Canadian National Breast Screening Study-2: 13-Year Results of a Randomized Trial in Women Aged 50–59 Years

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For the Canadian National Breast Screening Study-2

Background: **Screening for breast cancer with mammography in women aged 50 years or more has been shown to reduce mortality from breast cancer. However, the extent to which mammography contributes to the reduction of mortality in women who also undergo physical examination of the breasts is not known. This study was designed to compare breast cancer mortality following annual screening consisting of two-view mammography and physical examination of the breasts with mortality following annual screening by physical examination only. Breast self-examination was taught to all participants.** ***Methods:*** **This trial randomly and individually assigned 39 405 women aged 50–59 years, recruited from January 1980 through March 1985, to one of the study arms. The women were followed by record linkage with the Canadian National Cancer Registry and National Mortality Database to December 31, 1993, and by active follow-up of breast cancer patients to June 30, 1996.** ***Results:*** **Randomization achieved virtually equal distribution of demographic and breast cancer risk variables. At the first annual screen, 21% of the cancers found by mammography alone (in the mammography plus physical examination group) were 20 mm or more in size compared with 46% of those found by physical examination in the mammography plus physical examination group and 56% in the physical examination-only group. The corresponding percentages for screens 2–5 were 10%, 42%, and 50%, respectively. Screening detected 267 invasive breast cancers in the mammography plus physical examination group compared with 148 in the physical examination-only group. By December 31, 1993, 622 invasive and 71** ***in situ*** **breast carcinomas were ascertained in the mammography plus physical examination group, and 610 and 16 were ascertained in the physical examination-only group. At 13-year follow-up, with 107 and 105 deaths from breast cancer in the respective groups, the cumulative rate ratio was 1.02 (95% confidence interval = 0.78–1.33).** ***Conclusion:*** **In women aged 50–59 years, the addition of annual mammography screening to physical examination has no impact on breast cancer mortality. [J Natl Cancer Inst 2000;92:1490–9]**

The Canadian National Breast Screening Study-2 (CNBSS-2) is an individually randomized trial designed to evaluate in women aged 50–59 years on entry the contribution of annual mammography over and above annual physical examination of the breasts and the teaching of breast self-examination (BSE) in the reduction of mortality from breast cancer *(1,2).*

Screening for breast cancer in women aged 50 years or older with mammography alone or mammography plus physical examination of the breasts is believed to be effective in reducing mortality from breast cancer *(3).* However, it is not known how much mammography contributes to the effectiveness of combined screening over and above any benefit from physical examination and BSE. The Working Group to Review the National Cancer Institute–American Cancer Society U.S. Breast Cancer Detection Demonstration Projects *(4)* recommended that a trial to evaluate the magnitude of benefit and net benefit–risk in the use of mammography screening should be conducted. CNBSS-2 is the only trial designed to meet this need.

We report here the findings from the follow-up to 11–16 years from entry (mean, 13 years). The 7-year follow-up was reported previously *(2).*

Materials and Methods

The study methodology was reported previously *(2,5).* Fifteen screening centers were located in six Canadian provinces—Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia—and were supervised centrally at the University of Toronto, Canada. Special quality-control procedures were established for radiation physics and radiology *(6–8),* and a protocol was prepared for the local training of the physical examiners *(9–11).* Facilities and equipment for modern film-screen mammography were prerequisites *(12).*

Participants were recruited in the study by general publicity, by personal invitation letters from population lists, by group mailings, and through physicians *(13).* The eligibility criteria were as follows: age 50–59 years, no mammogram in the previous 12 months, no history of breast cancer, not pregnant, and signing the informed consent form approved by the University of Toronto. Randomization was individual and was stratified by the center and the 5-year age group.

Study Intervention

After an initial physical examination of the breasts and the teaching of BSE, women were randomly assigned to receive either annual mammography and physical examination or annual physical examination only. Two-view film-screen mammography was used throughout, craniocaudal and mediolateral

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See "Appendix" section for list of participants in the Canadian National Breast Screening Study-2.

See "Notes" following "References."

views were used until 1985, and craniocaudal and mediolateral oblique views were used thereafter *(12).* The breast physical examination technique has been described *(9).* This included a visual component as well as palpation, with all parts of the breast examined in a radial pattern from the periphery of the breast to the nipple. BSE was taught at the same time. The examination was thorough and took about 10 minutes. Five annual screening examinations were offered to the first 62% of the women entering the CNBSS-2 and four were offered to the remainder. The BSE technique of the woman was re-enforced on each rescreening visit *(14).*

Sample Size

The trial was planned with a fixed sample to evaluate whether a 40% reduction in breast cancer mortality would be seen in the mammography plus physical examination compared with the physical examination-only group, a reduction similar to the Health Insurance Plan (HIP) trial at 5 years from entry *(15).* It was assumed that nearly all of the mortality reduction would be derived from mammography *(1).* The sample size required to demonstrate this level of mortality reduction after 5 years of follow-up was computed to be 40 000 women, at an alpha level of 0.05 and a power of 80% *(1).* However, at 5 years, the number of breast cancer deaths was insufficient to achieve the planned power. Therefore, for the first mortality report, the follow-up was extended by 2 years, allowing the required number of deaths to accrue *(2).*

Study Procedures

In 12 of the 15 centers, nurses carried out the breast physical examinations; in the three Quebec centers, physicians performed the examinations. If physical examination of the breasts and/or mammography revealed an abnormality, the participant was referred to the CNBSS review clinic. At the review clinic, the study surgeon could discuss the mammography findings with the study radiologist, examined the participant, and decided whether further diagnostic procedures were indicated. The woman's physician determined if and how the study surgeon's recommendations should be implemented.

Follow-up Procedures

During the screening period, the center coordinators collected surgery and pathology reports for all diagnostic and therapeutic procedures. All slides were reviewed by a CNBSS pathologist. If the community and CNBSS pathologist disagreed, the slides were reviewed by a panel of three to five other CNBSS pathologists.

