Risk and Mortality of Recurrent Breast Cancer in Stockholm 1985-2005

Jonas Lundkvist[1,2], Frida Kasteng[2], Mathias Lidgren[1,6], Jan Adolfsson[3], Jonas Bergh[4], Tommy Fornander[5], Nils Wilking[1], Bengt Jönsson[6]

SSE/EFI Working Paper Series in Economics and Finance No 661
May, 2007

Abstract

The purpose of this study was to estimate the risk and mortality of breast cancer recurrences in Swedish women, and to analyse changes over time and variations between patients in different risk groups. Such estimates are of key importance for modelling the cost-effectiveness of different strategies for adjuvant treatment of breast cancer.

The study was based on all women diagnosed with breast cancer in Stockholm County between 1985 and 2005. Information about dates for locoregional recurrences, metastatic relapses, new contralateral tumours and death was collected. Cox proportional hazard and Weibull regression models were used to estimate survival functions, where year of diagnosis (dived into 5-year intervals), were included as explanatory variables in the models.

The risk of recurrences has decreased during the last 20 years for all three types of recurrence; for metastatic relapse the 5-year risk was reduced from 12.9% to 6.0% from 1985-90 to 2000-2005 . Mortality has also been reduced, resulting in an increased 5-year survival from 52.6% to 64.1% after locoregional recurrence and from 10.4% to 15.5% for metastatic relapse. For contralateral tumours, with a 5-year survival rate of 74.6% in 1985-1990 and 78% 2000-2005, no significant increase was observed. Analysis of risk groups according to TNM classification showed large difference in the risk of metastatic breast cancer between the three defined groups, but small differences for the risk of locoregional recurrences and new contralateral tumours.

The findings indicate that the early detection and new treatments have been successful in improving outcome for breast cancer patients and that it is important to use up-to-date information, when assessing the value of new treatment options.

Keywords: Breast cancer, Mortality, Survival, Recurrence, Sweden
JEL-code: I10

[1] Karolinska Institutet, Stockholm, Sweden
[2] European Health Economics, Stockholm, Sweden
[3] Onkologiskt Centrum, Karolinska University Hospital, Solna, Sweden
[4] Radiumhemmet, Karolinska Inst. & University Hospital, Stockholm, Sweden
[5] Department of Oncology, Karolinska University Hospital at Södersjukhuset, Stockholm, Sweden
[6] Centre for Health Economics, Stockholm School of Economics, Stockholm, Sweden

Introduction

Breast cancer is the most common cancer in women. The incidence has increased in Sweden and many other countries during the last decades[1, 2]. Survival has also increased[2-5], and the total mortality from breast cancer has therefore remained relatively constant in many western countries[6, 7]. The overall 5- and 10-year survival of breast cancer in Sweden has increased from 65% and 53%, respectively, for those diagnosed 1964-1966 to 84% and 74%, respectively, for those diagnosed in the 1990's[8]. The improved prognosis is likely a combination of early diagnosis[8-10] and improved treatment.

Adjuvant treatment of early breast cancer reduce the risk of disease recurrence, and also the risk of new contralateral tumours[11, 12]. However, recurrences and new contralateral tumours are still common and new treatments reducing the risk of these events, or improve the prognosis when they occur, are therefore welcome. However, the introduction of new, and often costly, adjuvant treatments increases the cost of breast cancer care, and since breast cancer is a common disease this will have significant effect on the overall cancer care budget. It is therefore important to assess the value for money, i.e. the cost-effectiveness, of these new therapies in order to find the optimal use of them in clinical practice. The main benefit of adjuvant treatment is to reduce the risk of metastatic disease, but also locoregional recurrences and new contralateral tumours are important targets for improved therapy. The risks and consequences of these events are therefore key variables in models for assessing the cost-effectiveness of these treatments[13, 14].

The risk of relapses also differs considerably between risk groups. Patients with large tumours and/or nodal involvement have higher risk of relapses[8]. The optimal adjuvant treatment may hence vary between risk groups and it is therefore also interesting to further explore variations in risk of relapses between groups of patients at different risk. The risk of recurrences/new contralateral tumours and the prognosis of patients having these events also vary over time as patient characteristics, diagnosis and treatment practices changes. This means that it is important to use relevant and up-to-date data when assessing the long-term benefits of new adjuvant treatments. It is also important to have specific Swedish data, since both treatment patterns and patients characteristics differ from those in other countries. We can thus not rely only on international studies if we like to have a reliable estimate of cost-effectiveness when new treatments are introduced for Swedish patients.

Since the early 1980's there has been several new treatments introduced. Tamoxifen, for example, was introduced in the 1970's and the first aromatase inhibitor was introduced in mid 1980's. Taxanes were approved for adjuvant treatment in Europe in 2005 and trastuzumab in 2006. Mammographic screening was introduced in Sweden in the mid 1980's. It is currently recommended for women aged between 40 and 70 years in Sweden. Studies have indicated that the introduction of screening has reduced the total mortality from breast cancer. Baker et al estimated a reduction in incidence of breast cancer death in Sweden to -9 cases per 100,000[15] and Duffy et al estimated that screening in seven Swedish counties resulted in a 40-45% reduction in breast cancer mortality[16-18]. The benefit of the endocrine treatments, such tamoxifen or aromatase inhibitors, is now also widely acknowledged[19, 20]. It is therefore likely that the risk of having a recurrent breast cancer, and also the prognosis once diagnosed with a recurrent disease, have improved during the last 20 years.

The purpose of this study was to evaluate trends and variation between different risk groups in the risk and mortality of breast cancer recurrences and new contralateral tumours in Swedish women.

Material and method

The study was based on all women diagnosed with breast cancer in Stockholm County between 1985 and 2005. The women were identified from the cancer registry at the regional oncology centre in Stockholm. Information about age at diagnosis, TNM classification, and dates for recurrences, new contralateral tumours and death were collected.

Data on four specific events was collected and used for the estimates: locoregional recurrence, metastatic disease (distant recurrence) contralateral cancer, and death. Risk is calculated as the probability of each event occurring for the first time. Time is measure from first diagnosis of the primary breast cancer. Mortality is analysed both as a first event (after primary diagnosis of breast cancer) and as conditional on a recurrence/contralateral tumour event. In the latter case, time to death is measured from diagnosis of the recurrence/contralateral tumour. The age of the patient is the age at the first diagnosis of the primary breast cancer.

Risk variations over time
Two models to compare risks over time are used: The Cox proportional hazard regression model and the Weibull regression models. The Cox model is suitable for analyzing the effect of risk factors, but does not give a functional form that can be used to calculate risks. The Weibull distribution, on the other hand, is suitable for modelling data with hazard rates that increase or decrease over time and can be used to derive a functional form of the risks.

Separate regression models were estimated for the risks and the mortalities of locoregional recurrence, contralateral cancer and metastatic relapse. Date of diagnosis was dived into 5-year intervals: 1985-1989, 1990-1994, 1995-1999 and 2000-, and were included as dichotomous explanatory variables in the regression models. The year of diagnosis corresponds to the year of the primary diagnosis in the estimation of risks of recurrences/contralateral cancer and the year of recurrence/contralateral cancer for the estimation of mortality.

