MINISTRY OF HEALTH
MANATŪ HAUORA

# Ascertaining and reporting interval cancers in BreastScreen Aotearoa: A protocol

## NATIONAL SCREENING UNIT (NSU)

## MINISTRY OF HEALTH

**Dr. Simon Baker**
**National Screening Unit**
**Ministry of Health**
**October 2005**
**Revised Dr Madeleine Wall**
**Mr Andrew Palmer**
**National Screening Unit**
**Ministry of Health**
**May 2006**

Table of contents

# Introduction

The aim of BreastScreen Aotearoa (BSA) is to reduce mortality from breast cancer in New Zealand. This will only be possible if all aspects of the programme are of the highest quality. The BSA National Policy and Quality Standards (NP&QS) sets out the Indicators, Criteria, Processes and Targets that all BSA service providers are required to meet to ensure that the quality of the programme is maximised.[1]

Breast screening is a complex process, and has the potential to prevent premature death and disability and to improve quality of life. However, it also has the potential to harm. It is incumbent on the National Screening Unit (NSU) to ensure that services operate within an effective quality assurance programme.[1]

Mammographic screening is able to identify cancers at an early stage, thereby increasing the likelihood of cure. However, mammography cannot detect all cancers, and some cancers will develop between one screen and the next.

## What is an interval cancer?

In the Glossary to the NP&QS, an Interval Cancer is defined as;

> *"..a cancer that is diagnosed between a negative screen, and the time the next screen would have occurred. In BSA, this is a cancer diagnosed within two years of a negative screen."*[1]

A highly effective screening programme should have a minimum number of interval cancers. A programme with a lot of interval cancers will not meet mortality reduction targets for the eligible population.[2]

## What is the interval cancer rate?

In the Glossary to the NP&QS the Interval Cancer Rate is defined as:

> *"..the number of interval cancers diagnosed in a given population during a given period of time. The interval cancer rate is usually expressed per 1000 people per year. The interval cancer rate should be calculated by 12-month intervals from the time of the last screen, and by using the entire time interval from the previous screening."*[1]

The BSA Data Management Manual (DMM) contains a list of indicators for monitoring the performance of BSA. The Interval Cancer Rate is one of the 'surrogate mortality indicators' for BSA.[2]

Each indicator in the DMM includes a Monitoring Definition for calculation of the indicator, and states the Data Elements needed to calculate the indicator.[2] This level of detail means that the interval cancer rate is precisely defined for BSA.

Most of the indicators for the monitoring of BSA can be calculated from the national monitoring data set (NMDS), for each lead provider (LP), and for BSA as a whole. However, some of the data elements required to calculate the interval cancer rate are not contained within the NMDS, and must be collected from other sources, such as the New Zealand Cancer Registry (NZCR).

The interval cancer rate will be calculated as:

*The number of women with interval cancers / The number of women screened during that screening round*

### Australia

In Australia, the interval cancer rate is expressed per 10,000 women years, and calculated as:

*The number of interval breast cancers x 10,000 / The number of women years at risk*[3]

### Europe

In the European Guidelines, the interval cancer rate is defined as the;

*The number of interval cancers diagnosed within a defined time period since the last negative screening examination per 10,000 women screened negative*[4]

## Why is the interval cancer rate important?

The monitoring of interval cancers is a crucial part of the evaluation of a mammography screening programme, and a key performance indicator. It provides a mechanism to evaluate some of the technical processes involved in screening (such as the interpretation of mammograms), and to evaluate the likely impact of the programme on breast cancer mortality in the target population.[5] If the interval cancer rate is high, BSA is unlikely to have a significant impact on breast cancer mortality.[3]

Calculating the interval cancer rate will also allow comparison between lead providers within New Zealand, comparison with overseas programmes, and allow the monitoring of trends in the performance of BSA over time. Interval

cancer monitoring is also important in evaluating the chosen screening interval.[4]

Calculation of the interval cancer rate also allows the calculation of other performance indicators, such as the proportional incidence, and programme sensitivity.

The documentation of all breast cancers in the target population requires access to systems to identify interval cancers, clear definitions for interval cancers, and mechanisms for distinguishing between the different categories of breast cancer.[5]

## What is the interval cancer rate target for BSA?

The NP&QS and DMM version 3.0 contain the following target:

> *There should be fewer than 6.9 interval cancers (including DCIS) within one calendar year of a woman's previous screen, per 10,000 women screened*[1 2]

The Data Management Manual states that this indicator should be reported annually. No interval cancer rate has yet been calculated for BSA.

