Title: Effect of age at diagnosis of breast cancer on the patterns and risk of mortality from all causes: a population-based study.

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Short running title: Mortality Risks and Patterns after Breast Cancer

Abstract

Aims: This retrospective population-based study investigated the patterns and risks of mortality from breast cancer, other cancers and non-cancer causes according to the age at diagnosis of breast cancer.

Methods: Mortality was assessed in 179,653 Australian women aged between 30 - 79 years who were diagnosed with breast cancer between 1982 and 2004, and who survived a minimum of 1 year. The mean subsequent follow-up was 6.3 years (range 0-23 years).

Results: Before December 2005, 52,934 women had died (34,459 of breast cancer, 5,019 of other cancers, and 13,456 of non-cancer causes). There was an inverse age-related relative risk of mortality (RR) from breast cancer (linear trend across age $p < 0.01$). For breast cancer survivors, the age-adjusted RR was 0.99 for other cancers and 0.81 ($p < 0.01$) for non-cancer causes in comparison with the general population. The RR from other cancers and non-cancer causes was highest in the 30-39 year age group (2.13, $p < 0.01$, and 2.15, $p < 0.01$, respectively), and progressively decreased with increasing age, with the 70-79 year age group having significantly reduced RR's (0.95, $p < 0.05$, and 0.78, $p < 0.01$, respectively).

Conclusions: There was an inverse age-related relative risk of death from breast cancer, other cancers and non-cancer causes. These findings suggest that younger Australian women require long-term surveillance for comorbidities which could lead to premature mortality while older women with limited comorbidities require optimal treatment of their breast cancer because their competing risks of mortality are lower than the age-matched general population.

Key words: breast cancer; causes of death; non-cancer causes of death; second primary cancer.

INTRODUCTION

Breast cancer survival rates are increasing and consequently premature mortality from any cause is an important consideration in the investigation of long-term outcomes. While premature mortality due to treatment related complications has been a focus of clinical concern, there is no evidence of an adverse effect of adjuvant systemic treatments on the patterns and risk of non-breast cancer mortality and only a small excess risks of vascular deaths after radiation treatment [1,2]. In contrast, population-based studies have reported an elevated risk of suicide [3-5] and other cancers [6-27] after a diagnosis of breast cancer. These findings suggest that breast cancer survivors are at increased risk of premature mortality due to a variety of causes but to date there has been relatively little investigation of all cause mortality after a diagnosis of breast cancer.

In considering the patterns of premature mortality after a diagnosis of breast cancer, the results of population-based studies confirm that breast cancer is the most common cause of death [28, 29]. However, the competing risks of death are influenced by numerous variables. For example, the results of trials of adjuvant endocrine treatments in older women report that non-cancer mortality represents the majority of deaths in long-term follow-up [30,31]. The age at diagnosis of breast cancer is also an important consideration because younger women have a higher risk of mortality from breast cancer than older women [32-36]. Younger women diagnosed with breast cancer are also reported to have a higher risk of other cancers [15, 20, 21, 23, 25-27, 37], and there is some evidence of an elevated relative risk of mortality (RR) from other cancers in women aged less than 50 years compared with older women [24, 25, 37].

However to date, no study has investigated in detail the relationship between age at breast cancer diagnosis and the long-term risk of mortality from other cancers and non-cancer causes.

In order to investigate the moderating influences of the wide age range of diagnosis of breast cancer and its long natural history on all causes of mortality, we assessed the patterns of death in Australian women aged 30-79 years, and calculated the RR from breast cancer between age groups as well as the RR from other cancers and non-cancer causes with the general population. The upper age limit was set at 79 years because Australian female life expectancy is 83.3 years [38] but no limit was set on the age of death despite the acknowledged difficulty of accurately coding causes of death amongst the eldest of the elderly [39, 40]. While premature mortality was the focus of this study, deaths in the first 12 months were excluded because we and others have reported substantially increased mortality rates in the first 12 months after a cancer diagnosis that might be explained by the incidental diagnosis of a cancer in the setting of a serious comorbidity [39, 41].