After the screening centers closed in 1988, annual follow-up by the CNBSS central office continued for all women known to have breast cancer, whether screen-, interval-, or incident-detected until June 30, 1996, the cutoff for this analysis. Passive follow-up was carried out for the remaining participants: New diagnoses of breast cancer in study participants to December 31, 1993, were identified by linkage with the National Cancer Registry maintained by Statistics Canada, Ottawa. Surgery and pathology reports for breast cancers ascertained after the end of the screening period were collected by the CNBSS central office. These breast cancers were not reviewed by a CNBSS pathologist; the diagnosis by the local pathologist was accepted for study purposes.

Ascertainment of Death

Deaths were identified in three ways: 1) by responses of family members to the questionnaires mailed to all participants during their screening schedule, 2) by active individual follow-up of women diagnosed with breast cancer to June 30, 1996, through their physician irrespective of how they were diagnosed, and 3) by passive follow-up of all 39 405 participants through linkage with the Canadian Mortality Data Base (CMDB) at Statistics Canada to December 31, 1993. The CMDB also includes deaths in Canadians resident in the United States at the time of death.

Verification of Cause of Death

Death review procedures were described previously *(5).* Death certificates were obtained for all participants. Relevant clinical records were collected for all women with breast cancer who had died, for those whose death certificate mentioned breast cancer, and for those with a cause of death specified as unknown, unknown primary, lung cancer, colon cancer, or liver cancer. Three oncologists independently reviewed each case, blind to allocation status and identity. A majority had to conclude that death was due or probably due to breast cancer or not due to breast cancer. All other causes of death were accepted as certified. For the current record linkage, the majority of deaths due to breast or lung cancer, due to other causes in women known to have breast cancer, or due to "primary unknown" was verified (C. J. Baines), with only a few hospitals refusing to release clinical records. Deaths due to lung and colorectal cancers were not verified. All other causes of deaths were analyzed as coded by the Nosology Division of Statistics Canada.

CNBSS-2 Database

The database includes records for 39 459 women aged 50–59 years randomly assigned to both study arms in CNBSS-2 from January 1980 through March 1985. Extensive ongoing quality control was carried out while data collection was in progress. Risk factor data were collected from information given on the initial enrollment form and epidemiologic questionnaire. Information on screening received after cessation of the study was not obtained.

For breast cancers, copies of the surgical and pathology reports were obtained; thus, information was obtained on surgical therapy, but not on adjuvant chemotherapy, radiotherapy, or hormone therapy. The size of the tumor and axillary lymph node status were determined by pathologists in community hospitals who followed their own standards of practice. For mixed *in situ* and invasive tumors, the invasive component was not always measured. Therefore, subsequent to the 1992 mortality report *(2),* all available material for screen-detected and interval cancers was collected again from the institutions where the original diagnosis was made and reviewed by one of the CNBSS pathologists (F. Alexander [Tom Baker Cancer Center, Calgary, AL, Canada] or a colleague. It was possible to obtain slides for review for nearly 80% of the requested cases. For those submitted, the pathologist reclassified the cancers by tumor size, when necessary, measuring the size of the invasive component for mixed invasive and *in situ* tumors.

CNBSS-2 Terminology

The terms "screen 1–5" are used to denote events associated with screening examinations. Screen-detected cancers are defined as those diagnosed as a result of a recommendation made at the CNBSS review clinic. Interval cancers are those occurring less than 12 months after a screening examination that did not generate a recommendation for diagnostic evaluation. Incident cancers are defined as those occurring 12 or more months after the previous CNBSS screening examination.

Methods of Analysis

The chi-square test was used to determine the statistical significance of differences in proportions. A two-sided alpha level of 0.05 was used as the cutoff for statistical significance. Only those values <0.05 are cited in the text. For all rate ratios, 95% confidence intervals (CIs) were computed.

Death due to or probably due to breast cancer is the major end point. Death rates are computed using person-years based on stratification by quinquennium of age, assuming all of those not known to be dead are alive. Age is defined in the analysis as age at entry. As indicated below, compliance with the interventions was high. Because all eligible subjects were included in the analysis and the follow-up, this can be regarded as an "intention-to-treat" analysis.

Results

Participants

Of the 39 459 women who entered the study, 54 were excluded from the analysis (Fig. 1). The mean follow-up from entry is 13 years (range, 11.3–16 years). Detailed analyses of all of the epidemiologic variables reported on the questionnaire were reported previously *(2,16).* There were no differences by study arm.

Compliance

After screen 1, when compliance with attendance was 100%, compliance varied between 90.4% at screen 2 and 86.7% at screen 5 in the mammography plus physical examination group *(2).* A few women (1.8%–3.2% at various years) accepted physical examination but refused mammography. The compliance of