## International variation in calculating interval cancer rates

While it is generally accepted that an interval cancer is a cancer that is diagnosed between a negative screen and the time the next screen would have occurred, there is some variation in how interval cancers are actually defined, identified and reported in different programmes.[3] Some programmes include DCIS as interval cancers, while others exclude them on the grounds that they are not invasive. Some programmes include cancers diagnosed at extended assessment or early recall as interval cancers, while other programmes categorise these as screen-detected. Some programmes include cancers detected at early rescreen as interval cancers, whereas others do

not. Most programmes exclude cancers where histological confirmation is absent.[6]

Applying different definitions for interval cancers in the UK programs could alter the calculated rates by up to 30 %.[3] This variation in calculating the interval cancer rate makes it vital that a clearly defined New Zealand protocol is established for the definition, identification and reporting of interval cancers.

## What is the Proportional Incidence?

Although the interval cancer rate is a key performance indicator for BSA, it is affected by the underlying incidence of disease in the population screened. For example, breast cancer incidence increases with age, so the interval cancer rate in 45–49 year old women may be lower than in women older than 50 years, even though mammographic screening is less sensitive and therefore less effective in 45–49 year old women.[3]

To address the problem of variation in the underlying incidence a related measure has been developed – the proportional incidence. This is the number of interval breast cancers, expressed as a proportion of the number of breast cancers expected in the absence of screening. The proportional incidence can be used to estimate the likely impact of a mammographic screening program on mortality. The higher the proportional incidence, the less likely it is that the programme will reduce mortality from breast cancer. As the proportional incidence approaches one, the effect of screening diminishes to zero.

Applying the age-specific underlying incidence to the population screened derives the expected number of cancers. However, it is impossible to know the underlying incidence with certainty, except in the context of randomised controlled trials. The incidence of breast cancer prior to the onset of the program may also differ from the current underlying incidence of disease. Blanks and Moss have proposed methods for estimating the underlying rate of breast cancer that is based on modelling the UK data prior to the commencement of screening.[3]

The underlying rate of breast cancer has been calculated for women aged 50-64 in New Zealand; there is little geographic variation in the background incidence, at 2.3 invasive cancers/1000 women. An analysis of the underlying rate of breast cancer for 45-49 and 65-69 year old women in New Zealand is underway.

## What is Sensitivity in the context of screening?

The sensitivity is the proportion of people with the disease who are detected as having it by the test. A test with a low sensitivity will miss a lot of cancers. A test with a sensitivity of 100% will detect all cancers present.

Unfortunately, it is not possible to directly measure the sensitivity in breast screening, since this requires the application of a 'gold standard' to ascertain whether any cancers were missed by either mammography, or the programme. Sensitivity can only be estimated, by waiting a period of time and counting the number of breast cancers that develop, and making an assumption that all these cancers were 'missed' at the time of screening. Obviously, in reality, this will include new cancers that develop after screening, so the number of cancers missed will always be overestimated, and the sensitivity will always be underestimated, using this method.

## What is the Programme Sensitivity?

The program sensitivity is the number of women with screen detected breast cancers, expressed as a percentage of the number of women with all breast cancers diagnosed in BSA within two years (and therefore including both screen-detected and interval cancers).[3] It is calculated as:

> *The number of screen-detected breast cancers / The number of screen-detected breast cancers + the number of interval breast cancers following a normal screen or assessment* [3]

Screen-detected cancers are invasive breast cancers diagnosed during a screening episode. Interval cancers are invasive breast cancers diagnosed following a negative screening episode and prior to the next scheduled screening examination.[3]

If programme sensitivity is calculated, a woman with a suspicious mammogram, who is cleared on screening or assessment but develops breast cancer within the next 24 months, is included as having an interval cancer.[6]

A programme needs to achieve a high sensitivity in order to be effective. The program sensitivity may be more easily interpretable than the proportional incidence and, unlike the interval cancer rate, is not dependent on the underlying incidence of disease in the screened population.[3]

The sensitivity is bound to be lower as the time interval since screening increases, since a greater proportion of cancers will arise *de novo* since the last screen.

## What is the Mammographic (Screening) Sensitivity?

In contrast, if screening sensitivity is calculated, a woman with an abnormal mammogram, who is cleared on assessment but develops breast cancer within the next 24 months, is *not* included as having an interval cancer, since the mammogram did not 'fail' to detect the cancer.[6] It is calculated as:

> *The Number of screen-detected breast cancers / The Number of screen-detected breast cancers + the number of interval breast cancers following a normal mammogram*

Some screening programmes stipulate that only interval cancers that could have been detected by mammography on radiological review should be included in the denominator.[6] However, there is no standardised way of carrying out a radiological review to determine, with any certainty, whether a breast cancer could have been detected prospectively. The radiological

review process for BSA, set out in the NPQS, is primarily an educational tool for radiologists rather than a gold standard for determining whether or not an interval cancer was missed.

