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Time from breast cancer diagnosis to therapeutic surgery and breast cancer prognosis: a population-based cohort study

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Novelty and Impact

Theoretically, time from breast cancer diagnosis to therapeutic surgery should affect survival but it is uncertain whether this holds true in a modern healthcare setting. The present study shows that even fairly short intervals from breast cancer diagnosis to surgery are associated with survival. Our findings suggest that the time interval between diagnosis and therapeutic surgery should be kept as short as possible without hampering diagnostic work-up and pre-operative patient optimization.

Abstract

Theoretically, time from breast cancer diagnosis to therapeutic surgery should affect survival. However, it is unclear whether this holds true in a modern healthcare setting in which breast cancer surgery is carried out within weeks to months of diagnosis.

This is a population- and register-based study of all women diagnosed with invasive breast cancer in the Stockholm-Gotland healthcare region in Sweden, 2001 - 2008, and who were initially operated. Follow-up of vital status ended 2014. 7017 women were included in analysis. Our main outcome was overall survival. Main analyses were carried out using Cox proportional hazards models. We adjusted for likely confounders and stratified on mode of detection, tumor size and lymph node metastasis.

We found that a longer interval between date of morphological diagnosis and therapeutic surgery was associated with a poorer prognosis. Assuming a linear association, the hazard rate of death from all causes increased by 1.011 (95% CI 1.006 to 1.017) per day. Comparing, e.g., surgery 6 weeks after diagnosis to surgery 3 weeks after diagnosis, thereby confers a 1.26-fold increased hazard rate. The increase in hazard rate associated with surgical delay was strongest in women with largest tumors. Whilst there was a clear association between delays and survival in women without lymph node metastasis, the association may be attenuated in subgroups with increasing number of lymph node metastases. We found no evidence of an interaction between time to surgery and mode of detection.

In conclusion, unwarranted delays to primary treatment of breast cancer should be avoided.

Introduction

In women worldwide, breast cancer is the most common cancer and leading cause of cancer death. Although breast cancer incidence has risen during the past decades, mortality has decreased. Surgery is the primary treatment for most breast cancers. Depending on patient characteristics, surgical radicality, stage, and tumor characteristics, adjuvant treatment with systemic therapy and radiotherapy may be given postoperatively. Delaying time to surgery will postpone all following oncologic treatment.

The magnitudes of the benefits and harms of mammography screening have been much debated due to controversies regarding the validity and relevance of the performed randomized controlled trials [1-5]. However, most reviews have concluded that mammography screening does reduce breast cancer-specific mortality [6-9]. If early detection decreases mortality, then shorter intervals to therapeutic surgery should also improve prognosis. However, whereas screening intervals are recommended to be 18 to 24 months long in Sweden, most patients are operated within weeks to months. Lastly, many advances in breast cancer treatment have been made, radically improving breast cancer prognosis [10-13]. Thus, although the time interval between date of breast cancer diagnosis and surgery theoretically should have an impact on prognosis, the interval may be too short and/or the effect too small to influence survival in the modern healthcare setting.

Studies that have investigated the association between time from breast cancer diagnosis to first treatment and survival are inconclusive [14-21], possibly owing to

differences in calendar periods, study populations, cut-offs and starting (e.g. physician referral vs morphological diagnosis) and end (e.g. surgery vs neoadjuvant therapy) points for calculating delays. The two, to date, largest studies, both published by Bleicher et al., [19] have found an association between increased time to surgery and worse survival. However, they included delays up to 180 days which may introduce bias since delays of this length are not random but could rather be due to e.g. severe comorbidity. The studies were further based on the SEER-Medicare and National Cancer Database (NCDB) populations, respectively. The former database only includes patients covered by Medicare and the latter is a hospital-based registry including 73% of breast cancer patients and with lower completeness for certain ethnicities and elderly patients [22]. The Swedish healthcare system, on the other hand, includes all Swedish residents, and the Regional Breast Cancer Register of Stockholm-Gotland, on which this study is based, has a completeness of 98% [23].

It is known that there is an increased risk of tumor cell dissemination in higher stage disease [24]. Hence, there may be an association between time to surgery and prognosis in higher stage breast cancer due to the postponement of systemic therapy. On the other hand, other factors, such as tumor aggressiveness and chemotherapy sensitivity, may be more important than timing in women who already have micrometastatic spread. Previous studies that have investigated possible differences in the relationship between time to surgery and survival based on stage are inconsistent [15, 19]. Stage is a variable composed of both tumor size and lymph node status (as well as assessment of distant metastasis). Whereas both of these tumor characteristics can be proxies for aggressiveness, they reflect different aspects of tumor biology. Thus, it may be important to study these factors individually.

Using a population-based breast cancer cohort capturing in principle all of the breast cancer cases within a Swedish healthcare region, we sought to investigate if also shorter intervals from breast cancer diagnosis to therapeutic surgery are associated with survival. We further wished to study this association stratifying on mode of detection, and separately stratifying on tumor size and lymph node metastasis, which, to our knowledge, has not been previously studied.

Materials and Methods

Women diagnosed with an invasive breast cancer between January 1, 2001 and December 31, 2008 in the healthcare region of Stockholm-Gotland in Sweden, were identified through the Regional Breast Cancer Register. The register includes information on diagnosis, surgery, postoperative treatment, tumor characteristics, and follow-up and has a completeness of 98% [23]. Using the unique personal identity number assigned to all Swedish residents, additional information was retrieved from the nationwide Swedish Cancer Register, the National Patient Register, the Mammography Screening Database, and the Cause of Death Register. The Cause of Death Register covers all residents in Sweden with essentially no missing deaths and has been shown to correctly classify 98% of breast cancer deaths [25]. The follow-up of vital status is therefore virtually complete. The Mammography Screening Database kept at the Stockholm-Gotland Regional Cancer Center holds information on attendance, outcomes and dates of all visits within the population-based mammography screening program in Stockholm-Gotland. We retrieved information on somatic and psychiatric comorbidity using the National Patient Register which has nationwide coverage for inpatient hospitalizations in Sweden since 1987. Specialized

outpatient clinics are also obligated to report to the National Patient Register since 2001. Diagnoses are coded according to the International Code of Diseases (ICD). Inpatient and outpatient coverage is approximately 100% [26] and 87% [27], respectively, and validity is high [26, 28, 29] We thus had information on all reported primary and secondary diagnoses for all inpatient hospitalizations and specialized outpatient visits since 1987 and 2001, respectively, and to end of follow-up for our study subjects.

