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# Nonbreast cancer incidence, treatment received and outcomes: Are there differences in breast screening attendees *versus* nonattendees?

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**While reductions in breast cancer mortality have been evident since the introduction of population-based breast screening in women aged 50–74 years, participation in cancer screening programs can be influenced by several factors, including health system and those related to the individual. In our study, we compared cancer incidence and mortality for several cancer types other than breast cancer, noncancer mortality and patterns of treatment amongst women who did and did not participate in mammography screening. All women aged 50–65 years enrolled on the Queensland Electoral Roll in 2000 were included. The study population was then linked to records from the population-based breast screening program and private fee-for-service screening options to establish screened and unscreened cohorts. Diagnostic details for selected cancers and cause of death were obtained from the Queensland Oncology Repository. We calculated incidence rate ratios and hazard ratios comparing screened and unscreened cohorts. Among screened compared to unscreened women, we found a lower incidence of cancers of the lung, cervix, head and neck and esophagus and an increase in colorectal cancers. Cancer mortality (excluding breast cancer) was 35% lower among screened compared to unscreened women and they were also about 23% less likely to be diagnosed with distant disease. Screened compared to unscreened women were more likely to receive surgery and less likely to receive no treatment. Our study adds further to the population data examining outcomes among women participating in mammography screening.**



## Introduction

In Australia, the outcomes for people diagnosed with cancer are among the best in the world.[1] Despite this, there remain significant variations in outcomes, related to Indigenous, regional and socioeconomic status.[2] Understanding the reasons for this variance is complex with many potential causes suggested, including lower rates of cancer screening, less access to care, poorer compliance with treatment and late presentations.[2]

**Key words:** screening, breast neoplasms, epidemiology, mortality, health literacy

**Abbreviations:** BSQ: BreastScreen Queensland; DCIS: ductal carcinoma *in situ*; ER: electoral roll; HR: hazard ratio; OR: odds ratio; QOR: Queensland Oncology Repository; RR: rate ratio; SES: socioeconomic status; WBSC: Wesley Breast Screening Clinic

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There is good evidence that screening for cervical and colorectal cancer has resulted in reductions in mortality, and in rates of advanced cancer—a primary goal of a cancer screening programme.[3,4] Breast cancer screening was introduced into many countries in the 1990s after randomized trials showed reductions in breast cancer mortality.[5,6] While some of the published findings have been disputed, primarily based on methodological issues,[7] more recent cohort and case–control studies have additionally shown a mortality-benefit for mammography and as such, the International Agency for Research on Cancer (IARC) states there is sufficient evidence that mammography reduces breast cancer mortality in women aged 50–69 years.[8] Controversy has however continued on the relative benefits from diagnosis of early stage cancers and the limited effects on diagnosis of later stage disease.[9] The over-representation of early stage disease has also raised questions of over-treatment of cancers that might not have been clinically relevant.[10,11] This has been exemplified by the increase in diagnosis and treatment of ductal carcinoma *in situ* (DCIS) with no corresponding decrease in rates of invasive cancers.[9]

While the risk of death from breast cancer is lower for women participating in mammography screening, all-cause mortality is also lower among patients with screen-detected,

**What's new?**

**Women whose breast cancers are detected *via* mammography screening are at reduced risk of breast cancer death. These women also experience reductions in overall cancer mortality, suggesting that mammography impacts outcomes of cancers other than breast cancer. In this population-based study of women who did and did not undergo mammography screening, overall non-breast cancer mortality was 35 percent lower among screened women. Incidence was reduced specifically for cancers of the cervix, esophagus, head and neck, and lungs, which frequently are associated with lifestyle behaviors. Screening further impacted early detection of non-breast cancers, potentially facilitating treatment and improving outcome.**



compared to those with nonscreen detected breast cancers.[12] A Canadian study found the risk of cancer death in women (excluding breast cancer) was about 26% lower amongst breast screening participants compared to nonparticipants.[13] The study also found the overall incidence of cancers other than breast cancer was about 17% lower in the screened cohort.

Given these results, the question arises whether it is the actual participation in screening that confers this reduction in risk of other cancers and (or) cancer death (excluding breast cancer), or is it perhaps other factors related to individuals who choose to participate in screening. Participation in cancer screening can be influenced by several factors, including those related to the health system (such as access) and those related to the individual (such as health literacy, cancer-related knowledge and beliefs). The likelihood of participation in screening can also be influenced by the presence of comorbidities in individuals, with a recent systematic review finding that women with comorbidities were less likely to participate in breast screening.[14] Additionally, low health literacy levels are reported to be a barrier to participation in screening.[15] Evidence also suggests that individuals who do not participate in screening are also less likely to undertake other primary prevention strategies.[16] However, data from a population-based study of women attending breast screening in Queensland, Australia showed that levels of modifiable breast cancer risk factors in screening participants and a sample of the general population were in fact similar.[17]

Australia introduced a biennial mammography screening program in the 1990s (BreastScreen Australia). The program is free of charge to all women in the age group of 50–74 years. Each State breast screening program utilizes the Australian Electoral Roll (ER) to identify women within the target age range (voting is compulsory in Australia and it is estimated that the ER is about 92% complete in Queensland.[18]) All women identified in the target screening age range are sent letters inviting them to a free screening mammogram with reminders sent every 2 years to those who have been screened. Presentation for screening is then a decision of the woman to attend or not. Rates of breast screening within the Australian population are about 54% and have remained relatively stable over the last couple of decades.[19] In addition to the free national BreastScreen program, women in Australia can also elect to have their mammogram through a private fee-for-service screening clinic. Furthermore, women with a prior history of breast cancer or a family history of breast cancer are eligible for a screening mammogram at any radiology practice, with the cost covered through Australia's public health system (Medicare). While population data on the number of women attending private screening facilities in Australia is unknown, in Queensland a recent population-based study of 3,200 women diagnosed with breast cancer found that for approximately 20% of screen detected breast cancers, the screening mammogram was performed in the private system.[20] Thus, overall participation in breast screening is likely to be higher than the numbers recorded by BreastScreen Australia.

