Time-dependent risk of developing distant metastasis in breast cancer patients according to treatment, age and tumour characteristics

E Colzani *,1, A L V Johansson 1, A Liljegren 2, T Foukakis 2, M Clements 1, J Adolfsson 3, P Hall 1 and K Czene 1

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden; 2Department of Oncology, Radiumhemmet, Karolinska University Hospital, Karolinska Institutet, SE-171 77 Stockholm, Sweden and 3Department of Clinical Science, Intervention and Technology, Karolinska Institutet, SE-171 77 Stockholm, Sweden

Background: Metastatic breast cancer is a severe condition without curative treatment. How relative and absolute risk of distant metastasis varies over time since diagnosis, as a function of treatment, age and tumour characteristics, has not been studied in detail.

Methods: A total of 9514 women under the age of 75 when diagnosed with breast cancer in Stockholm and Gotland regions during 1990–2006 were followed up for metastasis (mean follow-up = 5.7 years). Time-dependent development of distant metastasis was analysed using flexible parametric survival models and presented as hazard ratio (HR) and cumulative risk.

Results: A total of 995 (10.4%) patients developed distant metastasis; the most common sites were skeleton (32.5%) and multiple sites (28.3%). Women younger than 50 years at diagnosis, with lymph node-positive, oestrogen receptor (ER)-negative, > 20 mm tumours and treated only locally, had the highest risk of distant metastasis (0–5 years’ cumulative risk = 0.55; 95% confidence interval (CI): 0.47–0.64). Women older than 50 years at diagnosis, with ER-positive, lymph node-negative and ≤ 20-mm tumours, had the same and lowest cumulative risk of developing metastasis 0–5 and 5–10 years (cumulative risk = 0.03; 95% CI: 0.02–0.04). In the period of 5–10 years after diagnosis, women with ER-positive, lymph node-positive and > 20-mm tumours were at highest risk of distant recurrence. Women with ER-negative tumours showed a decline in risk during this period.

Conclusion: Our data show no support for discontinuation at 5 years of clinical follow-up in breast cancer patients and suggest further investigation on differential clinical follow-up for different subgroups of patients.

The overall survival of breast cancer patients has increased quite remarkably in the past decades because of substantial improvements in diagnosis and treatment reaching 79% 5-year survival by the early 2000s (Verdecchia et al, 2007). In particular, new polychemotherapy regimens have contributed to about 25% decrease in annual death rates from 1980s and, in combination with 5-year tamoxifen treatment, have approximately halved death rates among middle-aged women with oestrogen receptor (ER)-positive tumours (Early Breast Cancer Trialists’ Collaborative Group, 2005). However, the development of distant metastasis still means that the patient is beyond cure (Clarke et al, 2005; Early Breast Cancer Trialists’ Collaborative Group, 2005; Verdecchia et al, 2007; Liu et al, 2010).

Whereas it is well known that molecular profiles of breast tumours influence prognosis and likelihood of distant recurrences (Grann et al, 2005; Dunning et al, 2007; Hsieh et al, 2009;...
Alford et al, 2012), it has only recently been shown that gene expression profiles of breast tumour samples could be used to predict relapses and metastatic pattern in breast cancer patients and to be potential candidate targets for new drugs (van de Vijver et al, 2002; Chambers et al, 2002; Brenton et al, 2005; Minn et al, 2005).

Several studies have already investigated the prognosis of breast cancer patients after developing distant metastasis, showing that age at initial diagnosis, hormonal receptor status and site of metastasis are the most relevant factors for predicting survival from occurrence of metastasis (Largillier et al, 2008; Foukakis et al, 2011; Schneider et al, 2011). Dent et al (2009a,b) have shown that triple-negative tumours metastasise earlier and more frequently than other breast tumours; however, following 5 years from diagnosis the difference tends to disappear. Apart from the effect of ER-receptor status, not much is known about how time to first distant metastasis is influenced by age and tumour characteristics and how site of first distant metastasis changes by time since diagnosis (Biganzoli et al, 2003; Dent et al, 2007; Jensen et al, 2011; Frisk et al, 2012).

The risk of developing first distant metastasis may in fact vary over time since diagnosis across different subgroups of patients, and it is of importance to be able to more accurately predict the risk of tumour dissemination over time. We aimed to undertake a comprehensive analysis of factors affecting development, time and site of distant metastasis using a Swedish population-based cohort of breast cancer patients.