METHODS

Patient Population

The study cohort was all women aged 30-79 years diagnosed with invasive breast cancer (ICD9: 174; ICD10: C50) between January 1982 and December 2004. Cancer notification is required by law in Australia and is collated by the National Cancer Statistics Clearing House which is maintained by the Australian Institute of Health and Welfare (AIHW). Incident cases of invasive breast cancer were matched to the National Death Index dataset collated by the AIHW. Coded death information utilized ICD-9 and ICD-10 classifications, and non-cancer mortality groups were categorized according to previously published mortality concordances [41-43]. Mortality in the breast cancer cohort was compared with the mortality of the Australian female

population according to the same ICD-9 and ICD-10 classifications, adjusting for age and calendar period.

Variables extracted for the cohort dataset included year of diagnosis, year of death, age (5 year age groups to 85+), sex, time (years) since diagnosis and cause of death. Time since diagnosis was taken as the difference between the date of diagnosis and the date of death for people who died, and between the date of diagnosis and the censor date (31 December 2005) for people still alive. Cases not known to have died before the censor date were considered to be alive at that date. There was a small number of female breast cancer cases (0.2%) who were known to have died but were unable to be matched to the National Death Index. These deaths were excluded from the analysis. Women who were diagnosed with breast cancer under the age of 30 years were also excluded from the study because the small numbers (less than 1% of all breast cancer cases) would create unstable estimates.

Cohort Analysis

Person-years at risk was accumulated for each person in the female breast cancer cohort from the date of diagnosis of breast cancer up to the date of death or December 31st 2005, whichever came first. The expected number of deaths was calculated by applying the 5-year age decade of diagnosis-specific mortality rate for each cause of death in Australia to the person-years at risk among the breast cancer cohort. RR was calculated using the indirectly age-standardised mortality ratio (SMR). The SMR was calculated for each cause of death as the ratio of the observed number of deaths to the expected number of deaths. Ninety-five percent confidence intervals (95% CIs) were calculated assuming a Poisson distribution for the observed cases.

Poisson regression models were used to calculate adjusted mortality rate ratios (MRR) among the breast cancer cohort. The MRR compares the RR of dying from a condition in one population subgroup to the corresponding RR in another subgroup. Separate models were used for each cause of death. The outcome variable was the observed age-specific mortality counts, with the age group and time (years) since diagnosis included as explanatory variables. The log of the expected mortality counts was included as the offset variable in the Poisson model.

Data extractions and analyses utilized SAS (SAS Institute Inc, Cary NC USA) and Stata (StataCorp, TX USA). The SAS program code was sent electronically to AIHW staff who submitted the programs and returned the aggregated results. No potentially identifying information was released outside the AIHW and therefore the AIHW Ethics Committee waived the requirement for Ethics Committee approval of this study.

RESULTS

Patient Population

Between 1982 and 2004, 201,334 women were diagnosed with breast cancer, of whom 179,653 (89%) were aged 30-79 years at diagnosis. Among this cohort, 13,024 (7%) women were aged 30-39 years when diagnosed with breast cancer, 38,385 (21%) were aged 40-49 years, 47,424 (26%) were 50-59 years, 45,065 (25%) were 60-69 years, and 35,755 (20%) were 70-79 years. Before 31 December 2005, 52,934 (29%) of women aged 30-79 years had died (Table 1). Of these, 34,459 had died of breast cancer, 5,019 of other cancers and 13,456 of non-cancer causes. Excluding the first year after diagnosis, the cohort of 1-year breast cancer survivors was nearly 1.27 million person-years at risk, with a mean subsequent follow-up of 6.3 years and range of 0-23 years. During the same time, 1.34 million Australian women aged 30 years and over had died, and of these 1.01 million (75.2%) were of non-cancer causes.

Effect of Age on Patterns and Risk of Death

The RR for all causes of death combined in the breast cancer cohort was significantly elevated at 2.35 (CI 2.33-2.37) and this finding was due predominantly to the excess deaths from breast cancer (Table 1). The RR for deaths from other cancers showed no significant difference (0.99) between the breast cancer cohort and the Australian female population after adjusting for age and calendar period. In contrast, the RR was significantly lower for non-cancer causes (0.81, CI 0.80-0.83). When considered by age at breast cancer diagnosis, there were inverse age-associated RR's for deaths from other cancers and non-cancer causes in comparison with the age-matched general population. The 30-39 year age group had statistically significantly higher RR's for deaths from other cancers and non-cancer causes, and there was a progressive decline in RR as the age group decade of diagnosis of breast cancer increased. The 60-69 and 70-79 year age groups had statistically significantly lower RR's for deaths from other cancers and non-cancer causes in comparison with the age-matched general population.

