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Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study

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Background: We investigate whether differences in breast cancer survival in six high-income countries can be explained by differences in stage at diagnosis using routine data from population-based cancer registries.

Methods: We analysed the data on 257 362 women diagnosed with breast cancer during 2000–7 and registered in 13 population-based cancer registries in Australia, Canada, Denmark, Norway, Sweden and the UK. Flexible parametric hazard models were used to estimate net survival and the excess hazard of dying from breast cancer up to 3 years after diagnosis.

Results: Age-standardised 3-year net survival was 87–89% in the UK and Denmark, and 91–94% in the other four countries. Stage at diagnosis was relatively advanced in Denmark: only 30% of women had Tumour, Nodes, Metastasis (TNM) stage I disease, compared with 42–45% elsewhere. Women in the UK had low survival for TNM stage III–IV disease compared with other countries.

Conclusion: International differences in breast cancer survival are partly explained by differences in stage at diagnosis, and partly by differences in stage-specific survival. Low overall survival arises if the stage distribution is adverse (e.g. Denmark) but stage-specific survival is normal; or if the stage distribution is typical but stage-specific survival is low (e.g. UK). International differences in staging diagnostics and stage-specific cancer therapies should be investigated.

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²⁰See appendix.

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There are large international differences in survival from breast cancer, both between European countries (Berrino *et al*, 2007) and worldwide (Coleman *et al*, 2008; Sankaranarayanan *et al*, 2010). The International Cancer Benchmarking Partnership (ICBP) analysed population-based data for women diagnosed with breast cancer during 1995–2007 in six countries with comparable wealth, access to universal health care and high-quality cancer registration. Survival was highest in Sweden, Australia and Canada; intermediate in Norway; lower in Denmark; and lowest in the UK. Inequalities persisted in 2005–7, when 1-year survival was 4% lower in the UK than in Sweden (Coleman *et al*, 2011).

These survival differences may be due to variations in stage at diagnosis arising because of differences in screening, cancer awareness or referral pathways. Alternatively, international differences may exist in stage-specific survival, indicating differences in treatment, co-morbidity or staging accuracy. Understanding the balance of these explanations is important to cancer control strategies. Routinely collected data on stage are difficult to compare, because of variations in clinical classification and coding, and in how stage is recorded and processed by cancer registries. Internationally recognised staging systems such as the Tumour, Nodes, Metastasis (TNM) classification for malignant tumours (Sobin *et al*, 2009) are not universally adopted, and locally defined systems remain in use (Walters *et al*, 2013). Furthermore, cancer registries do not routinely collect full information on the source of stage data, such as the TNM version used, the timeframe after diagnosis within which stage was recorded, whether it was defined clinically or pathologically, and whether tumour size was recorded before or after neo-adjuvant therapy.

Population-based comparisons of breast cancer survival by stage have generally been limited to pair-wise contrasts between countries with similar registration processes (Christensen *et al*, 2004; Jensen *et al*, 2004; Woods *et al*, 2009), or 'high-resolution' studies that abstract stage from the medical records of large, representative samples of patients from cancer registries (Sant *et al*, 2003; Allemani *et al*, 2013). International high-resolution studies are costly and time-consuming, and dependent on the accessibility of medical records. Survival comparisons that use routinely collected data on stage for all patients in each jurisdiction would clearly be desirable, and may be possible if extensive quality control is conducted (Walters *et al*, 2013). Here, we analyse survival with routinely collected data for all women registered with breast cancer in regional or national registries in these six countries, thereby enabling the largest international comparison of survival by stage at diagnosis.

We show how the distribution of stage at diagnosis varies in these six countries. Age-specific and age-standardised net survival and the excess hazard of dying up to 3 years are presented by stage at diagnosis.

MATERIALS AND METHODS

Data. The ICBP obtained data from population-based cancer registries in Australia, Canada, Denmark, Norway, Sweden and the UK on 926 179 women diagnosed with breast cancer during 1995–2007 and followed up to 31 December 2007. National data were available from Denmark and Norway. Data from Australia and Canada were from state registries in New South Wales and Victoria (Australia) and Alberta, British Columbia, Manitoba and Ontario (Canada), representing 59.7% (11.4 of 19.2 million) and 64.9% (19.9 of 31.0 million) of the respective populations. For the UK, data were obtained from England, Northern Ireland and Wales, but not from Scotland (91.7% of the UK population; 54 of 59 million). The Swedish data were from the Uppsala-Örebro and Stockholm-Gotland health regions (42.8% of the Swedish

population; 3.8 of 8.9 million), and were clinical data covering 97% of patients in the regional cancer registry.

We restricted analysis to women diagnosed with a primary, invasive, malignant neoplasm of the breast (ICD-10 codes: C50.0–C50.9). Tumours that were benign, *in situ* or of uncertain behaviour were excluded: of the remaining 860 971 women, a further 3.2% (27 621) were excluded because their vital status was unknown, key dates were invalid or their cancer was registered only from a death certificate or at autopsy. Ductal carcinoma *in situ* tumours were excluded because they are not systematically or consistently recorded by cancer registries. These are standard exclusion criteria designed to improve internal validity and consistency in population-based cancer survival studies. Full details of quality control procedures have been described (Coleman *et al*, 2011).

We restricted analysis of survival by stage to women diagnosed during 2000–7 (535 537 women) when stage data were more complete (Walters *et al*, 2013). We further restricted analysis to those registries where over half of all patients had a valid stage, and where there was no sudden change in the availability of stage over time. This led to the exclusion of Victoria (Australia), and Alberta and Ontario (Canada). Only 49% of patients in England had a valid stage, but we could include five of the eight regional registries with stage data for 50% or more of registered patients. The Danish data were restricted to 2004–7, because earlier data were not coded to TNM and were known to be unreliable for international comparisons. The final sample consisted of 257 362 women.

To define 'valid stage', we consolidated the available data on stage, which had been coded to a variety of classification systems. For most countries, we could use the raw data to construct a TNM stage. In Australia, stage was categorised as 'localised, regional, distant'. The Australian system is equivalent to the US Surveillance and Epidemiology End Results Summary Stage 2000 (SEER SS2000) (Young *et al*, 2001), which is more widely known and better documented. In order to include Australia in the comparisons, we mapped the TNM system used in all the other countries to SEER SS2000. This mapping relied on the availability of the component T, N and M codes, whereas in England, only TNM stage I–IV data were available. We therefore present two sets of analyses, one based on the TNM classification, which is more relevant for clinicians but does not include Australia, and another based on SEER SS2000, which enables comparisons with Australia but excludes England (Walters *et al*, 2013).

Ethical approval. The study protocol was approved by the South East Research Ethics Committee of the National Health Service on 21 April 2010 (10/H1102/19). The study protocol and the Cancer Research UK Cancer Survival Group's system-level security policy at LSHTM were approved by the Ethics and Confidentiality Committee of the National Information Governance Board on 21 April 2010 (extension of PIAG 1-05(c)2007). Registries outside the UK obtained ethical approvals in their jurisdictions (details available on request).

Net survival and excess mortality. Net survival is the recommended method for estimating cancer survival using population-based data (Pohar-Perme *et al*, 2012), because cause of death data may be incomplete or unavailable, and death certification may not accurately record cancer as the underlying cause of death in comparable fashion between countries and over time (Laurenti *et al*, 2000). Net survival is the survival of cancer patients, after controlling for other causes of death (background mortality). Background mortality is estimated by fitting life tables specific to calendar year, region of residence, sex and single year of age (Coleman *et al*, 2011).

Net survival was modelled on the log cumulative excess hazard scale in a flexible parametric framework using the *stpm2* (Lambert and Royston, 2009) command in Stata version 12 (StataCorp LP,

College Station, TX, USA). The availability of follow-up data beyond the last boundary for which we want to estimate survival is important for the stability of the model, so we present survival estimates up to 3 years, even though we had longer follow-up for some patients (Remontet *et al*, 2007). We also present the excess hazard, the mortality counterpart to net survival, which is the instantaneous rate of dying from breast cancer, over and above all other causes of death, and which shows how breast cancer mortality changes with time after diagnosis.

We ran stratified, stage-specific models, treating patients with missing stage as a distinct category. Restricted cubic splines were used to allow for non-linearity in the effect of age and time since diagnosis on the excess hazard (Durrleman and Simon, 1989). We allowed for non-proportional effects of country and age on the hazard of dying, by introducing interactions with the splines of time. We used a range of tests to ascertain goodness of fit and to select our final model for each stage of diagnosis, including the Akaike Information Criterion, log-likelihood ratio tests, and examination of the Martingale residuals. Where possible, we compared the results of our selected model with those from a slightly more flexible model (e.g. by introducing an interaction term or an extra degree of freedom in the baseline hazard). Our selected models were robust to this increased flexibility.