The Cox proportional hazard models are in general modelled as:
$H(t) = H_0(t)e^{(a_1X_1+a_2X_2+...+a_nX_n)}$, where X_1 ... X_n are the explanatory variables and $H_0(t)$ is the baseline hazard at time t, representing the hazard for a person with the value 0 for all the explanatory variables. In our model, X_i corresponds to the dichotomous variables for the year interval of diagnosis, and $H_0(t)$ corresponds to the hazard function for patients diagnosed 1985-1989. The hazard ratio is then obtained by dividing both sides of the equation above by $H_0(t)$ and taking logarithms. The hazard ratio shows the relative risk reduction.

In the Weibull model it was thus assumed that time to recurrence and death (T) follows Weibull distributions. For t, a particular value of T, the Weibull survivor S(t) and hazard function $\lambda(t)$ are defined according to: $S(t) = e^{-(\gamma t^p)}$ and $\lambda(t) = \gamma\, pt^{p-1}$, where p and γ are non-negative parameters to be estimated. When p = 1, the Weibull distribution reduces to the exponential with a constant hazard rate and if $p > 1$ ($p < 1$) the hazard rate is monotonically increasing (decreasing) in t. To introduce covariates in the model, γ in the equations above is replaced by $e^{(\alpha+a_1X_1+a_2X_2+...+a_nX_n)}$.

Risk variations between patient groups
Risk of the locoregional recurrence, metastatic relapse and new contralateral tumours were also assessed in different risk groups. The TNM classification was used to divide patients into

three groups: Group 1 was patients with nodal involvement (T0-, N1-), group 2 those with large tumours without nodal involvement (T2-, N0) and group 3 were those with small tumours without nodal involvement (T0-1, N0). Separate analyses were also made for women below and above 55 years to explore differences between pre- and postmenopausal women.

Results

Information from 20,624 women diagnosed with breast cancer over the 20 year period was obtained. The mean age at diagnosis was 61 years and remained rather constant during the time interval. Screening did not seem to have an influence on the age at diagnosis. The mean follow-up time was 89 months. 23% of the women had had a recurrence or contralateral tumour and 33% had died during the follow-up period.

Risk of recurrence/contralateral tumour
Figures 1a-c in the appendix shows the Kaplan-Meier survival functions for risks of locoregional recurrence (figure 1a), metastatic relapse (figure 1b) and new contralateral tumour (figure 1c). Four separate curves, representing patients diagnosed 1985-1989, 1990-1994, 1995-1999 or 2000-2004, are shown. The figures indicate a trend towards lower risk for patients diagnosed more recently.

Table 1 presents the estimated parameter values in the Cox proportional hazard model. The coefficients for the explanatory variables show the differences in hazard rates between the various diagnosis year-intervals, compared to the first time period (i.e. 1985-1989). The hazard ratios are decreasing with year of diagnosis for all three types of events, which confirms that patients diagnosed recently have lower risk of recurrences/contralateral tumours. All hazard ratios are statistically significant (at a 0.05 level) except the risk for contralateral tumours in patients diagnosed between 1990 and 1994.

The risk of metastatic recurrence was reduced with two thirds during the period, while for locoregional recurrence and contralateral tumour, where the risk is much smaller, the risk reduction was just over fifty per cent.
.

Table 1. Parameters estimated in the Cox proportional hazard model for risk of recurrence/contralateral tumour

Events	Diagnosis year	Hazard ratio	p value	95% confidence interval
Locoregional recurrence	1990-1994	0.875	0.043	0.769-0.996
	1995-1999	0.692	0.000	0.601-0.796
	2000-2005	0.439	0.000	0.363-0.531
Metastatic relapse	1990-1994	0.690	0.000	0.630-0.756
	1995-1999	0.476	0.000	0.429-0.528
	2000-2005	0.333	0.000	0.289-0.385
Contralateral tumour	1990-1994	0.925	0.411	0.769-1.113
	1995-1999	0.598	0.000	0.477-0.751
	2000-2005	0.455	0.000	0.330-0.628

Risks of recurrences/contralateral tumours were calculated from the estimated Weibull regression models. Table 2 presents the calculated risks for the different diagnosis year-intervals. The results, for example, show that the 10-year risk of metastatic disease has decreased from 21.7% for patients diagnosed 1985-1989 to an estimated risk of 10.4% for patients diagnosed after 2000.

Table 2. Estimated 5- and 10-year risks for recurrence/contralateral tumour (from Weibull regression models)

	Locoregional recurrence		Metastatic relapse		Contralateral tumour	
Diagnosis year	*5-year risk*	*10-year risk*	*5-year risk*	*10-year risk*	*5-year risk*	*10-year risk*
1985-1989	6.4%	11.2%	12.9%	21.7%	2.6%	5.2%
1990-1994	6.0%*	10.5%*	10.0%	17.0%	2.6%*	5.3%*
1995-1999	5.5%	9.6%	8.1%	13.9%	1.7%	3.6%
2000-2005	3.8%	6.7%	6.0%	10.4%	1.4%	2.8%

* Not statistically significantly different from the result for the group diagnosed 1985-1989

Figure 2a-f in the appendix shows the risks of locoregional recurrence (figure 2a-b), metastatic relapse (figure 2c-d) and new contralateral tumour (figure 2e-f) for patients under and over 55 years of age respectively, and for the three defined risk groups. There is a large difference in the risk of metastatic relapse between the risk groups, where small node negative tumours are associated with a much better prognosis. There were fairly small differences for locoregional recurrence and new contralateral tumour, and also the differences between pre- and postmenopausal women were small.

Survival after primary breast cancer tumour

Figure 3 in the appendix shows the Kaplan-Meier function for survival after primary breast cancer diagnosis. Four separate curves, representing patients diagnosed with the primary tumour 1985-1989, 1990-1994, 1995-1999 or 2000-2004, are again shown. The results indicate an increased survival from breast cancer over time, which is also confirmed in analyses using a Cox proportional hazard model. The coefficients for the explanatory variables, presented in table 3 shows, the differences in survival for the various diagnosis year-intervals compared to patients diagnosed between 1985 and 1989.

Table 3. Parameters estimated in the Cox proportional hazard model for mortality after primary breast cancer diagnosis

Diagnosis year	Hazard ratio	p value	95% confidence interval
1990-1994	0.777	0.000	0.732-0.824
1995-1999	0.700	0.000	0.655-0.749
2000-2005	0.535	0.000	0.486-0.588

Survival after recurrence/contralateral tumour

Figure 4a-c in the appendix shows the Kaplan-Meier functions for survival after locoregional recurrence (figure 3a), metastatic relapse (figure 3b) and new contralateral tumour (figure 3c). Four separate curves, representing patients diagnosed with the recurrence/contralateral tumour 1985-1989, 1990-1994, 1995-1999 or 2000-2004, are again shown. The curve for locoregional recurrence indicates a trend towards increased survival for patients diagnosed more recently. This trend can, however, only be observed for survival after metastatic relapse for those diagnosed after 1994 and could not be observed for contralateral tumours.

Table 4 presents the estimated parameter values in the Cox proportional hazard model. The coefficients for the explanatory variables show the differences in survival between the various diagnosis year-intervals. The hazard ratios are decreasing with year of diagnosis for locoregional recurrence, which confirm that patients diagnosed with this event recently have increased survival compared to those diagnosed in the 1980's. The hazard ratio in patients diagnosed after 1994 is statistically significant for metastatic relapse.

