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Running title: Differences in breast cancer incidence in Australia and England

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Abstract

Objective
To compare breast cancer incidence in England and Australia by age, extent of disease and deprivation.

Methods
We analysed data for women aged 15-99 years diagnosed with breast cancer in England or Australia during 1990-1994, and in West Midlands or New South Wales during 1980-2002. We calculated three-year rolling average incidence rates and incidence rate ratios (IRR) between West Midlands and New South Wales by age, extent of disease and category of deprivation.

Results
Breast cancer incidence was higher in England than in Australia, and in West Midlands than in New South Wales but became more similar over time. Socio-economic differences in incidence were greater in New South Wales than in West Midlands. The most deprived women in West Midlands were diagnosed at a later stage of disease than the most deprived women in New South Wales. Incidence amongst elderly women was higher in West Midlands than in New South Wales. There were also high proportions of tumours with unknown stage amongst elderly women in West Midlands.

Conclusions
Although the overall incidence of breast cancer is similar, differences by age, extent of disease and deprivation exist.

Implications
The underlying reasons for these patterns require further examination.

Keywords: breast cancer, incidence, Australia, England, women
Introduction

Breast cancer in women constitutes one of the most important public health issues of the twenty-first century in more developed countries. Recent estimates suggest that there are over one million new cases and 400,000 deaths each year due to the disease.\textsuperscript{1,2} Incidence is highest in westernised settings where the prevalence of known risk factors is high, including early menarche,\textsuperscript{3} nulliparity or late first pregnancy,\textsuperscript{4} short periods of lactation,\textsuperscript{5-7} low parity,\textsuperscript{7} late menopause,\textsuperscript{8} high dietary fat intake,\textsuperscript{9-12} and exposure to exogenous oestrogen.\textsuperscript{13-15}

International comparisons of cancer incidence are conducted on a regular basis by the International Agency for Research on Cancer (IARC).\textsuperscript{16-19} However, little is known about how similar or different cancer incidence is between different nations by factors other than age or period of diagnosis. In this study we compare trends in breast cancer incidence in England with those of Australia during the period 1980-2002. Using the West Midlands and New South Wales as exemplar regions for each country, we examine how incidence differs according to deprivation status and extent of disease at diagnosis.

Materials and Methods

All invasive breast cancers diagnosed amongst women aged 15-99 years in England or Australia during the period 1990-1994, and in West Midlands or New South Wales during the period 1980-2002, were eligible for inclusion.

Data were obtained from the regional cancer registries for New South Wales (64,731 tumours amongst 64,705 women) and West Midlands (68,725 tumours registered amongst 68,396 women). Tumour records included information on age and extent of disease at diagnosis. In each region, patient records were linked to an ecologically defined deprivation category based upon the quintile of unemployment of their small area of residence. We used the unemployment rate as the primary measure of deprivation because it was both temporally and internationally comparable. Women
diagnosed between 1996 and 2002 were also allocated to a deprivation category based upon the income domain score of the Indices of Multiple Deprivation (IMD) 2004 in England and the index of disadvantage of the Socio-Economic Indexes for Areas (SEIFA) 2001 in Australia. This enabled the international and temporal results using the unemployment rate to be contrasted with those obtained when a local, validated definition of income deprivation was applied. We used the smallest geographic areas available for each census to maximise the accuracy of the ecological data. We used data from the 1991 and 2001 census in each country. We did not use data from the 1981 census because the very small-area data were not obtainable for Australia, nor did we use data from either the 1986 or 1996 Australian census because there was no corresponding survey conducted in England. Unemployment rates in New South Wales from the 1991 census were calculated for each Collection District (CD, mean population size 544, s.d. 248) and in the West Midlands for each Enumeration District (ED, mean population size 469, s.d. 153). These were linked to records for women diagnosed 1980-1995. Unemployment rates in New South Wales from the 2001 census were calculated for each CD (mean population size 539, s.d. 254) and in West Midlands for each Lower-Level Super-Output Area (LL-SOA, mean population size 1,513, s.d. 194). These were linked to women diagnosed 1996-2002. Less than 1% of records in the West Midlands and 1.5% of records in New South Wales failed to match due to missing address data. These records were excluded from all deprivation-specific analyses.