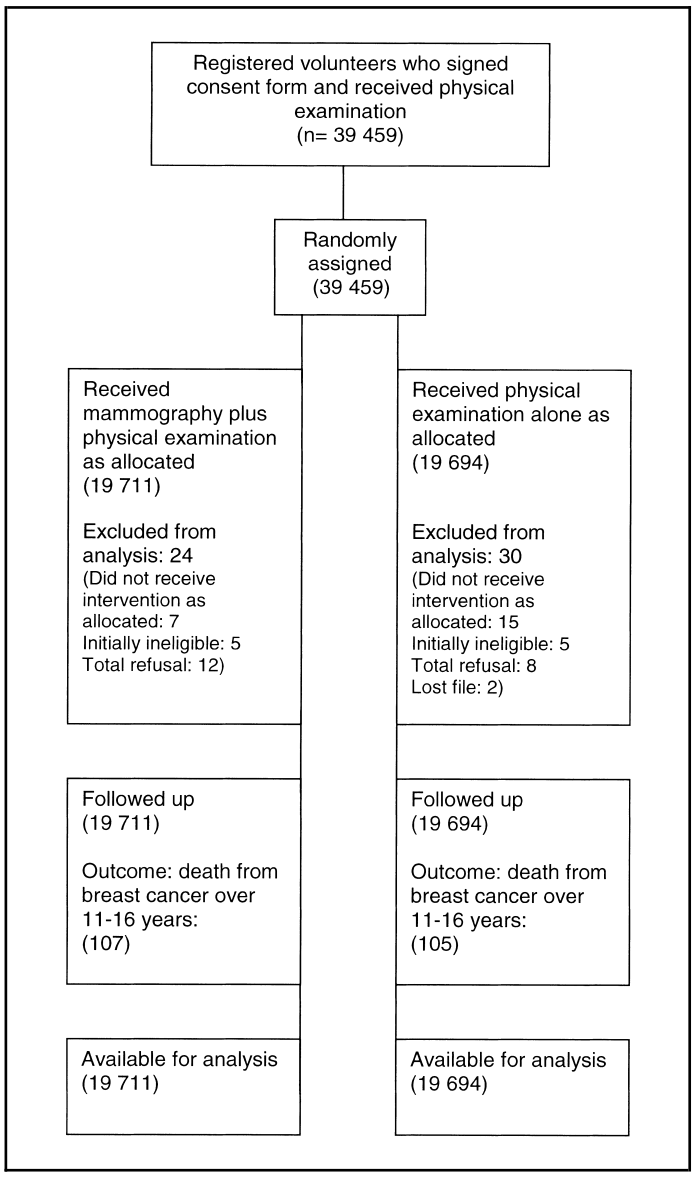

Fig. 1. Randomization and follow-up of volunteers who signed the informed consent form in the Canadian National Breast Screening Study-2 (CNBSS-2). There was no defined list of potential subjects from which the numbers not randomized can be determined. Volunteers into CNBSS-2 were sought largely by general publicity, and only they attended the screening centers and were registered *(13).* All 39 459 subjects received physical breast examination and instruction in breast self-examination prior to randomization.

physical examination-only participants after screen 1 varied between 89.1% at screen 2 and 85.4% at screen 5.

During the CNBSS-2 screening schedule, 1196 (6.1%) of mammography plus physical examination participants and 3330 (16.9%) of physical examination-only participants reported one or more interval mammograms. The proportions of mammography plus physical examination participants reporting interval mammograms remained stable across screening years, ranging between 1.9% and 2.2%, but increased slightly among women in the physical examination-only group, with 5.3% reporting mammograms between screens 1 and 2 and 8.0% between screens 4 and 5.

Referral to Review and Procedures Performed

At screen 1, 17.1% of mammography plus physical examination participants and 11.2% of physical examination-only participants were referred to the CNBSS review clinic; the difference was due to mammographic abnormalities in the absence of physical findings in the mammography plus physical examination group *(2).* In both groups, the proportions referred to review declined after screen 1, being 7.3% and 5.9% at screen 2 and lower subsequently. The contribution of physical findings to the referral rate was 11.0% in the mammography plus physical examination participants and 11.2% in the physical examination-only participants at screen 1, 5.7% and 5.9% at screen 2, and lower subsequently. In general, more diagnostic procedures were recommended and performed in mammography plus physical examination participants than in physical examination-only participants, and more were performed at screen 1 than at subsequent screens.

Biopsy rates for physical examination-only participants ranged from 8.7 per 1000 at screen 1 to 2.7 per 1000 at screen 5 *(2).* The corresponding rates for mammography plus physical examination participants were 24.3 and 7.1, respectively.

Cancer Detection

Screen-detection rates for all cancers were reported previously *(2).* The rate at screen 1 in the mammography plus physical examination group was 7.20 per 1000 and for the physical examination-only group was 3.45 per 1000. At subsequent screens, detection rates were just under half the initial rates. Throughout, interval-detected cancers were fewer in the mammography plus physical examination group than in the physical examination-only group, with totals of 50 and 88, respectively ($P<.0002$).

Seventy-one *in situ* breast carcinomas were detected in the mammography plus physical examination group compared with 16 in the physical examination-only group, a cumulative rate to December 31, 1993, of 38.3 per 1000 and 8.6 per 1000, respectively. A total of 267 invasive breast cancers were screen detected in the mammography plus physical examination group compared with 148 in the physical examination-only group. This excess of 119 screen-detected invasive cancers was reduced to 66 by the end of year 5 because of the larger number of interval and incident cancers diagnosed in the physical examination-only group, resulting in 5-year totals of 349 and 283, respectively. The residual excess of invasive cancers in the mammography plus physical examination group largely disappeared with continued follow-up. By December 31, 1993, a total of 622 invasive breast cancers had been ascertained in the mammography plus physical examination arm and 610 were ascertained in the physical examination-only group. Fig. 2 shows this by screening year. The area between the two curves is the lead time gained by the mammography-alone-detected cancers. The average lead time for the mammography plus physical examination group has been estimated to be 3.6 years (95% CI = 2.7–5.5) and that for the physical examination-only group was 1.5 years (95% CI = 1.0–3.3 years); therefore, the lead time gained by mammography was, on average, 2.1 years.

Table 1 presents tumor size for screen-detected, interval, and incident invasive cancers ascertained in the first 9 years of follow-up. Size distribution of cancers detected by mammography alone was more favorable than for those found by physical examination. Thus, at screen 1, only 21% of the cancers found by mammography alone were 20 mm or more in size compared with 46% of those found by physical examination with or without mammography in the mammography plus physical exami-