Table 4. Parameters estimated in the Cox proportional hazard model for mortality after recurrence/contralateral tumour

Events	Diagnosis year	Hazard ratio	p value	95% confidence interval
Locoregional recurrence	1990-1994	0.745	0.005	0.606-0.916
	1995-1999	0.590	0.000	0.474-0.736
	2000-2005	0.556	0.000	0.430-0.718
Metastatic relapse	1990-1994	0.972	0.665	0.855-1.105
	1995-1999	0.880	0.049	0.774-0.999
	2000-2005	0.775	0.000	0.675-0.889
Contralateral tumour	1990-1994	1.037	0.206	0.639-1.101
	1995-1999	0.383	0.453	0.529-1.329
	2000-2005	0.690	0.170	0.406-1.173

Survivals rates after recurrences/contralateral tumours were estimated from the Weibull regression models. Table 5 presents the survival for the different diagnosis year-intervals. There are very significant differences in survival after the different types of events. Most noticeable is the much lower 5 and 10 year survival after diagnosis of metastatic disease. However, both 5 and 10 year survival increased significantly over the period. Also after locoregional recurrence has the survival increased significantly over time. The 10-year survival increased from 28% for patients diagnosed 1985-1989 to 42% for patients diagnosed after 2000.

Table 5. Estimated 5- and 10-year survival rates after recurrence/contralateral tumour (from Weibull regression models)

	Locoregional recurrence		Metastatic relapse		Contralateral tumour	
Diagnosis year	*5-year survival*	*10-year survival*	*5-year survival*	*10-year survival*	*5-year survival*	*10-year survival*
1985-1989	52.6%	28.3%	10.4%	1.9%	74.6%	54.8%
1990-1994	60.9%	37.7%	11.1%*	2.1%*	73.5%*	53.1%*
1995-1999	64.8%	42.6%	12.7%*	2.7%*	75.2%*	55.6%*
2000-2005	64.1%	41.7%	15.5%	3.8%	78.0%*	59.9%*

* Not statistically significantly different from the result for the group diagnosed 1985-1989

Discussion

We have in this study assessed variations over time and across risk groups in the risk and mortality of breast cancer recurrences/new contralateral tumours. Obtaining up-to-date information about the long-term risks is difficult since we do not have long-term data on patients recently diagnosed. We estimated Cox proportional hazard and Weibull regression models and included years of diagnosis as explanatory variables in the models. By using the Weibull regression models, we can use the most recent information from patients diagnosed during the last years to estimate the long-term risk for these patients, based on information from all patients in the sample. Although it is based on specific assumptions about the characteristics of the survival function, we think that this method provides a relevant estimation of the current risk of, and mortality from, recurrences.

The findings show a reduction in the risk of and mortality from most types of breast cancer recurrences/new contralateral tumours over time. For metastatic disease, only patients diagnosed during the last 5-10 years showed an improved survival. The analysis also indicated that there was a large difference in the risk of metastatic relapse between the defined risk groups, but fairly small differences for locoregional recurrence and new contralateral tumours. Differences between pre- and postmenopausal women were also indicated to be small. No significant improvement in survival after contralateral tumours could be observed, but this may be due to the fairly small number of patients with contralateral tumours in the sample.

We have in this study not attempted to explain causes for the reductions in risks and mortality. We can assume that these reductions are caused both by early diagnosis (and hence more tumours detected at an early stage) and improved surgery, radiotherapy and pharmacological treatments. A quantification of the contribution of various factors to the overall improved outcome is an interesting and important subject for future studies[21].

The calculation of risks and mortality of disease recurrences is important for the quantification of the benefits of treatments aimed at reducing the risk of recurrences. It is also important for evaluating treatments aimed at reducing the mortality of recurrences. The data show that risks of and mortality from most types of recurrences and new contralateral cancers have decreased during the last 20 years. This stresses the need to use relevant, up-to-date, information reflecting the current clinical practice in evaluations of the clinical and economic benefit of new therapies. The findings also indicate that the efforts made during the last decades to develop new treatments and ways to detect tumours early have been successful in improving outcome for breast cancer patients. It is, however, not possible to say anything about the value of individual intervention, or what the costs of the interventions are in relation to their benefits, i.e. their cost-effectiveness.

The study was based on patients from only one county in Sweden. It is known that the risk and mortality of breast cancers varies between countries[22, 23], and sometimes also within countries. The exact risks and mortalities presented here may therefore not be representative of patients in other countries, but it is likely that the trend towards a reduced risk and mortality of recurrences identified here is transferable to many other settings. One of the implication of the findings, that it is important to use up-to-date information about risk and mortality of recurrences and new contralateral cancers for assessing the value of new treatments, is, however, relevant in most settings.

Acknowledgement and disclosure

Bengt Jönsson and Nils Wilking took the initiative to the study, and reviewed the final manuscript. Mathias Lidgren did the data extraction for the study. Jonas Lundkvist, Frida Kasteng and Mathias Lidgren did the statistical analysis. Jonas Lundkvist also made the first draft of the manuscript. Jan Adolfsson, Jonas Bergh and Tommy Fornander (The Stockholm Breast Cancer Group) have been responsible for the registry from which the data were selected.

The estimates derived have been used in the following economic evaluation studies of adjuvant treatment of breast cancer:

1. Lundkvist J, Wilking N, Holmberg S, Jönsson L. Cost-effectiveness of exemestane versus tamoxifen as adjuvant therapy for early-stage breast cancer after 2-3 years treatment with tamoxifen in Sweden. (presented as abstract at European Breast Cancer Conference, 2006 i and published in Breast Cancer Research and Treatment)
2. Lundkvist J, Borgström F, Kasteng F, Sobocki P, Lidgren M, Paulsson T, Henriksson R. Cost-effectiveness of anastrozole versus tamoxifen as adjuvant therapy for postmenopausal women with early hormone-receptor positive breast cancer – An evaluation of the ATAC-trial. (presented as abstract at San Antonio Breast Cancer Symposium, 2006)
3. Lidgren M, Jönsson B, Rehnberg C, Wilking N, Berg, J. Cost-effectiveness of HER2 testing and 1 year adjuvant trastuzumab therapy for early breast cancer. In Lidgren, M. Health Economics of Breast Cancer, , Dept of Learning, Informatics, Management and ethics, Medical management Centre, Karolinska Institutet, Stockholm, Sweden, 2007 (diss)

4. Lundkvist J, Jönsson L, Wilson K, Moledina A, Coleman R. Cost-effectiveness of various treatment strategies for aromatase inhibitors as adjuvant treatment in early breast cancer for post menopausal women in the UK.