Imputation of stage data. To determine the likely stage distribution among women with missing data on stage in each registry, we conducted multiple imputation using chained equations with the *ice* command in Stata 12, specifying an ordered logistic model (Nur *et al*, 2010; White *et al*, 2011). We imputed TNM stage I–IV and SEER SS2000. We first used logistic regression models to determine which variables significantly predicted the pattern of missingness or were associated with stage. These variables were included in the imputation models. In all models, we included vital status, the non-linear effect of the log cumulative excess hazard and the non-linear effect of age at diagnosis. Where necessary, we also included subsite, year of diagnosis and interactions between the log cumulative excess hazard and age, year and subsite. We ran each imputation model 15 times and combined the results under Rubin's rules (White *et al*, 2011).

We repeated the modelling strategy for stage-specific survival on each of the 15 imputed data sets. The range of estimates generated from these iterations was compared with the survival estimate based on the observed stage data.

All-ages estimates were age-standardised using stage-specific weights derived from the age distribution of patients in all jurisdictions combined, in the age categories 15–44, 45–54, 55–64, 65–74, 75–84 and 85–99 years (see web appendix 1).

RESULTS

Distribution of age and stage. The mean age at diagnosis ranged from 61 years in Australia to 63 years in the UK, Denmark and Sweden (Table 1). The proportion of women with a valid stage ranged from 74.7% in the UK to 92.1% in Australia. Women aged 70–99 years were more likely than younger women to be missing stage in all countries, except Sweden (Figure 1).

Among women with TNM stage, the proportion with stage I disease was 30.1% in Denmark, compared with 42–45% in other countries. The proportion with stage III or IV disease ranged from 8% in Sweden to 22% in Denmark (Table 1). For SEER SS2000 stage, the proportion of women with 'localised' disease ranged from 45.7% in Denmark to 69.9% in Sweden, and for 'distant' disease from 1.7% in the UK (Northern Ireland and Wales only) to 6.9% in Denmark.

Imputation of missing data only had a slight impact on these stage distributions. The proportion with TNM stage III–IV was

0.1–3.8% higher after imputation, and the effect was similarly small for SEER SS2000.

Both TNM and SEER SS2000 stage distributions were generally more favourable for women aged 50–69 (the 'screened age group'). Older women were more likely to have metastatic disease than younger women (Figure 1).

Net survival. In the analyses using TNM, age-standardised net survival (all stages combined) at 1 year ranged from 94.3% in the UK to 98.4% in Sweden (Table 2) and at 3 years from 87.4% in the UK to 94.1% in Sweden (Table 3). Survival in Denmark and the UK was significantly lower than in the other countries, at both 1 and 3 years, and it was highest in Sweden.

For women with TNM stage I–II disease, 1-year age-standardised net survival was close to 100% in all countries. The international range was wider for women with more advanced disease. One-year survival for stage IV disease varied from 53.0% in the UK to 66.9% in Sweden, a range of 13.9%. The range was also wide for women with missing data, for whom 1-year survival varied from 87.3% in the UK to 96.8% in Sweden. Women missing TNM stage in Denmark and the UK had 3-year survival that was 8.6–16.1% lower than in other countries (Table 3).

International differences in overall survival (all stages combined) were widest for women aged 70–99 years, at both 1 and 3 years. For example, 3-year survival was 4.1% higher in Sweden than in the UK for women aged 50–69 years, but 12.3% higher for women aged 70–99 years. The wider international differences for older women were also evident for stage-specific survival.

The international pattern of survival differs between the TNM and SEER SS2000 analyses because patients in England were only included in the TNM analyses (51% of all TNM-staged patients, 114 557 out of 225 033), and Australian patients were only included in the SEER SS2000 analyses (23% of all SEER SS2000 patients, 32 329 out of 142 805).

Survival for women with SEER SS2000 'localised' and 'regional' disease was high in all countries (over 97% at 1 year). Among women with 'distant' disease, 1-year survival varied from 62.4% in Norway to 70.1% in Australia. The international range for women with distant disease was wider at 3 years, when net survival was significantly lower in Norway than elsewhere, intermediate in Canada, Denmark and Sweden, and 9.1–22.5% higher in the UK (Northern Ireland and Wales) and Australia than in the other four countries. One- and three-year net survival for unstaged women was lowest in Denmark and the UK.

In all six countries, women aged 70–99 years generally had lower overall and stage-specific survival at both 1 and 3 years than women aged 50–69 years. This difference was widest in the UK. Women aged 70–99 years with TNM stage IV disease in the UK had much lower 1-year survival than women aged 50–69 years (42.2% vs 60.0%); the difference in Sweden was smaller (58.5% vs 69.1%).

Excess hazards. The stage-specific excess hazard of dying from breast cancer for women with TNM stage I–III disease generally rose with time since diagnosis (Figure 2). However, for patients with distant disease, excess mortality declined slightly with time, probably because the most frail patients, and those with the most extensive disease, died soon after diagnosis. Among women with TNM stage I disease, those diagnosed in Denmark had particularly high excess mortality up to 1 year after diagnosis. Women in the UK had relatively high excess mortality in the first year for stages II–IV, and at all stages at 3 years.

The excess hazard rose with time since diagnosis for women with SEER SS2000 'localised' and 'regional' cancers in all countries, and fell for those with 'distant' disease. International differences in the excess hazard were most notable soon after diagnosis, particularly among women with 'regional' disease.

Table 1. Number and mean age at diagnosis of breast cancer patients diagnosed in 2000–2007, country and stage at diagnosis (TNM and SEER Summary Stage 2000), before and after multiple imputation

	TNM stage					SEER Summary Stage 2000				
	Stage	Number ^a	Mean age	Observed (%)	After imputation (%)	Stage	Number ^a	Mean age	Observed (%)	After imputation (%)
Australia ^b						All patients	32 329	60.7		
						Missing stage	2569	67.7	7.9	
						Localised	16 739	61.0	56.2	55.9
						Regional	11 299	58.2	38.0	38.1
						Distant	1 722	63.4	5.8	6.0
Canada ^c	All patients	25 652	62.3			All patients	25 652	62.3		
	Missing stage	5341	67.8	20.8		Missing stage	5399	67.8	21.0	
	I	8912	61.6	43.9	41.0	Localised	12 242	61.8	60.4	57.0
	II	7924	60.2	39.0	38.1	Regional	6952	58.8	34.3	35.6
	III	2415	58.9	11.9	13.3	Distant	1059	62.9	5.2	7.4
	IV	1060	62.9	5.2	7.6					
Denmark ^d	All patients	16 190	63.3			All patients	16 190	63.3		
	Missing stage	1835	73.8	11.3		Missing stage	1835	73.8	11.3	
	I	4322	61.1	30.1	29.3	Localised	6557	62.2	45.7	44.8
	II	6849	61.9	47.7	47.2	Regional	6810	60.8	47.4	47.7
	III	2196	61.1	15.3	15.8	Distant	988	67.6	6.9	7.5
	IV	988	67.6	6.9	7.7					
Norway	All patients	21 964	62.4			All patients	21 964	62.4		
	Missing stage	2873	71.2	13.1		Missing stage	2862	71.2	13.0	
	I	8495	60.8	44.5	43.4	Localised	10 638	61.3	55.7	54.7
	II	8925	60.3	46.7	47.1	Regional	7465	60.1	39.1	39.7
	III	673	66.3	3.5	3.8	Distant	999	66.7	5.2	5.7
	IV	998	66.7	5.2	5.7					
Sweden ^e	All patients	20 659	62.7			All patients	20 659	62.7		
	Missing stage	3484	65.1	16.9		Missing stage	3484	65.1	16.9	
	I	7758	61.1	45.2	45.2	Localised	12 003	62.0	69.9	69.9
	II	8020	62.7	46.7	46.5	Regional	4678	62.3	27.2	27.2
	III	903	64.7	5.3	5.3	Distant	494	66.6	2.9	2.9
	IV	494	66.6	2.9	3.0					
UK ^f	All patients	140 568	63.0			All patients	26 011	63.3		
	Missing stage	35 517	67.7	25.3		Missing stage	9163	68.6	35.2	
	I	44 135	60.6	42.0	40.0	Localised	10 176	60.8	60.4	56.8
	II	47 738	61.2	45.4	45.4	Regional	6378	59.9	37.9	39.9
	III	8663	63.3	8.2	9.2	Distant	294	66.0	1.7	3.3
	IV	4515	67.6	4.3	5.4					

Abbreviation: TNM = Tumour, Nodes, Metastasis staging system.

