristic	Participants without Self-Reported Lump		*P* Value*	Participants with Self-Reported Lump		*P* Value*
	Mammography Group (*n* = 23 367)	Usual Care Group (*n* = 23 381)		Mammography Group (*n* = 1847)	Usual Care Group (*n* = 1835)	
	n (%)			*n (%)*		
Marital status						
Never married	1494 (6.5)	1505 (6.5)	>0.2	139 (6.5)	120 (6.5)	>0.2
Married	18 575 (80.6)	18 599 (80.8)		1461 (79.1)	1450 (80.7)	
Other	2941 (12.7)	2907 (12.7)		247 (13.3)	264 (14.4)	
Live births						
0	2139 (10.0)	2168 (10.1)	>0.2	164 (9.6)	177 (10.4)	>0.2
1	2113 (9.8)	2214 (10.3)		198 (11.6)	202 (11.8)	
2	7265 (33.8)	7086 (33.0)		585 (34.4)	591 (34.6)	
3	5740 (26.7)	5689 (26.5)		470 (27.8)	426 (24.9)	
≥4	4226 (19.6)	4310 (20.1)		284 (16.7)	314 (18.3)	
Reproductive status						
Premenopausal	15 300 (67.2)	15 480 (68.0)	>0.2	1230 (67.4)	1216 (67.1)	0.10
Perimenopausal	285 (1.3)	272 (1.2)		9 (0.5)	22 (1.2)	
Postmenopausal	1181 (5.2)	1156 (5.1)		44 (2.4)	36 (2.0)	
Hysterectomy with or without oophorectomy	5988 (27.1)	5858 (25.7)		541 (29.7)	542 (29.8)	
Education						
Grade 8	1674 (8.0)	1763 (8.4)	>0.2	170 (10.1)	156 (9.4)	>0.2
Grades 9–13	6392 (30.4)	6416 (30.6)		523 (31.1)	513 (30.9)	
Trade school, etc.	8175 (38.9)	7990 (38.1)		653 (38.8)	639 (38.5)	
University	4776 (22.7)	4789 (22.9)		337 (20.0)	353 (21.3)	
Family history of breast cancer						
Mother	1864 (8.1)	1892 (8.2)	>0.2	162 (8.8)	140 (7.6)	>0.2
Sister	765 (3.3)	800 (3.5)		52 (2.8)	54 (2.9)	
Daughter	1 (0.0)	4 (0.0)		1 (0.1)	0 (0.0)	
Second-degree relative	4516 (19.6)	4587 (19.9)		391 (21.2)	401 (21.9)	
Place of birth						
North America	19 231 (83.5)	19 290 (83.7)	>0.2	1574 (85.2)	1557 (84.9)	>0.2
Europe	3201 (13.9)	3144 (13.6)		219 (11.9)	219 (11.9)	
Elsewhere	565 (2.5)	592 (2.6)		50 (2.7)	56 (3.1)	
Cigarette smoking						
Never	11 039 (48.0)	11 020 (47.9)	>0.2	853 (46.3)	827 (45.2)	>0.2
Smoker						
1–10 y	1457 (27.4)	1368 (26.1)	>0.2	102 (20.0)	128 (25.3)	0.01
11–20 y	1978 (37.2)	1962 (37.4)		184 (36.2)	203 (40.0)	
>20 y	1884 (35.4)	1910 (36.5)		224 (43.8)	176 (34.7)	
Ex-smoker	6426 (27.9)	6530 (28.3)	>0.2	460 (24.9)	484 (26.4)	>0.2
Occupation						
None	7257 (33.2)	7195 (32.9)	>0.2	551 (31.8)	564 (32.8)	>0.2
Clerical	4779 (21.8)	4859 (22.2)		366 (21.1)	376 (21.9)	
Health	2346 (10.7)	2354 (10.8)		237 (13.7)	189 (11.0)	
Teaching	1983 (9.1)	1984 (9.1)		136 (7.9)	146 (8.5)	
Managerial	1684 (7.7)	1658 (7.6)		122 (7.0)	124 (7.2)	
Science	716 (3.3)	721 (3.3)		45 (2.6)	53 (3.1)	
Sales, service	1955 (8.9)	2010 (9.2)		173 (10.0)	167 (9.7)	
Other	1160 (5.3)	1110 (5.1)		102 (5.9)	98 (5.7)	

* For differences in the distributions between the mammography and usual care groups calculated by chi-square statistics.