References

1. Coombes, R.C., et al., *A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.* N Engl J Med, 2004. **350**(11): p. 1081-92.
2. Crocetti, E., et al., *Population-based incidence and mortality cancer trends (1986-1997) from the network of Italian cancer registries.* Eur J Cancer Prev, 2004. **13**(4): p. 287-95.
3. Chu, K.C., et al., *Recent trends in U.S. breast cancer incidence, survival, and mortality rates.* J Natl Cancer Inst, 1996. **88**(21): p. 1571-9.
4. Talback, M., et al., *Cancer survival in Sweden 1960-1998--developments across four decades.* Acta Oncol, 2003. **42**(7): p. 637-59.
5. Ugnat, A.M., et al., *Survival patterns for the top four cancers in Canada: the effects of age, region and period.* Eur J Cancer Prev, 2005. **14**(2): p. 91-100.
6. Bornefalk, A., I. Persson, and R. Bergstrom, *Trends in breast cancer mortality among Swedish women 1953-92: analyses by age, period and birth cohort.* Br J Cancer, 1995. **72**(2): p. 493-7.
7. Doll, R. and J. Boreham, *Recent trends in cancer mortality in the UK.* Br J Cancer, 2005. **92**(7): p. 1329-35.
8. Tejler, G., et al., *Survival after treatment for breast cancer in a geographically defined population.* Br J Surg, 2004. **91**(10): p. 1307-12.
9. Jensen, A.R., et al., *Does stage at diagnosis explain the difference in survival after breast cancer in Denmark and Sweden?* Acta Oncol, 2004. **43**(8): p. 719-26.
10. Sant, M., et al., *Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe.* Int J Cancer, 2003. **106**(3): p. 416-22.
11. *Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group.* Lancet, 1998. **351**(9114): p. 1451-67.
12. Bergh, J., et al., *A systematic overview of chemotherapy effects in breast cancer.* Acta Oncol, 2001. **40**(2-3): p. 253-81.
13. Karnon, J., *Aromatase inhibitors in breast cancer: a review of cost considerations and cost effectiveness.* Pharmacoeconomics, 2006. **24**(3): p. 215-32.
14. Kilian, R. and F. Porzsolt, *When to recommend and to pay for first-line adjuvant breast cancer treatment? A structured review of the literature.* Breast, 2005. **14**(6): p. 636-42.
15. Baker, S.G., B.S. Kramer, and P.C. Prorok, *Comparing breast cancer mortality rates before-and-after a change in availability of screening in different regions: extension of the paired availability design.* BMC Med Res Methodol, 2004. **4**: p. 12.
16. *Reduction in breast cancer mortality from the organised service screening with mammography: 2. Validation with alternative analytic methods.* Cancer Epidemiol Biomarkers Prev, 2006. **15**(1): p. 52-6.
17. *Cancer Research UK (http://info.cancerresearchuk.org/).* 2006.
18. Duffy, S.W., et al., *The impact of organized mammography service screening on breast carcinoma mortality in seven Swedish counties.* Cancer, 2002. **95**(3): p. 458-69.
19. Hennessy, B.T. and L. Pusztai, *Adjuvant therapy for breast cancer.* Minerva Ginecol, 2005. **57**(3): p. 305-26.
20. Kaklamani, V.G. and W.J. Gradishar, *Adjuvant therapy of breast cancer.* Cancer Invest, 2005. **23**(6): p. 548-60.
21. Lichtenberg, F., *Pharmaceutical innovation and cancer survival: US and international evidence. In Wilking and Jönsson. A pan-European comparison regarding patient access to cancer drugs. Report Karolinska Institutet.* 2005.

22. Coleman, M.P., et al., *EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century.* Ann Oncol, 2003. **14 Suppl 5**: p. v128-49.
23. Sant, M., et al., *Cancer survival increases in Europe, but international differences remain wide.* Eur J Cancer, 2001. **37**(13): p. 1659-67.