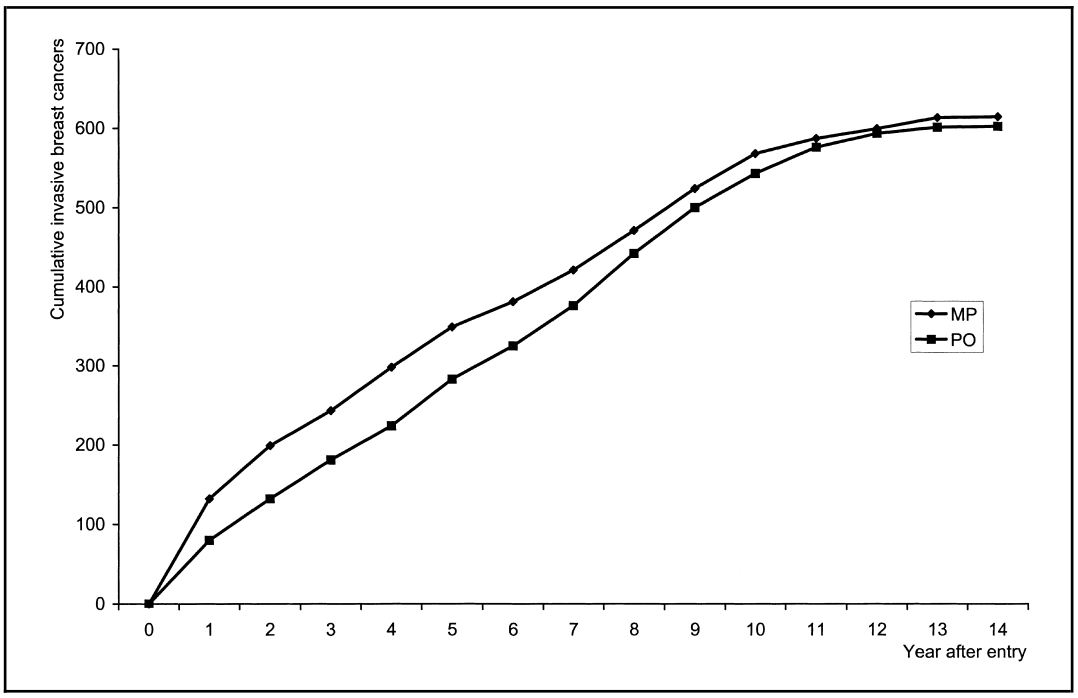

Fig. 2. Cumulative numbers of invasive breast cancers ascertained, by year after entry into the Canadian National Breast Screening Study-2. MP = mammography plus physical examination arm; PO = physical examination-only arm.

nation group and 56% in the physical examination-only group. The corresponding percentages for screens 2–5 were 10%, 42%, and 50%. The sizes of interval cancers were similar to those found by physical examination, 47% of those in the mammography plus physical examination group and 42% in the physical examination-only group being 20 mm or larger. Of the incident cancers, 29% in the mammography plus physical examination group and 31% in the physical examination-only group were

Table 1. Size of invasive breast cancers, ascertained in the first 9 years of follow-up, by year and mode of detection*

	Screen-detected cancer, No.				Interval cancer, No.		Incident cancer, No.		All cancers, No.	
Tumor size, mm	All MP	MP/MA	MP/PE	PO	MP	PO	MP	PO	MP	PO
Year 1										
<9	17	13	4	3	0	1	—	—	17	4
10–14	18	5	13	9	1	3	—	—	19	12
15–19	27	14	13	13	7	4	—	—	34	17
20–39	40	10	30	32	6	4	—	—	46	36
⩾40	2	0	2	4	0	1	—	—	2	5
Unknown	14	6	8	3	0	3	—	—	14	6
Total	118	48	70	64	14	16	—	—	132	80
Years 2–5										
<9	31	24	7	3	2	8	3	4	36	15
10–14	36	24	12	20	6	12	2	5	44	37
15–19	36	16	20	16	6	9	8	7	50	32
20–39	32	7	25	35	14	25	7	20	53	80
⩾40	6	1	5	7	3	5	4	3	13	15
Unknown	8	6	2	3	5	13	8	8	21	24
Total	149	78	71	84	36	72	32	47	217	203
Years 6–9										
<9	—	—	—	—	—	—	22	31	22	31
10–14	—	—	—	—	—	—	30	23	30	23
15–19	—	—	—	—	—	—	28	27	28	27
20–39	—	—	—	—	—	—	42	50	42	50
⩾40	—	—	—	—	—	—	6	11	6	11
Unknown	—	—	—	—	—	—	47	75	47	75
Total	—	—	—	—	—	—	175	217	175	217
Total to year 9										
<9	48	37	11	6	2	9	25	35	75	50
10–14	54	29	25	29	7	15	32	28	93	72
15–19	63	30	33	29	13	13	36	34	112	76
20–39	72	17	55	67	20	29	49	70	141	166
40–49	8	1	7	11	3	6	10	14	21	31
Unknown	22	12	10	6	5	16	55	83	82	105
Total	267	126	141	148	50	88	207	264	524	500

*MP = mammography plus physical examination arm, MA = detected by mammography alone, PE = detected by physical examination with or without mammographic findings, PO = physical examination only arm.

Table 2. Cross-classification of size of screen-detected invasive breast cancers with lymph node status, by study arm*

	Lymph node status											
	MP, No.								PO, No.			
	All methods of detection				MA							
Tumor size, mm	None	1–3	⩾4	Unknown	None	1–3	⩾4	Unknown	None	1–3	⩾4	Unknown
Year 1												
<9	13	1	1	2	10	1	0	2	2	0	0	1
10–14	13	2	0	3	4	0	0	1	9	0	0	0
15–19	17	7	0	3	8	4	0	2	10	1	2	0
20–39	20	11	7	2	5	4	0	1	13	9	8	2
⩾40	0	1	1	0	0	0	0	0	2	1	1	0
Unknown	11	1	0	2	5	0	0	1	1	0	0	2
Total	74	23	9	12	32	9	0	7	37	11	11	5
Years 2–5												
<9	22	3	2	4	17	1	2	4	3	0	0	0
10–14	28	5	1	2	19	2	1	2	15	4	0	1
15–19	24	9	3	0	8	7	1	0	6	8	1	1
20–39	18	10	3	1	5	1	0	1	21	6	7	1
⩾40	1	1	3	1	0	0	1	0	3	3	1	0
Unknown	6	0	0	2	5	0	0	1	2	1	0	0
Total	99	28	12	10	54	11	5	8	50	22	9	3

*Study arms: MP = mammography plus physical examination study arm, PO = physical examination-only study arm, and MA = detected by mammography alone.

known to be 20 mm or larger. However, size had not been recorded for 24% and 28%, respectively, of these cancers. Most could not be included in the CNBSS review of tumor size, so the apparent differences between the size of the incident cancers and those detected in the screening period must be interpreted with caution.