We identified 9191 women with a diagnosis of invasive breast cancer in Stockholm-Gotland during the study inclusion period of which 8229 women were initially operated. Hence, only women with stage 1 to 3 disease and women who did not receive neoadjuvant therapy were eligible. Exclusions are depicted in Figure 1. Women who had the same recorded date for both breast cancer diagnosis and surgery were excluded since these women either 1) underwent diagnostic operations; 2) were pre-operatively diagnosed with in situ breast cancer but where postoperative, pathology reports showed an invasive component; or 3) had an incorrectly recorded date of diagnosis. Patients in the first group are more likely to have non-symptomatic, small lesions with no axillary involvement [30, 31], since these are most difficult to detect preoperatively. The same rationale applies to the second group – i.e. that these patients are more likely to have smaller invasive components and no axillary involvement since they were not detected preoperatively. These two groups will therefore to a greater extent be composed of cancers of a lower stage than the general breast cancer population (which we also found in our study population (data not shown)), and, thus, also have a better survival which would skew the association between time to surgery and prognosis. We further excluded all women who had >63 days from date of diagnosis to date of surgery. Delays of this magnitude are not

spurious but rather due to e.g. more severe comorbidity or possibly erroneous coding of neoadjuvant therapy, both of which would affect the analysis of prognosis. The cut-off of 63 days was selected since this is the minimum time in which four cycles of neoadjuvant chemotherapy could be administered and this was a commonly administered amount of cycles in the neoadjuvant setting in the Stockholm-Gotland healthcare region during the inclusion period. Our final study population comprised 7017 women.

For all outcomes, follow-up started at date of morphological diagnosis (code 5 diagnosis based on a fine needle aspiration or a core needle biopsy). Since information on vital status was available until November, 2014, but information on cause of death only was available throughout 2013, follow-up ended on date of death, emigration, or, if these events did not occur, in November, 2014, for overall survival and December, 2013, for breast cancer-specific survival. Follow-up of distant recurrence ended five years after date of diagnosis, date of distant metastasis, death, or emigration, whichever came first. We restricted the follow-up of distant metastasis to five years in order to try to achieve as high completeness as possible.

Statistical analysis

Time to surgery was primarily considered as a continuous variable since the fit of regression models for survival times were superior to when it was treated as a categorical variable. However, for the purpose of descriptive statistics and in order to construct Kaplan Meier curves, time to surgery was à priori categorized accordingly: 0 to 14 days, 15 to 28 days, 29 to 42 days and 43 to 63 days.

Our main outcome of interest, decided on à priori, was overall survival since it contained more events and included one more year of follow-up than breast cancer-specific survival which increases power to detect subtle differences. However, we also studied breast cancer-specific survival and risk of distant metastasis in order to confirm results. Survival analysis was performed using Kaplan Meier survival curves and the Cox proportional hazards model. The proportional hazards assumptions were examined using Schoenfeld residuals. All the assumptions of the Cox proportional hazards model were satisfied. We also used restricted cubic splines to investigate a possible non-linear relationship between time to surgery and overall survival. In order to compare the fits of these models which included different degrees of freedom, we used the Akaike Information Criterion (AIC) [32].

We studied the association of time to surgery and prognosis in the population as a whole. Since mode of detection, tumor size and lymph node status could modify associations, we thereafter stratified on mode of detection (screen- vs non-screen-detected tumors), tumor size (≤20 mm, >20 to 40mm, or >40 mm) and number of lymph node metastasis (0, 1 to 3, or ≥4). Categories were decided upon à priori.

Age, immigration status, comorbidity according to the Charlson Comorbidity Index (CCI) score [33], diagnosis of a psychiatric disorder including substance abuse before date of breast cancer surgery, mode of detection, synchronous contralateral breast cancer (within three months of the primary tumor), tumor size and lymph node status according to pathology reports, immediate breast reconstruction, operating hospital, calendar period were included as potential confounders in multivariate analyses. We

also adjusted for planned adjuvant therapy - chemotherapy and/or trastuzumab (only 148 women received trastuzumab and all but four of these individuals received chemotherapy), radiotherapy, and endocrine therapy - in order to investigate whether time to surgery was independently associated with survival. All of the aforementioned covariates were included in what was considered our main model. For approximately 60% of our study population we could extract information on education level, BMI and smoking status based on questionnaire data obtained in 2009 since these individuals were also included in the LIBRO-1 study [34]. We thus carried out sensitivity analyses further adjusting for these factors. For all other covariates there was a very low degree of missingness (0 to <3%) except for immediate breast reconstruction which had a missingness of 22%. A missing category was created for all variables that had missing values and included in analyses. In the regression analyses, all covariates were treated/categorized as in Table 1.

Analyses were carried out using the statistical software, STATA 13.1.

Results

Descriptive statistics are summarized in Table 1 and includes all the covariates adjusted for. The median time to surgery was 27 days. The median follow-up time was 8.9 years (range 23 days to 13.9 years). There was no statistically significant difference in follow-up time based on time to surgery (p=0.235).