Appendix

Figure 1a. Kaplan-Meier estimates of risk for locoregional recurrences

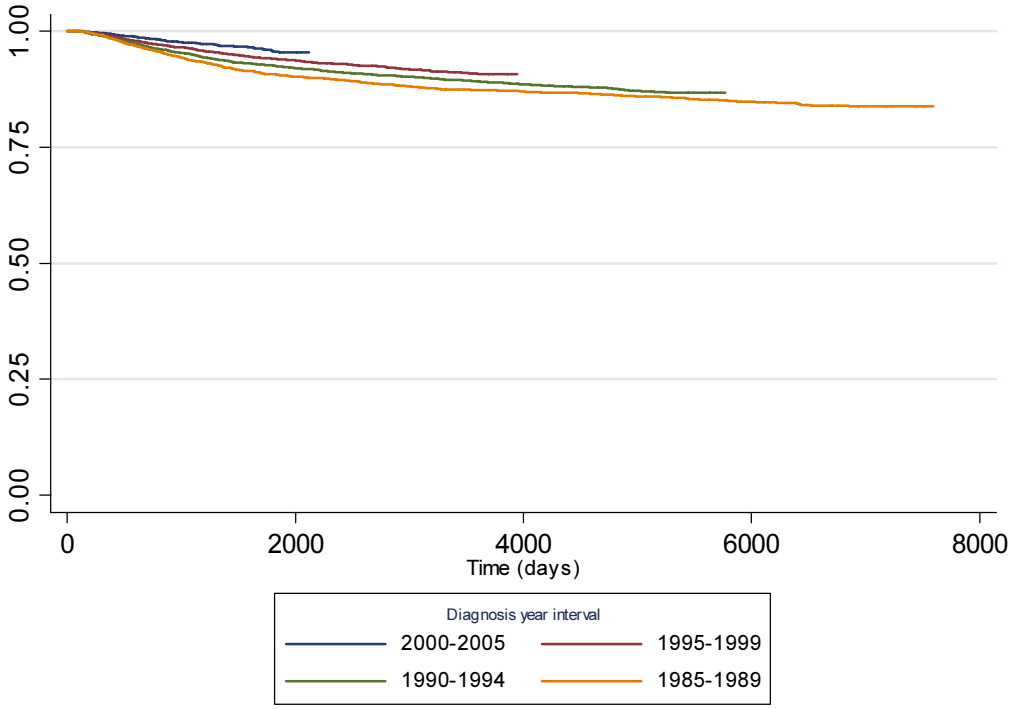


Figure 1b. Kaplan-Meier estimates of risk for distant relapses

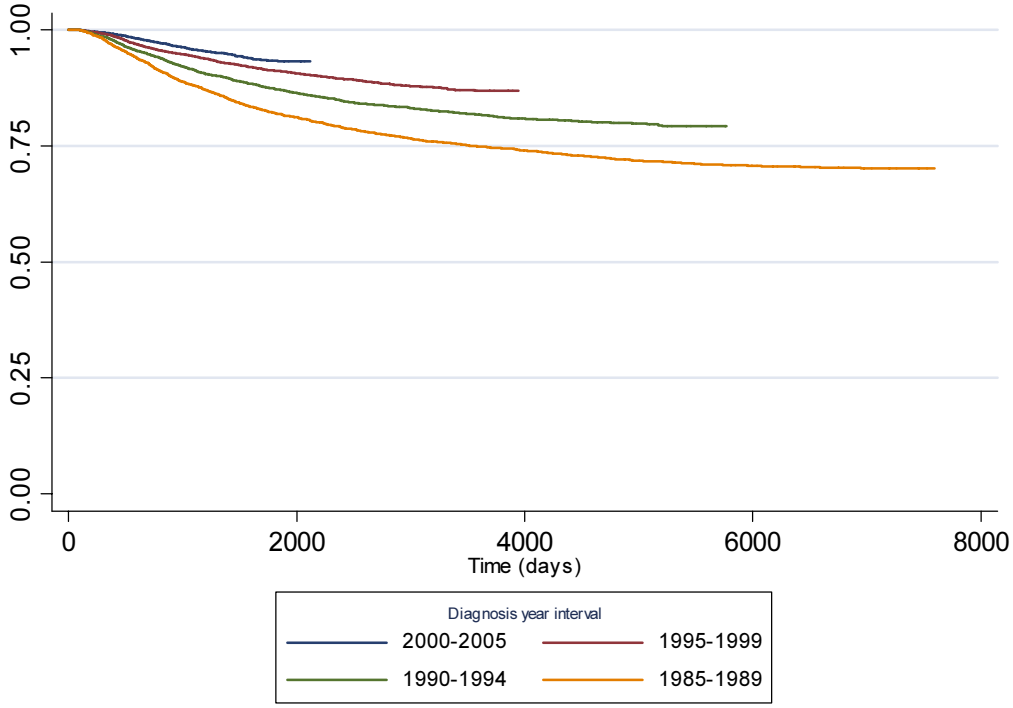


Figure 1c. Kaplan-Meier estimates of risk for contralateral tumour

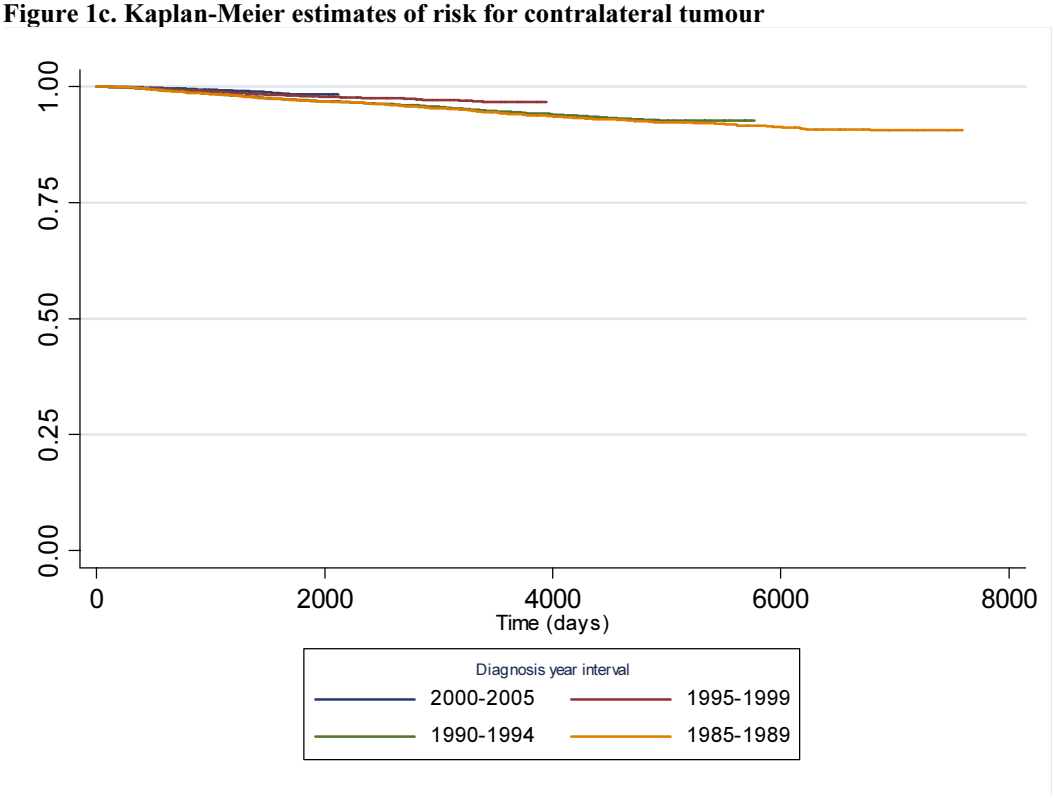
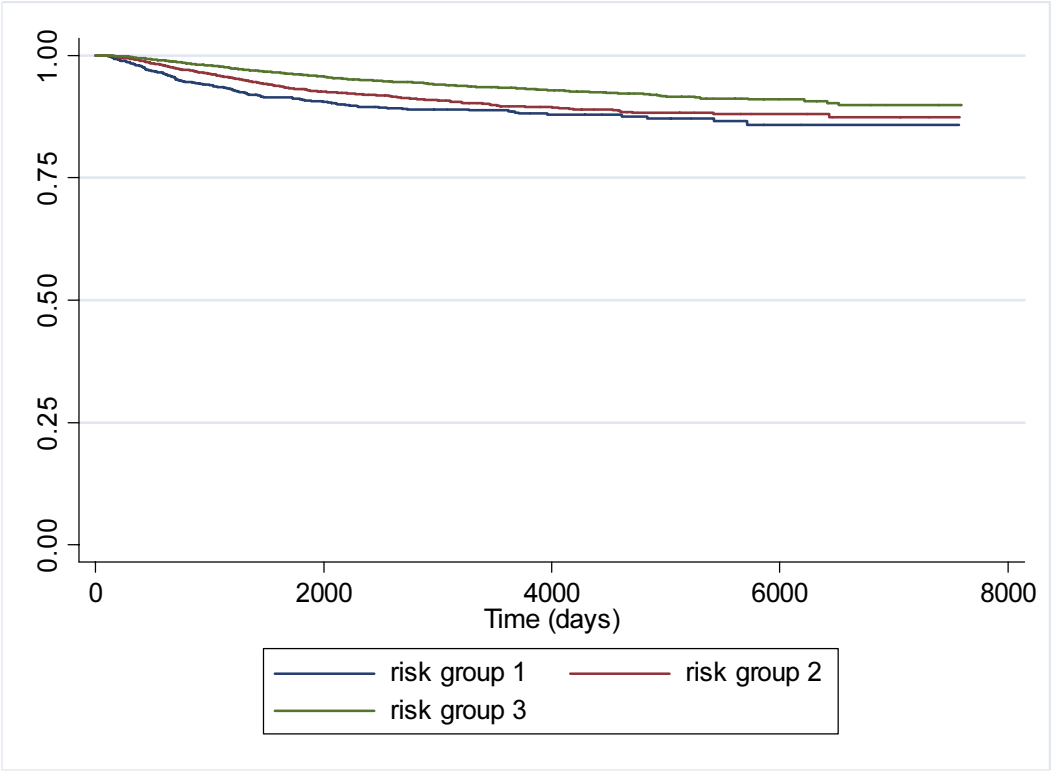
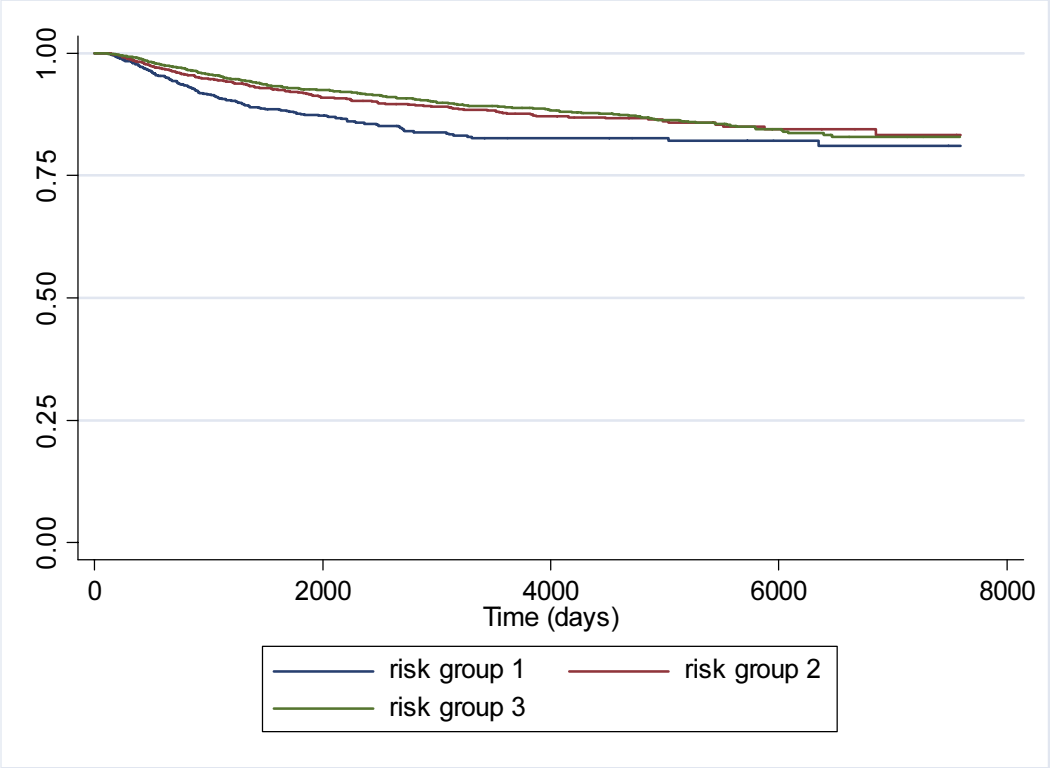