# Definitions

It is vital that the interval cancer rate is precisely defined for BSA. In order to support this, it is necessary that some key definitions are agreed in advance.

## Screen-detected cancer

For the purposes of this protocol, a screen-detected cancer is a breast cancer diagnosed during a screening episode.[3]

## Interval cancer

An interval cancer is any breast cancer that is diagnosed after completion of a negative screening episode, and before the next screen is due. Cancers diagnosed in women who have passed the upper age limit of BSA will be included as potential interval cancers, as long as the interval cancer occurs before 24 months from the date of the index screen.

## Definitions of other key terms

For the purposes of this protocol the following definitions will also apply:[3]

- A *screening episode* consists of the screening examination and assessment, if necessary. For the purpose of determining interval cancer rates, early review, early recall or extended assessment within 12 months of initial screen is not considered part of the screening episode.

- *Assessment* consists of the further investigation of a mammographic abnormality reported at screening.

- The *next scheduled screening examination* is defined as 24 months after the previous screen.

- *Time since screen* is calculated from the date of the previous mammographic screening examination

- *Index screening year* refers to the year for which we are determining the interval cancer rate and programme and screening sensitivity.

- *Index screens* refer to all screening examinations performed in the index screening year.

- *First round screening* includes all women who attend BSA for the first time

- *Subsequent* screening includes all women who have previously been screened by BSA

- *Rescreening* refers to the next screening examination after the screening episode in the index screening year being evaluated.

- *Symptoms* in refer to the self-report of a breast lump and/or blood-stained or watery nipple discharge.

- *Early review, early recall or extended assessment* refers to a woman who is assessed and not cleared for routine rescreening, but is referred for further assessment within 12 months of the index screen.

- *Early rescreen* occurs when a woman attends for routine rescreen less than 20 months from a previous negative screen.[3]

## Inclusion and Exclusion criteria

Just as it is necessary that some key definitions are agreed in advance, it is also necessary to consider the inclusion and exclusion criteria for calculating the interval cancer rate. Different programmes have calculated their interval cancer rates using different inclusion and exclusion criteria; these are indicated in brackets below. Where there has been international variation, the factor will be counted, and either included or excluded, depending on which overseas programme the BSA rate is being compared to.

All women who have had a mammogram as part of BSA will be included for calculating the interval cancer rate.

Women who are recommended for routine rescreening are only at risk of an interval breast cancer up until 24 months after the screening examination.

Women who have reported a personal history of invasive breast cancer or DCIS will have their potential interval cancers counted, and these will be either included as interval cancers if it has been at least ten years since their diagnosis (WA, NSW, SA, Tas and ACT) or excluded (Vic, Aus and Swe).

Cancers diagnosed in women at or before early review, early recall or extended assessment will be counted, and analysis carried out with these cancers both included (Swe, Aus and SA) or excluded (Eur, Ita, Vic and NSW) as interval cancers.

Cancers diagnosed in women presenting symptomatically, either before or at their scheduled next screen, will be counted as interval cancers, as long as the symptom is in the same breast as the cancer subsequently diagnosed (Aus).

Cancers diagnosed in women attending for rescreening within 24 months with symptoms will be counted and either included (as long as the symptom is in

the same breast as the cancer subsequently diagnosed) (RoW) or excluded (SA and Tas) as interval cancers

Cancers diagnosed in women attending for rescreening (early rescreen) within 20 months without symptoms will be counted and either included (RoW) or excluded (Aus, WA and Vic) as interval cancers.

Cancers diagnosed in women who attend early for a routine rescreen (following an invite) and are asymptomatic will not be included as interval cancers, as long as the rescreen is 20 months or more after the last screen.

Cancers that are classified as DCIS will be counted, and analysis carried out with DCIS both excluded (base case) and included as interval cancers.

Cancers that are classified as DCIS with micro-invasion will be counted, and analysis carried out with 'DCIS with micro-invasion' both included (base case) and excluded as interval cancers.

Interval cancers without histological or cytological confirmation will be counted and either included (Que) or excluded (RoW) as interval cancers. Interval cancers without histological confirmation but with cytological confirmation, or confirmation from laboratories treating physicians or hospitals, will be excluded as interval cancers. Self reported cancers will not be included as interval cancers.