Unadjusted Kaplan Meier curves for overall survival showed a poorer survival with increasing time to surgery (p<0.0001) (Figure 2) which was also replicated in

multivariate analyses using the Cox proportional hazards model (Table 2). We found a statistically significant association between time to surgery and each of the three outcomes. Each day's delay conferred an increased hazard rate of death from all causes by 1.011 (95% CI 1.006 to 1.016) after full adjustment. Comparing surgery after 6 weeks to surgery after 3 weeks (a difference of 21 days), thus confers a 1.26-fold ($1.011^{\wedge 21}$) increased hazard rate of death. Hazard ratios (HR) were somewhat lower for breast cancer-specific death (1.007, 95% CI 1.000 to 1.014) and risk of distant metastasis within five years (1.008, 95% CI 1.001 to 1.016). We further adjusted for education level, BMI, and smoking status and found that point estimates remained unchanged for breast cancer-specific survival and risk of distant metastasis and virtually unchanged for overall survival (HR 1.010, 95% CI 1.006 to 1.015). Since associations with delays were stronger for overall survival than for breast cancer-specific survival and distant metastasis, we hypothesized that this could be due to residual confounding by comorbidity since comorbidity affects both timing and type of surgery, timing and type of adjuvant therapy, and both breast cancer-specific deaths and deaths due to other causes. We therefore carried out post hoc analyses of the association between time to surgery and overall survival restricted to women with no somatic nor psychiatric comorbidity (n=5762, 849 deaths, 52193 years at risk). Results were somewhat attenuated and similar to point estimates for breast cancer-specific survival and risk of distant metastasis; HR for overall survival was 1.008 (95% CI 1.002 to 1.013, p=0.010) based on our main model and 1.007 (95% CI 1.002 to 1.013, p=0.012) after further adjustment for education level, BMI and smoking status.

We proceeded by allowing for a smooth nonlinear covariate effect using splines. Although we did not find convincing evidence to reject the linear model (the linear model had lowest AIC value, a value of 20163.4, compared to values of 20165.0 and 20166.5 for the 2 and 3 degrees of freedom models, respectively,) the nonlinear models suggested that an association between time to surgery and survival may be strongest after around 20 days (Figure 3). The HRs comparing surgery after 6 weeks to surgery after 3 weeks were similar for all three models. Post-hoc, stratified analysis lent further support to the observation that a day's "delay" may carry different weight according to its time from diagnosis; in women operated within 20 days, there was no statistically significant association with overall survival (HR 1.004 for each day's delay; 95% CI 0.975-1.033, after full adjustment), whereas the hazard rate increased by 1.012 (95% CI 1.006-1.019, after full adjustment) for each day's delay in the group operated 21-63 days after diagnosis.

We lastly performed analyses stratifying on tumor size and lymph node metastases, the results of which are presented in Table 3. On the multiplicative scale (Cox proportional hazards model) the increase in hazard rate (from an increase in surgical delay), independent of outcome, was largest in the group of women with largest tumors (and, of course, large tumors are associated with high hazard rates). The interaction between time to surgery and tumor size was statistically significant for all three outcomes (p=0.0019 for the main model for overall survival). Based on our main model, the hazard rate for death from all causes increased by a factor of 1.030 (95% CI 1.014 to 1.046) for women with tumors >40 mm, and by a factor of 1.007 (95% CI 1.000 to 1.014) for women with tumors ≤20 mm per day's delay. Survival analyses stratified on lymph node metastases revealed that, on the multiplicative

scale, the association between a surgical delay and an increased hazard rate of death was attenuated with an increasing amount of lymph node metastases (p=0.0001 for an interaction between time to surgery and lymph node status). Based on our main model, the hazard rate for death from all causes increased by a factor of 1.012 (95% CI 1.005 to 1.019) for women with no lymph node metastases, and by a factor of 1.003 (95% CI 0.993 to 1.012) for women with >=4 lymph node metastases per day's delay. Similar point estimates of association within each of the strata were seen for breast cancer-specific survival and risk of distant metastasis within five years, as were seen of overall survival, although they were not statistically significant.

The association between time to surgery and overall survival was only statistically significant in non-screen-detected cancers (HR 1.010, 95% CI 1.004 to 1.015, and 1.003, 95% CI 0.992 to 1.014, for non-screen-detected cancers and screen-detected cancers, respectively). However, there was no statistically, significant interaction between time to surgery and mode of detection (p=0.6576 for overall survival).

Discussion

Despite relatively short intervals, we found that time to therapeutic surgery from breast cancer diagnosis was associated with prognosis (overall survival, breast cancer-specific survival, and risk of distant metastasis within five years). Assuming a linear relationship, we found that the hazard rate of death from all causes increased by 1.011 per day, which, comparing e.g. surgery at 6 weeks after diagnosis to surgery at 3 weeks after diagnosis, would confer a 1.26-fold increased hazard rate of death. The association between time to surgery and survival was especially

pronounced in women with larger tumors. Whereas this association also was present in women with no lymph node metastases, the association was attenuated in subgroups with increasing number of lymph node metastases.

A certain interval from date of diagnosis to surgery is needed to complete diagnostic work-up, optimize patients pre-operatively, and may also be crucial for patients to adjust to their cancer diagnosis and awaiting surgery. Results from non-linear models suggested that a day's "delay" carried different weight according to its time from diagnosis; the association with overall survival seemed to be strongest after 20 days and weaker, if at all present, in the interval before that. Future studies with more power are needed to further examine this.

Our finding of an association between surgical delay and an inferior survival in breast cancer patients is consistent with the three, previously published, population-based studies that have used morphological diagnosis as starting point and were confined to women who had surgery as initial treatment [18, 19]. It is further in line with most studies on early detection and breast cancer mortality [6-9]. Our results from analyses stratified on tumor size and lymph node metastasis are related to the findings of the NCDB cohort in the study conducted by Bleicher et al. [19] who found an association between time to surgery and an increased risk of death in women who had stage I and II disease, but not in women with stage III disease. This was not clearly seen in the SEER study by Bleicher et al. [19]. Conversely, McLaughlin et al. only found an association between time to first treatment (surgery, radiotherapy or systemic treatment) and survival in late stage disease [15]. However, the NCDB study is the only study with a study population comparable to ours since the SEER cohort only

included individuals over 65 years of age and the study by McLaughlin et al. was based on a cohort of low income women and included patients independent of type of first treatment which could explain the discrepant results. The differences in associations we found in subgroup analyses would be in agreement with the spectrum theory in which breast cancer is viewed as a heterogeneous disease; from tumors that remain localized throughout their entire life spans to those that already are disseminated at onset [35]. The theory states that many breast cancers fall in between these two extremities, being localized at first, but, if left untreated, at some time point acquiring the potential to spread [35].