Figure 2a. Kaplan-Meier estimates of risk for locoregional recurrences (patient above 55 years)



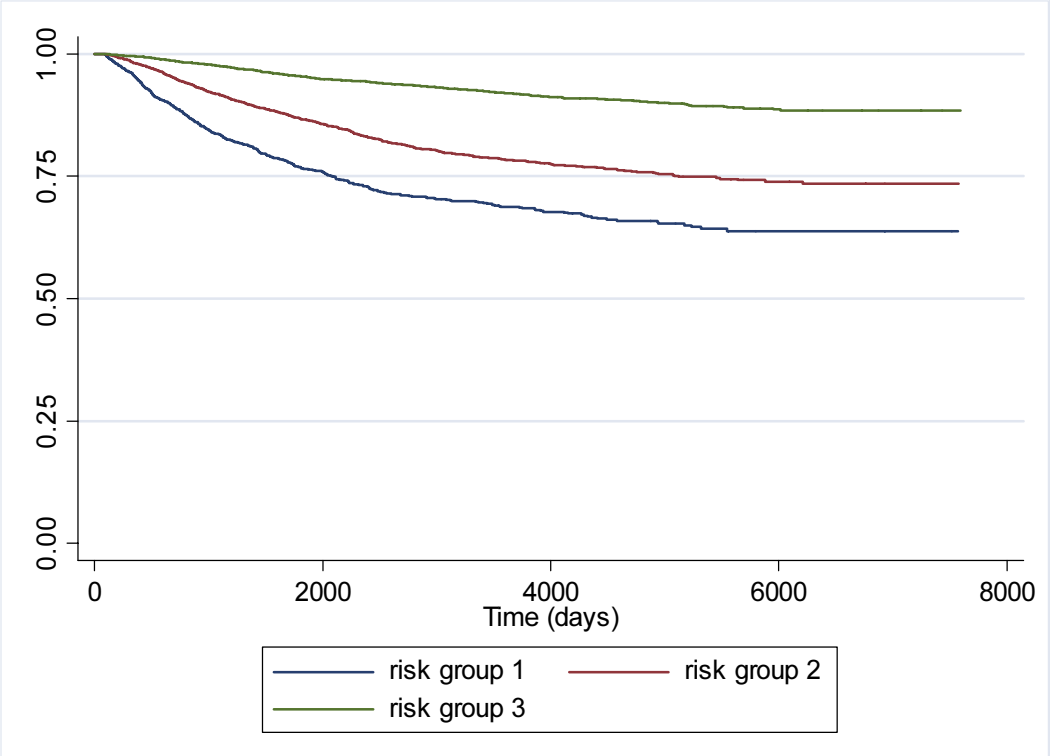
Group 1: T0-, N1-, group 2: T2-, N0 and group 3: T0-1, N0

Figure 2b. Kaplan-Meier estimates of risk for locoregional recurrences (patient below 55 years)



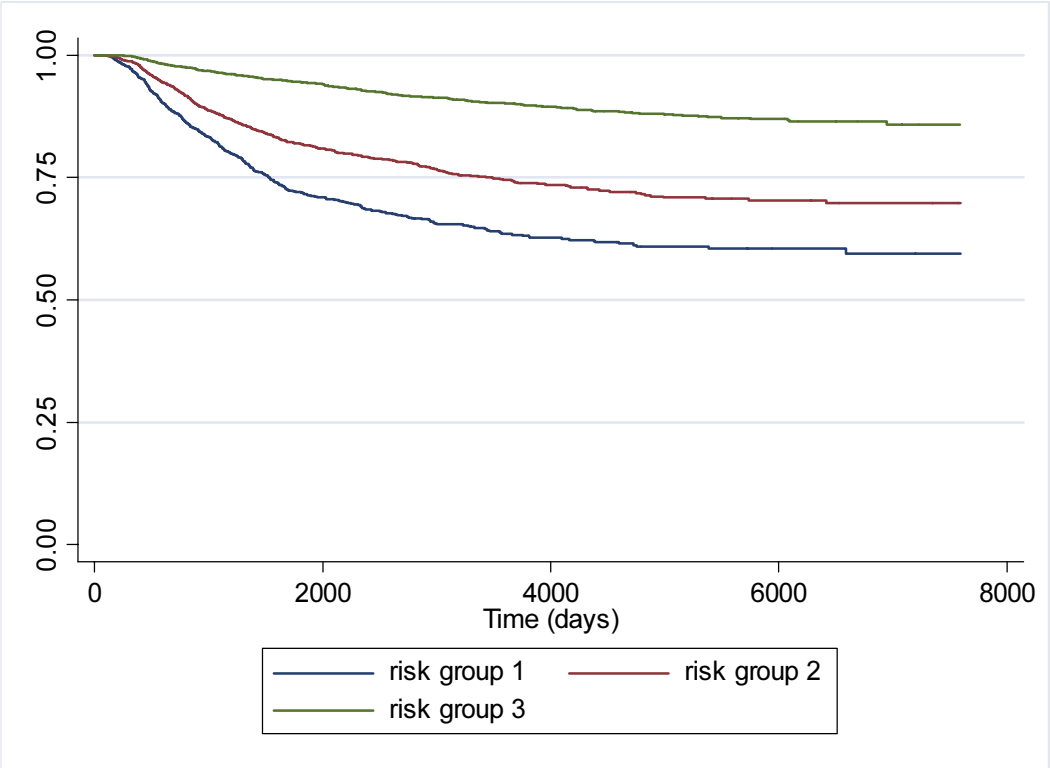
Group 1: T0-, N1-, group 2: T2-, N0 and group 3: T0-1, N0