Data on primary invasive breast cancers for England and Australia were originally collected as part of the CONCORD study. Information on age at diagnosis was available for 143,645 tumours diagnosed amongst 143,526 women in England and 38,819 tumours amongst 38,811 women in Australia.

Estimated mid-year population counts by region, age and sex were obtained from the Office for National Statistics for England and Wales and the Australian Bureau of Statistics for each year 1980-2002. These counts are widely used for the purposes of research and public-sector planning in both
countries. Counts for each small area in West Midlands and New South Wales in 1991 and 2001 were also obtained. These small-area populations were summed across deprivation groups to produce a set of age-, sex- and deprivation-specific populations for each region in 1991 and 2001. The proportions in each age-, sex- and deprivation- group for these census years were then applied to the region-specific population estimates for the non-census years, in order to produce a continuous annual series of deprivation- and region-specific counts by age and sex. For the years 1980-1995, deprivation categories were defined by quintiles of unemployment from the 1991 census, and for the years 1996-2002, according to quintiles of unemployment in 2001.

Three-year rolling incidence rates per 100,000 woman-years were obtained by dividing the mean number of breast tumours in the index year and the years immediately before and after that year, by the mid-year population. At the start and end of the period, a two-year average was used (1980-1981 and 2001-2002, respectively). Incidence rates were directly age-standardised using the combined numbers of women diagnosed with breast cancer in the West Midlands and New South Wales during the period 2000-2002 as the standard. This ensured that the age-standardised rates were as close as possible to their non-standardised equivalents in the last period of diagnosis.

Estimates of the incidence rate ratio (IRR) were obtained using Poisson regression modelling. The IRR was used to describe the differences in incidence between West Midlands (or England) and New South Wales (or Australia), the mean annual increase in incidence, and the ‘deprivation gap’ between the highest and lowest unemployment categories. When estimating this socio-economic differential, both linear and quadratic models were examined. The fit of the two models was evaluated using the Pearson chi-squared statistic. The likelihood ratio test was used to compare nested models.

Results
There was a continuous increase in breast cancer incidence in both West Midlands and New South Wales during the period 1980-2002. Incidence in West Midlands was higher than in New South Wales
except for 1994-1997 although the increase in incidence was steeper in New South Wales (Figure 1). The difference in incidence between West Midlands and New South Wales mirrored the incidence for Australia and England as a whole during the period 1990-1994. Mammographic screening was introduced in both West Midlands and New South Wales during this period. In both populations, the introduction of screening was associated with an increase in incidence. Following the ‘prevalent wave’ there was no significant difference between the incidence rates in New South Wales and West Midlands for the years 2001 and 2002 (p-value 0.09). During these years both screening programmes had reached ‘steady-state’, that is, the prevalent round of screening had been completed for all women in both West Midlands and New South Wales. Despite this similarity in incidence for the most recent years, notable differences in the incidence patterns were evident according to age, deprivation status and extent of disease.

Age
In New South Wales, incidence rose rapidly with age up to 50 years (around the menopause) after which the rates tended to plateau, particularly after 1992 (Figure 2). In contrast, the incidence of breast cancer in the West Midlands continued to increase with age, each group displaying a significantly higher rate than the previous group between 70-74 and 85-99 years in all six calendar periods examined (p-values all <0.001). These patterns were reflected nationally in both countries (data not shown). Trends in the incidence rate amongst women 40-79 years at diagnosis reflected the different ways in which screening mammography was introduced in each region (Figure 3). Large differences in the incidence rate between New South Wales and West Midlands were observed for women aged 80 years or more at diagnosis. These increased over time, despite the fact that the overall incidence rate in the two regions became more similar. In contrast, the incidence rates amongst women aged less than 50 years or 70-79 years at diagnosis were comparable.