To further assess the risk of mortality between age groups for different causes, we calculated MRR's according to age at breast cancer diagnosis. In assessing the MRR according to age group, the 60-69 year cohort was used as the reference group. In comparison with this group, younger age groups had significantly elevated MRR for deaths from breast cancer, other cancers and non-cancer causes while the 70-79 year age group had a significantly reduced MRR (Table 1). When we re-fitted the Poisson models using an ordinal variable for age group, the linear trend across age categories was highly significant ($p < 0.01$).

Patterns of Non-Cancer Mortality

Table 2 presents the patterns of non-cancer mortality according to ICD groupings for non-cancer causes. Overall, there were three causes of death for which breast cancer patients had a higher RR compared with the general female population: suicide, infectious diseases and diseases of the liver (Table 2). For most of the remaining causes of death categories, breast cancer survivors had significantly reduced RR's. Numerically, the greatest impact was for cardiovascular (especially ischaemic heart and cerebrovascular), respiratory and digestive diseases. Statistically significantly reduced RR's were also documented in the numerically smaller ICD groups of endocrine, nutritional and metabolic diseases, mental and behavioural disorders, and diseases of the central nervous, genitourinary and musculoskeletal systems. There were significantly higher than expected RR's from respiratory disease in the 30-39 year age group, and from diseases of the oesophagus, stomach and duodenum in the 40-49 year age group. When considered by age at breast cancer diagnosis, the RR was significantly lower for multiple ICD groupings in women 50-79 years, but numerically the greatest reduction was for cardiovascular and respiratory diseases, including chronic obstructive pulmonary disease.

Discussion

The purpose of this population-based study was to investigate the patterns and competing risks of mortality in a large population of women diagnosed with breast cancer. Consistent with other reports, the results show that deaths from breast cancer were more common than other causes [28, 29], that the risk of death due to breast cancer decreased with increasing time after diagnosis [29], that young age was associated with an increased RR from breast cancer [32-36], and that there were age-related differences in the patterns of mortality from breast cancer and other causes [44-46]. An important novel finding of this study was a continuum of declining RR from breast cancer, other cancers and non-cancer causes as the age at diagnosis of breast cancer increased. Furthermore, the RR's from other cancers and non-cancer causes were

significantly higher than the age-matched female population in the 30-39 year age group, and significantly lower in the 70-79 year age group.

Since adverse functional and comorbidity outcomes after treatment of breast cancer could potentially translate into premature mortality, we investigated the patterns and RR from non-cancer causes for different ages according to ICD groupings. Overall, there were significantly reduced RR's at multiple sites but numerically the greatest impact was for cardiovascular, respiratory and digestive diseases. There was a significantly elevated RR from suicide, a finding previously described [3-5], and for infectious and liver diseases. There were also important age-related differences in the patterns of non-cancer mortality. For the 50-79 year group, there were marked reductions of RR from cardiovascular disease, including the subgroups of ischaemic heart and cerebrovascular disease, as well as for respiratory disease. Importantly, there was a significantly lower RR from chronic obstructive pulmonary disease, a surrogate marker of cigarette smoking, and consequently the reduced RR's from cardiovascular, ischaemic heart, cerebrovascular and respiratory diseases in this group might be explained by lower smoking rates and higher socioeconomic status [47-48].

In contrast to older women, the RR from non-cancer causes was significantly elevated in the 30-49 year age group. The highest RR was in the 30-39 year group and there was a progressive decline of RR as the age decade grouping increased. The RR from respiratory disease was elevated in the 30-39 year group and from diseases of the oesophagus, duodenum and stomach in the 40-49 year age group. However, since there were only a small number of events for each ICD code, this study is underpowered to accurately identify specific causes of elevated mortality risks in younger women.