Figure 2c. Kaplan-Meier estimates of risk for distant relapses (patient above 55 years)



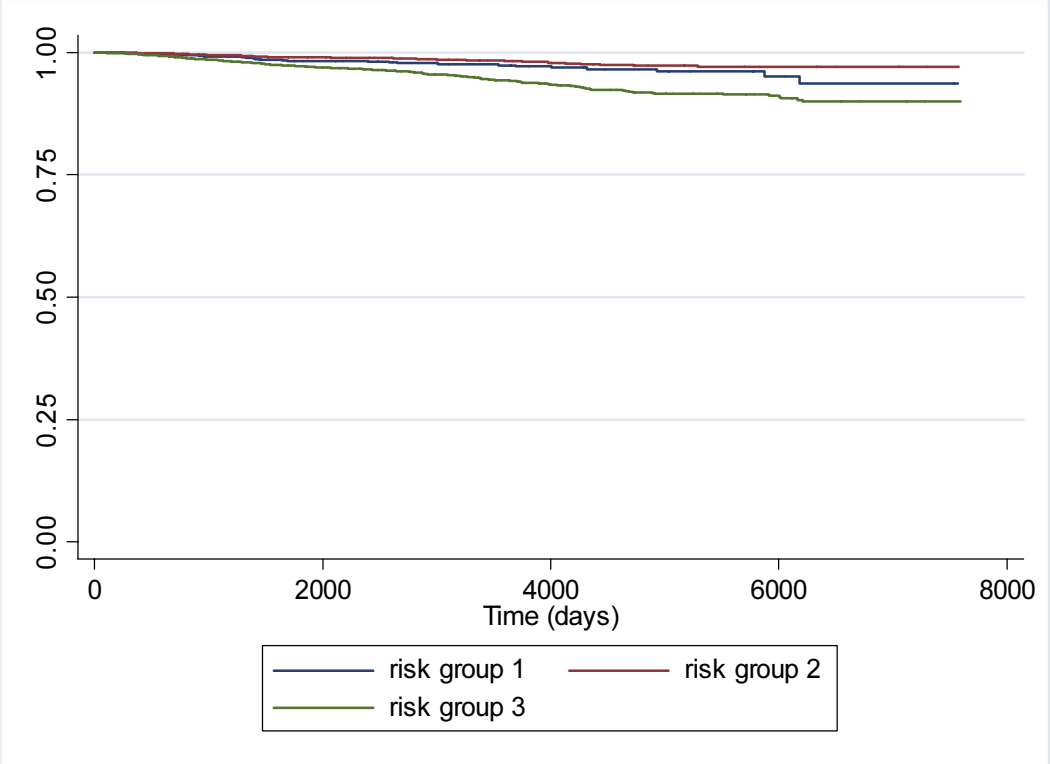
Group 1: T0-, N1-, group 2: T2-, N0 and group 3: T0-1, N0

Figure 2d. Kaplan-Meier estimates of risk for distant relapses (patient below 55 years)



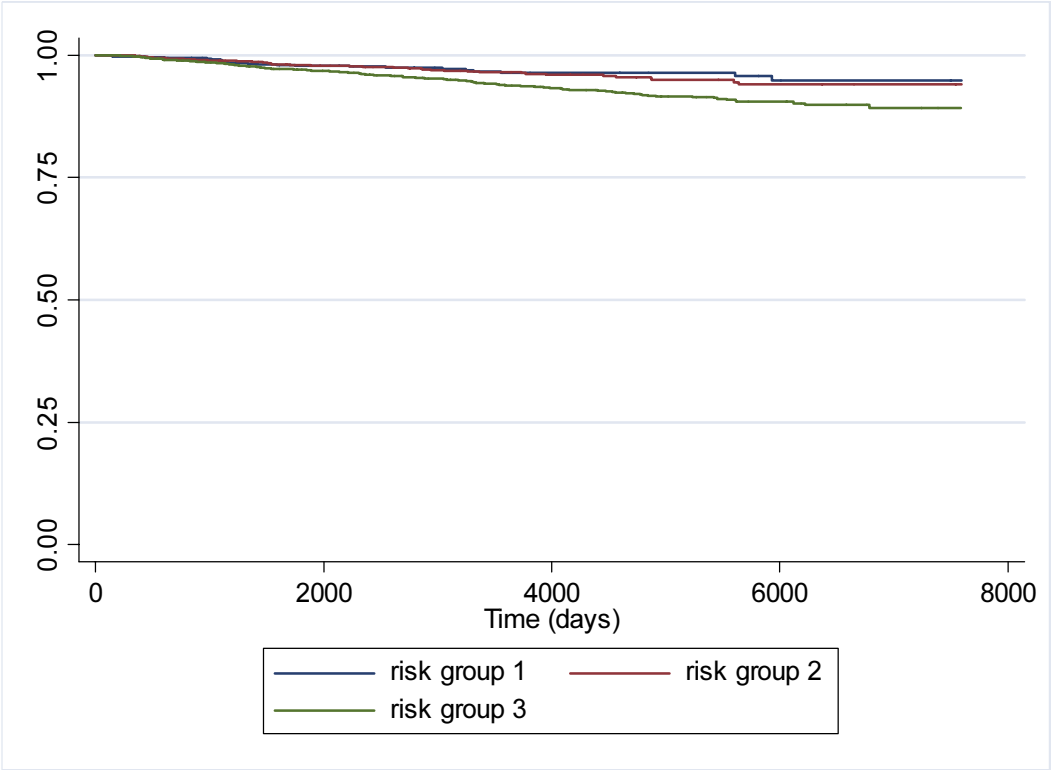
Group 1: T0-, N1-, group 2: T2-, N0 and group 3: T0-1, N0

Figure 2e. Kaplan-Meier estimates of risk for contralateral tumour (patient above 55 years)



Group 1: T0-, N1-, group 2: T2-, N0 and group 3: T0-1, N0

Figure 2f. Kaplan-Meier estimates of risk for contralateral tumour (patient below 55 years)



Group 1: T0-, N1-, group 2: T2-, N0 and group 3: T0-1, N0

Figure 3. Kaplan-Meier estimates of mortality after primary breast cancer diagnosis