MATERIALS AND METHODS

Data source. The Stockholm Breast Cancer Register (SBCR) is a population-based clinical register held by the Regional Cancer Centre of Stockholm–Gotland region, Sweden. The register contains data about all breast cancer diagnoses occurring in the Swedish counties of Stockholm and Gotland since 1976. The SBCR provides detailed clinical information, such as tumour characteristics and intention of treatment, for each patient.

Study cohort. A population-based cohort was selected from the SBCR, including all women diagnosed with first invasive breast cancer in the period of 1 January 1990 and 31 December 2006, younger than 75 years at diagnosis and without any previous occurrence of cancer. Patients were followed up for at most 10 years from the date of breast cancer diagnosis until the development of first distant metastasis (event), until death, diagnosis of second primary cancer or end of study period (31 December 2006). The records were linked to the Swedish Cancer Register (Barlow et al, 2009) for information on other invasive cancers through linkage by the personal identification number (unique for each Swedish resident and included in all Swedish population registers).

The cohort comprised 14 188 women. Those who had a metastatic disease at diagnosis (stage IV, n=264), were diagnosed with first distant metastasis occurring within 3 months from breast cancer diagnosis (n=44), had tumour size less than 1 mm (n=52), received neoadjuvant treatment (n=798) and did not undergo surgery for breast cancer (n=217) were excluded. Women who were diagnosed with second primary cancer at the time of breast cancer diagnosis (n=226) were also excluded because of impossibility to infer origin of metastasis. Finally, women who were referred as dying from breast cancer without any record of distant metastasis were also excluded (n=240), as it was not possible to assess whether this was due to missing information about metastatic status or due to the inaccurate in the reported underlying cause of death. Of the remaining patients (n=12 322), 1189 (9.7%) had subsequent distant metastasis within 10 years of initial diagnosis.

Information on date of breast cancer diagnosis, planned adjuvant treatment and site of first distant metastasis was complete for all patients. Information on number of positive lymph nodes and tumour size was available for 94.6% and 98.4% of patients, respectively. Information on ER status was available for 80.3% of patients. For this reason, in the analysis we eventually included only patients with information available for each covariate used in the models (n=9514), of which 995 (10.4%) developed distant metastasis within 10 years of initial diagnosis.

Information on the cause of death was obtained from the Swedish Cause of Death Register (Rutqvist, 1985). Patients with underlying cause of death other than breast cancer (International Classification of Diseases (ICD) version 8 = 174, ICD9 = 174, ICD10 = C50) were censored. Information on the site of first metastasis was obtained from the SBCR and was divided into eight groups according to the ICD code: skeleton, lung, pleura, liver, central nervous system (CNS), skin, other sites and multiple sites of first distant metastasis (defined as distant metastasis diagnosed within 2 months from the first distant metastasis diagnosis).

Ethics. This study has an ethical permission from the regional ethics committee at the Karolinska Institutet.

Statistical analysis. This cohort study was analysed using survival methodology with adjustment for competing risks. All women were followed up and they contributed to risk–time from the date of diagnosis until the date of first distant metastasis (event) or diagnosis of second primary cancer, date of death, 10 years of follow-up or end of study, 31 December 2006 (censoring).

Rates of first distant metastasis were calculated as number of events (development of first distant metastasis) divided by total risk–time. These rates were modelled using flexible parametric survival models (FPMs) that use a restricted cubic spline function for the cumulative baseline hazard function (Royston and Parmar, 2002; Lambert and Royston, 2009). The models estimate hazard ratios (HRs) with 95% confidence intervals (CIs) as measure of association between exposures and outcome. For the baseline rate, we used a spline with five degrees of freedom (two knots at each boundary and four intermediate knots placed at quintiles of the distribution of events). The underlying timescale used in the analysis was time since diagnosis of breast cancer.

From the FPM it is also possible to post estimate the cumulative risk of developing metastasis in the presence of competing risks (Hinichliffe and Lambert, 2012). We estimated the cumulative risk for first distant metastasis within 5 years from diagnosis for various covariate patterns in the presence of competing event death due to causes other than breast cancer. We further estimated the cumulative risk of metastasis during the period of 5–10 years after diagnosis, conditional upon surviving and being metastasis-free at 5 years (that is, conditional probabilities). Variables were categorised as follows: age at breast cancer diagnosis (<50, 51–60, 61–74 years), calendar period at breast cancer diagnosis (1990–1994, 1995–1999, 2000–2006), tumour size (<20 mm, >20 mm), lymph node status (positive/negative), ER status (ER-positive/negative) and treatment. Treatment was categorised as local treatment (surgery without adjuvant treatment; surgery with radiotherapy only (RT)) and systemic treatment (any combination with either chemotherapy (CT) or hormone therapy (HT)).