Appendix Table 2. **Cases of Cancer according to Year, Size of Invasive Breast Tumors, and Mode of Detection**

Year and Tumor Size	Cases of Cancer, *n*							
	Screening Detected Cancer				Interval Cancer		Incident Cancer	
	Mammography Group			Usual Care Group	Mammography Group	Usual Care Group	Mammography Group	Usual Care Group
	All	Mammography*	Mammography + Exam†					
Year 1								
<9 mm	7	4	3	7	3	2	–	–
10–14 mm	17	4	13	6	1	4	–	–
15–19 mm	21	5	16	12	1	5	–	–
20–39 mm	28	4	24	26	4	8	–	–
≥40 mm	4	0	4	3	6	3	–	–
Unknown	10	4	6	4	2	2	–	–
Total	87	21	66	58	17	24	–	–
Years 2–5								
<9 mm	27	17	10	–	2	–	3	10
10–14 mm	18	10	8	–	7	–	3	24
15–19 mm	21	5	16	–	10	–	3	28
20–39 mm	32	7	25	–	13	–	8	59
≥40 mm	10	2	8	–	3	–	3	16
Unknown	13	7	6	–	5	–	5	18
Total	121	48	73	–	40	–	25	155
Years 6–9								
<9 mm	–	–	–	–	–	–	17	14
10–14 mm	–	–	–	–	–	–	22	32
15–19 mm	–	–	–	–	–	–	29	22
20–39 mm	–	–	–	–	–	–	63	49
≥40 mm	–	–	–	–	–	–	15	17
Unknown	–	–	–	–	–	–	58	69
Total	–	–	–	–	–	–	204	203
Total to year 9								
<9 mm	34	23	13	7	5	2	20	24
10–14 mm	35	14	21	6	8	4	25	56
15–19 mm	42	10	32	12	11	5	32	50
20–39 mm	60	11	49	26	17	8	71	108
≥40 mm	14	2	12	3	9	3	18	33
Unknown	23	11	12	4	7	2	63	87
Total	208	69	139	58	57	24	229	358

* Detected by mammography alone.
† Detected by physical examination alone or with mammography.

Appendix Table 3. **Cross-Classification of Size of Screening-Detected Invasive Breast Cancer with Nodal Status**

Year and Tumor Size	Cases of Cancer, *n*											
	Mammography Group								Usual Care Group			
	All				Mammography Alone*							
	0 Positive Nodes	1–3 Positive Nodes	≥4 Positive Nodes	Unknown Nodal Status	0 Positive Nodes	1–3 Positive Nodes	≥4 Positive Nodes	Unknown Nodal Status	0 Positive Nodes	1–3 Positive Nodes	≥4 Positive Nodes	Unknown Nodal Status
Screen 1												
<9 mm	5	1	0	1	3	0	0	1	2	3	0	2
10–14 mm	14	1	2	0	3	0	1	0	3	3	0	0
15–19 mm	14	2	5	0	5	0	0	0	10	1	0	1
20–39 mm	12	7	9	0	2	1	1	0	15	7	4	0
≥40 mm	1	2	1	0	0	0	0	0	0	2	1	0
Unknown	6	2	1	1	4	0	0	0	3	0	0	1
Total	52	15	18	2	17	2	2	1	33	16	5	4
Screen 2–5												
<9 mm	19	6	1	1	11	4	1	1	–	–	–	–
10–14 mm	13	3	1	1	8	2	0	0	–	–	–	–
15–19 mm	17	3	1	0	4	1	0	0	–	–	–	–
20–39 mm	20	8	4	0	7	0	0	0	–	–	–	–
≥40 mm	6	2	1	1	2	0	0	0	–	–	–	–
Unknown	7	2	1	3	4	1	0	2	–	–	–	–
Total	82	24	9	6	36	8	1	3	–	–	–	–

* Detected by mammography alone.

Appendix Table 4. **Nodal Status of Invasive Breast Cancer Ascertained in Women Who Reported a Lump at the Initial Physical Examination**

Time of Detection	Cases of Cancer, *n*									
	Mammography Group (*n* = 1847)					Usual Care Group (*n* = 1835)				
	0 Positive Nodes	1–3 Positive Nodes	≥4 Positive Nodes	Unknown Nodal Status	Total	0 Positive Nodes	1–3 Positive Nodes	≥4 Positive Nodes	Unknown Nodal Status	Total
Screen 1	15	7	6	0	28	13	7	2	2	24
Screens 2–5	8	3	4	0	15	–	–	–	–	–
Interval 1	1	0	3	0	4	1	1	0	0	2
Interval 2–5	2	0	0	0	2	–	–	–	–	–
Incident 2–5	1	2	0	0	3	9	2	3	2	16
Incident after screening	10	5	1	8	24	9	5	2	13	29
Total	37	17	14	8	76	32	15	7	17	71