Lymph node status is the single most significant prognostic factor of distant recurrence and death in women with breast cancer [36]. Women with lymph node metastases thus reflect the women at largest risk of tumor cell dissemination which implies that tumor cells have spread beyond the breast and locoregional lymph nodes. Local treatment with e.g. surgery will therefore not have a curative potential, which could explain the null association between time to surgery and prognosis in this group. However, delaying surgery also automatically delays all following systemic treatment, yet initiation of adjuvant chemotherapy could have been prioritized in women with more advanced disease. Alternatively, other factors such as tumor biology and treatment efficacy may outweigh the aspect of timing of adjuvant, systemic therapy, for these individuals, at least within the relatively short intervals investigated in this study.

The topic of this study is highly clinically relevant. Since it would be unethical to perform a randomized controlled trial with the same objective, one must rely on

observational studies. As with all such studies, our study has certain caveats. We cannot discern whether the poorer prognosis seen with increased time to surgery is due to delayed surgery, delayed adjuvant treatment or a combination of the two. There may be patient factors, other than the ones adjusted for, associated with both postponement of surgery and adjuvant treatment or treatment adherence. Yet, we believe that we adjusted for all relevant, systematic confounders, including patient factors such as somatic and psychiatric comorbidity. We further only allowed a fairly short interval to surgery, thereby excluding extremes. For a subcohort of women [34] we had additional information on education level, BMI and smoking. Point estimates remained unchanged for breast cancer-specific survival and distant metastasis within five years and virtually unchanged for overall survival after additional adjustment. Thus, by adjusting for the other factors included in our main model, we believe that we take into account effects of socioeconomic factors on the relationship between time to surgery and prognosis. This may be expected in a country like Sweden where healthcare, including both mammography screening and breast cancer treatment, is publically financed, and all Swedish residents are automatically covered by the National Healthcare System [37]. Because this study excluded women who received neoadjuvant therapy and women who had a diagnostic resection performed, we did not take tumor subtype into account since no other information on tumor characteristics other than tumor size and lymph node metastasis would have been available prior to surgery. Hence, tumor subtype could not have influenced time to surgery other than indirectly via age, stage and mode of detection, which were all adjusted for. A null association between time to surgery and subtype was also found in the subpopulation that had information on tumor subtype according to the St Gallen method [38] (n=1574) [39].

In observational studies, there is always a risk of residual confounding. We hypothesized that the differences in effect sizes between time to surgery and overall survival compared to the more breast cancer specific outcomes breast cancer-specific survival and risk of distant metastasis could be due to residual confounding by comorbidity since comorbidity can affect timing and type of surgery as well as adjuvant therapy and both breast cancer specific deaths and deaths by other causes. After exclusion of women with both somatic and psychiatric comorbidities, we found that point estimates for overall survival were somewhat attenuated and similar to point estimates for breast cancer-specific survival and risk of distant metastasis. Thus, the discrepancy in effect sizes may largely be due to residual confounding by comorbidity.

Strengths of this study include its prospective, cohort design. Furthermore, it is based on high quality registers with a nearly 100% coverage of breast cancer cases. Hence, it includes almost all women initially operated for breast cancer within the healthcare region of Stockholm-Gotland, independent of e.g. insurance status or survival. Additional strengths include the high quality of previously validated variables including mode of detection, low degree of missingness, virtually complete follow-up of vital status, and long follow-up time.

Conclusion

We have shown that even a few weeks delay from breast cancer diagnosis to therapeutic surgery is associated with an impaired prognosis. There may, however, be certain subgroups, such as women with lymph node metastases, for whom time to

surgery might be of less importance. For women with large tumors it may be particularly crucial to keep this interval at a minimum. In conclusion, the time interval between diagnosis and therapeutic surgery should be kept as short as possible without hampering diagnostic work-up and preoperative, patient optimization.

Footnotes

Author contributions: LE and KC conceived the study. LE, KC, JB, and FW designed the study and the other authors provided critical input. KC and ST managed the data collection and LE extracted and managed the data. LE and KH carried out the data analysis. All authors helped in the interpretation of data. LE wrote the first draft of the manuscript which all authors critically reviewed. All authors approved the final draft.

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Ethical approval: This study was approved by the Regional Ethical Review Board in Stockholm, Sweden, with reference number 2009/254-31/4. The data analyzed for the

main analyses were obtained from registry data and informed consent of individual participants was therefore not required. All individuals included in the LIBRO1 study provided written informed consent.

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Figure 1. Flow chart of study population