Extent of disease at diagnosis
Breast cancers were diagnosed at an increasingly earlier stage in both New South Wales and West Midlands, although the proportion of earlier disease tended to be higher in New South Wales (Figure 4). An increase in the numbers of unstaged cancers was observed between 1992 and 1996 in New South Wales and between 1986 and 1991 in West Midlands. This pattern is likely to be due to the introduction of electronic notification in New South Wales during these years, and to the fact that not all available information about nodes and distant metastases that exists in patients’ notes has been entered into the database at the West Midlands Cancer Intelligence Unit for these years. The increase in the incidence of localised disease was greatest in West Midlands amongst women aged 50 – 64 years at diagnosis. In New South Wales the incidence of localised disease was greatest amongst women aged 50 – 79 years at diagnosis. In both areas, the incidence of localised disease was much less marked amongst women younger than 50 years or older than 80 years (data not shown). In West Midlands, but not in New South Wales, the decrease in the incidence of distant disease was most marked amongst the oldest women.

The numbers of unstaged cancers were much greater amongst elderly women in the West Midlands, during the period 1993-2002. After adjustment for the underlying increase in risk of disease with age, the incidence of tumours of unknown stage in the West Midlands amongst women aged 80-99 years was 12 times greater than women aged 40-49 years (adjusted IRR 11.5; 7.2-18.4). In New South Wales, the equivalent analysis revealed a four-fold increase (adjusted IRR 4.2; 2.7-6.6).

**Deprivation**

Incidence was higher amongst the most affluent women than the most deprived women in New South Wales throughout 1980-2002. In contrast, in West Midlands during the years 1980-1987, whilst the incidence in the most affluent women was similar to that in New South Wales, it was lower than the incidence in the most deprived women (Table 1). Later, during the years 1988-2002, this West Midlands pattern reversed, with a higher incidence amongst the most affluent women similar to that seen in New South Wales. During 1988-1995, the period which includes the initial roll out of
screening, the rolling incidence rate increased for women in all deprivation groups in West Midlands except the most deprived. The incidence rate for this group did not increase until 1996-2002, almost 10 years after the NHS Screening Programme was first introduced. In New South Wales, where diagnostic mammography was subsidised by the universal health insurance scheme Medicare from 1984, the incidence rate increased for women in all deprivation groups simultaneously (data not shown).

The difference between the most affluent and the most deprived groups was larger in New South Wales than in West Midlands both in 1988-1995 and 1996-2002 (p-value of interaction term 0.005 and <0.001 respectively). The socio-economic gradient was most evident for localised tumours in West Midlands. In contrast, in New South Wales, a gradient was evident for both localised and regional disease (Table 1, Figure 5). The incidence of distant disease was persistently higher amongst the more deprived women in West Midlands while no such socio-economic differences were observed in New South Wales. There was no consistent pattern for unstaged disease in either region.

The difference in incidence of the most affluent compared to the most deprived observed during the period 1996-2002 was slightly greater when defined by quintiles of the IMD income domain score or SEIFA disadvantage score in comparison to the unemployment rate (data not shown).

Discussion
During the period 1980-2002 incidence of breast cancer increased in both England and Australia, and became more similar over time. The population of women with breast cancer in West Midlands was older, and diagnosed at a later stage of disease than their counterparts in New South Wales. The socio-economic difference in the incidence rate between the most affluent and the most deprived was greater in New South Wales than in West Midlands. However, our data suggest that the more deprived women in West Midlands were diagnosed at a later stage of disease than the more deprived women in New South Wales.
Incidence was increasing in New South Wales before the state screening programme was rolled out to women aged 50-69 years (1988-1996). This is likely to be due to screening pilots in some areas of the state prior to the introduction of the universal screening programme, as well as the availability of diagnostic mammography in private clinics and some public hospitals in New South Wales. The frequency of these mammograms has been shown to have increased substantially before the state screening programme was universally available (but when its existence was widely publicised\textsuperscript{24}). This has previously been interpreted as diagnostic mammography amongst women without clinical symptoms.\textsuperscript{25} This would be consistent with our data which shows increasing incidence prior to the introduction of screening, even amongst women aged 40-49 years and 70-79 years at diagnosis who were not offered screening but could self-refer in New South Wales. Breast cancer incidence was increasing more slowly in West Midlands than in New South Wales prior to the introduction of the NHS Breast Screening Programme in 1988. It then rose more rapidly in the first prevalent screening round (1989-1993) to reach the same levels as those seen in New South Wales. These incidence changes occurred mainly in women aged 50-64 years old, implying that the NHS Breast Screening Programme was the main, if not the only, means for women in West Midlands to obtain mammography.