^aNumber of patients before imputation.^bAustralia: New South Wales.^cCanada: British Columbia and Manitoba.^dIn Denmark we analysed women diagnosed during 2004–7.^eSweden: Uppsala-Örebro and Stockholm-Gotland health regions.^fUnited Kingdom (TNM analysis): Northern Ireland, Wales and the Northern and Yorkshire Cancer Registry and Information Service, Eastern Cancer Registration and Information Centre, Oxford Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit in England; United Kingdom (SEER analysis): Northern Ireland and Wales.

Effect of imputing stage on net survival. Imputation of missing data on stage had little impact on survival for women with early-stage breast cancer. For those with TNM stage III–IV, survival was generally lower when imputed data were included. This was especially true in the UK (five English registries, Northern Ireland, Wales), which had the lowest stage-specific survival for all except TNM stage I disease. For women with TNM stage IV disease, 1-year survival in the UK ranged from 50.3–51.2% in the 15 imputed data sets, whereas the range was 59.4–69.1% in the other five countries (Figure 3). In the analyses including imputed SEER SS2000 data, 1-year survival for women with ‘distant’ disease in the UK (Northern Ireland, Wales) was 47.0–55.9%, compared with 61.8–70.5% elsewhere.

Women in the UK with SEER SS2000 ‘distant’ disease had comparatively high 3-year survival (54.8%), but this was not evident after inclusion of imputed stage data (35.6–43.0%) (see Supplementary additional file 2).

DISCUSSION

Age-standardised net survival for women with breast cancer varied from 94.3% in the UK to 98.4% in Sweden 1 year after diagnosis, and from 87.4% (UK) to 94.1% (Sweden) at 3 years. International differences were widest for women who were older, or with more advanced disease, or with missing stage at diagnosis. The

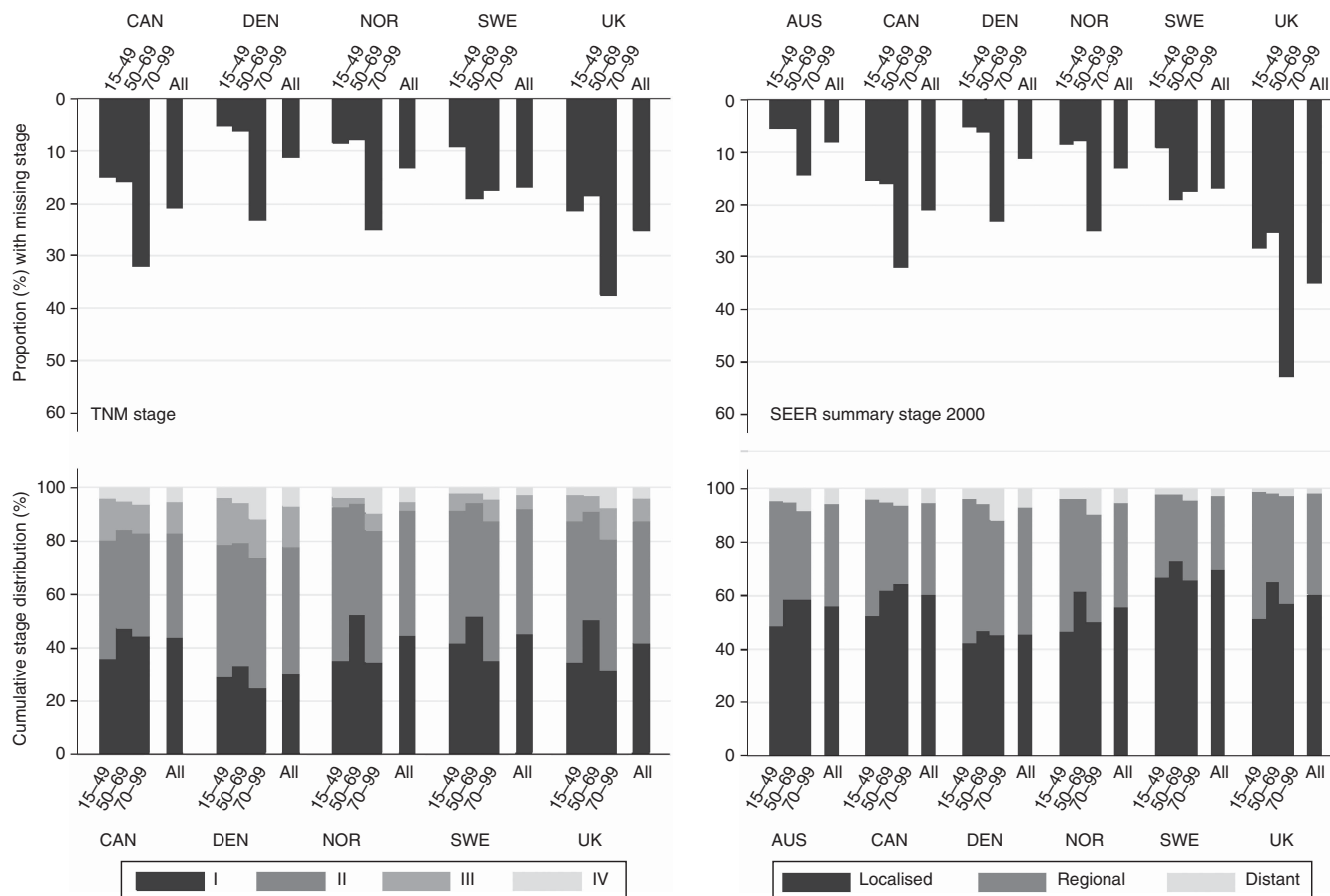


Figure 1. Proportions of breast cancer patients with missing stage (upper figure) and cumulative stage distribution among staged patients (lower figure). Results presented by age at diagnosis and country: TNM (left) and SEER Summary Stage 2000 (right). Notes: Denmark and Norway: national data; Australia: New South Wales; Canada: British Columbia and Manitoba; Sweden: Uppsala-Örebro and Stockholm-Gotland health regions; UK (TNM analysis): Northern Ireland, Wales and the Northern and Yorkshire Cancer Registry and Information Service, Eastern Cancer Registration and Information Centre, Oxford Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit in England; UK (SEER SS2000 analysis): Northern Ireland and Wales. In Denmark, we analysed women diagnosed during 2004–7.

distribution of stage at diagnosis was least favourable in Denmark, where survival was relatively low, but stage-specific survival was average. In contrast, the stage distribution in the UK was similar to that in countries with higher overall survival, but survival was lower within each category of stage. Differences in stage at diagnosis explain some of the international variation in survival, but other factors, such as treatment, co-morbidity and staging procedures, must also be important (Coleman, 1999).

We analysed routinely collected data from population-based cancer registries, handled under a single protocol, to produce a rigorously comparable, up-to-date, international study of breast cancer survival by stage at diagnosis for over 250 000 women. We have described a new method to harmonise the different clinical staging systems, and the problems of coding and classification that remain (Walters *et al*, 2013). Such problems include the high proportion of patients for whom data on stage are not available, and the lack of consistency in how stage data are recorded and processed by cancer registries. For the International Association of Cancer Registries (IACR), stage at diagnosis is a 'recommended' (not 'essential') variable, and IACR guidance on recording stage does not currently ensure standardisation of practice (Jensen *et al*, 1991; Parkin, 2006).

Nonetheless, by consolidating the available stage data, we have produced a robust stage variable for a high proportion of patients. The stage distributions are generally consistent with previous national and age-specific estimates (Sant *et al*, 2003; Allemani *et al*,

2010; Wishart *et al*, 2010), and they changed very little when stage was imputed where it was missing. The patterns of survival by stage, age and time since diagnosis are internally and clinically coherent.

Stage-specific survival was lower after imputation of missing stage, particularly for late-stage disease, and especially in the UK regions, where over 25% of patients had missing data on stage. Older women and those with poor prognosis were particularly likely to be in this category. The lack of change in the stage distribution after imputation, yet lower stage-specific survival, is at face value confusing. It arises because women with missing stage data were on average much older than women with known stage, and older patients generally have lower net survival, even within each stage category. Women with missing stage data may also have more co-morbidity or other adverse prognostic factors than women with known stage, contributing to lower survival within each stage. This was particularly true in the UK and Denmark, whereas in Norway and Sweden stage appeared to be missing more completely at random, the prognosis for women with missing stage being closer to those with known stage, leading to smaller changes in stage-specific survival following imputation (White *et al*, 2011). A richer data set, with full data on treatment and co-morbidity, might have enabled more precise imputations of stage, because the main assumption behind imputation is that stage can be predicted from other variables in the data set. Nonetheless, even when the number of covariables is limited, multiple imputation remains the least biased approach for handling missing data (Nur *et al*, 2010).