Our aim was to examine outcomes such as cancer incidence and mortality (excluding breast cancer), noncancer mortality and patterns of treatment, in two cohorts of women in Queensland who did and did not participate in mammography screening.

## Materials and Methods

Our study was conducted in Queensland, a state of Australia with a population of 5 million. We used the state electoral roll for Queensland, to identify women aged 50–65 in the year 2000. ER records were then linked to BreastScreen Queensland (BSQ), Queensland's state-based free screening program, the Wesley Breast Screening Clinic (WBSC; the largest provider of fee-for-service mammography in Queensland) and then linked to mammograms performed in other private radiology practices for women eligible for a Medicare-funded mammogram. Our study population included two cohorts: a screened cohort (women who had received at least one mammography screen from 2000 to 2005) and an unscreened cohort (women with no history of mammography screening during the same period; Fig. 1).

Cohort members were linked to state records in the Queensland Oncology Repository (QOR). QOR consolidates patient information on cancer diagnoses and deaths from the Queensland Cancer Register, Queensland Hospital Admitted Data Collection which includes data on surgery, radiation therapy and intravenous systemic therapy for all public and private health facilities. In Queensland, notification of cancer is a statutory requirement for all public and private hospitals. Death data is obtained from Registry of Births, Deaths and Marriages by the Australian Bureau of Statistics (ABS). ABS uses the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) to code causes of death. Further, the ABS uses the Mortality Medical Data System (MMDS) which allows the classification of multiple causes of death in

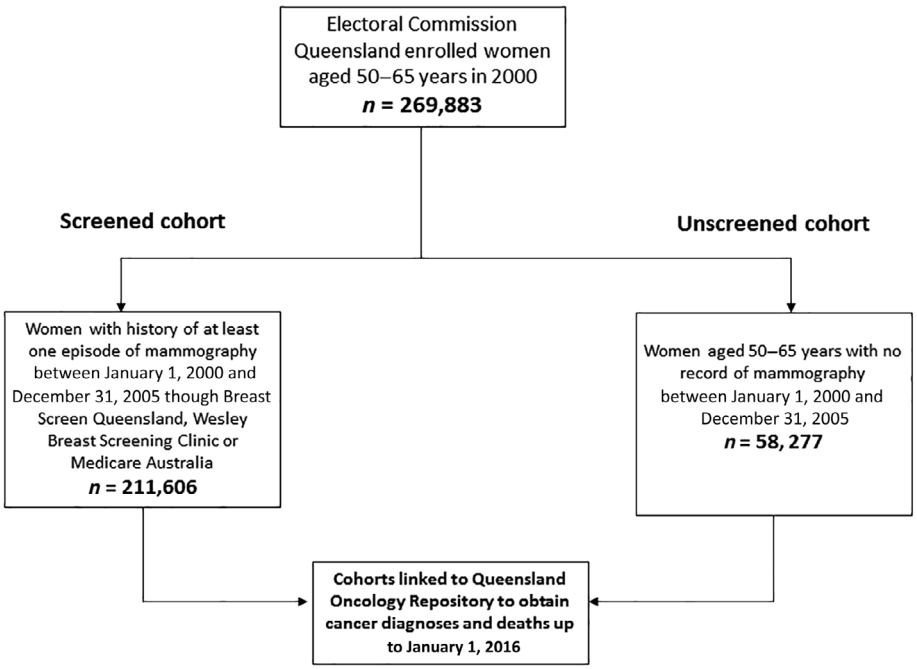


**Figure 1.** Flow chart showing screening and nonscreened study cohorts.

accordance with the current version of the International Classification of Diseases (ICD).[21] Follow up commenced on January 1, 2000, and women accrued time in the unscreened cohort until the date of their first screen during the 6-year period 2000–2005 at which point they began to accrue person-time in the screened cohort. Women remained in the unscreened group even if they had a record of screening prior to 2000. Follow up of the study population concluded on January 1, 2016.

### Variables included

We included age, socioeconomic status (SES) and residential location. SES was assigned according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), a census-based measure of social and economic well-being.[22] Residence was categorized into urban or rural, based on the Australian Geographical Classification.[23] Primary cancer site, histology and stage at diagnosis were extracted from QOR and grouped as regional, distant (metastatic), or other. We identified patients whose cancer stage was regional or distant through health administrative data using staging algorithms with reasonable confidence. However, due to the complexities of cancer staging by site (if regional or metastatic spread is not present) we elected to assign patients without evidence of regional or metastatic spread to the "other" category. We included eight cancers in the analysis. Lung, cervix, head and neck and esophageal cancers were chosen based on their known association with lifestyle risk factors such as smoking, alcohol and obesity.[24] We also included pancreatic, brain and ovarian cancers, where lifestyle-associated risk factors have not been established.[24]

### Statistical analysis

Incidence rates (per 10,000) were calculated for each cancer and overall in screened and unscreened cohorts, using the number of cancers observed and person-years at risk. We calculated rate ratios for incidence, and hazard ratios for all-cause mortality adjusted for age, SES and residential location using Cox regression models for all cancers combined and for individual cancers in the screened compared to the unscreened cohort. Women diagnosed with different cancer types during the follow-up period were included in each relevant cancer group. Those diagnosed with any cancers prior to January 1, 2000, were excluded from the mortality analysis ($n$ = 6,985). We additionally examined rate ratios of treatment received in the screened compared to the unscreened cohort adjusted for age, SES, residential location and stage at diagnosis. We excluded Indigenous status in the analyses due to underidentification of Indigenous women in the unscreened cohort.