Cancers developing in women who were recommended for, and did not attend for further assessment (or exited BSA before assessment), will be counted, and analysis carried out with these cancers both included (UK and Aus) and excluded (Can and WA) as interval cancers.

LCIS, ADH and secondary tumours of non-breast primaries will not be counted as cancers.

Secondary breast cancers will not be counted as interval cancers (Aus)

Paget's disease will only be considered a cancer if there is underlying evidence of malignancy.

Cases diagnosed within two months of screening will be excluded as interval cancers (Que).

The inclusion and exclusion criteria used for the routine reporting of interval cancer rates in BSA Monitoring Reports will be determined in discussion with the BSA Independent Monitoring Group, and the BSA Advisory Group.

Women at high risk of breast cancer will frequently be screened two-yearly in BSA, but have additional mammograms – outside BSA – in alternate years. The discussion with the BSA Independent Monitoring Group and the BSA Advisory Group will also determine how high-risk women will be identified, how they will be categorised, whether they will be analysed separately, and, if so, what processes will be used.

## Denominators

Interval cancer rates will be measured per 10,000 women. In Australia, rates are calculated per 10,000 women years.[3] This denominator is used by Australia since, in reality, the denominator for the interval cancer rate varies with years since screen because the 'at risk' population changes. Therefore the denominator is expressed as the 'number of years at risk' rather than the number of women screened. In New Zealand, women do not have annual screening, or move across state boundaries – and therefore into different screening registries – so the denominator of 'per 10,0000 women' will essentially be the same as the denominator of 'per 10,000 women years'.

The number of women years at risk for the different time periods is:

- **First year (0–<12 months):** All women screened in the *index screening year* (who have not reported a personal history of breast cancer).

- **Second year (12–<24 months):** All women screened in the *index screening year* (who have not reported a personal history of breast cancer).

- **First and second year (0–<24 months):** The sum of the first and second year denominators.[3]

# Methodology

## Data collection

Women diagnosed with breast cancer fall into four groups;

1. women whose screening and assessment records are recorded in BSA
2. women screened in BSA, but who exit before assessment
3. women screened and assessed outside BSA
4. women not screened.[6]

Women in categories 1. and 2. will provide the information required for calculating the BSA interval cancer rate.

Information will be requested from the New Zealand Cancer Registry (NZCR) on all women diagnosed with breast cancer from 31 December 1999. Women aged 50-68 up to July 04, and women aged 45 to 73 from July 04, will be considered as potentially having interval cancers. The upper age-range allows for women who were eligible at the time of screening, but have since aged out of the eligible age range, to be included.

## Matching

Identification of interval breast cancer cases will be carried out through the matching of BSA data with NZCR data.

The NSU will provide an extract containing all women screened in the specified time period, **but excluding those recalled and diagnosed with cancer by BSA between 20 and 24 months.** The NSU extract will contain 'NHI' and 'date of birth' fields.

The NZCR will match the NSU 'NHI' field against all possible parent and child 'NHI' fields contained in the NHI database to match the maximum possible combinations. The NZCR will then provide an extract containing all demographic and breast cancer records contained in the NZCR matched against all parent and child 'NHI' fields, to create a list of possible interval cancers.

## Data storage

Information will be extracted and entered into a secure database, and all paper records will be kept in a locked filing cabinet. All data transfers will be carried out securely, and all other requirements for data security and strict confidentiality will be adhered to, in line with NZHIS security policies.

It will be necessary to record a large amount of data on each woman, so that analysis can be undertaken after varying the inclusion and exclusion criteria, and varying other input variables, such as date used for 'date of diagnosis'.

## Confirmation of diagnosis

Once matches have been made between the BSA database and the NZCR, cancer stage information will be extracted, to enable the stage distribution of interval cancers to be examined.

A list of women with provisional interval cancers will be created. To confirm that this list is accurate, a spreadsheet containing a list of these women, complete with all variables, will be sent to the appropriate LPs. Lead Providers will be able check the data contained against their own records to ensure that for BSA screen detected cancers;

- the woman really did develop a cancer
- the histological diagnosis is correct
- the site, size and grade are correct
- the dates in the NZCR are correct

Lead Providers will be able to feed back this information to the NSU, so that records can be corrected.

Lead providers will manually review each exact and possible match using the data available from the NSU, and any other data source available e.g. the lead provider database, the woman's GP, telephone directories, the electoral roll, hospitals or the treating doctor in order to confirm that women without BSA detected cancers:

1. were screened in BSA;
2. if screened, the screen dates are correct; and
3. if they had a BSA biopsy matching the NCR record date, the NCR diagnosis is correct.[3]

Lead providers will also have the last opportunity to add extra interval cancers that were not recorded by the NZCR. This list of interval cancers will be useful to LPs carrying out the mandatory Interval Cancer Radiological Review.