Table 2. All-ages, age-specific and age-standardised 1-year net survival (%) with 95% CI, by stage at diagnosis and country for women diagnosed with breast cancer during 2000–2007

	Australia ^a		Canada ^b		Denmark ^c		Norway		Sweden ^d		UK ^e						
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI					
TNM stage																	
All patients																	
All ages			96.9	96.6	97.1	95.6	95.3	96.0	96.5	96.2	96.8	98.4	98.2	98.7	94.2	94.1	94.3
Age-standardised			96.8	96.6	97.0	95.6	95.4	95.9	96.5	96.3	96.6	98.4	98.2	98.5	94.3	94.2	94.4
15–49			98.5	98.3	98.8	98.6	98.8	98.8	98.6	98.5	98.8	99.3	99.2	99.5	98.0	97.8	98.1
50–69			97.9	97.8	98.1	97.2	96.9	97.5	98.1	98.0	98.3	99.0	98.9	99.2	96.9	96.8	97.0
70–99			94.2	93.6	94.8	91.4	90.5	92.3	92.2	91.5	93.0	96.9	96.3	97.4	87.9	87.6	88.2
Stage I																	
All ages			100.0	100.0	100.0	100.0	99.9	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Age-standardised			100.0	100.0	100.0	100.0	99.9	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
15–49			100.0	99.9	100.0	99.9	100.0	100.0	100.0	99.9	100.0	100.0	100.0	100.0	100.0	99.9	100.0
50–69			100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
70–99			100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Stage II																	
All ages			99.7	NA	NA	99.7	99.6	99.9	99.1	98.9	99.3	99.4	99.3	99.6	99.2	99.1	99.3
Age-standardised			99.7	99.7	99.8	99.7	99.6	99.8	99.1	99.0	99.2	99.4	99.3	99.5	99.2	99.2	99.3
15–49			99.7	99.6	99.8	99.7	99.6	99.9	99.2	99.0	99.4	99.5	99.4	99.7	99.2	99.1	99.3
50–69			99.7	99.6	99.8	99.8	99.7	99.9	99.3	99.1	99.4	99.5	99.3	99.6	99.3	99.2	99.4
70–99			99.8	99.7	99.9	99.6	99.3	99.9	98.6	98.2	99.0	99.3	99.0	99.5	99.1	99.0	99.3
Stage III																	
All ages			96.5	95.8	97.3	96.6	95.7	97.5	94.0	92.2	95.8	94.1	92.4	95.7	90.6	90.0	91.2
Age-standardised			96.0	95.5	96.4	96.2	95.7	96.6	95.0	94.3	95.7	94.7	94.0	95.4	90.9	90.5	91.4
15–49			98.0	97.5	98.5	98.1	97.6	98.7	97.5	96.7	98.4	97.4	96.5	98.2	95.5	94.8	96.2
50–69			97.4	96.8	98.0	97.4	96.7	98.1	96.7	95.6	97.7	96.6	95.6	97.6	93.9	93.3	94.5
70–99			92.9	91.3	94.6	93.6	91.9	95.3	90.6	87.8	93.4	90.3	87.6	93.1	84.2	82.9	85.4
Stage IV																	
All ages			69.0	66.4	71.6	63.8	60.8	66.8	61.6	58.7	64.4	66.9	62.9	70.8	52.3	50.9	53.7
Age-standardised			66.7	64.8	68.6	64.2	62.2	66.2	61.7	59.8	63.6	66.9	64.3	69.5	53.0	52.0	54.0
15–49			82.7	79.7	85.7	82.2	77.5	86.9	71.4	66.9	75.9	85.7	81.4	83.0	68.3	65.5	71.1
50–69			70.4	67.3	73.5	69.9	66.4	73.5	68.4	65.1	71.8	69.1	64.3	74.0	60.0	58.2	61.9
70–99			59.1	54.7	63.6	53.5	49.2	57.9	52.5	48.4	56.6	58.5	52.7	64.4	42.2	40.3	44.1
Missing stage																	
All ages			91.7	90.9	92.5	87.2	85.4	89.0	93.1	91.9	94.2	97.7	97.0	98.4	87.3	86.9	87.7
Age-standardised			91.6	91.0	92.2	88.5	87.4	89.6	94.0	93.3	94.7	96.8	96.2	97.5	87.3	87.1	87.6
15–49			97.6	97.1	98.1	96.8	95.2	98.4	98.2	98.2	98.2	99.3	98.9	99.7	96.4	96.0	96.7
50–69			95.3	94.6	95.9	89.5	87.4	91.6	97.1	96.4	97.8	99.1	98.8	99.4	93.2	92.9	93.6
70–99			87.2	85.8	88.6	84.9	82.4	87.4	89.5	87.7	91.3	94.4	92.6	96.1	79.9	79.2	80.5

Table 2. (Continued)

	Australia ^a		Canada ^b		Denmark ^c		Norway		Sweden ^d		UK ^e						
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI					
SEER Summary Stage 2000																	
All patients																	
All ages	97.1	96.9	97.3	96.6	95.6	95.2	96.0	96.5	96.2	96.8	98.4	98.2	98.7	92.9	92.6	93.2	93.5
Age-standardised	96.9	96.7	97.0	96.7	95.7	95.5	96.0	96.6	96.4	96.8	98.4	98.3	98.6	93.3	93.1	93.5	93.5
15-49	98.6	98.5	98.8	98.3	98.6	98.3	98.8	98.6	98.5	98.8	99.4	99.2	99.5	97.6	97.3	97.8	97.8
50-69	98.1	98.0	98.3	97.7	97.1	96.8	97.4	98.1	97.9	98.3	99.0	98.8	99.2	96.1	95.9	96.4	96.4
70-99	93.8	93.3	94.4	93.6	91.4	90.5	92.3	92.2	91.5	93.0	96.9	96.3	97.4	85.7	84.9	86.4	86.4
Localised																	
All ages	100.0	99.9	100.0	100.0	100.0	99.9	100.0	99.9	NA	NA	99.9	99.9	100.0	99.9	99.9	100.0	100.0
Age-standardised	99.9	99.9	100.0	100.0	100.0	99.9	100.0	99.9	99.9	100.0	99.9	99.9	100.0	99.9	99.9	100.0	100.0
15-49	99.9	99.8	100.0	99.9	99.9	99.8	100.0	99.9	99.9	100.0	99.9	99.8	100.0	99.9	99.8	100.0	100.0
50-69	99.9	99.9	100.0	100.0	99.9	99.9	100.0	100.0	99.9	100.0	99.9	99.9	100.0	99.9	99.9	100.0	100.0
70-99	99.9	99.9	100.0	100.0	100.0	100.0	100.0	99.9	99.9	100.0	99.9	99.9	100.0	100.0	100.0	100.0	100.0
Regional																	
All ages	98.6	98.4	98.9	98.5	98.7	98.2	99.1	97.9	97.5	98.3	98.0	97.5	98.5	97.7	97.3	98.1	98.1
Age-standardised	98.6	98.4	98.7	98.6	98.6	98.4	98.9	98.0	97.8	98.3	98.3	98.1	98.6	97.7	97.4	97.9	97.9
15-49	99.0	98.8	99.3	99.2	99.2	98.9	99.5	99.0	98.7	99.3	99.2	98.9	99.4	98.6	98.2	98.9	98.9
50-69	99.0	98.8	99.2	99.0	99.0	98.7	99.3	98.8	98.5	99.1	98.9	98.6	99.2	98.2	97.8	98.5	98.5
70-99	97.3	96.5	98.0	96.8	97.4	96.4	98.4	95.1	94.0	96.3	96.0	94.8	97.1	95.9	95.0	96.9	96.9
Distant																	
All ages	71.6	69.7	73.6	66.2	63.7	60.7	66.7	61.2	58.4	64.1	66.7	62.7	70.6	69.3	64.3	74.3	74.3
Age-standardised	70.1	68.7	71.5	65.7	65.5	63.5	67.5	62.4	60.5	64.3	67.8	65.3	70.4	69.4	65.8	72.9	72.9
15-49	87.2	84.9	89.6	79.2	82.0	77.3	86.8	70.8	66.1	75.5	85.5	81.0	90.0	81.9	73.6	90.2	90.2
50-69	78.2	75.9	80.5	66.9	69.7	66.2	73.3	67.8	64.4	71.2	68.6	63.7	73.5	76.5	71.0	82.0	82.0
70-99	54.4	50.8	57.9	54.8	53.6	49.2	57.9	52.5	48.3	56.6	58.6	52.8	64.5	56.5	48.1	64.8	64.8
Missing stage																	
All ages	90.8	89.7	92.0	90.8	87.2	85.4	89.0	92.8	91.7	93.9	97.6	96.9	98.3	82.8	82.0	83.6	83.6
Age-standardised	90.8	89.9	91.6	90.7	88.3	87.2	89.5	93.6	92.9	94.4	96.7	96.0	97.4	82.9	82.3	83.5	83.5
15-49	96.6	95.7	97.5	96.8	96.8	95.1	98.5	98.5	97.9	99.1	99.2	98.8	99.7	94.1	93.2	95.0	95.0
50-69	94.7	93.7	95.7	95.0	89.2	87.1	91.4	96.9	96.2	97.7	99.1	98.7	99.4	89.1	88.3	89.9	89.9
70-99	86.0	83.9	88.0	87.2	85.1	82.6	87.5	89.3	87.4	91.1	94.3	92.5	96.1	75.0	73.7	76.4	76.4

Abbreviations: CI = confidence interval; NA = not available; NS = net survival; TNM = Tumour, Nodes, Metastasis staging system.