Ethical approval for our study was granted by the Metro South Health Human Research Ethics Committee, by the Uniting Care Health HREC (with respect to WBSC data) and by the Australian Institute of Health and Welfare HREC (with respect to linkage of Medicare-funded data).

### Data availability

Ethical restrictions apply to the availability of these data, which were used under agreement for our study. Result tables of the complete analyses and further covariables are available upon reasonable request from the corresponding author.

**Table 1.** Sociodemographic characteristics of 269,883 women aged 50–65 years

| | Screened | | | Screened *versus* unscreened | |
|---|---|---|---|---|---|
| | Yes[1] (*n* = 211,606) | No (*n* = 58,277) | Percent screened | OR (95%CI) | *p*-value |
| Age group | | | | | ‹0.001 |
| 50–54 | 84,506 | 23,611 | 78.2 | ref | |
| 55–59 | 66,303 | 17,451 | 79.2 | 1.06 (1.04–1.09) | |
| 60–64 | 51,991 | 14,503 | 78.2 | 1.00 (0.98–1.02) | |
| 65 | 8,806 | 2,712 | 76.4 | 0.91 (0.87–0.95) | |
| SES | | | | | ‹0.001 |
| Affluent | 32,215 | 8,372 | 79.4 | ref | |
| Middle | 136,138 | 36,708 | 78.8 | 0.96 (0.94–0.99) | |
| Disadvantaged | 42,305 | 12,941 | 76.6 | 0.85 (0.82–0.88) | |
| Unknown | 948 | 256 | 78.7 | 0.96 (0.84–1.11) | |
| Location | | | | | 0.02 |
| Urban | 134,394 | 37,389 | 78.2 | ref | |
| Rural | 76,286 | 30,639 | 78.7 | 1.03 (1.01–1.05) | |
| Unknown | 926 | 249 | 78.8 | 1.03 (0.90–1.19) | |

[1]Includes women having a record of at least one mammogram from 2000 to 2005.
Abbreviations: OR, odds ratio; SES, socioeconomic status.

**Table 2.** Cancer incidence and the proportion identified as having regional or distant disease at diagnosis for selected cancers amongst 269,883 women aged 50–65 years

| | Incidence | | Stage at diagnosis | | | |
|---|---|---|---|---|---|---|
| Cancer type | Number diagnosed | Rate/10,000[1] | Regional (%) | Distant (%) | Other[2] (%) | Unadjusted p-value[3] |
| *Lung* | | | | | | 0.002 |
| Screened | 2,649 | 8.6 | 21.9 | 39.2 | 38.9 | |
| Unscreened | 966 | 11.8 | 19.2 | 45.7 | 35.2 | |
| *Cervix* | | | | | | 0.04 |
| Screened | 207 | 0.7 | 14.5 | 6.3 | 79.2 | |
| Unscreened | 138 | 1.7 | 11.6 | 14.5 | 73.9 | |
| *Head and neck* | | | | | | 0.001 |
| Screened | 435 | 1.4 | 26.9 | 3.7 | 69.4 | |
| Unscreened | 156 | 1.9 | 42.3 | 3.8 | 53.8 | |
| *Esophagus* | | | | | | 0.69 |
| Screened | 188 | 0.6 | 19.7 | 17.0 | 63.3 | |
| Unscreened | 72 | 0.9 | 15.3 | 19.4 | 65.3 | |
| *Ovarian* | | | | | | 0.17 |
| Screened | 839 | 2.7 | 4.3 | 51.8 | 43.9 | |
| Unscreened | 218 | 2.7 | 2.3 | 57.8 | 39.9 | |
| *Colorectal* | | | | | | |
| Screened | 4,083 | 13.3 | 23.3 | 14.1 | 62.5 | ‹ 0.001 |
| Unscreened | 947 | 11.6 | 23.9 | 23.1 | 53.0 | |
| *Brain* | | | | | | |
| Screened | 371 | 1.2 | N/A[4] | N/A[4] | N/A[4] | |
| Unscreened | 101 | 1.2 | | | | |
| *Pancreas* | | | | | | 0.17 |
| Screened | 616 | 2.0 | 12.0 | 48.4 | 39.6 | |
| Unscreened | 176 | 2.1 | 13.1 | 55.1 | 31.8 | |

[1]Incidence rate expressed as the number of cancers per 10,000 person-years.
[2]Other includes all cases excluding those with regional or distant disease.
[3]*p*-value based on chi-square for differences across stage.
[4]The above stage categories not appropriate for brain cancers.