Firstly, we estimated HRs by age and tumour characteristics using non-proportional hazards models, which allow HR to vary over follow-up (that is, time-dependent effects).

Secondly, we estimated 5-year cumulative risks of developing a first distant metastasis in the presence of competing event death due to other causes. As cumulative risk is an absolute measure, results are shown for a given set of characteristics (covariate patterns). We also report cumulative risks during 5–10 years after
diagnosis conditional on surviving 5 years answering the question: what is the probability that a patient who has survived 5 years without metastasis will develop first distant metastasis in the coming years? The data were analysed using Stata Intercooled 12.0 (StataCorp, 2009, Stata Statistical Software: Release 12, College Station, TX, USA: StataCorp LP) and R package version 2.15.1 for calculating CIFs 5–10 years.

## RESULTS

The mean age of the patients was 56.4 years at diagnosis. The tumour characteristics were distributed as follows: 63.5% of patients had lymph node-negative tumours, 69% had tumours of size 20 mm or less and 82.3% had ER-positive tumours (Table 1). In our cohort, 87.9% of women underwent systemic adjuvant treatment. The overall rate of first distant metastasis was 19.4 per 1000 person–years (95% CI: 18.2–20.6).

Table 1. Frequency distributions and rates of first distant metastasis in the study cohort of breast cancer patients in the Stockholm and Gotland Swedish counties, 1990–2006, followed for up to 10 years since diagnosis

| Age at diagnosis | Total N (%) | First distant metastasis N (%) | Rate of metastasis per 1000 person–years (95% CI) |
|------------------|-------------|-------------------------------|-----------------------------------------------|
| ≤50 Years        | 2913 (30.6) | 400 (40.2)                    | 25.0 (22.6–27.6)                              |
| 51–60 Years      | 3039 (31.9) | 271 (27.2)                    | 16.6 (14.7–18.7)                              |
| 61–74 Years      | 3562 (37.4) | 324 (32.6)                    | 17.1 (15.3–19.1)                              |

### Period of breast cancer diagnosis

| Period of breast cancer diagnosis | Total N (%) | First distant metastasis N (%) | Rate of metastasis per 1000 person–years (95% CI) |
|----------------------------------|-------------|-------------------------------|-----------------------------------------------|
| 1990–1994                        | 2623 (27.6) | 496 (49.8)                    | 24.2 (22.2–26.4)                              |
| 1995–1999                        | 2242 (23.6) | 324 (32.6)                    | 18.9 (16.9–21.0)                              |
| 2000–2006                        | 4650 (48.9) | 175 (17.6)                    | 12.8 (11.1–14.9)                              |

### ER status

| ER status | Total N (%) | First distant metastasis N (%) | Rate of metastasis per 1000 person–years (95% CI) |
|-----------|-------------|-------------------------------|-----------------------------------------------|
| Positive  | 7830 (82.3) | 688 (69.1)                    | 16.1 (14.9–17.4)                              |
| Negative  | 1684 (17.7) | 307 (30.9)                    | 35.7 (32.0–40.0)                              |

### Lymph nodes status

| Lymph nodes status | Total N (%) | First distant metastasis N (%) | Rate of metastasis per 1000 person–years (95% CI) |
|--------------------|-------------|-------------------------------|-----------------------------------------------|
| Positive           | 6043 (63.3) | 354 (32.4)                    | 12.4 (9.4–11.3)                               |
| Negative           | 3471 (36.5) | 463 (44.6)                    | 36.9 (34.1–39.9)                              |

### Tumour size

| Tumour size | Total N (%) | First distant metastasis N (%) | Rate of metastasis per 1000 person–years (95% CI) |
|-------------|-------------|-------------------------------|-----------------------------------------------|
| ≤20 mm      | 6567 (69.0) | 457 (45.9)                    | 12.5 (11.4–13.7)                              |
| >20 mm      | 2947 (31.0) | 538 (54.1)                    | 36.2 (33.3–39.4)                              |

### Treatment

| Treatment | Total N (%) | First distant metastasis N (%) | Rate of metastasis per 1000 person–years (95% CI) |
|-----------|-------------|-------------------------------|-----------------------------------------------|
| Local (surgery + /− RT only)  | 9514 (100.0) | 955 (100.0)                   | 19.4 (18.2–20.6)                              |
| Systemic (with CT and/or HT)  | 1147 (12.1)  | 193 (16.9)                    | 24.5 (21.3–28.2)                              |
| Total     | 13371 (99.9) | 1148 (8.6)                    | 19.4 (18.2–20.6)                              |

Abbreviations: CI = confidence interval; CT = chemotherapy; ER = oestrogen receptor; HT = hormone therapy; RT = radiation therapy.