Increases in the incidence rate for breast cancer may also be related to increased use of hormone replacement therapy (HRT) during this period. HRT has been shown to increase a woman’s risk of developing breast cancer,\textsuperscript{14,15} and is most commonly prescribed to menopausal women. Use of HRT increased from the early 1990s in both the UK\textsuperscript{26} and in Australia.\textsuperscript{27,28} This may explain some of the accelerated increase in incidence we observed amongst these age groups after 1988.

The drop in incidence after age 65 and the continuing rise in incidence into old age in West Midlands are both distinctive patterns and contrast with the patterns observed in New South Wales. However, they are consistent with the most recently published data for these regions.\textsuperscript{19} The drop in incidence after age 65 highlights the differing nature of screening in West Midlands. It is possible that the much
higher incidence rates observed amongst the oldest women in England and West Midlands are at least in part due to the more frequent (biennial as opposed to triennial) and extended age range screening programme in New South Wales (50-69 with self referral reminders sent to women aged up to 74 compared with 50-64 in West Midlands). These differences could result in the detection in New South Wales of slow growing cancers through screening which would only become symptomatic in the very elderly, whereas in the West Midlands, where screening stops at 64, these cancers have more time to grow and are detected at a later stage of diagnosis when the women are older. However, higher incidence amongst the elderly was observed as early as 1980, so such an effect of the screening programme cannot fully explain higher incidence amongst the elderly during the years 1980-1988. One alternative explanation is that incident breast cancers amongst elderly women are missed more frequently by the New South Wales Central Cancer Registry. However, it is unlikely that this fully explains the large differences in incidence that we observed for this age group. It remains possible, therefore, that the underlying risk factors for breast cancer differed for elderly women between these two populations during this period. It is known, for example, that prior to 1980 fertility rates were higher and the age of first birth lower in Australia compared to England.29-31 It is also likely that because a large minority elderly of Australian women were born outside Australia (34% of those over 75 in the 200132) they would have been exposed to different levels dietary, reproductive and lifestyle risk factors for breast cancer in early and middle age compared to elderly women in England.

The much lower probability of having complete information on extent of disease recorded amongst elderly women in West Midlands is striking. Some of these are death certificate only registrations (DCOs), the proportion of which was higher in West Midlands (1.4% compared to 0.5% in New South Wales). Some are likely to be women whose cancer was initially made known to the registry via a death certificate, but for whom the date of diagnosis has subsequently been traced (death certificate initiated (DCI) cases). These cases are more likely to be older, and less likely to have accurate clinical information available than non-DCO or DCI cases. This pattern may also be a result of the fact that during the late 1980s and the early 1990s, it was more common to treat elderly women with
tamoxifen alone without surgery.\textsuperscript{33} These women would be more likely to be classified as unstaged since, in the absence of a surgical intervention, they have little or no information on their tumour recorded. It is also possible that this pattern represents less thorough diagnostic work-up of elderly women. It has been previously documented in the UK that older women are less likely to receive triple assessment, to have a steroid receptor test or axillary staging with at least four nodes examined.\textsuperscript{34,35} These patterns are not explained by differences in stage, size, histological type, or hormonal status of these women’s tumours\textsuperscript{35} but could in part be due to co-existing co-morbidity which means that surgical intervention is not possible.

