

Quantifying Breast Cancer Over-diagnosis in an Organised Mammography Screening Program

KERRI BECKMANN

BSc (Hons) MPH

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Discipline of Public Health
School of Population Health
Faculty of Health Sciences
University of Adelaide
Australia

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Thesis Abstract

Mammography screening is effective in reducing breast cancer (BC) mortality; however there are widespread concerns that it may also lead to over-diagnosis, i.e. the detection of BC that would not have emerged clinically in a woman's lifetime had she not participated in screening. The extent of over-diagnosis due to mammography is contested, with published estimates varying from 0% to 54%. The principal aim of this research is to quantify the level of over-diagnosis of BC associated with population-based mammography screening in South Australia (SA).

The following questions are addressed: (1) Have BC incidence rates increased following the introduction of screening in SA and is the increase greater than expected based on projections of pre-screening trends?, (2) Has the prevalence of key breast cancer risk factors also increased?, (3) To what extent does hormone replacement therapy (HRT) use affect breast cancer risk and screening outcomes?, (4) Are there any differences in the underlying risk of BC among screening participants and non-participants?, and the central question (5) What is the level of over-diagnosis due to organised mammography screening in SA? Questions 2-4 relate to the potential for estimates of over-diagnosis to be confounded by risk factor differences/temporal changes. A review of previous studies of over-diagnosis due to mammography screening is included, which highlights methodological complexities relating to measurement of over-diagnosis and offers some explanations for why published estimates vary to such a great extent.

The first two questions were answered through descriptive analyses of BC incidence trends in SA from 1977-2009, as well as trends in the prevalence several key breast cancer risk factors collected via the SA Health Omnibus Surveys during 1991-2009 (alcohol use, body weight, HRT use) and Australian Bureau of Statistics (fertility rates and age at first birth). The effect of HRT on various screening outcomes (e.g. screen-detection rates, interval cancer rates, recall to assessment) was examined through multivariable Poisson regression modelling using individual person level data from BreastScreen SA, which included self-reported HRT use at the time of each screening episode. Differences in underlying risk of BC between screening participants and non-

participants were investigated using 2012 South Australian Health Omnibus Survey data.

Two different methods were used to quantify over-diagnosis. Method 1 used a case-control design to compare screening histories for women with and without BC. Odds ratios (OR) were determined across different time intervals after screening to allow for lead time effects and applied to background reference rates based on pre-screening incidence trends. Over-diagnosis estimates were obtained by comparing cumulative incidence with and without screening. Method 2 used a lead time modelling approach in which estimates of lead time duration and screening sensitivity, and screening participation data were used to adjust the background incidence rates (without screening). This was achieved by iteratively adding the number of cancers expected to be brought forward by screening each year, then subtracting this number from the pool of cancers in future years. Over-diagnosis was calculated by comparing the lead time adjusted cumulative incidence with the observed cumulative incidence.

Studies presented in this thesis demonstrate that: (1) screening led to an increase in breast cancer incidence that was sustained beyond what was expected, based on projection of pre-screening incidence, however age-specific patterns suggest changing prevalence of HRT use have also impacted on incidence trends, (2) the prevalence of key risk factors also increased over this period, potentially contributing to an increase in background incidence rates, (3) HRT use among South Australian women is causally associated with increased risk of breast cancer which complicates estimation of over-diagnosis due to the marked changes in prevalence of HRT use, (4) women who participated in screening had a higher prevalence of breast cancer risk factors (most notably HRT use), indicating the potential for estimates to be confounded by underlying risk differences, (5) mammography screening is likely to result in a modest level of over-diagnosis (8% for IBC and 12-14% for all BC among women eligible to participate in screening). Estimates were lower after adjustment for confounding. These results are comparable with findings from long-term follow-up of screening trials and with several recent cohort studies of European screening programs, but are lower than many other estimates.

Thesis Declaration

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Kerri Beckmann (Candidate)

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Publications/manuscripts contributing to this thesis

Beckmann KR, Farshid G, Roder DM, Hiller JE and Lynch JW. Impact of hormone replacement therapy use on mammographic screening outcomes. *Cancer Causes Control*. 2013; 24: 1417-26.

Beckmann KR, Roder DM, Hiller JE, Farshid G, Lynch JW. Do breast cancer risk factors differ among those who do and do not undertake mammography screening? *Journal of Medical Screening* 2013; 20:208-19.

Beckmann KR, Roder DM, Hiller JE, Farshid G, Lynch JW. The influence of mammographic screening on breast cancer incidence trends in South Australia. *Asian Pacific Journal of Cancer Prevention* 2014; 15:3105-12.

Beckmann KR, Lynch JW, Hiller JE, Farshid G, Houssami N, Duffy Sw, Roder DM. A novel case-control design to estimate the extent of over-diagnosis of breast cancer due to organised mammography screening. *International Journal of Cancer* 2014. Aug 5. doi: 10.1002/ijc.29124. [Epub ahead of print]

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Beckmann KR, Farshid G, Roder DM, Hiller JE, Lynch JW Impact of hormone replacement therapy use on mammographic screening outcomes. Sydney International Breast Cancer Congress 2012, Sydney, Australia, October 2012. (E-poster)

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ABBREVIATIONS

ABS:	Australian Bureau of Statistics
APC:	Annual percent change
ARIA:	Accessibility and Remoteness Index for Australia
ASR:	Age-standardised rate
BC:	Breast cancer
BMI:	Body mass index
BSSA:	BreastScreen SA
CI:	Confidence interval
CISNET:	Cancer Intervention and Surveillance Modelling Network
DCIS:	Ductal carcinoma in-situ
ER:	Electoral roll
ERP:	Estimated residential population
FNA:	Fine needle aspiration
GP:	General Practitioner
HRT:	Hormone replacement therapy
IARC:	International Agency for Research on Cancer
IBC:	Invasive breast cancer
IDC:	Invasive ductal cancer
IRR:	Incidence rate ratio
IRSAD:	Index of Socioeconomic Advantage and Disadvantage
MET:	Metabolic equivalent time
MI:	Multiply imputed
MST:	Mean sojourn time
NSW:	New South Wales
OD:	Over-diagnosis
OR:	Odds ratio
PCNB:	Percutaneous needle biopsy
PPV:	Positive predictive value
RCT:	Randomised controlled trial
RR:	Relative risk
SA:	South Australia
SACR:	South Australian Cancer Registry
SEP:	Socioeconomic position
UK:	United Kingdom
US:	United States of America
WHI:	Women's Health Initiative