## Screening history

Non-identifiable screening records are held in the BSA database, including information on screening history and clinical management.

## Data definitions

For the purposes of calculating indicators, the date of screening will be the date of the screening examination, and the date of diagnosis will be the date of first pathological confirmation **(cytology or histopathology),** of breast cancer following that screening examination. To allow direct comparison with overseas programmes, other 'dates of diagnosis' should also be used – such as date of surgery,[4] however, the cancer registry only records the date of the procedure that led to first notification, which is often not the definitive treatment surgery date.

Women who are not rescreened between 24 months and 36 months, and who are diagnosed with breast cancer either at screening or by presenting with symptoms, will be tabulated as 'cancers occurring within 24-36 months of a negative screen'. The records of each of these women will then be reviewed to determine whether the woman was offered screening at the appropriate time.

## Categorisation

Women identified from the NZCR as having had breast cancer can then be divided into five groups;

1. women whose breast cancers were BSA screen-detected
2. women who had a suspicious mammogram, who was cleared by assessment, but then developed breast cancer
3. women whose breast cancers were diagnosed following a normal mammogram
4. women with an abnormal mammogram who were placed on extended assessment, early recall or early review
5. women who have had a mammogram in BSA, but not within the last two years (lapsed attender)
6. women who have never had a mammogram in BSA.[6 7]

No further information will be sought concerning women who have not participated in BSA.

## Data analysis

Analysis will be carried out for the following groups of women with cancer;

1. women with a suspicious mammogram and a diagnosis of cancer at assessment
2. women with a suspicious mammogram, but cleared of cancer at assessment
3. women with a suspicious mammogram, then placed on extended assessment
4. women with a normal mammogram

## Reporting Results

The interval cancer rate will be examined separately;

- for all women aged 50-64
- by five- and ten-year age group
- by ethnicity
- by screening round (first and subsequent)
- by time since screen (up to 12 months, 12 to 24 months, up to 24 months) (Aus)
- by LP.

Where numbers are sufficient, analysis will by two or more of the above variables.

Proportional incidence, screening sensitivity and programme sensitivity will all be calculated, and also analysed by the above variables.

Rates will be calculated per 10,000 women screened (RoW).

Stage distribution (UICC classification), tumour size (in mm), histological grade (modified Bloom and Richardson system) and nodal status of interval cancers will be presented.

The stage distribution, tumour size, histological grade and nodal status of interval cancers will be presented alongside these variables in cancers detected by BSA, cancers in women who did not take part in BSA, and cancers diagnosed in women before BSA began.

Results will be categorised and presented in such a way that direct comparison can be made with key overseas programmes.

## Potential Implementation Barriers

There are issues that need to be addressed to ensure that the ascertainment of interval cancers is accurate and complete. These include:

### Cancer registrations

For the timely calculation of the interval cancer rate and program sensitivity, it is necessary for breast cancer registrations to be completed as soon as possible after diagnosis. The longer the period of time between the index screen and the calculation of rates for that period, the less valuable the data will be in determining the performance of the programme and informing policy decisions within BSA.

### Unique identification of each woman

This is necessary so that each woman is only counted once, regardless of the site at which she was screened. It is also necessary to be able to link a woman's records over successive screening rounds, in case a woman is screened at a different service less than 20 months after their index screen.

# References

1. National Screening Unit. National Policy and Quality Standards. Wellington: National Screening Unit, 2004.
2. National Screening Unit. Data Management Manual. Auckland: National Screening Unit, 2003.
3. Kavanagh AM, Amos AF, Marr GM. The ascertainment and reporting of interval cancers within the BreastScreen Australia Program. Sydney: NHMRC National Breast Cancer Centre, 1999.
4. European Commission. European guidelines for quality assurance in mammography screening. In: Perry N, Broeders M, de Wolf C, et al., editors. Luxembourg: Europe Against Cancer, 2001.
5. Tornberg S, Codd M, Rodrigues V, et al. Ascertainment and evaluation of interval cancers in population-based mammography screening programmes: A collaborative study in four European centres. *Journal of Medical Screening* 2005;12(1):43-49.
6. BreastScreen Aotearoa Independent Monitoring Group. BSAIMG Interval Cancer Protocol. Dunedin: University of Otago, 2001.
7. Liston J, Wilson R. Quality Assurance Guidelines for Breast Cancer Screening Radiology (NHSBSP Publication No 59). Sheffield: National Health Service Breast Screening Programme, 2005.