More lymph node-positive tumors were found on screening in the mammography plus physical examination group compared with the physical examination-only group, the numbers being 32 and 22 at screen 1 and 40 and 32, respectively, at screens 2–5. However, 17 and 28, respectively, of the interval cancers were lymph node positive. Including the incident cancers, by the end of year 5 after entry to the study, 100 lymph node-positive tumors had been diagnosed in the mammography plus physical examination group and 95 had been diagnosed in the physical examination-only group. Of the 524 invasive breast cancers ascertained in the mammography plus physical examination group in the first 9 years, 163 (31%) were known to be lymph node positive compared with 500 and 173 (35%) , respectively, in the physical examination-only group, a statistically nonsignificant difference ($P>.1$).

A cross-classification of tumor size by lymph node status is presented for screen-detected cancers in Table 2. Cancers detected by mammography alone were less likely to be lymph node positive than those detected by physical examination, and small tumors were less likely to be lymph node positive than large tumors. However, some small impalpable cancers were lymph node positive, including four at screens 2–5 with four or more lymph nodes microscopically involved with tumor. (None of the lymph node-positive cancers detected on mammography alone had palpable axillary lymph nodes.) Similar data for the interval and incident cancers are available from the authors on request.

Mortality

Table 3 provides the underlying causes of death ascertained through record linkage to the CMDB to December 31, 1993. The total numbers of deaths were similar in the mammography plus physical examination and physical examination-only groups, 734 and 690, respectively. There were 88 deaths from breast cancer in the mammography plus physical examination group and 90 deaths in the physical examination-only group, for a cumulative rate ratio of 0.98 (95% CI = 0.73–1.31). There were more deaths in the mammography plus physical examination group than in the physical examination-only group for pancreas, ovary, hematopoietic, and other cancers and more deaths in the physical examination-only group than in the mammography plus physical examination group for lung cancer, colorectal cancer, other causes, and external causes. Only the difference for pan-

Table 3. Causes of death from record linkage to Canadian Mortality Database to the end of 1993, by study arm*

	Study arm			
	MP		PO	
Cause of death†	No.	%	No.	%
Breast cancer	88	11.9	90	12.9
Lung cancer	74	10.0	82	11.8
Colorectum cancer	45	6.1	51	7.4
Stomach cancer	12	1.6	12	1.7
Pancreas cancer	42	5.7	18	2.7
All uterus cancer	19	2.6	10	1.6
Ovary cancer	46	6.3	31	4.5
Hematopoietic neoplasms	47	6.4	35	5.1
Other neoplasms	91	12.4	74	10.7
Infectious/parasitic diseases	5	0.7	6	0.9
Endocrine/metabolic cause	14	1.9	11	1.8
Central nervous system (nonvascular) cause	12	1.6	14	1.9
Circulatory disease	148	20.2	144	20.9
Respiratory disease	17	2.3	19	2.7
External cause	43	5.9	50	7.2
Other cause	30	4.0	42	6.1
Unknown cause	1	0.1	1	0.1
Total	734		690	

*MP = mammography plus physical examination study arm and PO = physical examination-only study arm.

†*See* text for explanation of verification procedures.

creas cancer is nominally statistically significant ($P<.01$); however, in view of the numbers of comparisons made, the difference can be ascribed to chance.

Table 4 presents the numbers of deaths due to breast cancer according to time and method of breast cancer detection over the total period of follow-up to June 30, 1996. There were more deaths in the mammography plus physical examination group from cancers detected at screen 1 than in the physical examination-only group. In contrast, there were more deaths in the physical examination-only group than in the mammography plus physical examination group from interval 2–5 cancers. Deaths from incident cancers are presented for those diagnosed during years 2–5 and then yearly to 9 or more years after entry.

If only breast cancer deaths occurring in those diagnosed with breast cancer in the first 5 years after entry are considered (top section, Table 4), the rate ratio is 1.09 (95% CI = 0.78–1.51). Similar rate ratios are found as each successive year of ascertaining breast cancers is added to this baseline. Including deaths from all breast cancers ascertained through December 31, 1993 (bottom section, Table 4), yields 107 in the mammography plus physical examination arm and 105 in the physical examination-only arm, for a cumulative rate ratio of 1.02 (95% CI = 0.78–1.33).

An analysis of the data in Table 4 dividing the study population into those aged 50–54 and those aged 55–59 years on entry has also been performed (not shown). There is no material difference from the findings in Table 4, although the CIs are wider because of the smaller numbers of deaths in each subgroup.

Discussion

CNBSS-2 is the only trial that has evaluated the effect of mammography over and above physical examination of the breasts and BSE in women aged 50–59 years. All of the other studies of this age group have compared screening to no screening. This analysis has confirmed our preliminary conclusion that screening women aged 50–59 years with yearly mammography in addition to physical examination detected considerably more lymph node-negative and small breast cancers than screening

Table 4. Cumulative number of deaths from breast cancer to June 30, 1996, by study arm and time of breast cancer detection*