Figure 1 shows rates of first distant metastasis in relation to time since breast cancer diagnosis for different age groups of patients and tumour characteristics. Women younger than 50 years at breast cancer diagnosis, women with ER-negative tumours, positive lymph nodes and tumours larger than 20 mm, all showed a peak in the rate of first distant metastasis at about 2 years, in comparison with fairly stable rates in other subgroups of patients. In particular, women with ER-negative tumours showed a sharp decrease in the rate of first distant metastasis after 2 years since breast cancer diagnosis, whereas women with ER-positive tumours showed rather stable rates of first distant metastasis over time from about 1 year up until 10 years since breast cancer diagnosis.

Table 2 shows frequency distribution of sites of first distant metastasis by time-to-first distant metastasis subdivided into 0–2, 2–5 and 5–10 years since diagnosis. Overall, metastasis to the skeleton (32.5%) and multiple sites of metastasis (28.3%) were the most frequent presentations of distant metastasis within 10 years. No particular combination pattern of multiple sites of first distant metastasis was found in the cohort. The site distribution of first distant metastasis changed significantly (P<0.05) over time for the following sites: skeleton, CNS and liver. The proportion of first distant metastasis to the skeleton increased from 29.9% of all first distant metastasis in the first 2 years to 36.5% in the period of 5–10 years since breast cancer diagnosis. The proportion of CNS and liver metastasis instead decreased from 6.8% and 15.4%, respectively, in the first 2 years to 1.8% and 8.0%, respectively, in 5–10 years since breast cancer diagnosis. Between 5 and 10 years since breast cancer diagnosis, 274 (27.5%) of all first distant metastasis were diagnosed.

Table 3 shows time-dependent HRs of developing first distant metastasis by age and tumour characteristics at 2, 5 and 10 years from breast cancer diagnosis. For women with positive lymph nodes, the hazard of developing metastasis was still significantly increased at 10 years after diagnosis (HR = 2.6; 95% CI: 1.9–3.5) compared with women with negative lymph nodes. Women with ER-negative tumours had an increased hazard at 2 (HR = 2.7; 95% CI: 2.2–3.3) and 5 (HR = 1.4; 95% CI: 1.1–1.7) years from breast cancer diagnosis compared with women with ER-positive tumours; at 10 years from diagnosis, the same HR was not significantly increased anymore (HR = 0.9; 95% CI: 0.6–1.4). Having a tumour larger than 20 mm at breast cancer diagnosis was still causing an increased hazard of developing first distant metastasis at 10 years (HR = 1.5; 95% CI: 1.1–2.0).

Table 4 shows cumulative risks of developing first distant metastasis within 5 years of diagnosis, and within 10 years surviving 5 years without metastasis, according to all different covariate patterns. Among those with an adjuvant treatment combination including CT and/or HT, the highest risk of first distant metastasis in the period of 0–5 years was found in patients of 50 years of age or less, with tumour size ≥ 20 mm, positive lymph nodes and ER-negative tumours at breast cancer diagnosis (cumulative risk = 0.45; 95% CI: 0.38–0.53); whereas the lowest risk was among patients aged 51–74 years with negative lymph nodes, tumour size ≤ 20 mm and with ER-positive tumours at breast cancer diagnosis (cumulative risk = 0.03; 95% CI: 0.02–0.04). For the same two groups of patients in the period of 5–10 years following diagnosis (that is, among those who survived metastasis-free until 5 years), the risk dropped (cumulative risk = 0.09; 95% CI: 0.05–0.17) for the group originally at the highest risk, whereas it remained the same (cumulative risk = 0.03; 95% CI: 0.02–0.04) for the group at the lowest risk. The risk at 5–10 years following diagnosis was similar to the risk for the period of 0–5 years in all women with ER-positive tumours and negative lymph nodes, regardless of treatment, tumour size and age. This was also true for women with ER-negative tumours and positive lymph nodes, if the tumour size at diagnosis was ≤ 20 mm. For all patients with ER-negative tumours instead, the risk at 5–10 years following diagnosis was significantly lower compared with the risk for the period of 0–5 years regardless of age, tumour size and nodes. Women treated with systemic adjuvant treatment (that is, CT and/or HT) always had lower risks compared to women treated with surgery only, with or without RT.