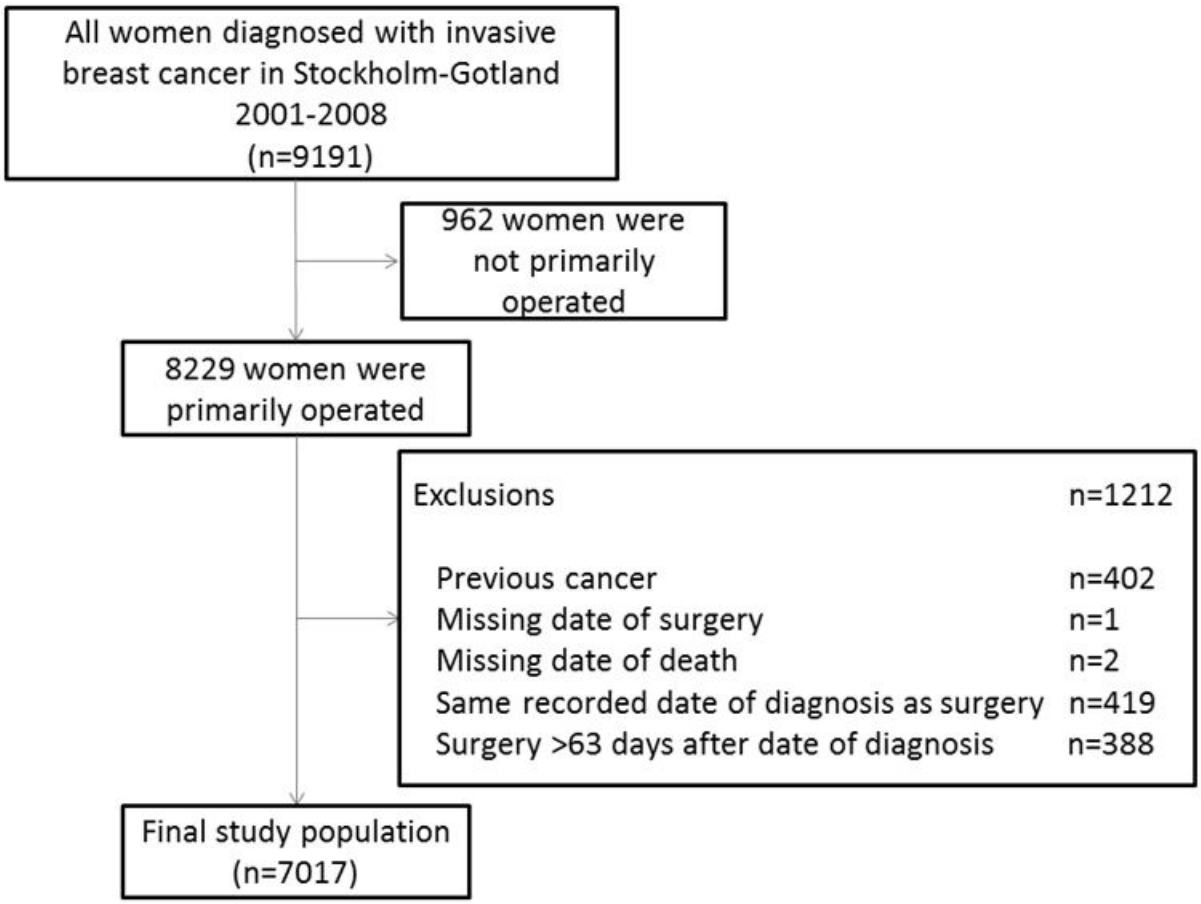


Table 1. Patient, tumor, treatment and follow-up characteristics by time to surgery

		Time to therapeutic breast cancer surgery			
	All[a] n=7017	**1 day - 2 weeks** n=745	**>2-4 weeks** n=3283	**>4-6 weeks** n=2166	**>6-9 weeks** n=823
Characteristic	Mean (SD) /n (%)	Mean (SD) /n (%)	Mean (SD) /n (%)	Mean (SD) /n (%)	Mean (SD) /n (%)
Age	58.2 (10.8)	56.0 (10.6)	57.8 (10.7)	59.2 (10.8)	59.0 (11.5)
BMI					
<25	2138 (30%)	257 (35%)	1013 (31%)	643 (30%)	225 (27%)
25-30	1322 (19%)	114 (15%)	645 (20%)	431 (20%)	132 (16%)
>=30	496 (7%)	53 (7%)	213 (6%)	167 (8%)	63 (8%)
Unknown	3061 (44%)	321 (43%)	1412 (43%)	925 (43%)	403 (49%)
Smoking status					
Non-smoker	1570 (22%)	172 (23%)	738 (22%)	499 (23%)	161 (20%)
Current smoker	1319 (19%)	138 (19%)	653 (19%)	396 (18%)	132 (16%)
Former smoker	286 (4%)	33 (4%)	135 (4%)	84 (4%)	34 (4%)
Unknown	3842 (55%)	402 (54%)	1757 (54%)	1187 (55%)	496 (60%)
Education level					
Low	2262 (32%)	236 (32%)	1036 (32%)	725 (33%)	265 (32%)
High	1716 (24%)	196 (26%)	839 (26%)	520 (24%)	161 (20%)
Unknown	3039 (43%)	313 (42%)	1408 (43%)	921 (43%)	397 (48%)
CCI[b]					
0	6173 (88%)	677 (91%)	2918 (89%)	1886 (87%)	692 (84%)
1	460 (7%)	37 (5%)	203 (6%)	159 (7%)	61 (7%)
≥2	343 (5%)	28 (4%)	145 (4%)	108 (5%)	62 (8%)
Unknown	41 (1%)	3 (0%)	17 (1%)	13 (1%)	8 (1%)
Psychiatric disorder[c]					
No	6484 (92%)	702 (94%)	3040 (93%)	1992 (92%)	750 (91%)
Yes	533 (8%)	43 (6%)	243 (7%)	174 (8%)	73 (9%)
Born in Sweden					
No	1205 (17%)	112 (15%)	525 (16%)	419 (19%)	149 (18%)
Yes	5812 (83%)	633 (85%)	2758 (84%)	1747 (81%)	674 (82%)
Mode of detection					
Screen-detected breast cancers	2392 (34%)	273 (37%)	1230 (37%)	692 (32%)	197 (24%)
Non-screen-detected breast cancers	4535 (65%)	461 (62%)	2014 (61%)	1445 (67%)	615 (75%)
Unknown	90 (1%)	11 (1%)	39 (1%)	29 (1%)	11 (1%)
Calendar period					
2001-2003	2601 (37%)	306 (41%)	1235 (38%)	752 (35%)	308 (37%)
2004-2006	2539 (36%)	263 (35%)	1205 (37%)	774 (36%)	297 (36%)
2007-2008	1877 (27%)	176 (24%)	843 (26%)	640 (30%)	218 (26%)
Synchronous CBC[d]					
No	6885 (98%)	734 (99%)	3235 (99%)	2115 (98%)	801 (97%)
Yes	132 (2%)	11 (1%)	48 (1%)	51 (2%)	22 (3%)
Operating hospital					