Time of detection	Study arm, No. of deaths	
	MP	PO
Including only breast cancers identified to 5 years from entry		
Screen 1	25	12
Screens 2–5	28	22
Interval 1	7	7
Intervals 2–5	10	20
Incidents 2–5	4	7
Total	74	68
Cumulative breast cancer death rates per 10 000†	3.42	3.15
Mortality rate ratio (95% CI)	1.09 (0.78–1.51)	
Including breast cancers identified to 6 years from entry		
Among breast cancers detected to year 5	74	68
Among breast cancers detected during year 6	10	8
Total	84	76
Cumulative breast cancer death rates per 10 000†	3.89	3.52
Mortality rate ratio (95% CI)	1.10 (0.81–1.51)	
Including breast cancers identified to 7 years from entry		
Among breast cancers detected to year 6	84	76
Among breast cancers detected during year 8	9	7
Total	93	83
Cumulative breast cancer death rates per 10 000†	4.30	3.84
Mortality rate ratio (95% CI)	1.12 (0.83–1.50)	
Including breast cancers identified to 8 years from entry		
Among breast cancers detected to year 7	93	83
Among breast cancers detected during year 8	6	6
Total	99	89
Cumulative breast cancer death rates per 10 000†	4.58	4.12
Mortality rate ratio (95% CI)	1.11 (0.84–1.48)	
Including breast cancers identified to 9 years from entry		
Among breast cancers detected to year 8	99	89
Among breast cancers detected during year 9	5	8
Total	104	97
Cumulative breast cancer death rates per 10 000†	4.81	4.49
Mortality rate ratio (95% CI)	1.07 (0.81–1.41)	
Including breast cancers identified 9 or more years from entry		
Among breast cancers detected to year 9	104	97
Among breast cancers detected beyond year 9	3	8
Total	107	105
Cumulative breast cancer death rates per 10 000†	4.95	4.86
Mortality rate ratio (95% CI)	1.02 (0.78–1.33)	

*MP = mammography plus physical examination arm, PO = physical examination-only arm, and CI = confidence interval.

†Based on 216 133 person-years of observation in the mammography plus physical examination arm and 216 042 in the physical examination-only arm.

with physical examination alone but had no impact on mortality from breast cancer *(2).* However, the period of observation has now been extended to 11.3–16 years from entry.

Possible explanations for our findings include chance, bias in allocation, quality of CNBSS mammograms, lack of compliance with mammography in the mammography plus physical examination group, mammography received by physical examination-only participants, incomplete ascertainment of outcomes, and lack of efficacy of mammography on breast cancer mortality among women who have annual physical breast examinations performed by highly trained health professionals and who practice BSE.

All CIs around our estimates of effect exclude a 30% reduction in breast cancer mortality from mammography screening. Although it is impossible to prove a null effect, chance is an unlikely explanation for our findings.

Evaluation of the characteristics of the participants confirmed that they were well matched by allocation *(2,16),* and the proportions of women referred to review on the basis of findings on physical examination were similar. Our allocation procedures have been criticized, but no evidence that the process was subverted has been found *(17–19).* A recent review *(20)* has again found that CNBSS was randomized adequately. The main reason for concern over CNBSS-1 relating to women aged 40–49 years was an excess of cancers with four or more lymph nodes at screen 1 in the mammography plus physical examination group compared with the usual-care group. This excess was probably due to earlier detection of lymph node-positive as well as lymph node-negative cancers by mammography screening *(17)* or may have been due to chance *(21).* In CNBSS-2, an initial excess of lymph node-positive tumors identified by mammography largely comprised those with one to three lymph nodes but was clearly caused by lead time, since it disappeared within 5 years of the initial screen.

The CNBSS is the only mammography screening study to have subjected films to independent evaluation *(12).* Unfortunately, the external reviewers chose not to evaluate the films from the early 1980s in relation to the study protocol, which, until 1985, required a mediolateral view, but chose instead to evaluate these films in relation to what they perceived the state of the art to be in 1987, requiring a mediolateral oblique view. This practice led to the unjustified accusation that, in the early part of the trial, 50% of the films were unsatisfactory *(22).* This and other adverse comments have ignored the evidence that CNBSS mammograms achieved high sensitivity and the expected cancer detection rates *(16,23–25).* Detection rates were higher in the mammography plus physical examination than in the physical examination-only allocation throughout screening. These detection rates were achieved at the cost of high biopsy rates for benign lesions [similar to a U.S. experience *(26)*], and an excess of mastectomies in the mammography plus physical examination arm *(27),* largely due to uncertainty over the appropriate treatment of the excess of *in situ* carcinomas found.

Compliance with mammography in the mammography plus physical examination group was excellent throughout the period of screening *(2).* In addition, there was relatively little mammography in the physical examination only-group, most being prescribed for diagnostic purposes *(2).* The reasons for the low rates of mammography in this group include the fact that the subjects were recruited with informed consent and that breast-screening programs were not initiated in Canada until after CNBSS screening had been concluded. We do not have information on the extent that mammography was given to participants in either group subsequent to the study schedule. Organized screening programs began in British Columbia in 1988 and were subsequently extended to Ontario and Alberta in 1990 and other provinces *(28).* It seems unlikely that differential uptake of screening mammography subsequent to CNBSS screens could explain the lack of mortality differential that we have seen.

There is no guidance from the published literature on the cancer-detection rates to be expected from physical examination-only screening. Although detection rates have been published for the U.K. trial for the examinations in rounds 2, 4, and 6 when physical examinations alone were given *(29),* these are not comparable to the rates reported previously for the CNBSS-2 physical examination-only allocation *(2).* The U.K. study included women aged 45–64 years on entry and, more important, the physical examination-only screens followed screens in which mammography was given a year before. Thus, cancers with a prolonged lead time detected by mammography would not have been "available" for detection by physical examination in the following year.

Our procedures ensured complete ascertainment of cancers in both groups for at least 5.5 years after the cessation of screening. Such prolonged follow-up was essential to determine the eventual outcomes both of cancers detected on screening and of cancers that would have been detected in the physical examination-only group if mammography screening had been performed. However, all of the cancers diagnosed after the cessation of screening in the mammography plus physical examination group and many in the physical examination-only group could not have been influenced by the screening in the study. Nevertheless, because the relevant cancers in the physical examination-only group cannot be identified, it is necessary to include deaths from breast cancer diagnosed well past the end of screening to enable the breast cancers comparable to those diagnosed early in the mammography-screened group to appear later in those screened with physical examination only. The time required theoretically is that period until the numbers of breast cancers equalize in the two arms *(30).* Such a time point will never arise if mammography results in overdiagnosis of trivial occult cancers. However, in this analysis, the numbers of invasive cancers approximately equalize by the end of the period of observation (Fig. 2) so that the mortality rate ratio, including all breast cancers ascertained, is closest to the theoretical ideal.

