

The Canadian National Breast Screening (CNBSS) Trials

Anthony B. Miller MD

Professor Emeritus,

Dalla Lana School of Public
Health, University of Toronto

The Society for Clinical Trials,
May 21, 2012

The Context

- In 1971, Shapiro, Strax and Venet published initial mortality results from the HIP trial
- In 1972 the Canadian Association of Radiologists established an “ad hoc” committee on mammography
- There was much concern on risk of radiation from mammography
- In 1974 this committee recommended against routine mammography screening but that a Canadian study of the evaluation of breast screening should be conducted.

cf The United States

- After HIP, no Randomized Trials of breast screening have been conducted in the US
- Instead the American Cancer Society established the Breast Cancer Detection and Demonstration Project (BCDDP), with additional funding from the NCI (using cancer control, non-research, funds)
- NCI rejected an application to enable 3 US centers to join the CNBSS in evaluating screening for women age 40-49

The process in Canada

- Extensive consultations were held, culminating in a national workshop funded by H&W in 1974
- I submitted my first grant application to NCIC in 1975 – it was rejected because of the cost (\$5m)
- Pilot studies were funded for Montreal, Toronto and Vancouver, conducted 1976-77

Design of the CNBSS

- Initially intended to be a replication of HIP, i.e. MA + CBE vs no screening
- The design for women age 50+ was modified because of one of the recommendations of Beahrs et al (1979) after Review of the BCDDP – “Randomized controlled studies in breast cancer screening should be started on questions not answerable from the BCDDP-

Beahrs et al (1979) conclusions on RST, contd.

“These include the magnitude of benefit and net benefit-risk in the use of mammography, the benefit in screening women 40-49 years of age, and the effect of increasing the interval between screenings.

CNBSS-1 addressed screening women age 40-49,

CNBSS-2 the benefit of mammography over CBE in women age 50-59

Canadian National Breast Screening Study (CNBSS)-1

- 50,430 volunteers age 40-49 randomized with informed consent to:
 - ◆ Annual two-view mammography + physical examination (CBE) + BSE (MP)
 - ◆ Initial physical examination (CBE) + BSE only (UC), with annual follow-up by mail
- 5 or 4 screens and follow-up to 25 years

Canadian National Breast Screening Study (CNBSS)-2

- 39,405 volunteers age 50-59 randomized with informed consent to:
 - ◆ Annual two-view mammography + physical examination (CBE) + BSE (MP)
 - ◆ Annual physical examination (CBE) + BSE only (PO)
- 5 or 4 screens and follow-up to 25 years

The centers

- Selected as recognized institutions where the expertise (radiology, surgery, pathology) was already present, optimally capable of recruiting 9000 women
- Funded for two in 1979
- Three more in 1981
- The remainder (to 15) in 1983-4
- Situated in 6/10 provinces

Recruitment

- General publicity (radio, newspapers and TV)
- Efforts by local branches of the Canadian Cancer Society
- Mailed invitations to special groups
- In Nova Scotia letters to women in the Provincial Health Plan
- In Toronto phone calls to women identified through municipal registers
- An invitation from the Federal Minister of Health with Family Allowance checks

Randomization

- Individual randomization after informed consent was required by the ERBs
- The trials were initiated before distributed randomization by computer was possible
- Sealed envelopes and telephone calls for assignment were deemed impractical
- Lists supplied by the central office with preprinted identification numbers and group designations controlled by a trained coordinator was piloted in Toronto and worked well

Quality control of mammography

- All centers required to use film-screen mammography rather than Xerography
- Reference physicist periodically checked radiation dose and image quality
- All positive screens and 10% random samples of negatives reviewed by Reference Radiologist
- Meetings held of CNBSS radiologists with external experts (Moskovitz, Tabar)
- Samples of mammograms reviewed by external radiologists

Quality control of physical examinations (CBE)

- Special protocol developed (Bassett)
- Nurse examiners trained by study surgeon in each center for one month
- Nurse examiners attended review clinic for all positive screens providing opportunity for study surgeon to correct errors
- Random quality checks by Deputy Director (CJB)

Pathology Reviews

- Pathology reports collected for all breast biopsies
- All biopsies reviewed by CNBSS center pathologist
- Discrepancies between local and CNBSS pathologist reviewed by a panel of CNBSS pathologists
- Meeting held of all breast pathologists with external expert (Page)
- Review of slides of all tumors with no size recorded in report by a CNBSS pathologist

Death review during screening period

- Records of terminal illness collected for all deaths certified as breast cancer or unknown causes and all deaths of women diagnosed with breast cancer
- Records reviewed by a team of breast specialists (medical oncology, radiotherapy, surgical oncology)
- Consensus achieved as to cause of death

Diagnosis and Treatment

- Positive screening tests reported to participant and family physician
- They decided on referral and treatment
- Diagnosis and treatment fully covered by Provincial health plans
- Review by medical oncologist and radiotherapist confirmed treatment met accepted guidelines (1984).
 - i.e. adjuvant chemotherapy or tamoxifen given for stage 2+ breast cancer

Follow-up

- Individual follow-up during screening period (1980-88), by attendance at screening centers or mail
- Breast cancers followed up through treating physician annually to 1996
- Subsequent follow-up through record linkage to Canadian Cancer Registry and National Death Index to 2005

Challenges

- Irwin Bross accused me of inducing cancer by mammography (1980)
- Radiologists invited to review samples of mammograms applied 1988 criteria to 1980+ films
- Many of our radiologists and our reference physicist refused to accept the results
- A prominent NCI statistician did not understand that screening can bring forward the diagnosis of advanced, as well as early disease
- I and my colleagues continue to be attacked for “obtaining the wrong answer”!

Acknowledgements

- The CNBSS has been a national endeavor supported throughout by Health and Welfare Canada and the National Cancer Institute of Canada and their successors
- We are indebted to the participants, their physicians, the CNBSS radiologists, study surgeons, local coordinators, nurse-examiners and our consultants for its success

Especial Acknowledgements to:

- ✓ Cornelia Baines, Deputy Director
- ✓ Geoffrey Howe* and Teresa To, Statisticians
- ✓ Claus Wall, Data Manager
- ✓ Andrew White, Programmer
- ✓ Martin Yaffe, Reference Physicist
- ✓ Douglas MacFarlane*, Reference Radiologist
- ✓ Charlotte Turnbull, National Coordinator
- ✓ The Canadian Tumor Reference Centre

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