**Table 3.** Multivariate models showing incidence, mortality and risk of distant disease in the screened *versus* unscreened cohorts

| | Incidence[1] | | Mortality[1,2] | | Distant[1] | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *p*-value | HR (95% CI) | *p*-value | RR (95% CI) | *p*-value |
| Lung | 0.73 (0.68–0.79) | ‹0.001 | 0.63 (0.57–0.68) | ‹0.01 | 0.86 (0.79–0.94) | 0.001 |
| Cervix | 0.41 (0.33–0.50) | ‹0.001 | 0.21 (0.14–0.31) | ‹0.001 | 0.44 (0.22–0.86) | 0.017 |
| Head and Neck | 0.74 (0.62–0.89) | 0.001 | 0.40 (0.30–0.52) | ‹0.001 | 0.94 (0.39–2.30) | 0.89 |
| Esophagus | 0.70 (0.53–0.92) | 0.01 | 0.54 (0.39–0.76) | ‹0.001 | 0.83 (0.47–1.47) | 0.53 |
| Ovarian | 1.01 (0.87–1.18) | 0.85 | 0.69 (0.57–0.84) | ‹0.001 | 0.89 (0.78–1.02) | 0.09 |
| Colorectal | 1.14 (1.06–1.23) | ‹0.001 | 0.69 (0.60–0.78) | ‹0.001 | 0.61 (0.53–0.70) | ‹0.001 |
| Brain | 0.96 (0.77–1.20) | 0.72 | 0.89 (0.71–1.13) | 0.34 | N/A[3] | |
| Pancreas | 0.92 (0.78–1.09) | 0.34 | 0.87 (0.72–1.04) | 0.87 | 0.89 (0.76–1.05) | 0.16 |
| All selected cancers | 0.94 (0.90–0.98) | 0.005 | 0.65 (0.61–0.69) | ‹0.001 | 0.77 (0.72–0.82) | ‹0.001 |

Cohorts in the mortality analysis and model additionally adjusted for differences in incidence.
[1]All models adjusted for age, SES and residence.
[2]Participants diagnosed with cancers prior to January 1, 2000 were excluded from both screened and unscreened.
[3]Brain cancers excluded from stage analysis.
Abbreviations: HR, hazard ratio; RR, rate ratio.

## Results

In 2000, there were 269,883 women aged 50–65 eligible for mammography screening. Of the study population, 211,606 (78.4%) had at least one episode of mammography screening in the following 6 years. Table 1 shows the demographic characteristics of the study population for screened and unscreened women. There were some modest differences in screening participation according to age, SES and location.

**Table 4.** Treatment received by cancer type according to stage in screened and unscreened cohorts

| | Regional | | | | Distant | | | | Other[1] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Surgery (%) | RT (%) | CT (%) | None[2] (%) | Surgery (%) | RT (%) | CT (%) | None (%) | Surgery (%) | RT (%) | CT (%) | None (%) |
| *Lung* | | | | | | | | | | | | |
| Screened | 29.1 | 71.0 | 75.7 | 7.6 | 3.8 | 55.1 | 52.1 | 23.4 | 48.8 | 41.5 | 38.2 | 16.6 |
| Unscreened | 17.3 | 70.3 | 60.0 | 16.8 | 1.8 | 47.6 | 41.7 | 33.1 | 23.0 | 40.9 | 39.4 | 30.3 |
| *Cervix* | | | | | | | | | | | | |
| Screened | 60.0 | 93.3 | 70.0 | 0.0 | 23.1 | 46.2 | 30.8 | 30.8 | 65.0 | 48.0 | 43.1 | 9.8 |
| Unscreened | 37.5 | 93.8 | 87.5 | 0.0 | 10.0 | 50.0 | 35.0 | 25.0 | 27.0 | 71.4 | 61.9 | 7.9 |
| *Head & Neck* | | | | | | | | | | | | |
| Screened | 41.0 | 94.9 | 58.1 | 0.0 | 50.0 | 81.3 | 62.5 | 0.0 | 72.8 | 62.5 | 26.1 | 0.0 |
| Unscreened | 33.3 | 89.4 | 65.2 | 0.0 | 50.0 | 66.7 | 0.0 | 0.0 | 70.5 | 64.1 | 23.1 | 0.0 |
| *Esophagus* | | | | | | | | | | | | |
| Screened | 16.2 | 86.5 | 70.3 | 5.4 | 3.1 | 50.0 | 40.6 | 34.4 | 39.3 | 60.7 | 57.1 | 17.9 |
| Unscreened | 9.1 | 90.9 | 63.6 | 0.0 | 7.1 | 50.0 | 35.7 | 42.9 | 13.6 | 65.9 | 50.0 | 27.3 |
| *Ovarian* | | | | | | | | | | | | |
| Screened | 83.3 | 22.2 | 94.4 | 2.8 | 77.7 | 11.3 | 92.9 | 4.8 | 88.7 | 10.1 | 70.4 | 5.3 |
| Unscreened | 80.0 | 20.0 | 100.0 | 0.0 | 54.0 | 10.3 | 87.9 | 12.7 | 78.7 | 8.5 | 68.1 | 12.8 |
| *Colorectal* | | | | | | | | | | | | |
| Screened | 99.6 | 20.9 | 77.3 | 0.1 | 88.2 | 21.3 | 68.6 | 5.7 | 99.0 | 15.4 | 24.2 | 0.5 |
| Unscreened | 98.2 | 20.4 | 66.8 | 0.4 | 87.7 | 19.6 | 56.2 | 10.5 | 96.6 | 17.9 | 26.2 | 2.2 |
| *Pancreas* | | | | | | | | | | | | |
| Screened | 68.9 | 17.6 | 64.9 | 12.2 | 6.7 | 10.1 | 59.1 | 36.6 | 35.0 | 16.4 | 48.1 | 34.1 |
| Unscreened | 65.2 | 8.7 | 60.9 | 17.4 | 3.1 | 10.3 | 49.5 | 47.4 | 25.0 | 11.4 | 38.6 | 52.3 |

[1]Other includes all cases excluding those with regional or distant disease.
[2]No treatment received.
Abbreviations: CT, intravenous chemotherapy; RT, radiation therapy.