As pointed out previously *(5),* our interval cancer rates are not comparable to those from other studies, since we included women with abnormal mammographic or physical findings on the previous screen, but for whom a recommendation for further investigation was not made at the CNBSS review clinic. Thus, our interval cancer rates cannot be compared with studies that included only women with a negative previous screen. All participants were taught and urged to practice BSE. In some cases, interval cancers were detected as a result of BSE, thus potentially reducing delay in diagnosis. Even so, mammography reduced the interval cancer rates by about 43% overall in the mammography plus physical examination group compared with the physical examination-only group. Thus, high interval cancer rates seem unlikely to be an explanation for the lack of a mortality benefit from mammography.

A substantial excess of small and lymph node-negative tu-

mors during the screening period resulted from the addition of mammography to physical examination screening, but the addition of mammography to physical examination of the breasts did not reduce the cumulative incidence of lymph node-positive breast cancers. In other words, the stage shift that resulted from mammography screening did not result in a decrease in the absolute rate of advanced breast cancers. Reduction in the absolute cumulative incidence rate of advanced cancer is a prerequisite for mortality reduction following screening *(31).* Lead time without benefit has recently been demonstrated for lung cancer screening (Marcus PM, Bergstrahl EJ, Fagerstrom RM, Williams DE, Fontana R, Taylor WF, et al: unpublished data). CNBSS-2 is the first study to demonstrate lead time without benefit for breast cancer screening.

The benefit derived from mammography screening is usually ascribed to the detection of impalpable and perhaps also *in situ* breast carcinomas. Our findings suggest that a different paradigm may be in order *(32).* It is striking that the successive trials of breast cancer screening have failed to show a greater reduction in breast cancer mortality than the HIP trial, despite the substantial technologic improvements in mammography since the 1960s. The benefits of screening in the HIP trial were seen rapidly, beginning about 3 years after entry, and maximizing by 5 years *(15).* This seems to place some doubt on the role of impalpable cancers detected by mammography. The excellent survival of women with such cancers (also found in CNBSS-2, 87.5% alive at 10 years, data not presented) is almost certainly due to a combination of lead time and length bias. Of interest, excellent survival at 10 years was also found in CNBSS-2 for women with those cancers detected by physical examination alone (89.9%), which compares to the 75.7% 10-year survival of those detected by both mammography and physical examination. In the HIP trial, at least 70% of the benefit may have come from the physical examinations *(33).* This suggests that the earlier detection and earlier treatment of more advanced cancers with a smaller tumor burden may make a major contribution to the benefit derived from screening. That benefit may derive from a shift to earlier detection within stage, rather than stage shift itself, has been suggested to explain the HIP results among women aged 40–49 years *(34)* as well as an apparent benefit from BSE *(35).* A case–control analysis within the CNBSS found that efficient practice of BSE contributed to mortality reduction in both the mammography plus physical examination and physical examination-only allocations *(36).* It, therefore, seems likely that benefit was derived from the physical examinations together with BSE conducted in both groups in the trial.

When the data from trials comparing mammography screening to no screening are evaluated by 5-year age at entry group, there is some evidence of lesser effectiveness at age 50–54 years than at older ages. This phenomenon was first seen in one of the case–control studies in The Netherlands *(37)* and was also seen in the Edinburgh trial *(38)* and, to a lesser extent, in the U.K. trial as a whole *(39).* However, that cannot be the explanation for the absence of an effect in CNBSS-2, since an analysis by 5-year age at entry group failed to find any difference in the null effect comparing women aged 55–59 years on entry with those aged 50–54 years.

One further possible explanation for the lack of difference in breast cancer mortality between the two arms in this trial is that treatment of breast cancer has improved to such an extent that there is no longer any benefit from screening. Without an unscreened control group (deemed unethical at the time this study was designed), we cannot confirm that screening in either arm was beneficial. We demonstrated previously that CNBSS-2 participants had a higher incidence of breast cancer and lower breast cancer mortality than those expected from the Canadian population *(2).* This finding suggests some benefit from screening in both study arms. It has been pointed out that the tumor size distribution in the control subjects in the Swedish mammography trials was substantially less favorable than that in the control subjects in CNBSS 1 and 2 *(40),* suggesting that the difference in mortality seen in Canada would be less than that seen in Sweden. Thus, the estimates of 15%–20% breast cancer mortality reduction following screening made for the Dutch and U.K. populations *(41)* may be more realistic than the 30% reduction often derived by extrapolation from the overview analysis of the Swedish trials *(42).*

We re-emphasize that the CNBSS-2 comparison of screening with mammography plus physical examination and BSE to screening with physical examination and BSE alone is unique. It is in the group aged 50 years or more that an early benefit of combined screening or of mammography alone has been reported *(3).* Although it could have been anticipated that, if mammography makes the major contribution to the benefit of combined screening, we would have observed it after 7 years' follow-up *(2),* we have now conducted sufficient additional follow-up to be able to conclude that it does not do so. We are not aware of any mammography screening trial that has shown a widening of benefit beyond 7–10 years after entry. It, therefore, seems extremely unlikely that benefit might be detectable after further follow-up. However, our findings do not negate the reported benefit from mammography screening compared with no screening. Rather, they suggest another option for screening women over the age of 50 years: annual physical examination and the teaching of BSE by skilled health professionals. This option may prove to be of particular interest in countries where breast cancer is an increasing problem but where mammography services are almost nonexistent. The option should also, however, be considered by physicians in practice *(43).* Nevertheless it must be emphasized that physical examinations for screening involve far more skilled attention to relatively minor signs than those often rather casually performed by health-care workers who have not been trained to recognize the signs of early breast cancer *(9,43).*