## DISCUSSION

We found that the site distribution of first distant metastasis over time changed significantly for metastasis to the skeleton, CNS and
The risk of developing distant metastasis within 10 years of breast cancer diagnosis significantly varied in different subgroups of patients. The risk remained non-negligible up to 10 years since diagnosis particularly among women with positive lymph nodes. The risk was high in particular among patients with ER-negative tumours within the first 5 years of diagnosis, whereas it significantly decreased after 5 years since diagnosis. The risk of developing distant metastasis remained instead rather stable for most subgroups of patients with ER-positive tumours independent of age and other tumour characteristics.

In our cohort, one-third of first distant metastasis was diagnosed in the skeleton. This proportion significantly increased over time since diagnosis, whereas the proportion of metastasis to the liver and CNS significantly decreased. This seems to reflect the natural history of distant recurrences as women with ER-positive tumours more often develop metastasis to the skeleton later during follow-up, whereas women with ER-negative tumours more often develop early liver and CNS metastasis (Kennecke et al, 2010).

Interestingly, the risk for developing distant metastasis over time since diagnosis mirrors the pattern observed for breast cancer patients with different characteristics. The risk is higher in the early years after diagnosis and then decreases, especially among ER-negative patients. This is consistent with the natural history of breast cancer metastases.

Table 2. Frequencies and proportion of first distant metastases, by time since diagnosis and site, in the study cohort of breast cancer patients in the Stockholm and Gotland Swedish counties, 1990–2006, followed for up to 10 years since diagnosis

| Site of first distant metastasis | 0–2 Years, n (%) | 2–5 Years, n (%) | 5–10 Years, n (%) | 0–10 Years, n (%) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Skeleton                        | 97 (29.9)       | 126 (31.7)      | 100 (36.5)      | 323 (32.5)      |
| Lung                            | 24 (7.4)        | 41 (10.3)       | 22 (8.0)        | 87 (8.7)        |
| Liver                           | 50 (15.4)       | 36 (9.1)        | 22 (8.0)        | 108 (10.9)      |
| Pleura                          | 12 (3.7)        | 17 (4.3)        | 16 (5.8)        | 45 (4.5)        |
| CNS                             | 22 (6.8)        | 17 (4.3)        | 5 (1.8)         | 44 (4.4)        |
| Other                           | 31 (10.0)       | 32 (8.1)        | 43 (15.7)       | 106 (10.7)      |
| Multiple                        | 88 (27.2)       | 128 (32.2)      | 66 (24.1)       | 282 (28.3)      |
| Total (any site)                | 324 (100.0)     | 397 (100.0)     | 274 (100.0)     | 995 (100.0)     |

Abbreviation: CNS = central nervous system.

Table 3. Adjusted HR and 95% CIs of developing a first distant metastasis by patient and tumour characteristics in the study cohort of breast cancer patients in the Stockholm and Gotland Swedish counties, 1990–2006, followed for up to 10 years since diagnosis

| Age               | At 2 years, HR (95% CI) | At 5 years, HR (95% CI) | At 10 years, HR (95% CI) |
|-------------------|-------------------------|-------------------------|--------------------------|
| <50 Years         | 1.5 (1.2–1.9)           | 1.1 (0.9–1.3)           | 1.1 (0.8–1.5)            |
| 51–60 Years       | 1.0 (0.8–1.3)           | 0.9 (0.8–1.1)           | 1.0 (0.7–1.4)            |
| 61–74 Years       | 1.0                      | 1.0                      | 1.0                      |

| Lymph nodal status | At 2 years, HR (95% CI) | At 5 years, HR (95% CI) | At 10 years, HR (95% CI) |
|-------------------|-------------------------|-------------------------|--------------------------|
| Negative lymph nodes | 1.0                    | 1.0                     | 1.0                      |
| Positive lymph nodes | 3.2 (2.4–4)           | 2.9 (2.5–3.4)           | 2.6 (1.9–3.5)            |

| ER status | At 2 years, HR (95% CI) | At 5 years, HR (95% CI) | At 10 years, HR (95% CI) |
|-----------|-------------------------|-------------------------|--------------------------|
| ER +      | 1.0                     | 1.0                     | 1.0                      |
| ER -      | 2.7 (2.2–3.3)           | 1.4 (1.1–1.7)           | 0.9 (0.6–1.4)            |

| Tumour size | At 2 years, HR (95% CI) | At 5 years, HR (95% CI) | At 10 years, HR (95% CI) |
|-------------|-------------------------|-------------------------|--------------------------|
| 1–20 mm     | 1.0                     | 1.0                     | 1.0                      |
| >20 mm      | 2.7 (2.2–3.3)           | 1.8 (1.6–2.1)           | 1.5 (1.1–2)              |

Abbreviations: CI = confidence intervals; ER = oestrogen receptor; HR = hazard ratios.