^aAustralia: New South Wales.^bCanada: British Columbia and Manitoba.^cIn Denmark we analysed women diagnosed during 2004-7.^dSweden: Uppsala-Örebro and Stockholm-Gotland health regions.^eUnited Kingdom (TNM analysis): Northern Ireland, Wales and the Northern and Yorkshire Cancer Registry and Information Service, Eastern Cancer Registration and Information Centre, Oxford Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit in England; United Kingdom (SEER analysis): Northern Ireland and Wales.

Table 3. All-ages, age-specific and age-standardised 3-year net survival (%) with 95% CI, by stage at diagnosis and country for women diagnosed with breast cancer during 2000-2007

	Australia ^a		Canada ^b		Denmark ^c		Norway		Sweden ^d		UK ^e		
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	
TNM stage													
All patients													
All ages			92.4	92.0	88.2	89.8	90.6	90.1	91.1	93.8	94.8	87.3	87.1
Age-standardised			92.4	92.0	88.4	89.6	90.5	90.1	90.9	93.8	94.5	87.4	87.3
15-49			93.4	93.1	92.1	94.2	93.5	92.1	93.5	94.9	96.1	91.1	90.8
50-69			94.1	93.7	90.8	92.3	93.8	93.4	94.2	95.3	96.1	91.6	91.4
70-99			89.2	88.2	80.7	84.4	83.5	82.1	84.8	89.7	92.2	78.6	78.1
Stage I													
All ages			99.7	99.5	99.4	99.8	99.5	99.3	99.8	99.0	99.6	99.3	99.2
Age-standardised			99.7	99.6	99.1	99.6	99.5	99.4	99.7	99.1	99.4	99.3	99.2
15-49			99.3	98.9	97.6	99.7	99.0	98.6	99.5	97.9	99.1	98.5	98.2
50-69			99.7	99.5	99.4	99.9	99.6	99.3	99.8	99.1	99.6	99.4	99.2
70-99			99.9	99.8	99.5	100.0	99.8	99.7	99.9	99.6	99.9	99.7	99.6
Stage II													
All ages			96.4	NA	94.4	96.6	91.5	90.7	92.3	94.1	94.8	92.4	92.1
Age-standardised			96.4	96.0	94.4	96.2	91.4	90.8	92.0	94.1	93.6	92.4	92.2
15-49			96.0	95.2	94.1	96.9	92.7	91.8	93.7	94.9	94.0	92.4	92.9
50-69			96.2	95.5	95.8	97.7	96.9	92.6	94.1	94.7	95.5	93.1	92.8
70-99			97.2	95.8	90.0	96.3	87.1	84.8	89.3	92.5	90.8	91.2	90.4
Stage III													
All ages			83.1	81.2	80.2	85.1	79.2	75.6	82.9	72.8	79.7	70.2	69.0
Age-standardised			82.0	81.1	80.7	83.0	80.7	79.2	82.2	77.3	78.8	70.7	69.9
15-49			85.8	84.1	83.5	87.9	84.6	81.6	87.6	81.7	84.7	76.5	74.8
50-69			84.9	83.2	82.1	86.7	83.4	80.3	86.5	80.7	83.7	74.6	73.3
70-99			76.2	73.4	73.1	79.9	73.8	69.2	78.5	69.7	74.1	61.9	59.9
Stage IV													
All ages			39.9	36.9	31.7	39.5	31.6	28.7	34.5	41.8	46.2	27.4	26.1
Age-standardised			37.8	35.6	33.4	38.8	31.6	29.6	33.7	41.8	45.0	27.9	26.9
15-49			55.4	49.7	44.4	64.1	34.9	29.0	40.8	64.8	56.1	36.2	33.1
50-69			39.6	35.8	35.4	45.3	37.4	33.5	41.4	41.6	47.5	33.1	31.2
70-99			31.5	26.6	21.6	31.5	25.5	21.5	29.5	34.2	40.9	20.8	19.0
Missing stage													
All ages			85.9	84.7	71.2	77.9	85.6	83.7	87.6	94.3	95.5	77.0	76.5
Age-standardised			85.8	84.9	74.1	78.4	87.3	86.1	88.5	92.3	93.7	77.1	76.7
15-49			93.0	91.6	83.0	94.4	90.6	93.1	96.8	96.8	95.4	88.0	87.2
50-69			90.7	89.6	72.2	80.6	92.9	91.5	94.4	97.5	98.2	85.7	85.2
70-99			80.1	78.1	67.4	76.3	79.5	76.3	82.7	87.2	90.6	66.9	66.0

Table 3. (Continued)

	Australia ^a			Canada ^b			Denmark ^c			Norway			Sweden ^d			UK ^e		
	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI	NS (%)	95% CI
SEER Summary Stage 2000																		
All patients																		
All ages	92.5	92.2	92.9	92.4	92.0	92.8	89.0	88.3	89.8	90.6	90.0	91.1	94.3	93.8	94.8	86.1	85.6	86.7
Age-standardised	92.2	91.9	92.5	92.1	92.8	89.2	88.7	89.8	90.7	90.3	91.1	94.2	93.9	94.6	86.6	86.3	87.0	
15-49	93.7	93.2	94.2	93.4	94.0	93.2	92.1	94.2	92.9	92.2	93.6	95.5	94.9	96.1	90.6	89.9	91.3	
50-69	94.4	94.1	94.8	94.1	93.7	94.5	91.5	90.8	93.7	93.3	94.2	95.7	95.3	96.1	90.6	90.1	91.1	
70-99	88.0	87.0	89.0	89.2	88.2	90.3	82.6	80.8	84.4	83.5	82.1	84.9	90.9	89.7	92.2	77.2	76.0	78.4
Localised																		
All ages	98.8	98.3	99.1	99.4	99.1	99.6	98.9	98.4	99.5	98.7	NA	NA	98.3	97.9	98.7	98.5	98.2	98.9
Age-standardised	98.7	98.5	99.0	99.3	99.2	99.5	98.9	98.6	99.2	98.7	98.4	99.0	98.3	98.0	98.5	98.6	98.3	98.8
15-49	98.2	97.7	98.6	98.7	98.2	99.1	98.4	97.4	99.4	98.3	97.7	98.9	97.7	97.2	98.3	96.9	96.2	97.7
50-69	98.9	98.6	99.2	99.3	99.0	99.6	98.6	97.8	99.5	99.0	98.7	99.4	98.2	97.8	98.6	98.5	98.1	99.0
70-99	98.8	97.5	100.0	100.0	99.9	100.0	99.8	99.4	100.0	98.3	96.8	99.7	98.8	97.8	99.7	99.8	99.3	100.0
Regional																		
All ages	91.6	90.9	92.3	91.2	90.3	92.1	91.2	90.0	92.4	88.6	87.7	89.6	88.0	86.8	89.3	87.2	86.1	88.2
Age-standardised	91.4	90.9	91.9	91.1	90.5	91.8	91.1	90.3	92.0	89.0	88.3	89.6	89.0	88.2	89.8	87.2	86.5	88.0
15-49	92.2	91.3	93.0	91.8	90.7	92.9	92.5	91.0	94.1	91.7	90.6	92.9	92.0	90.5	93.5	89.3	88.0	90.7
50-69	92.9	92.2	93.6	92.9	92.0	93.8	92.4	91.3	93.6	91.7	90.8	92.6	91.2	90.1	92.4	88.5	87.4	89.6
70-99	87.8	85.9	89.7	87.0	84.5	89.5	87.1	83.9	90.4	79.8	77.1	82.4	80.5	77.6	83.4	82.5	79.9	85.0
Distant																		
All ages	53.7	51.4	56.0	39.7	36.8	42.7	35.3	31.5	39.2	31.4	28.6	34.3	41.7	37.2	46.1	54.8	49.1	60.6
Age-standardised	52.0	50.3	53.6	38.6	36.4	40.8	37.2	34.4	39.9	32.3	30.2	34.3	42.9	39.7	46.1	54.8	50.3	59.2
15-49	71.3	67.2	75.3	55.2	49.5	60.9	54.2	44.4	64.1	34.9	29.0	40.8	64.9	56.2	73.5	65.8	52.5	79.2
50-69	60.8	57.9	63.8	39.8	36.0	43.6	40.8	35.8	45.7	37.8	33.8	41.8	41.9	36.0	47.8	62.5	55.6	69.4
70-99	34.5	30.8	38.3	30.8	26.0	35.6	25.6	20.7	30.4	24.9	21.0	28.8	33.6	27.0	40.3	41.9	32.6	51.2
Missing stage																		
All ages	80.6	78.7	82.5	85.6	84.4	86.7	74.3	71.0	77.6	85.2	83.3	87.2	94.1	92.9	95.4	71.2	70.0	72.3
Age-standardised	80.6	79.1	82.0	85.2	84.2	86.1	75.9	73.7	78.1	86.7	85.4	88.0	92.1	90.7	93.5	71.3	70.4	72.1
15-49	88.1	85.6	90.7	92.9	91.5	94.3	89.5	84.0	95.0	94.8	92.9	96.7	96.9	95.4	98.4	83.8	82.1	85.5
50-69	87.3	85.5	89.2	90.5	89.3	91.6	76.3	72.1	80.6	92.7	91.2	97.4	97.1	96.7	98.1	79.6	78.4	80.9
70-99	73.0	69.6	76.4	79.6	77.5	81.7	71.5	67.0	76.0	79.0	75.8	82.2	86.9	83.5	90.4	61.5	59.7	63.3