Appendix: Participants in the CNBSS-2

Center Directors: A. A. Bassett (Mt. Sinai Hospital, Toronto, ON), D. C. G. Bethune (Victoria General Hospital, Halifax, NS), D. M. Bowman (Manitoba Cancer Treatment and Research Foundation, Winnipeg, MB), H. Bush (London Regional Cancer Centre, ON), J. Cantin (Hôtel-Dieu Hospital, Montreal, PQ), L. Deschênes (Hôpital St. Sacrement, Quebec), J. E. Devitt (Ottawa Civic Hospital, ON), D. N. Graham (Central Alberta Cancer Centre, Red Deer, AB), G. Hislop (Cancer Control Agency of British Columbia, Vancouver), A. W. Lees (Cross Cancer Institute, Edmonton, AB), B. M. Lefèbvre (Ottawa General Hospital, Ottawa, ON), L. Mahoney (St. Michael's Hospital, Toronto), S. E. O'Brien (Henderson General Hospital, Hamilton, ON), A. Simard (Notre-Dame Hospital, Montreal, PQ), and W. J. Temple (Tom Baker Cancer Centre, Calgary, AB).

Surgeons: C. P. Armstrong (Tom Baker Cancer Centre), R. M. Baird (Cancer Control Agency of British Columbia), A. A. Bassett (Mt. Sinai Hospital), D. J. Beatty (Manitoba Cancer Treatment and Research

Foundation), W. Beecroft (deceased; Manitoba Cancer Treatment and Research Foundation), W. J. Buie (Tom Baker Cancer Centre), R. Bury (Cross Cancer Institute), C. D. J. Chadwick (Ottawa Civic and General Hospitals, ON), W. G. Chipperfield (Tom Baker Cancer Centre), D. Currie (St. Michael's Hospital), G. J. Dewar (Central Alberta Cancer Centre), M. Falardeau (Notre-Dame Hospital), G. J. Francis (Central Alberta Cancer Centre and Tom Baker Cancer Centre), M. H. Friedman (Cross Cancer Institute), N. Gagic (Henderson General Hospital), D. Girvin (Victoria Hospital, London, ON), H. R. Harse (Tom Baker Cancer Centre), I. Koven (Mt. Sinai Hospital), U. Kuusk (Cancer Control Agency of British Columbia), R. D. Marriott (Central Alberta Cancer Centre), A. B. McCarten (Cross Cancer Institute), J. McCredie (Victorial Hospital), W. O. Onerheim (Central Alberta Cancer Centre), A. Péloquin (Notre-Dame Hospital), C. Potvin (Hôtel-Dieu Hospital), R. E. Pow (Tom Baker Cancer Centre), J. Purves (Victorial General Hospital), P. M. Rebbeck (Cancer Control Agency of British Columbia), J. Robert (Hôpital St. Sacrement), A. Robidoux (Hôtel-Dieu Hospital), J. T. Sandy (Cancer Control Agency of British Columbia), S. Sidlofsky (Mt. Sinai Hospital), E. R. Sigurdson (Mt. Sinai Hospital), B. Steele (Victoria General Hospital), R. M. Stone (Mt. Sinai Hospital), J. B. Taillefer (Ottawa General Hospital, Ottawa), W. J. Temple (Tom Baker Cancer Centre), T. K. Thorlakson (Manitoba Cancer Treatment and Research Foundation), and G. K. Thorson (Henderson General Hospital).

Radiologists: L. Audet (Hôpital St. Sacrement), B. L. Bird (St. Michael's Hospital), M. J. Burns (St. Michael's Hospital), B. Capusten (Central Alberta Cancer Centre), W. R. Castor (Cross Cancer Institute), G. M. Cooke (St. Michael's Hospital), C. M. Copeland (Central Alberta Cancer Centre and Cross Cancer Institute), J. W. Davidson (Henderson General Hospital), G. D. Davis (Victoria General Hospital), J. E. Desautels (Tom Baker Cancer Centre), R. L. Desmarais (Ottawa Civic and General Hospitals), L. A. Fried (Victoria General Hospital), A. Grégoire (Hôtel-Dieu Hospital), G. Hardy (Manitoba Cancer Treatment and Research Foundation), P. Hassell (Cancer Control Agency of British Columbia), G. Hébert (Notre-Dame Hospital), R. Jong (Mt. Sinai Hospital), S. M. Kelly (Ottawa Civic and General Hospitals), J. Ladouceur (deceased; Notre-Dame Hospital), J. Laperrière (Hôtel-Dieu Hospital), J. D. Longley (Cancer Control Agency of British Columbia), R. N. Ludwig (Cross Cancer Institute), J. H. MacGregor (Victoria General Hospital), J. S. Manchester (Victoria General Hospital), J. McCallum (Victoria Hospital), T. Minuk (Henderson General Hospital), H. F. Morrish (Tom Baker Cancer Centre), H. A. Mueller (Cancer Control Agency of British Columbia), D. Ouimet-Oliva (Notre-Dame Hospital), N. L. Patt (St. Michael's Hospital), M. Petitclerc (Hopital St. Sacrement), P. Poon (St. Michael's Hospital), O. Prosmanne (Hôtel-Dieu Hospital), P. Rasuli (Ottawa Civic and General Hospitals), J. W. Radomsky (Central Alberta Cancer Centre), P. Rasuli, J. L. Robillard (Central Alberta Cancer Centre), I. S. Simor (Mt. Sinai Hospital), B. J. Shapiro (Mt. Sinai Hospital), S. L. Share (Tom Baker Cancer Centre), R. K. Sparrow (Victoria Hospital), H. K. Standing (Manitoba Cancer Treatment and Research Foundation), W. J. Weiser (St. Michael's Hospital), and A. H. Zalev (St. Michael's Hospital).

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Reference physicist: M. Yaffe (The Toronto General Hospital).

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NOTES

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