Higher breast cancer incidence amongst the affluent is consistent with data from America, Canada and Finland.\textsuperscript{36} In New South Wales, incidence by socio-economic group has previously been examined for the period 1987-1991.\textsuperscript{37} The authors similarly report higher incidence amongst the affluent. Our data show that socio-economic differentials in incidence are greater in New South Wales than in West Midlands, but that this same socio-economic ‘gradient’ in incidence was associated with extent of disease more strongly in West Midlands than in New South Wales. Our data also suggest that the uptake of screening – or at least the impact of the availability of screening upon the incidence rate – was more constant across the socio-economic spectrum in New South Wales than in West Midlands. These patterns suggest first, that the relative differences in the underlying risk factors for breast cancer between social groups are greater in Australia than in England, but also, that the more deprived women in West Midlands may have been diagnosed relatively later than the more deprived women in New South Wales during this period. There are several possible sources of delay for breast cancer patients. These include the failure to attend an invitation to screening, the time between an abnormal routine mammographic screen and a diagnostic test to confirm the presence of cancer; the time between a woman becoming aware of symptoms of breast cancer and her seeking medical examination for these symptoms within primary care, and the time between primary care consultation and the point at which confirmatory diagnostic tests are carried out.\textsuperscript{38,39} Further research should
examine the relative contributions of these factors to differences in extent of disease at diagnosis between the more deprived and the more affluent women.

Incidence was higher amongst the more deprived women than the more affluent women diagnosed in the West Midlands prior to 1988, in contrast to New South Wales. The incidence rates for affluent women were, however, similar in the two regions. The pattern in West Midlands is remarkable because it is the reverse of socio-economic patterns observed in other populations. Although consistent with a previous socio-economic analysis of incidence for the West Midlands\textsuperscript{40}, this pattern is not easily explained. It is unlikely that breast cancer was under-reported amongst more affluent women during this early period since the overall incidence in West Midlands was similar to other regions of the UK\textsuperscript{16}. It is possible that underlying risk factors for breast cancer changed quickly for these women, specifically that affluent women born in the 1950s and 1960s experienced later menarche, delayed child-bearing, had fewer children and took HRT in comparison to their predecessors and less affluent contemporaries. All these changes would have increased the chances of the more affluent women having breast cancer from the late 1980s onwards. However, this pattern was not observed in New South Wales. A more likely explanation for this pattern may lie in the way in which deprivation status was obtained for the West Midlands. The accuracy of the deprivation measure for women diagnosed up to 1985 is almost certainly lower than that for women diagnosed 1986-2002. This is because there was no comparable measure of deprivation available in 1981. Consequently the unemployment rate derived for 1991 was applied to women diagnosed from 1980 onwards. Such misclassification would make the incidence rates similar in each deprivation group, rather than produce the reverse of the expected trend. It is also known that the distribution of deprivation in England changed substantially during the late 1980s and 1990s.\textsuperscript{41} In particular, gentrification of inner-city areas of the West Midlands may have led to a reversal in the socio-economic profile of particular communities over this period. This may have further impacted the accuracy of our results for the early 1980s.
The geographical basis for census data in England changed from census Enumeration Districts (EDs) in 1991 to Lower-Level Super-Output Areas (LL-SOAs) in 2001. This required a change from 1996 onward in the small areas we used to assign a woman's address at diagnosis to a deprivation category. The accuracy of the deprivation measure used in the West Midlands for 1996-2002 is unlikely to have been affected, however, because although LL-SOAs are larger than the older EDs, they were designed to be more socially homogenous, and we have previously shown that they do in fact have very similar properties to EDs for socio-economic differences in cancer.42

We used a temporally and internationally comparable measure of deprivation: the unemployment rate as our primary measure of deprivation. This enabled a direct comparison of socio-economic patterns as well as an assessment of how they changed over time. The unemployment rate in the area of residence is unlikely to be the most discriminatory measure of deprivation for elderly women. However, we observed similar patterns for women diagnosed 1996-2002 when using quintiles of two highly-validated and locally-defined deprivation measures; for West Midlands, the IMD income domain score 2004,20 and for New South Wales the index of disadvantage of the Socio-Economic Indexes For Areas (SEIFA) 2001.43 This suggests that our results are robust to the measure of deprivation applied.