An elevated risk of other cancers after a breast cancer diagnosis at younger age is well documented [15, 20, 21, 23, 25-27, 37] and, although an age-dependent risk of mortality has

also been reported [24, 25, 37], no study to date has investigated the nature of this association in detail. An important finding of our study was a significant inverse relationship between age at breast cancer diagnosis and the RR from other cancers. This risk was highest for the 30-39 year age group and progressively declined with increasing age, with the 60-69 and 70-79 year age groups having significantly reduced risks of mortality compared with the age-matched population. Since we did not assess cancer site-specific mortality, the possible role of lifestyle factors and treatment could not be evaluated in our study. However, it is possible that lower smoking rates in older women could have contributed to the reduced RR from other cancers. For younger women, there is widespread concern that treatment factors might contribute to an increased risk of other cancers [14, 15, 23, 37]. However, the Early Breast Cancer Trialists' Collaborative Group failed to demonstrate an increased risk of mortality from other cancers in women treated with either polychemotherapy or radiotherapy compared with untreated patients [1, 2]. These findings, together with the results of one study that reported an elevated risk of other cancers both prior to the era of adjuvant systemic treatment and outside the fields of radiation therapy, suggest that treatment does not fully explain the elevated risk of other cancers after a diagnosis of breast cancer [20].

Shared environmental and genetic characteristics are now widely considered as risk factors for the development and behavior of complex diseases, including cancer. Our findings of inverse age dependent RR's from other cancers and non-cancer causes together with an inverse age-related RR from breast cancer mortality suggest that contributing genetic and environmental risk factors are likely to be different across age groups. Evidence of the age dependent behavior of breast cancer is also supported by other epidemiological and clinical studies. For example, although the pattern of peak incidence of breast cancer differs markedly between Western and Asian societies, inverse age dependent mortality from other cancers after a breast cancer diagnosis has been reported in both Dutch and Taiwanese population-based studies [24, 25]

while the adverse prognostic characteristic of young age at diagnosis of breast cancer has been reported in Western and Korean women [32-36].

Limitations to the interpretation of our results include methodological concerns that apply to all registry-based studies as well as issues specific to our study. Death certification may not reflect a true picture of the cause of death, and misclassification of metastases as new primary cancers is also possible, especially in the elderly [38, 39, 49-51]. Disease classification has also changed over the years and, although we used established mortality concordances, misclassification of non-cancer causes of death is possible. Finally, we did not assess disease incidence or details of treatment. However, the purpose of this study was an assessment of the impact of a diagnosis of breast cancer on the patterns of mortality, and matching of a histological diagnosis of breast cancer with subsequent death was complete in 99.8% of cases. Furthermore, the use of a large national population sample with long follow-up provides confidence about the interpretation of the results, especially in younger women for whom premature mortality is likely to have the greatest social and economic impact.

To our knowledge, this is the first study to undertake a detailed investigation of the patterns and risks of all cause mortality across a wide range of ages, and the findings therefore require confirmation by other population-based studies. Larger studies of younger women are a particular priority in order to investigate in more detail the patterns and risk of premature mortality from non-breast cancer causes. For older women, optimal treatment of breast cancer is important for those with limited comorbidities since their competing risks of mortality are lower than the age-matched population. Until further information becomes available, the findings of this study suggest that women with breast cancer need to be informed of their risk of competing causes of mortality and, for younger women, risk adapted strategies of long-term surveillance need to be incorporated into models of survivorship care.

Table 1. Relative risk (RR) of mortality from breast cancer according to age, and RR of mortality from other cancers and non-cancer causes compared with the age-matched Australian female population (1982-2004)¹.