Karolinska University Hospital (Solna)[e]	1341 (19%)	88 (12%)	504 (15%)	538 (25%)	211 (26%)
Danderyd's University Hospital[e]	1321 (19%)	266 (36%)	758 (23%)	201 (9%)	96 (12%)
Stockholm South General Hospital[e]	961 (19%)	60 (8%)	371 (11%)	385 (18%)	145 (18%)
Huddinge Hospital[e]	626 (9%)	66 (9%)	263 (8%)	209 (10%)	88 (11%)
Capio St. Göran's Hospital[e]	1807 (26%)	158 (21%)	918 (28%)	556 (26%)	175 (21%)
Ersta Hospital and Queen Sophia Hospital[f]	664 (9%)	81 (11%)	332 (10%)	185 (9%)	66 (8%)
Others[g]	297 (4%)	26 (3%)	137 (4%)	92 (4%)	42 (5%)
Tumor size					
0-20 mm	4846 (69%)	539 (72%)	2310 (70%)	1449 (67%)	548 (67%)
>20-40 mm	1726 (25%)	163 (22%)	804 (24%)	559 (26%)	200 (24%)
>40	353 (5%)	34 (5%)	134 (4%)	131 (6%)	54 (7%)
missing	92 (1%)	9 (1%)	35 (1%)	27 (1%)	21 (3%)
Lymph node metastases					
0	4423 (63%)	478 (64%)	2092 (64%)	1392 (64%)	461 (56%)
1-3	1738 (25%)	174 (23%)	841 (26%)	503 (23%)	220 (27%)
>=4	668 (10%)	72 (10%)	261 (8%)	222 (10%)	113 (14%)
Unknown	188 (3%)	21 (3%)	89 (3%)	49 (2%)	29 (4%)
Immediate breast reconstruction					
No	5084 (72%)	540 (72%)	2415 (74%)	1565 (72%)	564 (69%)
Yes	361 (5%)	17 (2%)	120 (4%)	143 (7%)	81 (10%)
Unknown	1572 (22%)	188 (25%)	748 (23%)	458 (21%)	178 (22%)
Radiotherapy					
No	1654 (24%)	138 (19%)	735 (22%)	526 (24%)	255 (31%)
Yes	5316 (76%)	602 (81%)	2524 (77%)	1626 (75%)	564 (69%)
Unknown	47 (1%)	5 (1%)	24 (1%)	14 (1%)	4 (0%)
Chemotherapy[h]					
No	4362 (62%)	424 (57%)	2033 (62%)	1375 (63%)	530 (64%)
Yes	2595 (37%)	316 (42%)	1219 (37%)	776 (36%)	284 (35%)
Unknown	60 (1%)	5 (1%)	31 (1%)	15 (1%)	9 (1%)
Endocrine therapy					
No	1157 (16%)	130 (17%)	539 (16%)	366 (17%)	123 (15%)
Yes	5815 (83%)	609 (82%)	2723 (83%)	1787 (83%)	696 (85%)
Unknown	45 (1%)	6 (1%)	21 (1%)	14 (1%)	4 (0%)
Follow-up time of vital status (years)	8.9 (2.9)	9.2 (2.9)	9.0 (2.9)	8.7 (2.9)	8.5 (3.1)
Vital status[i]					
Alive	5811 (83%)	640 (86%)	2762 (84%)	1775 (82%)	634 (77%)
Dead	1206 (17%)	105 (14%)	521 (16%)	391 (18%)	189 (23%)
Breast cancer-specific death					
No	6417 (91%)	687 (92%)	3004 (92%)	1990 (92%)	736 (89%)
Yes	600 (9%)	58 (8%)	279 (9%)	176 (8%)	87 (11%)
Distant metastasis within 5 years					
No	6521 (93%)	690 (93%)	3064 (93%)	2025 (93%)	742 (90%)
Yes	496 (7%)	55 (7%)	219 (7%)	141 (7%)	81 (10%)

[a] The median time to surgery for the whole population was 27 days.

[b] Charlson Comorbidity Index.

[c] Diagnosis of psychiatric disorder before date of breast cancer surgery.

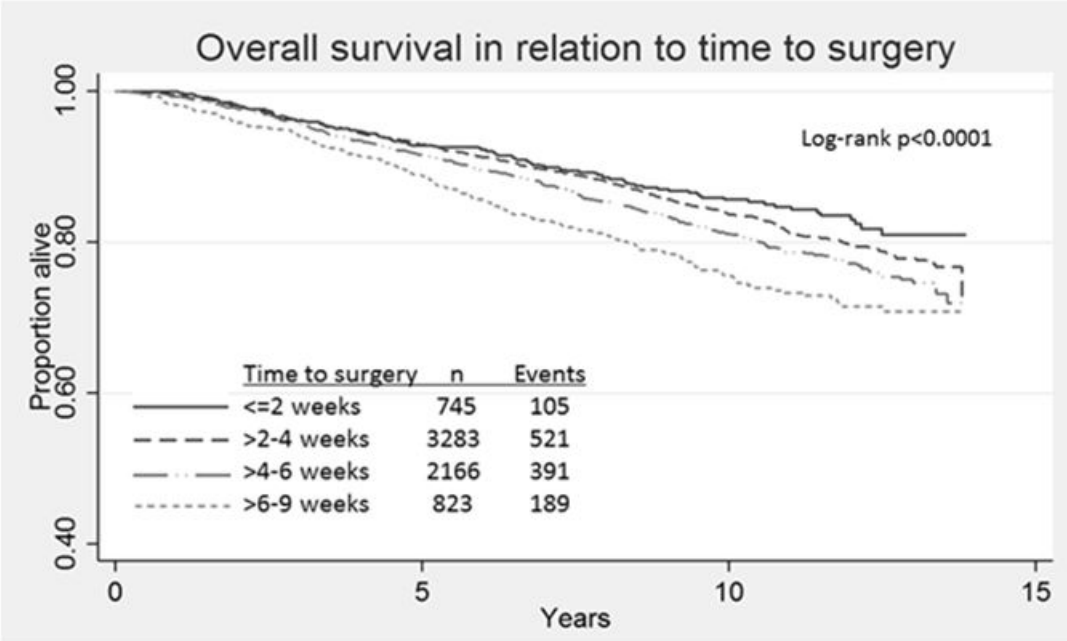
[d] Contralateral breast cancer diagnosed within three months of the first breast cancer.