Women aged 65 years were about 10% less likely to have had an episode of screening compared to those aged 50–54 (OR = 0.91, 95% CI = 0.87–0.95) and women living in disadvantaged areas were about 15% less likely to have been screened compared to those in affluent areas (OR = 0.85, 95% CI = 0.82–0.88).

### Incidence, stage and mortality

Within the study population, 12,162 women were diagnosed with one of the included cancers from January 1, 2000 to December 31, 2014. Incidence and stage of cancers at diagnosis are shown in Table 2. Incidence per 10,000 person-years was lower amongst the screened, compared to the unscreened cohort for cancers of the lung (8.6 and 11.8, respectively), cervix (0.7 and 1.7, respectively), head and neck (1.4 and 1.9, respectively) and esophagus (0.6 and 0.9, respectively). We observed a higher incidence of colorectal cancer in the screened compared to the unscreened cohort (13.3 and 11.6, respectively).

Across most cancers, a higher proportion of unscreened, compared to screened participants presented with regional or distant disease at diagnosis (Table 2). In the adjusted models (Table 3), the incidence rate ratio for lung, cervix, head and neck and esophageal cancers in the screened cohort was significantly lower compared to the unscreened cohort. The rate ratio was however higher for colorectal cancer in the screened compared to the unscreened cohort (RR = 1.14, 95% CI = 1.06–1.23; Table 3). While cancer incidence, (excluding breast cancer) was about 6% lower, cancer mortality (excluding breast cancer) was 35% (OR = 0.65, 95% CI = 0.61–0.69) lower in the screened compared to the unscreened cohort. When cancer was diagnosed, after adjustment, women in the screened compared to the unscreened cohort were 23% less likely to be diagnosed with distant disease (RR = 0.77, 95% CI = 0.72–0.82). The decreased likelihood of a cancer being diagnosed at a distant stage was observed across cancers of the lung, cervix, colon, rectum and pancreas (Table 3).

### Treatment

The treatment received by stage of cancer is presented in Table 4. While across all included cancers, a higher proportion of women in the screened cohort with regional disease had surgery compared to those in the unscreened cohort, the differences were more apparent for cancers of the lung, cervix and esophagus. For example, 29% of women with regional stage lung cancer in the screened cohort received surgery, compared to 17% of those in the unscreened cohort. The magnitude of the difference was even greater for cervical cancer.

After adjustment for age, SES, location and stage at diagnosis, surgery was more commonly used in those diagnosed with cervix, esophagus, ovarian, head and neck and colorectal cancers (Table 5) than for the other included cancers. In the screened cohort, there was a greater use of radiation therapy

**Table 5.** Multivariate analysis showing the rate ratios of treatment received comparing screened *versus* unscreened cohorts

| | Surgery | | Radiation therapy | | Chemotherapy[1] | | No treatment | |
|---|---|---|---|---|---|---|---|---|
| | RR[2] (95% CI) | *p*-value | RR[2] (95% CI) | *p*-value | RR[2] (95% CI) | *p*-value | RR[2] (95% CI) | *p*-value |
| Lung | 1.75 (1.49–2.06) | <0.001 | 1.09 (1.02–1.18) | 0.02 | 1.18 (1.09–1.28) | <0.001 | 0.59 (0.52–0.66) | <0.001 |
| Cervix | 2.00 (1.48–2.71) | <0.001 | 0.80 (0.70–0.92) | 0.002 | 0.73 (0.61–0.88) | 0.001 | 1.16 (0.61–1.88) | 0.65 |
| Head and neck | 1.05 (0.90–1.22) | 0.54 | 1.02 (0.92–1.13) | 0.77 | 1.06 (0.86–1.30) | 0.61 | N/A[3] | N/A[3] |
| Esophagus | 2.49 (1.24–4.98) | 0.01 | 0.92 (0.76–1.11) | 0.39 | 1.10 (0.85–1.43) | 0.47 | 0.76 (0.47–1.24) | 0.28 |
| Ovarian | 1.29 (1.16–1.43) | <0.001 | 1.12 (0.72–1.74) | 0.61 | 1.05 (0.98–1.12) | 0.13 | 0.47 (0.29–0.75) | 0.002 |
| Colorectal | 1.02 (1.00–1.04) | 0.02 | 0.93 (0.80–1.08) | 0.37 | 1.09 (1.01–1.17) | 0.03 | 0.41 (0.29–0.58) | <0.001 |
| Brain | 1.07 (0.97–1.18) | 0.20 | 1.19 (0.98–1.44) | 0.08 | 1.29 (0.78–2.14) | 0.32 | 0.57 (0.33–0.97) | 0.04 |
| Pancreas | 1.36 (1.00–1.85) | 0.05 | 1.15 (0.72–1.85) | 0.55 | 1.19 (1.00–1.41) | 0.05 | 0.74 (0.61–0.90) | 0.002 |
| All selected cancers | 1.32 (1.27–1.37) | <0.001 | 0.90 (0.79–0.91) | <0.001 | 1.05 (1.01–1.10) | 0.02 | 0.54 (0.48–0.59) | <0.001 |

[1]Intravenous chemotherapy only.
[2]Rate ratio adjusted for age, SES, residential location and stage at diagnosis.
[3]N/A indicates all patients received some form of treatment.