We have used a long, continuous data series including measures of the extent of disease and of deprivation status, in order to examine breast cancer incidence trends in the West Midlands, England and New South Wales, Australia during the period 1980-2002. Our findings show that there are differences in breast cancer incidence between the West Midlands and New South Wales, which are also reflected at a national level, but that the incidence in each region has become increasingly similar over time. However, there remain different incidence patterns by age in West Midlands in comparison to New South Wales, according to extent of disease at diagnosis and by deprivation category. It is unclear why the incidence amongst elderly women in West Midlands is so much higher than in New South Wales. This warrants further investigation. In particular, the underlying reasons for the much
higher proportion of women with unknown stage amongst the elderly in West Midlands should be examined in detail since differences in diagnostic work-up are likely to have implications for the treatment and subsequent survival of elderly women with breast cancer in England. These data also suggest that the more deprived women in the West Midlands are diagnosed with breast cancer relatively later than the more deprived women in New South Wales. Further research should confirm whether such differences are due to delays in diagnosis, be they patient or health service-orientated.

Text box:

**Screening implementation**

*West Midlands, England*

England’s National Health Service Breast Screening Programme began in 1988, inviting women aged 50 - 64 years every three years for mammography in every region of the country. The first screening centres opened in the West Midlands on 1 March 1988 screening women aged 50-64 years. Full geographical coverage of the region was achieved in mid-1991.

*New South Wales, Australia*

Australia’s centrally funded mammographic screening began in 1991, but the timing of its implementation varied by state. In New South Wales biennial mammography screening of women aged 50-69 was introduced progressively from 1988. State-wide coverage was achieved on 1 January 1996. Diagnostic mammography was also available in private clinics and some public hospitals in New South Wales during this period.
Ethics approval

Local ethics approval was obtained from the London School of Hygiene and Tropical Medicine ethics committee (7 December 2004, Application number 2071). Permission for use of the English cancer registry data for breast cancers diagnosed 1990-1994 was given by Dr Mike Quinn, Director, National Cancer Intelligence Centre, ONS, London (CONCORD Working Group member for England and Wales). Permission for use of the Australian cancer registry data for breast cancers diagnosed 1990-1994 given by Dr Paul Jelfs, Chair, The Australasian Association of Cancer Registries, (CONCORD Working Group member for Australia). Permission for use of the West Midlands cancer registry data for breast cancers diagnosed 1980-2002 was obtained from West Midlands Cancer Intelligence Unit. Ethical approval for use of the New South Wales cancer registry data for breast cancers diagnosed 1980-2002 was obtained from the Cancer Institute New South Wales Ethics Committee (5 January 2005 Reference number 2004/05/084). All data analysed were fully anonymised.

Funding

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References


Table 1: Incidence rate ratios (IRR) between the most affluent (reference) and most deprived groups, by period of diagnosis and extent of disease: women diagnosed with breast cancer in New South Wales and West Midlands 1980-2002

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* statistically significant at 5% level

<sup>a</sup> Incidence Rate Ratio (IRR): derived from a Poisson regression comparing the age-standardised rates of the most deprived with those of the most affluent (reference).

<sup>b</sup> Absolute difference in fitted age-standardised incidence rates per 100,000 woman-years between the most deprived and most affluent groups. Negative values mean that deprived women have lower incidence than affluent women.

<sup>c</sup> P-value derived from a Pearson chi-squared goodness-of-fit test of the whole model. Values smaller than 0.05 indicate a lack of adequate fit to the data.
Figure 1: Age-standardised incidence rates for primary invasive breast cancer in New South Wales and Australia in comparison with the West Midlands and England: women diagnosed 1980-2002

No centrally organised population-based screening

Screening offered universally in West Midlands and introduced gradually in New South Wales

Screening offered universally in New South Wales
Figure 2: Age-specific incidence of invasive breast cancer in New South Wales and the West Midlands, with an indication of screened age ranges by period of diagnosis: women diagnosed 1980-2002.
Figure 3 Three-year rolling average incidence rates for primary invasive breast cancer by age group at diagnosis: New South Wales (grey, solid) and Australia (grey, dashed) in comparison with the West Midlands (black, solid) and England (black, dashed), women diagnosed 1980-2002.
Figure 4: Age-standardised incidence of primary invasive breast cancer by extent of disease: New South Wales and West Midlands, women diagnosed 1980-2002
Figure 5: Age-standardised incidence of primary invasive breast cancer by extent of disease and deprivation category: New South Wales and West Midlands, women diagnosed 1980-2002