Abbreviations: CI = confidence interval; NA = not available; NS = net survival; TNM = Tumour, Nodes, Metastasis staging system.

^aAustralia: New South Wales^bCanada: British Columbia and Manitoba.^cIn Denmark we analysed women diagnosed during 2004-7.^dSweden: Uppsala-Örebro and Stockholm-Gotland health regions.^eUnited Kingdom (TNM analysis): Northern Ireland, Wales and the Northern and Yorkshire Cancer Registry and Information Service, Eastern Cancer Registration and Information Centre, Oxford Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit in England; United Kingdom (SEER analysis): Northern Ireland and Wales.

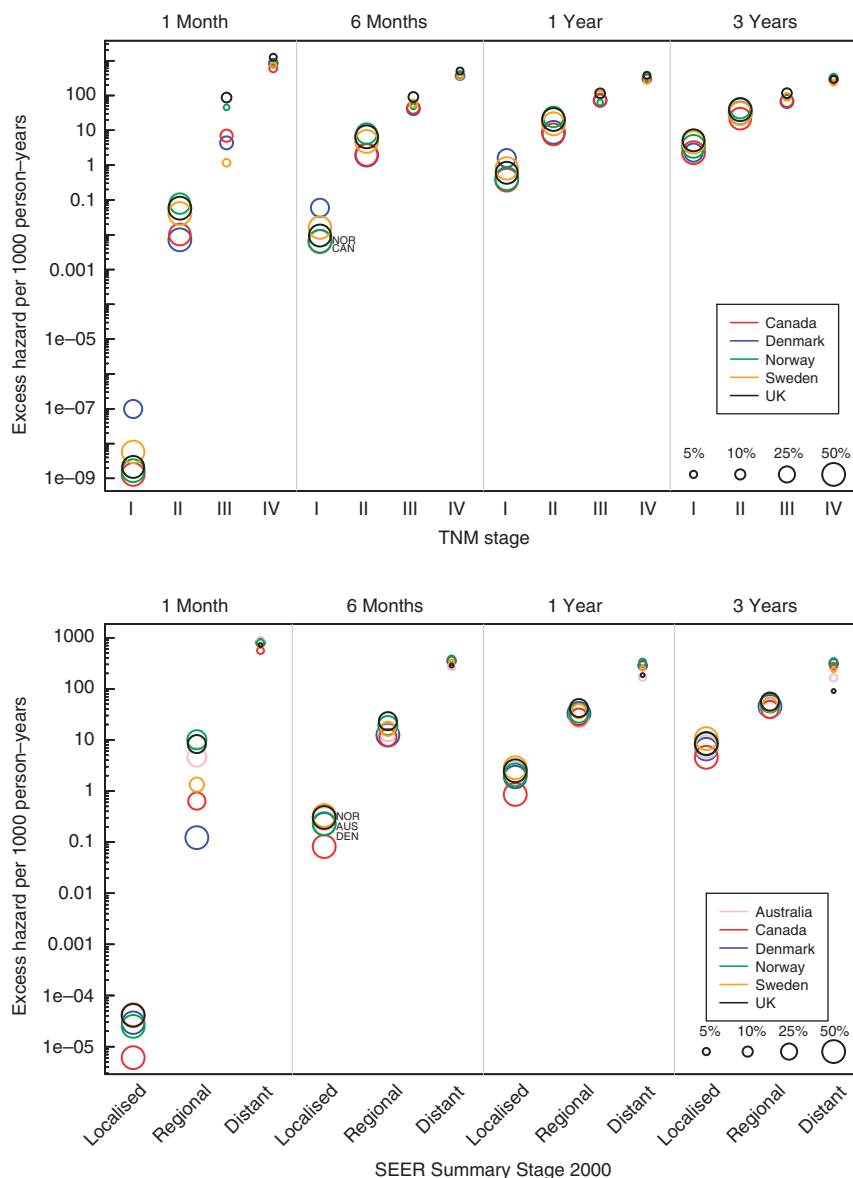


Figure 2. Age-standardised excess hazard of death (per 1000 person-years, log scale) from breast cancer. Results presented by TNM or SEER Summary Stage 2000 and time since diagnosis. *Notes:* (1) Denmark and Norway: national data; Australia: New South Wales; Canada: British Columbia and Manitoba; Sweden: Uppsala-Örebro and Stockholm-Gotland health regions; UK (TNM analysis): Northern Ireland, Wales and the Northern and Yorkshire Cancer Registry and Information Service, Eastern Cancer Registration and Information Centre, Oxford Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit in England; UK (SEER SS2000 analysis): Northern Ireland and Wales. In Denmark, we analysed women diagnosed during 2004–7. (2) Bubbles are scaled to represent the stage distribution at diagnosis.

National breast cancer screening programmes for women aged 50–69/70 years were being implemented in all of these countries except Denmark during 2000–7. Screening was initiated around 1990 (Dowling *et al*, 2010), although the date by which national coverage was achieved varied, for example from 1997 in Sweden to 2005 in Norway (Autier *et al*, 2011). Small differences existed in the timing and methods of screening, for example most countries employed an annual or biennial invitation, except the UK where women were invited every 3 years, and there was variation in the use of digital mammography and clinical breast examination (Dowling *et al*, 2010). Overall however, by 2004–5 the uptake of screening was consistently 65–75% of eligible women in the UK, Norway, Sweden (Dowling *et al*, 2010), New South Wales (Birch *et al*, 2007), British Columbia and Manitoba (Public Health Agency of Canada, 2012). Among these jurisdictions we do not consider that small differences in the screening programmes explain

differences in the stage distribution or in stage-specific survival. Instead, we note the consistency with which women in the ‘screened’ age-group had more favourable stage distributions than younger and older women, and that the largest between-country differences in survival were found among the older, ineligible, women.

Denmark is the only country in this study that did not implement national breast cancer screening during 2000–7. Up to 2006, just 20% of the population was covered by screening (Jorgensen *et al*, 2010). Screening is associated with an increase in the diagnosis of Stage I and II tumours (Jensena *et al*, 2003; Jensen *et al*, 2008), as well as the ‘overdiagnosis’ of indolent invasive cancers that might never have been diagnosed in the absence of screening (Hackshaw, 2012; Kalager *et al*, 2012; Marmot *et al*, 2012). It is likely that the slower implementation of screening in Denmark underlies the more advanced stage distribution in that