Cause of death	Age group	Observed deaths	Expected deaths	RR ² (95% CI)	MRR ^{2,3} (95% CI)
Deaths from breast cancer	30-79 combined	34459	935.0	36.86 [36.47-37.25] **	
	30-39 years	3531	24.2	145.75 [140.98-150.64] **	12.22 [11.37-13.13] **
	40-49 years	7598	136.7	55.60 [54.36-56.86] **	2.61 [2.47-2.77] **
	50-59 years	8562	219.4	39.02 [38.20-39.86] **	1.42 [1.34-1.50] **
	60-69 years	8248	289.6	28.48 [27.87-29.10] **	<u>1.00</u>
	70-79 years	6520	265.1	24.60 [24.00-25.20] **	0.88 [0.89-0.90] **
Deaths from other cancers	30-79 combined	5019	5072.3	0.99 [0.96-1.02]	
	30-39 years	107	50.3	2.13 [1.74-2.57] **	4.51 [3.10-6.57] **
	40-49 years	474	378.1	1.25 [1.14-1.37] **	1.38 [1.12-1.69] **
	50-59 years	966	943.1	1.02 [0.96-1.09]	1.20 [1.03-1.39] *
	60-69 years	1702	1828.0	0.93 [0.89-0.98] **	<u>1.00</u>
	70-79 years	1770	1863.1	0.95 [0.91-1.00] *	0.94 [0.83, 1.07]
All non-cancer deaths combined	30-79 combined	13456	16528.2	0.81 [0.80-0.83] **	
	30-39 years	145	67.6	2.15 [1.81-2.52] **	3.34 [2.46-4.52] **
	40-49 years	529	429.9	1.23 [1.13-1.34] **	1.99 [1.68-2.37] **
	50-59 years	1273	1335.6	0.95 [90-1.01] *	1.18 [1.04-1.34] **
	60-69 years	3916	4892.9	0.80 [0.78-0.83] **	<u>1.00</u>
	70-79 years	7593	9793.4	0.78 [0.76-0.79] **	0.76 [0.71-0.83] **
All causes of death combined – excluding breast cancer	30-79 combined	18475	21604.8	0.86 [0.84-0.87] **	
	30-39 years	252	120.3	2.10 [1.84-2.37] **	3.66 [2.90-4.64] **
	40-49 years	1003	811.9	1.24 [1.16-1.31] **	1.64 [1.44-1.88] **
	50-59 years	2239	2285.3	0.98 [0.94-1.02]	1.17 [1.06-1.28] **
	60-69 years	5618	6726.0	0.84 [0.81-0.86] **	<u>1.00</u>
	70-79 years	9363	11660.6	0.80 [0.79-0.82] **	0.80 [0.75-0.85] **
All causes of death combined	30-79 combined	52934	22539.8	2.35 [2.33-2.37] **	
	30-39 years	3783	145.3	26.03 [25.21-26.88] **	23.32 [21.87-24.88] **
	40-49 years	8601	948.5	9.07 [8.88-9.26] **	6.55 [6.23-6.87] **
	50-59 years	10801	2504.7	4.31 [4.23-4.39] **	2.65 [2.53-2.77] **
	60-69 years	13866	7015.6	1.98 [1.94-2.01] **	<u>1.00</u>
	70-79 years	15883	11925.7	1.33 [1.31-1.35] **	0.47 [0.45-0.49] **

1. Relative risk calculated as the indirectly age-standardized mortality ratio. Based on separate Poisson models for each cause of death, modelling the observed mortality counts by age group, years since diagnosis and the interaction between these two variables. Excludes first year after diagnosis 2. **: $p < 0.01$; *: $p < 0.05$ 3. Age-specific Mortality Rate Ratios (MRR) (reference=60-69 years), adjusted for years since diagnosis and the interaction between age group and years since diagnosis.

Table 2. Relative risk (RR) for non-cancer causes of mortality in the breast cancer cohort (1982-2004)^{1,2,3}