[e] University and county hospitals. [f] Private, non-county hospitals. [g] All other hospitals where study subjects were operated, including all rural hospitals.

[h] Chemotherapy="Yes" also includes women who received trastuzumab since only 148 women received trastuzumab and all but four of these women received chemotherapy.

[i] 119 deaths occurred during 2014 and were thus not classified. The remaining 1087 deaths were due to breast cancer (n=600), other cancers (n=125), cardiovascular disease (n=188), and other, less frequent causes (n=174).

Figure 2. Kaplan Meier plot of time from date of breast cancer diagnosis to therapeutic surgery and overall survival.



No. at risk				
<=2 weeks	745	686	335	59
>2-4 weeks	3283	3038	1301	269
>4-6 weeks	2166	1978	736	153
>6-9 weeks	823	728	272	52

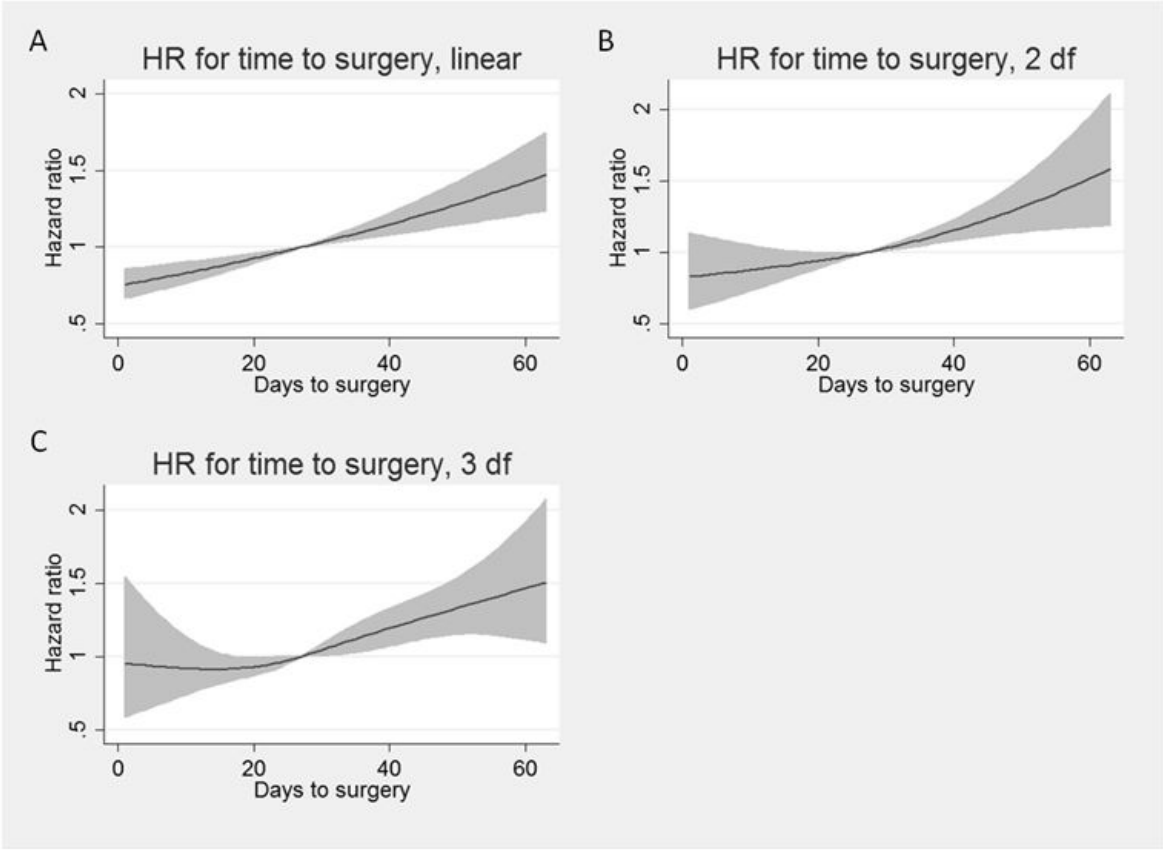
Table 2. Hazards ratios of overall survival, breast cancer-specific survival, and risk of distant metastasis, respectively, in relation to time to surgery

Overall survival				
n=7017, number of deaths=1206, time at risk=62474 years				
Estimate per one day's increase	**HR**	**95% CI**	**P-value**	**HR comparing a difference in time to surgery of 21 days**
Age-adjusted	1.011	1.007-1.016	<0.001	1.26
Main model[a]	1.011	1.006-1.016	<0.001	1.26
Additionally adjusted for questionnaire data[b]	1.010	1.006-1.015	<0.001	1.23
Breast cancer-specific survival				
n=7017, number of breast cancer-specific deaths=600, time at risk=57462 years				
Estimate per one day's increase	**HR**	**95% CI**	**P-value**	
Age-adjusted	1.008	1.001-1.015	0.021	1.18
Main model[a]	1.007	1.000-1.014	0.037	1.16
Additionally adjusted for questionnaire data[b]	1.007	1.000-1.014	0.048	1.16
Distant metastasis within 5 years				
n=7017, number of women with distant metastasis=496, time at risk=33259 years				
Estimate per one day's increase	**HR**	**95% CI**	**P-value**	
Age-adjusted	1.009	1.001-1.016	0.021	1.21
Main model[a]	1.008	1.001-1.016	0.028	1.18
Additionally adjusted for questionnaire data[b]	1.008	1.000-1.015	0.045	1.18

[a] Adjusted for age, comorbidity according to the Charlson Comorbidity Index, immigration, diagnosis of psychiatric disorder, mode of detection, calendar period, synchronous contralateral breast cancer, operating hospital, immediate breast reconstruction, tumor size, lymph node metastasis, radiotherapy, endocrine therapy and chemotherapy/trastuzumab.