*HRs adjusted for all variables in the table, treatment and calendar period. Time-varying effects for age, lymph node status, ER status and tumour size.

bReference group.

Figure 1. Estimated rates of first distant metastasis within 10 years of diagnosis of first invasive breast cancer in women diagnosed between 1990 and 2006 in Stockholm–Gotland Swedish counties, according to age and tumour characteristics.
Metastasis still indicates a very poor prognosis in breast cancer whereas ER status is not. These findings confirm that distant breast cancer death, at 10 years since breast cancer diagnosis, is a significant prognosticator of distant recurrence, as well as of breast cancer-specific mortality that has been previously studied in this same cohort: lymph node status and tumour size at diagnosis are significant prognosticators of distant recurrence as it allows a quantitative estimation of what is the actual cumulative risk as a function of time is of relevant clinical value. Time-dependent effects (interaction with time since diagnosis) for age and tumour characteristics. The use of cumulative risk as a function of time is of relevant clinical value as it allows a quantitative estimation of what is the actual probability of developing distant metastasis for any given subgroup of breast cancer patients at different time points. This measurement may help clinicians to better estimate the individual risk of developing first distant metastasis during the first 5 years as well as metastasis carries over significantly to the second 5 years of follow-up for most metastasis-free patients, particularly those patients with lymph node-positive tumours where the risk at 5–10 years up for most metastasis-free patients, particularly those patients with lymph node-positive tumours where the risk at 5–10 years after diagnosis.

Cumulative risk estimates of developing distant metastasis were obtained for specific subgroups of patients while taking into account the competing risk of dying from other causes and by allowing time-dependent effects (interaction with time since diagnosis) for age and tumour characteristics. The use of cumulative risk as a function of time is of relevant clinical value as it allows a quantitative estimation of what is the actual probability of developing distant metastasis for any given subgroup of breast cancer patients at different time points. This measurement may help clinicians to better estimate the individual risk of developing first distant metastasis during the first 5 years as well as metastasis carries over significantly to the second 5 years of follow-up for most metastasis-free patients, particularly those patients with lymph node-positive tumours where the risk at 5–10 years after diagnosis.
after diagnosis is always higher or equal to 8%. In addition, for some subgroups of patients with ER-positive tumours, the cumulative risk of developing distant metastasis in the period of 0–5 and 5–10 years is essentially the same.

Patients with ER-positive and lymph node-negative tumours show no change and very low risk over time. This could be explained by a very good effect of treatment, or alternatively even by overtreatment since patients undergoing local treatment show a similar low risk. More clinical attention should, however, be given to other subgroups in which follow-up could be intensified and treatment could be improved. In particular, women with ER-positive, lymph node-positive, >20 mm tumours still have a risk higher than 10% to develop first distant metastasis in the period of 5–10 years after diagnosis. Of note, all subgroups of patients with ER-negative tumours have a sharp significant decrease in risk of developing distant metastasis in the period of 5–10 years following diagnosis compared with the period of 0–5 years, independent of age and other tumour characteristics. The American Society of Clinical Oncology (ASCO) has recently concluded in a review of the clinical practice guidelines of years, independent of age and other tumour characteristics. The 5–10 years following diagnosis compared with the period of 0–5 and 5–10 years is essentially the same.

We thank the Stockholm Breast Cancer Registry and the Stockholm Breast Cancer Group for the data made available and for the help in the data cleaning and study design phase. This research was funded by the King Gustaf V Jubilee Fund, Swedish Research Council (grant no: 521-2008-2728); Swedish Cancer Society (grant no: CAN 2010/807); and the Swedish Cancer Society (grant no: 5128-B07-01PAF to KC). This study was supported by the Cancer Risk Prediction Center (CRiSP; www.crispcenter.org), a Linneus Centre (Contract ID 70867902) financed by the Swedish Research Council. We also thank Dr Paul Lambert from the University of Leicester (UK) for the methodological support in the analysis.

### ACKNOWLEDGEMENTS

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