Cause of death [ICD codes]	30-39 years RR (95% CI)	40-49 years RR (95% CI)	50-59 years RR (95% CI)	60-69 years RR (95% CI)	70-79 years RR (95% CI)	30-79 years RR (95% CI)	Total (n=7540)
Cardiovascular disease ⁴	132.0 [88-194]	95.4 [82-111]	75.6 [69-82]**	74.7 [72-78]**	74.5 [72-77]**	75.1 [73-77]**	(n=7540)
Ischaemic heart disease ⁵	N/A	82.3 [65-103]	75.1 [67-84]**	77.9 [73-82]**	75.3 [72-78]**	76.3 [74-79]**	(n=3830)
Cerebrovascular disease ⁶	N/A	91.7 [66-125]	75.8 [63-91]**	67.2 [61-73]**	74.9 [71-79]**	73.1 [70-76]**	(n=2022)
Respiratory Disease ⁷	226.6 [121-387]**	96.0 [72,126]	83.9 [72-98]*	79.2 [72-87]**	74.0 [69-80]**	77.9 [74-82]**	(n=1397)
Chronic obstructive pulmonary disease ⁸	N/A	89.5 [59-130]	70.7 [57-87]**	86.0 [76-96]**	76.4 [68-85]**	79.6 [74-86]**	(n=712)
Diseases of the digestive system ⁹	191.3 [95-342]	91.4 [62-130]	126.8 [104-154]*	97.4 [85-111]	80.5 [72-90]	91.8 [85-99]*	(n=704)
Diseases of the oesophagus, stomach and duodenum ¹⁰	N/A	366.5 [176-674]**	199.4 [120-311]**	102.4 [73-139]	69.6 [53-89]**	93.3 [78-111]	(n=130)
Endocrine, nutritional and metabolic diseases ¹¹	N/A	79.5 [50-119]	70.3 [54-90]**	86.5 [76-98]*	90.9 [82-101]*	86.4 [80-93]**	(n=676)
Diseases of the nervous system ¹²	N/A	99.5 [64-147]	79.7 [60-104]	60.7 [51-72]**	74.1 [66-83]**	72.0 [66-79]**	(n=506)
Injury and poisoning ¹³	94.2 [56-149]	115.4 [89-147]	102.8 [81-129]	95.6 [80-113]	84.6 [73-97]**	93.7 [86-102]	(n=498)
Suicide ¹⁴	136.6 [66-251]	138.8 [92-201]	127.0 [82-187]	120.5 [76-182]	83.6 [40-154]	122.7 [99-150]*	(n=95)
Diseases of the genitourinary system ¹⁵	N/A	124.1 [66-212]	79.9 [54-113]	82.3 [69-98]*	79.3 [70-90]**	81.7 [74-90]**	(n=434)
Mental and behavioural disorders ¹⁶	N/A	N/A	72.8 [41-120]	55.3 [43-69]**	65.2 [57-74]**	63.2 [57-70]**	(n=349)
Certain infectious and parasitic diseases ¹⁷	N/A	171.6 [91-293]*	213.3 [154-288]**	97.1 [74-126]	117.5 [97-142]	124.9 [109-142]**	(n=227)
Diseases of the liver ¹⁸	N/A	60.6 [31-106]	123.3 [89-167]	136.7 [104-176]*	109.1 [77-150]	117.2 [100-137]*	(n=158)
Diseases of the musculoskeletal system ¹⁹	N/A	176.03 [96-296]	75.9 [45-120]	79.2 [60-103]	83.7 [68-102]	84.7 [73-98]*	(n=97)
All non-cancer deaths ²⁰	214.5 [181-252]**	123.0 [113-134]**	95.3 [90-101]	80.0 [78-83]**	77.5 [76-79]**	81.4 [80-83]**	(n=13456)

1. Excludes first year after diagnosis. 2. **: p<0.01; *: p<0.05. 3. N/A indicates there were fewer than 10 deaths for this age group. 4. ICD9: 390-459; ICD10: I00-I99, G45, G46. 5. CD9: 410-414; ICD-10: I20-I25. 6. ICD9: 430-438; ICD10: I60-I69. 7. ICD9: 460-519; ICD10: J00-J99. 8. ICD9: 416.0, 416.9, 490-492, 495-496; ICD10: I27.0, I27.8, I27.9, J40-J44, I67. 9. ICD9: 520-579; ICD10: K00-K99. 10. ICD9: 530-537; ICD10: K20-K31. 11. ICD9: 2400' le cause le "2789" or "E000" le cause le "E909". 12. ICD9: 320-359; ICD10: G00-G99. 13. ICD9: 800-869, 880-929, 950-999; ICD10: V00-X99, Y00-Y39, Y85-Y87, Y89. 14. ICD9: 950-959; ICD10: X60-X84. 15. ICD9: 580-629; ICD10: N00-N99. 16. ICD9: 290-319; ICD10: F00-F99. 17. ICD9: 010-139; ICD10: A00-B99. 18. ICD9: 570-573; ICD10: K70-K78. 19. ICD9: 710-739; ICD10: M00-M99. 20. All deaths excluding CD9: 140-208; ICD10: C00-C97.

ACKNOWLEDGMENTS

This study was funded by the Breast Cancer Association of Queensland.

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