Table 6. Noncancer mortality risk in screened *versus* unscreened cohorts

| Cause of death | Number | HR (95% CI) | *p*-value |
|---|---|---|---|
| Diabetes | 554 | 0.46 (0.38–0.54) | ‹0.001 |
| Mental disorder/substance abuse | 346 | 0.75 (0.59–0.96) | 0.02 |
| Movement disorders | 127 | 1.39 (0.86–2.24) | 0.18 |
| Alzheimer's | 180 | 1.19 (0.81–1.75) | 0.37 |
| Influenza/pneumonia | 153 | 0.58 (0.41–0.82) | 0.002 |
| Emphysema | 143 | 0.39 (0.28–0.55) | ‹0.001 |
| Asthma | 63 | 0.53 (0.32–0.90) | 0.02 |
| Gastric disease | 44 | 0.56 (0.30–1.06) | 0.08 |
| Liver disease | 250 | 0.57 (0.44–0.74) | ‹0.001 |
| Renal failure | 145 | 0.49 (0.35–0.69) | ‹0.001 |
| *Any cardiovascular disease* | 3,667 | 0.55 (0.51–0.59) | ‹0.001 |
| Myocardial infarction | 851 | 0.54 (0.47–0.62) | ‹ 0.001 |
| Other ischemic heart disease | 809 | 0.50 (0.44–0.58) | ‹0.001 |
| Pericarditis | 2 | – | – |
| Valvular dysfunction | 131 | 0.48 (0.33–0.68) | ‹0.001 |
| Cardiomyopathy | 111 | 0.43 (0.29–0.64) | ‹0.001 |
| Arrhythmia | 110 | 0.52 (0.35–0.77) | 0.001 |
| Congestive heart failure | 115 | 0.51 (0.35–0.76) | ‹0.001 |
| Cerebrovascular disease | 904 | 0.63 (0.55–0.73) | ‹0.001 |
| Other cardiovascular | 634 | 0.57 (0.45–0.66) | ‹0.001 |

Abbreviation: HR, hazard ratio.

in lung cancer, but less use of radiation therapy in cervical cancer. Intravenous systemic chemotherapy use was more common among screened compared to unscreened women for lung cancer ($p < 0.001$), colorectal cancer ($p = 0.03$) and pancreatic cancer ($p = 0.02$). In the screened cohort, there was less likelihood of a patient not receiving any major treatment modality for lung, ovarian, colorectal, brain and pancreatic cancers (Table 5).

### Noncancer mortality

Outside of cancer, noncancer mortality was significantly lower among screened compared to unscreened women due to diabetes, mental disorder/substance abuse, influenza/pneumonia, emphysema, asthma, liver disease, renal disease or any cardiovascular cause including ischemic cardiac disease, heart failure and cerebrovascular disease. Noncancer mortality overall was 43% lower in the screened, compared to the unscreened cohort (Table 6).

## Discussion

There remains controversy over the interpretation of screening mammography data for breast cancer. Population and cohort studies have shown consistently lower mortality in screened *versus* unscreened cohorts.[25,26] However, the individually randomized Canadian study has raised concerns with the lack of reduction in late stage disease and breast cancer mortality.[10] A recent review focusing on the impact of mammography on incidence of advanced breast cancer noted issues around study design and statistical analysis of published research and does to some degree hamper a thorough review of the effectiveness of screening.[27] There is a suggestion that some of the perceived gain may occur due to overdiagnosis of clinically insignificant lesions (so-called lead-time bias).[28] The Surveillance, Epidemiology and End Results (SEER) registries in the United States have examined breast cancer diagnoses *versus* death at the county level to approximate screening outcomes. This showed an excess of breast cancer diagnosis was associated with screening, but breast cancer deaths remained unchanged.[29]

While controversy continues over the benefits of regular screening mammography across screening outcomes, in our study, we observed differences in outcomes across multiple cancers (excluding breast cancers). Overall, there was a modest but significant fall in the incidence of several of our included cancers. This was more marked for lung, cervix, head and neck and esophageal cancers. These are all cancers where a lower prevalence of lifestyle factors such as smoking is likely to exist in the screened population.[24] The lower incidence and the magnitude of the reduction we found are similar to a Canadian study of screening participants and nonparticipants.[13]

For cancers of the cervix, apart from its association with smoking, the lower incidence we observed among screened women may be due in some part to their participation in cervical screening (and thus the potential to identify precancerous lesions). Similar to the Canadian study,[13] we did not

observe any decrease or increase in the incidence of other cancers (such as ovarian, pancreas and brain). These are all cancers where lifestyle factors have not been shown to have a significant association. In our study, we did observe a higher incidence of colorectal cancer among screened, compared to unscreened women. While the exact reasons for this increased incidence in a cancer that is predominantly associated with lifestyle factors (such as diet, obesity and physical inactivity) is unknown, it may be that women who participated in mammography screening, also participated in Australia's national bowel screening program, thus providing the opportunity to identify early stage bowel cancers. Australia's national bowel screening program began a phased introduction in 2006.[29] In our study, we did observe about a 40% lower incidence of late stage colorectal cancer amongst the screened compared to the unscreened cohort. Further research may help shed light on these findings. While we did not have more extensive data on the lifestyle behaviors of the cohorts, previous studies have shown those attending mammography screening are less likely to be current smokers, less likely to be obese and more likely to have a physically active lifestyle.[30]