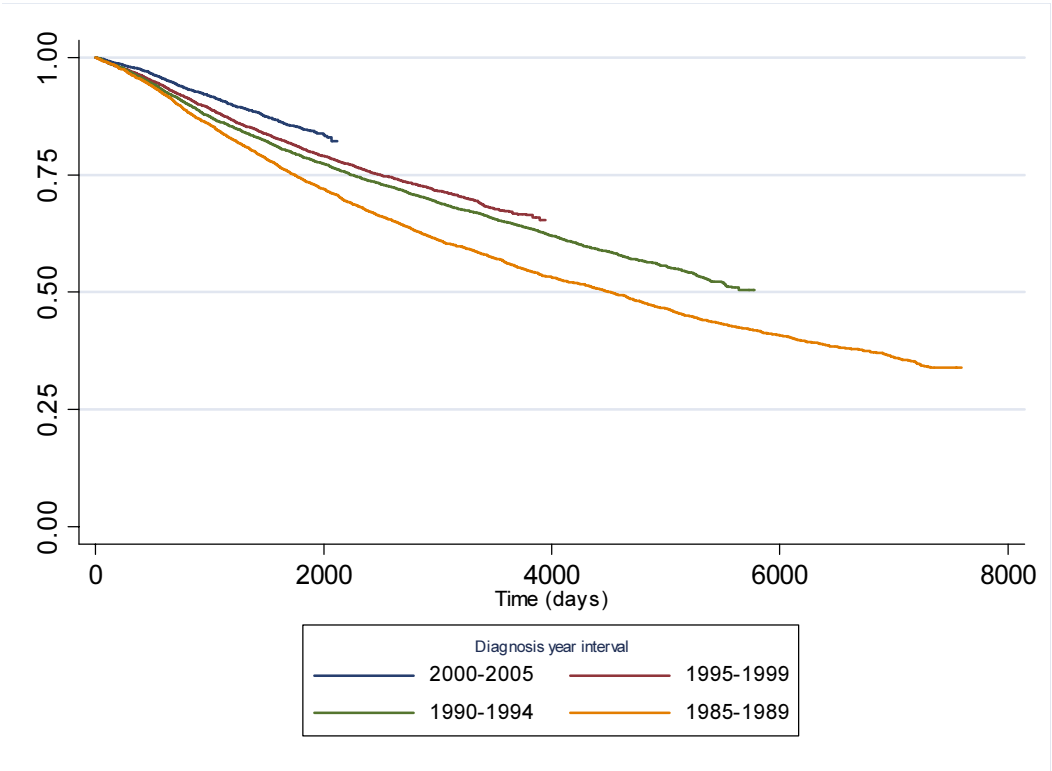
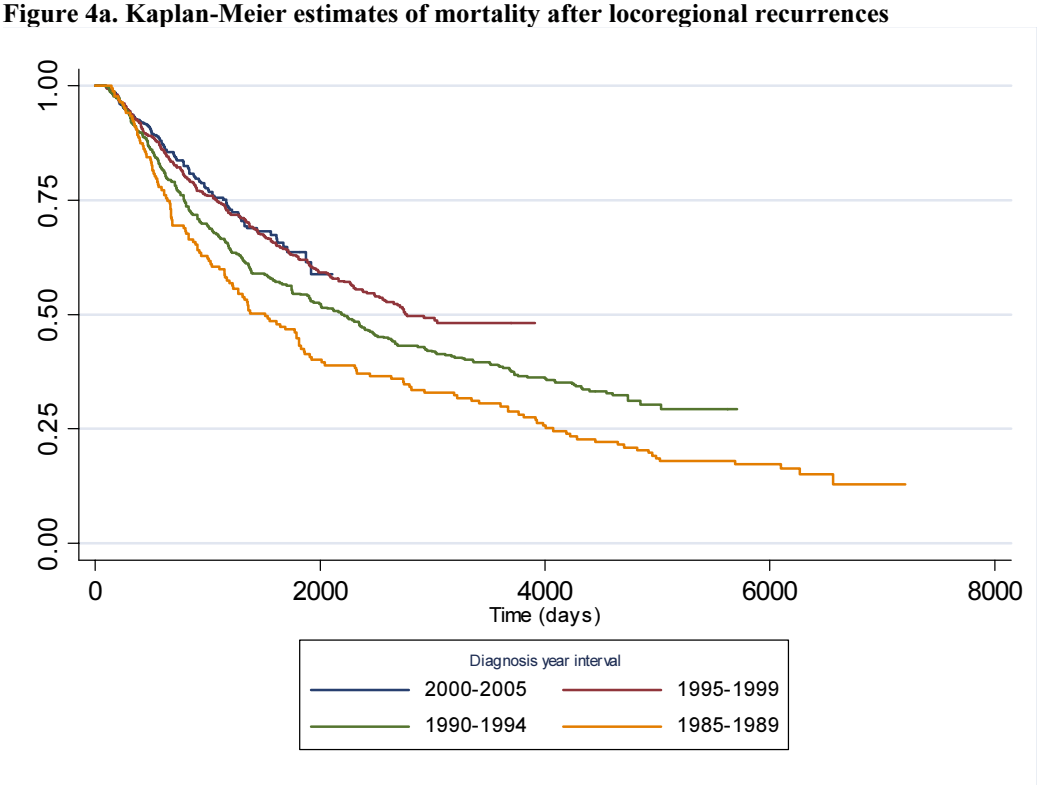


Figure 4a. Kaplan-Meier estimates of mortality after locoregional recurrences



4b. Kaplan-Meier estimates of mortality after distant relapses

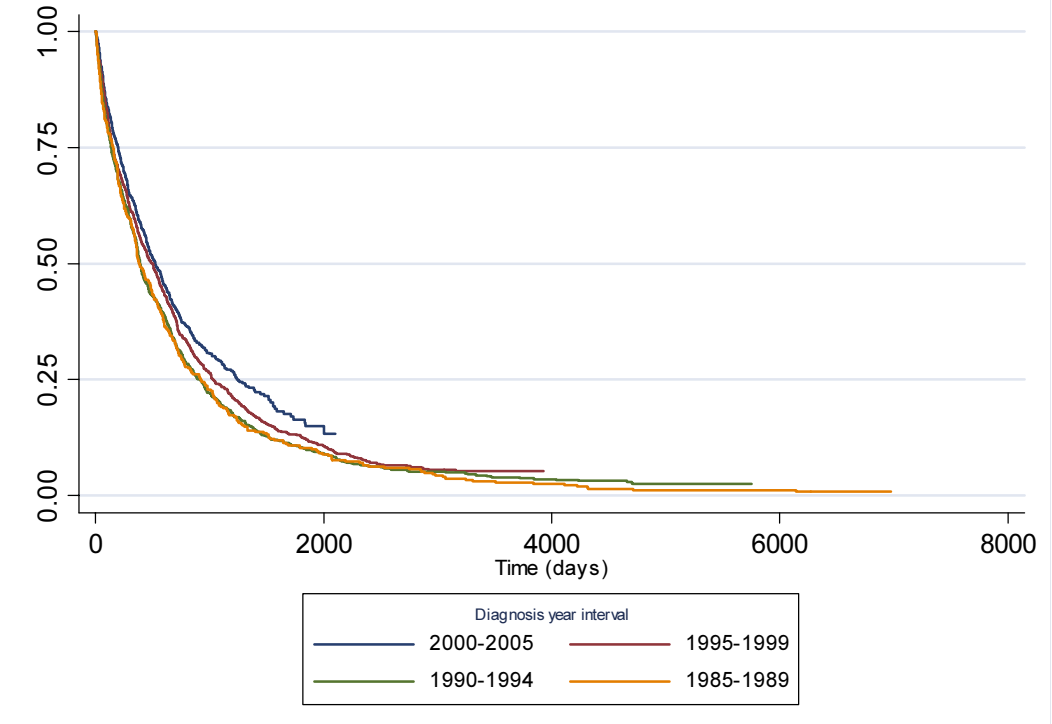


Figure 4c. Kaplan-Meier estimates of mortality after contralateral tumour