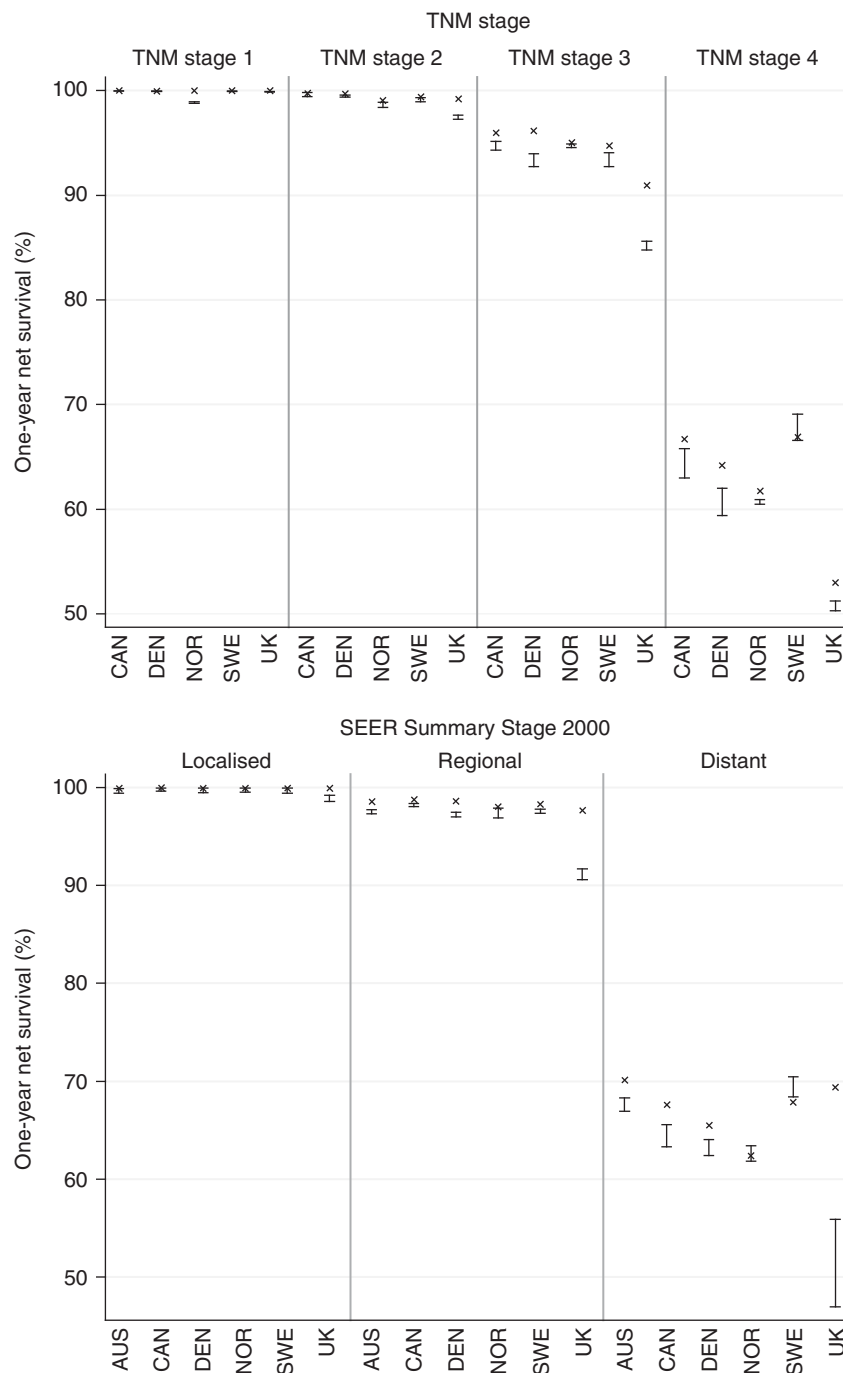


Figure 3. Age-standardised 1-year net survival for women diagnosed with breast cancer during 2000–7. Results presented by stage at diagnosis and country, using known stage and imputed stage: TNM (upper figure) and SEER Summary Stage 2000 (lower figure). ^x = survival estimate derived from women with known stage. \bar{I} = range of survival estimates derived for all women after imputation of stage where it was missing (see text). Notes: Denmark and Norway: national data; Australia: New South Wales; Canada: British Columbia and Manitoba; Sweden: Uppsala-Örebro and Stockholm-Gotland health regions; UK (TNM analysis): Northern Ireland, Wales and the Northern and Yorkshire Cancer Registry and Information Service, Eastern Cancer Registration and Information Centre, Oxford Cancer Intelligence Unit, West Midlands Cancer Intelligence Unit in England; UK (SEER SS2000 analysis): Northern Ireland and Wales. In Denmark, we analysed women diagnosed during 2004–7.

country (which is evident despite restriction of the analyses to 2004–7) (Christensen *et al*, 2004). It may also explain the lower survival of women with Stage I tumours compared with that group of women in other countries, where more women with ‘overdiagnosed’ indolent invasive tumours may have been included.

It is possible that the overall relatively low net survival in Denmark arises in small part because of lead time bias in the other countries, wherein diagnosis is brought forward by screening,

so that survival from the time of diagnosis is longer, regardless of whether screening actually extended life. However, this cannot fully explain low survival in Denmark, because survival in Denmark is relatively low even among non-screened age-groups.

It has been shown that lower survival in England than in Sweden and Norway arises mainly in the first few months after diagnosis (Møller *et al*, 2010; Lambert *et al*, 2011). Low survival in the first year may indicate delayed diagnosis, and it has led to promotion of ‘awareness of symptoms and early detection as the

main strategy to improve breast cancer survival in the United Kingdom' (Møller *et al*, 2010). Given the ecological studies cited above, we might expect later diagnosis to lead to a later stage distribution, but the stage distribution in the UK is actually fairly average among these countries, and it cannot fully explain the lower survival of UK breast cancer patients.

International differences in stage-specific survival may be explained by differences in treatment. Previous studies have identified differences between European countries in the proportion of women who receive 'standard care' for breast cancer (Allemani *et al*, 2010), especially a lower proportion receiving surgery in the UK (Sant *et al*, 2003). Given that the largest differences in survival were found for women with metastatic disease, we would expect this to be largely driven by differences in the use of systemic therapies (Koscielny *et al*, 2009). Further research is under way to determine whether differences in breast cancer treatment between these six countries in 2000–7 could help explain the inequalities in survival.

International differences in stage-specific survival may also reflect differences in the intensity and accuracy of staging. In the UK, it is recommended that asymptomatic women should not undergo staging investigations such as whole body bone and CT scans for metastatic disease (National Institute for Health and Clinical Excellence, 2012). If women with asymptomatic metastases are systematically diagnosed as having non-metastatic disease, this could help explain our finding of lower survival than elsewhere among women with both stage III and IV tumours in the UK (stage migration) (Feinstein *et al*, 1985). Previous studies have highlighted less aggressive staging in the UK than in other European countries (Sant *et al*, 2003). To ensure that future studies can control correctly for differences in the intensity of staging investigations between countries, details of these procedures should be systematically captured by cancer registries.

The largest international differences in survival were found among older women or those who were not staged, who had particularly low survival in the UK and Denmark. Treatment recommendations are less well defined for older women, who are rarely included in clinical trials and who often have more complex co-morbidities (Bastiaannet *et al*, 2010). Women in the UK and Denmark may be staged less often than in other countries if they are particularly frail and could be considered liable to suffer from invasive staging investigations. Unstaged women may also have shorter survival because treatment guidelines are less clear (Voogd and Coebergh, 2010; Wishart *et al*, 2010). Some of these women may actually have been staged, but the clinical data not transmitted to the cancer registry. The channels for reporting clinical information on stage to cancer registries should be improved to enable better international comparisons of cancer survival.

CONCLUSIONS

International variation in breast cancer survival is partly explained by stage at diagnosis. This was most clearly true in Denmark, where the stage distribution was most adverse and where overall survival was lower than in any other country except the UK. The national roll-out of mammographic screening in Denmark from 2007 will be expected to increase the proportion of women diagnosed at an early stage. In the UK, by contrast, the stage distribution was relatively favourable, but stage-specific survival was lower than in other countries. This suggests that the low survival in the UK must be explained by other factors, such as the intensity and accuracy of staging, and access to or the effectiveness of stage-specific treatment. Australia and Sweden had quite favourable stage distributions at diagnosis and relatively high survival at all stages of disease. There is scope for other countries to learn

from health policies and clinical practice in these countries. Women with early-stage disease in Canada and Norway had similar survival to that seen elsewhere, but those with late-stage disease had lower survival than in Australia and Sweden: the treatment of these women should be investigated, as should the relatively high proportion of women with TNM stage III disease in Canada.

The completeness and comparability of stage data routinely collected by population-based cancer registries needs considerable improvement to facilitate comparisons of survival by stage. Such data enable larger, more timely, more representative and more affordable comparisons of cancer survival than any other approach and they can be invaluable in monitoring the success of cancer control strategies. To this end, IACR should now identify stage as an 'essential' data item for collection by population-based cancer registries, and clinicians and registry staff should ensure that data on stage at diagnosis are complete, standardised and comparable between countries. Clinicians should be encouraged to conform to a single international staging system such as TNM. Meanwhile, the Union for International Cancer Control should ensure that the TNM system achieves a balance between meeting clinical demands for detail and retaining the simplicity required for surveillance of cancer survival worldwide.