We additionally found the hazard rates for cancer mortality (excluding breast cancer) were significantly lower in screening participants. This included all our included cancers except brain and pancreas where mortality is high regardless of stage of presentation.[31] Mortality differences in the included cancers were greater than the corresponding incidence differences. The lower mortality rates for cervical and colorectal cancer, we observed in our study may also be the result of participation in cervical and bowel screening programmes.[32,33] Again, our results here are similar to those reported elsewhere.[13] We also found screening participants were significantly less likely to present with later stage disease (staging conventions were not applicable to brain cancers). Lower incidence and mortality rates, and earlier stage at presentation for some cancers, all point toward heightened awareness and concern about health among screening participants. This is also apparent when noncancer mortality is examined, with generalized improvement across many causes of death, particularly those linked to modifiable risk factors. Screening behavior has been linked to other desirable health behaviors in several cohort studies in different populations.[34,35] A Danish study showed a 28% lower risk for all-cause mortality and 24% for cancer mortality amongst screening participants.[35]

In our study, we found screening participants were about 30% more likely to receive surgery and about 10% less likely to receive radiation therapy than nonparticipants across our selected cancers. Furthermore, screening participants were about 50% less likely to receive no treatment compared to nonparticipants. This is an interesting finding and while we adjusted for stage at diagnosis in our analysis, it is possible the results may be due to some residual confounding. Additionally, it is known that women with comorbidity are less likely to participate in breast screening,[14] and the presence of comorbidities may to some degree influence treatment options. It is also possible that screening participants are likely to have a healthier lifestyle (no smoking, healthy diet and adequate physical activity) and have established links with health care (such as a general practitioner who would provide ongoing advice and care) and these factors may impact the type of treatment offered (and completed).

### Strengths and limitations

Strengths of our study include the large population-based cohorts. Our cohorts included all women aged 50–65 years on the electoral roll. Voting is compulsory in Australia and the electoral roll is estimated to be approximately 92% complete and accurate.[18] A further strength is the linkage of the study population not only to the population-based breast screening program, but also to the largest provider of fee-for-service screening in Queensland as well as mammograms conducted in other private facilities covered by a Medicare (Australia's National Health System) rebate. Additionally, as cancer is a notifiable disease in Australia, we were able to link the study population to our Queensland Oncology Repository (QOR) to obtain details on cancer diagnoses, deaths and causes of death. Further, treatment data was obtained *via* surgical procedure codes collected with hospitalizations, radiation and intravenous chemotherapy treatment records.

While it is possible that errors occurred during the linkage of the study population to QOR, it is unlikely that errors would have been differential between the screened and unscreened cohorts and thus would not affect any of the estimates unduly. It is possible that women in the unscreened cohort may have had a mammogram outside of the three included sources used in our study. That said, these three sources represent the largest providers of mammogram services in Queensland, and our screening rate of around 78% is in line with published screening rates from BSQ (54%), plus estimates of an additional 20% performed in private facilities.[20,36] It should also be acknowledged that the findings in our study may be subject to some bias as our "unscreened" group included women with no history of screening for the period 2000–2005, that is, we made no provision for a history of screening prior to 2000. To address the potential biases due to "left truncation," we searched records from the screening facilities we were able to access prior to 2000 (it should be noted we did not have access to all screening records prior to 2000 due to ethics limitations). These records amounted to approximately 20% of all screening records used in the study. With these limitations in mind, we included an additional 9,093 women (15.6% of the original "unscreened" group) with a record of a mammogram prior to 2000 to the "screened" group and re-ran analyses. We found no substantial changes in the direction or magnitude of effect for any of the included outcomes. The greatest change we saw was for lung cancer incidence which increased in the screened group to 8.8/10,000

(from 8.6/10,000) and decreased in the unscreened group to 11.4/10,000 (from 11.8/10,000), however, the direction of effect remained the same. While we did undertake this exercise to examine potential biases, we recognize this process was limited and that caution should be exercised in extrapolating our sample estimates for the entire cohort.

We were unable to collect data on cancers that may have occurred in women who had moved out of Queensland following enrolment into the study. However, migration out of Queensland is relatively low, and census data shows 92% of women in the included age group remained at the same address for the previous 5 years prior to 2006.[37] Additionally, although stage is not routinely collected or recorded in QOR or anywhere in Australian cancer registries, staging algorithms were created to best capture the presence of regional or metastatic disease from health administration data sources for the cohorts. These algorithms have proven comparable against some cancers to SEER but further work needs to be done on each specific type of cancer. While we adjusted for SES in the multivariate analysis, the SES variable used was a broad measure based on an individual's location. We did find some modest correlation with SES and screening participation, but we did not have access to data on education. Education level has been shown to be a consistent predictor of screening participation.

## Conclusion

Our study adds further to the population data examining outcomes from mammographic screening. We observed significantly lower mortality from some cancers and in noncancer mortality amongst breast screening participants. Our study also showed breast screen attendees appear to be at lower risk of some cancers, heightened risk of other cancers and experience earlier presentation of some cancers, and have more treatment opportunities.

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## Conflict of interest

The authors have no conflicts of interest to declare.