[b] Adjusted for all of the factors included in the main model (see above) as well as BMI, smoking, education level and LIBRO-1 participation.

Figure 3. Hazards ratios (HR) based on Cox proportional hazards models of overall survival according to time to surgery in days



A. Linear model[a,b]

B. Nonlinear model including restricted cubic splines with 2 degrees of freedom[a,b]

C. Nonlinear model including restricted cubic splines with 3 degrees of freedom[a,b]

[a] The median time to surgery, 27 days, is set as reference.

[b] All models are adjusted for age, comorbidity according to the Charlson Comorbidity Index, immigration, diagnosis of psychiatric disorder, mode of detection, calendar period, synchronous contralateral breast cancer, operating hospital, immediate breast reconstruction, tumor size, lymph node metastasis, radiotherapy, endocrine therapy and chemotherapy/trastuzumab.

Table 3. Hazards ratios for risk of death from all causes, breast cancer-specific death, and distant metastasis in relation to time to breast cancer surgery, stratified by tumor size and lymph node metastases, respectively

Estimate per one day's increase	**Tumor size <=20 mm** (n=4846)			**Tumor size >20-40 mm** (n=1726)			**Tumor size>40 mm** (n=353)			**p-value for interaction**
	Overall survival									
	Deaths=613 Time at risk=44456 years			Deaths=451 Time at risk=14360 years			Deaths=127 Time at risk=2797 years			
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	
Age-adjusted model	1.008	1.001-1.014	0.026	1.012	1.004-1.020	0.002	1.022	1.007-1.037	0.004	0.0084
Main model[a]	1.007	1.000-1.014	0.052	1.012	1.004-1.020	0.003	1.030	1.014-1.046	<0.001	0.0018
	Breast cancer-specific survival									
	Breast cancer-specific deaths=228 Time at risk=40809 years			Breast cancer-specific deaths=276 Time at risk=13254 years			Breast cancer-specific deaths =87 Time at risk=2602 years			
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	
Age-adjusted model	1.003	0.992-1.014	0.601	1.008	0.998-1.018	0.131	1.015	0.998-1.033	0.091	<0.0001
Main model[a]	1.002	0.991-1.013	0.771	1.008	0.998-1.018	0.135	1.025	1.006-1.046	0.012	<0.0001
	Distant metastasis within 5 years									
	Events=177 Time at risk=23503 years			Events=240 Time at risk=7845 years			Events=73 Time at risk=1479 years			
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	
Age-adjusted model	1.005	0.993-1.018	0.423	1.005	0.994-1.016	0.357	1.018	0.999-1.038	0.067	0.0001
Main model[a]	1.004	0.992-1.017	0.532	1.005	0.994-1.016	0.376	1.026	1.005-1.047	0.015	<0.0001

Estimate per one day's increase	**No lymph node metastasis** (n=4423)			**1-3 lymph node metastases** (n=1738)			**>=4 lymph node metastases** (n=668)			**p-value for interaction**
	Overall survival									
	Deaths=581 Time at risk=40056 years			Deaths=305 Time at risk=15329 years			Deaths=274 Time at risk=5085 years			
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	
Age-adjusted model	1.013	1.006-1.020	<0.001	1.009	0.999-1.018	0.064	1.004	0.995-1.013	0.426	0.0001
Main model[b]	1.012	1.005-1.019	0.001	1.009	1.000-1.019	0.059	1.003	0.993-1.012	0.562	0.0001
	Breast cancer-specific survival									
	Breast cancer-specific deaths=206 Time at risk=36743 years			Breast cancer-specific deaths=182 Time at risk=14093 years			Breast cancer-specific deaths=204 Time at risk=4744 years			
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	
Age-adjusted model	1.007	0.995-1.019	0.247	1.003	0.990-1.015	0.682	1.004	0.993-1.015	0.489	0.1624
Main model[b]	1.005	0.993-1.017	0.412	1.003	0.990-1.015	0.686	1.003	0.993-1.014	0.537	0.1843
	Distant metastasis within 5 years									
	Events=171 Time at risk=21395 years			Events=149 Time at risk=8184 years			Events=173 Time at risk=2784 years			
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	
Age-adjusted model	1.011	0.998-1.024	0.108	0.999	0.986-1.013	0.933	1.003	0.991-1.014	0.674	0.0781
Main model[b]	1.009	0.996-1.022	0.163	0.998	0.984-1.012	0.806	1.003	0.991-1.015	0.680	0.1006

[a]Adjusted for age, comorbidity according to the Charlson comorbidity index, immigration, diagnosis of psychiatric disorder, mode of detection, calendar period, synchronous contralateral breast cancer, operating hospital, immediate breast reconstruction, chemotherapy/trastuzumab, radiotherapy, endocrine therapy, and lymph node metastasis.

[b]Adjusted for age, comorbidity according to the Charlson comorbidity index, immigration, diagnosis of psychiatric disorder, mode of detection, calendar period, synchronous contralateral breast cancer, operating hospital, immediate breast reconstruction, chemotherapy/trastuzumab, radiotherapy, endocrine therapy, and tumor size.