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CONFLICT OF INTEREST

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REFERENCES

- Allemani C, Sant M, Weir HK, Richardson LC, Baili P, Storm H, Siesling S, Torrella-Ramos A, Voogd AC, Aareleid T, Ardanaz E, Berrino F, Bielska-Lasota M, Bolick S, Cirilli C, Colonna M, Contiero P, Cress R, Crocetti E, Fulton JP, Grosclaude P, Hakulinen T, Izarzugaza MI, Malmstrom P, Peignaux K, Primic-Žakelj M, Rachtan J, Diba CS, Sanchez MJ, Schymura MJ, Shen T, Traina A, Tryggvadóttir L, Tumino R, Velten M, Vercelli M, Wolf HJ, Woronoff AS, Wu X, Coleman MP (2013) Breast cancer survival in the US and Europe: a CONCORD high-resolution study. *Int J Cancer* **132**(5): 1170–1181.
- Allemani C, Storm H, Voogd AC, Holli K, Izarzugaza I, Torrella-Ramos A, Bielska-Lasota M, Aareleid T, Ardanaz E, Colonna M, Crocetti E, Danzon A, Federico M, Garau I, Grosclaude P, Hédelin G, Martinez-Garcia C, Peignaux K, Pleško I, Primic-Žakelj M, Rachtan J, Tagliabue G, Tumino R, Traina A, Tryggvadóttir L, Vercelli M, Sant M (2010) Variation in 'standard care' for breast cancer across Europe: a EURO CARE-3 high resolution study. *Eur J Cancer* **46**(9): 1528–1536.
- Autier P, Boniol M, Gavin A, Vatten LJ (2011) Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. *BMJ* **343**: d4411.

- Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, van de Water W, Portielje JE, van der Geest LG, Janssen-Heijnen ML, Dekkers OM, van de Velde CJ, Westendorp RG (2010) Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127 805 unselected patients. *Breast Cancer Res Treat* **124**(3): 801–807.
- Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, Santaquilani M, EUROCARE Working Group (2007) Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. *Lancet Oncol* **8**(9): 773–783.
- Birch S, Haas M, Savage E, Van GK (2007) Targeting services to reduce social inequalities in utilisation: an analysis of breast cancer screening in New South Wales. *Aust New Zealand Health Policy* **4**: 12; PMID:17550622.
- Christensen LH, Engholm G, Ceberg J, Hein S, Perfekt R, Tange UB, Andersson M, Mouridsen HT, Möller T, Storm HH (2004) Can the survival difference between breast cancer patients in Denmark and Sweden 1989 and 1994 be explained by patho-anatomical variables? A population-based study. *Eur J Cancer* **40**(8): 1233–1243.
- Coleman MP (1999) Why the variation in breast cancer survival in Europe? *Breast Cancer Res* **1**(1): 22–26.
- Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, Nur U, Tracey E, Coory M, Hatcher J, McGahan CE, Turner D, Marrett L, Gjerstorff ML, Johannesen TB, Adolfsson J, Lambe M, Lawrence G, Meechan D, Morris EJ, Middleton R, Steward J, Richards MA. ICBP Module 1 Working Group (2011) Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* **377**: 127–138.
- Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, Azevedo e Silva G, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL, and CONCORD Working Group (2008) Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* **9**: 730–756.
- Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R (2010) Breast and cervical cancer screening programme implementation in 16 countries. *J Med Screen* **17**(3): 139–146.
- Durrleman S, Simon R (1989) Flexible regression models with cubic splines. *Stat Med* **8**(5): 551–561.
- Feinstein AR, Sosin DM, Wells CK (1985) The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* **312**(25): 1604–1608.
- Hackshaw A (2012) The benefits and harms of mammographic screening for breast cancer: building the evidence base using service screening programmes. *J Med Screen* **19**(Suppl 1): 1–2.
- Jensen AR, Garne JP, Storm HH, Engholm G, Möller T, Overgaard J (2004) Does stage at diagnosis explain the difference in survival after breast cancer in Denmark and Sweden? *Acta Oncol* **43**(8): 719–726.
- Jensen AR, Madsen AH, Overgaard J (2008) Trends in breast cancer during three decades in Denmark: stage at diagnosis, surgical management and survival. *Acta Oncol* **47**(4): 537–544.
- Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG (1991) Cancer registration: principles and methods (IARC Scientific Publications No. 95). International Agency for Research on Cancer: Lyon.
- Jensena AR, Ewertz M, Cold S, Storm HH, Overgaard J (2003) Time trends and regional differences in registration, stage distribution, surgical management and survival of breast cancer in Denmark. *Eur J Cancer* **39**(12): 1783–1793.
- Jorgensen KJ, Zahl PH, Gotzsche PC (2010) Breast cancer mortality in organised mammography screening in Denmark: comparative study. *Br Med J* **340**: c1241.
- Kalager M, Adami HO, Bretthauer M, Tamimi RM (2012) Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. *Ann Intern Med* **156**(7): 491–499.
- Koscielny S, Arriagada R, Adolfsson J, Fornander T, Bergh J (2009) Impact of tumour size on axillary involvement and distant dissemination in breast cancer. *Br J Cancer* **101**(6): 902–907.
- Lambert PC, Holmberg L, Sandin F, Bray F, Linklater KM, Purushotham A, Robinson D, Möller H (2011) Quantifying differences in breast cancer survival between England and Norway. *Cancer Epidemiol* **35**(6): 526–533.
- Lambert PC, Royston P (2009) Further development of flexible parametric models for survival analysis. *Stata J* **9**(2): 265–290.
- Laurenti R, Coleman MP, Aylin P (2000) Accuracy of statements of the cause of death on death certificates and the international comparability of mortality statistics. In *Death certification and mortality statistics: an international perspective*, Coleman MP, Aylin P (eds) (Office for National Statistics: London).
- Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M (2012) The benefits and harms of breast cancer screening: an independent review. *Lancet* **380**(9855): 1778–1786.
- Møller H, Sandin F, Bray F, Klint A, Linklater KM, Purushotham A, Robinson D, Holmberg L (2010) Breast cancer survival in England, Norway and Sweden: a population-based comparison. *Int J Cancer* **127**(11): 2630–2638.
- National Institute for Health and Clinical Excellence. Breast cancer quality standards. <http://www.nice.org.uk/guidance/qualitystandards/breastcancer/Staging.jsp>. Last accessed 2 May 2012.
- Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP (2010) Modelling relative survival in the presence of incomplete data: a tutorial. *Int J Epidemiol* **39**: 118–128.
- Parkin DM (2006) The evolution of the population-based cancer registry. *Nat Rev Cancer* **6**(8): 603–612.
- Pohar-Perme M, Stare J, Estève J (2012) On estimation in relative survival. *Biometrics* **68**(1): 113–120.
- Public Health Agency of Canada. Organized Breast Cancer Screening Programs in Canada—Report on Program Performance in 2005 and 2006 <http://www.phac-aspc.gc.ca/cd-mc/publications/cancer/obcsp-podcs05/1-eng.php>. Last accessed 4 December 2012.
- Remontet L, Bossard N, Belot A, Estève J. FRANCIM (2007) An overall strategy based on regression models to estimate relative survival and models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. *Stat Med* **26**(10): 2214–2228.
- Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, Law SC, Ahn YO, Xiang YB, Yeole BB, Shin HR, Shanta V, Woo ZH, Martin N, Sumitsawan Y, Sriplung H, Barboza AO, Eser S, Nene BM, Suwanrungruang K, Jayalekshmi P, Dikshit R, Wabinga H, Esteban DB, Laudico A, Bhurgri Y, Bah E, Al-Hamdan N (2010) Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* **11**(2): 165–173.
- Sant M, Allemani C, Capocaccia R, Hakulinen T, Aareleid T, Coebergh JW, Coleman MP, Grosclaude P, Martinez C, Bell J, Youngson J, Berrino F (2003) Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer* **106**(3): 416–422.
- Sobin LH, Gospodarowicz M, Wittekind C (2009) *TNM classification of malignant tumours*. 7th edition. Union for International Cancer Control (UICC) and Wiley-Blackwell: Oxford.
- Voogd AC, Coebergh JW (2010) Explaining variations in survival in breast cancer in the Eastern Region of England. *Ann Oncol* **21**(3): 669–670.
- Walters S, Maringe C, Butler J, Brierley JD, Rachet B, Coleman MP (2013) Comparability of stage data in cancer registries in six countries: Lessons from the International Cancer Benchmarking Partnership. *Int J Cancer* **132**(3): 676–685.
- White IR, Royston P, Wood AM (2011) Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* **30**(4): 377–399.
- Wishart GC, Greenberg DC, Chou P, Brown CH, Duffy S, Purushotham AD (2010) Treatment and survival in breast cancer in the Eastern Region of England. *Ann Oncol* **21**(2): 291–296.
- Woods LM, Rachet B, O'Connell D, Lawrence G, Tracey E, Willmore A, Coleman MP (2009) Large differences in patterns of breast cancer survival between Australia and England: a comparative study using cancer registry data. *Int J Cancer* **124**(10): 2391–2399.
- Young JL, Roffers SD, Ries LAG, Fritz AG, Hurlbut AA (2001) *SEER Summary Staging Manual—2000: Codes and Coding Instructions*. National Cancer Institute: Bethesda.

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APPENDIX

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