## References

1. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018;391:1023–75.
2. Cramb SM, Baade PD. *Atlas of cancer in Queensland: geographical variation in incidence and survival, 1998 to 2007*. Brisbane, Australia: Viertel Centre for Research in Cancer Control, Cancer Council Queensland, 2011.
3. International Agency for Research on Cancer (IARC), World Health Organisation. *Cervix cancer screening*, vol. 10. Lyon: IARC Press, 2005.
4. Holme O, Bretthauer M, Fretheim A, et al. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. *Cochrane Database Syst Rev* 2013;9:CD009259.
5. Tabar L, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the breast cancer screening working Group of the Swedish National Board of health and welfare. *Lancet* 1985;1:829–32.
6. Shapiro S, Venet W, Strax P, et al. Selection, follow-up, and analysis in the health insurance plan study: a randomized trial with breast cancer screening. *Natl Cancer Inst Monogr* 1985;67: 65–74.
7. Gotzsche PC, Jorgensen KJ. The benefits and harms of breast cancer screening. *Lancet* 2013; 381:799.
8. Lauby-Secretan B, Loomis D, Straif K. Breast-cancer screening—viewpoint of the IARC working group. *N Engl J Med* 2015;373:1479.
9. Autier P, Boniol M. Mammography screening: a major issue in medicine. *Eur J Cancer* 2018;90: 34–62.
10. Miller AB, Wall C, Baines CJ, et al. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ* 2014; 348:g366.
11. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998–2005.
12. Mook S, Van 't Veer LJ, Rutgers EJ, et al. Independent prognostic value of screen detection in invasive breast cancer. *J Natl Cancer Inst* 2011; 103:585–97.
13. Phillips N, Coldman A. Comparison of nonbreast cancer incidence, survival and mortality between breast screening program participants and non-participants. *Int J Cancer* 2008;122:197–201.
14. Diaz A, Kang J, Moore SP, et al. Association between comorbidity and participation in breast and cervical cancer screening: a systematic review and meta-analysis. *Cancer Epidemiol* 2017; 47:7–19.
15. Berkman ND, Sheridan SL, Donahue KE, et al. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* 2011; 155:97–107.
16. Paskett E, Tatum C, Rushing J, et al. Randomized trial of an intervention to improve mammography utilization among a triracial rural population of women. *J Natl Cancer Inst* 2006;98:1226–37.
17. Protani M, Page A, Taylor R, et al. Breast cancer risk factors in Queensland women attending population-based mammography screening. *Maturitas* 2012;71:279–86.
18. Australian Electoral Commission. Annual Roll Integrity. Available from https://www.aec.gov.au/Enrolling_to_vote/Enrolment_stats/annual-review/index.htm; 2018.
19. Australian Institute of Health and Welfare (AIHW). *BreastScreen Australia monitoring report 2014-2015. Cancer series no. 106. Cat. no CAN 105*. Canberra: AIHW, 2017.
20. Youl PH, Aitken JF, Turrell G, et al. The impact of Rurality and disadvantage on the diagnostic interval for breast cancer in a large population-based study of 3202 women in Queensland, Australia. *Int J Environ Res Public Health* 2016;13: E1156.
21. Australian Bureau of Statistics. *Information Paper: ABS Causes of Death Statistics: Concepts, Sources and Methods*. Canberra, Australia: Australian Bureau of Statistics. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/mf/3317.0.55.002, 2006.
22. Australian Bureau of Statistics. *Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA), Australia*. Canberra: ABS, 2011 Available from http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2033.0.55.001~2011~Main%20Features~Main%20Page~1. Accessed May 2, 2018.
23. Australian Bureau of Statistics. Australian Statistical Geography Standard (ASGS). *Volume 5 - remoteness structure*, vol. 2011. Canberra: ABS, 2013.
24. Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board. Lifestyle behaviors contributing to the burden of cancer. In: Curry SJ, Byers T, Hewitt M, eds *Fulfilling the Potential of Cancer Prevention and Early*

*Detection*. Washington, DC: National Academies Press (US), 2003.
25. Gotzsche PC, Jorgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2013;1:CD001877.
26. Fracheboud J, van Luijt PA, Sankatsing VD, et al. *National Evaluation of breast cancer screening in The Netherlands 1990–2011/12. Thirteenth evaluation report*. Rotterdam, Nijmegen: Department of Public Health. Available from: https://www.erasmusmc.nl/mage/publications-collaborations/pub/national-evaluation-breastcancer?lang=en, 2014.
27. Broeders MJM, Allgood P, Duffy SW, et al. The impact of mammography screening programmes on incidence of advanced breast cancer in Europe: a literature review. *BMC Cancer* 2018;18:860.
28. Alibhai SM. Cancer screening: the importance of outcome measures. *Crit Rev Oncol Hematol* 2006; 57:215–24.
29. Harding C, Pompei F, Burmistrov D, et al. Breast cancer screening, incidence, and mortality across US counties. *JAMA Intern Med* 2015;175:1483–9.
30. Martin-Lopez R, Jimenez-Garcia R, Lopez-de-Andres A, et al. Inequalities in uptake of breast cancer screening in Spain: analysis of a cross-sectional national survey. *Public Health* 2013;127:822–7.
31. Queensland Government. *Cancer in Queensland: a statistical overview*. Brisbane: Queensland Health, 2018.
32. Boyes DA, Worth AJ, Anderson GH. Experience with cervical screening in British Columbia. *Gynecol Oncol* 1981;12:S143–55.
33. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472–7.
34. Fillenbaum GG, Burchett BM, Kuchibhatla MN, et al. Effect of cancer screening and desirable health behaviors on functional status, self-rated health, health service use and mortality. *J Am Geriatr Soc* 2007;55:66–74.
35. Petersen KE, Johnsen NF, Olsen A, et al. The combined impact of adherence to five lifestyle factors on all-cause, cancer and cardiovascular mortality: a prospective cohort study among Danish men and women. *Br J Nutr* 2015;113: 849–58.
36. BreastScreen Australia. *Evaluation of the BreastScreen Australia program—evaluation final report (June 2009)*. Canberra: Australian Government Department of Health, 2009.
37. Australian Bureau of Statistics. *Census of Population and Housing*. Canberra, Australia: Australian Bureau of Statistics, 2006 Available from http://www.abs.gov.au/websitedbs/censushome.nsf/home/tablebuilderdata2006basic?opendocument&navpos=240.