The Breast 45 (2019) 75–81

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Potential gain in life years for Swedish women with breast cancer if stage and survival differences between education groups could be eliminated – Three what-if scenarios

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ARTICLE INFO

Article history:
Received 30 October 2018
Received in revised form
13 February 2019
Accepted 9 March 2019
Available online 12 March 2019

Keywords:
Breast cancer
Socioeconomic status
Survival differences
Postponable deaths
Gain in life years

ABSTRACT

Many studies have found evidence of socioeconomic differences in breast cancer survival. This study aimed to quantify the impact of removing differences in stage distribution and stage-specific relative survival between education groups in Swedish women with breast cancer. Using information from a breast cancer research database, the study population contained 62 121 women diagnosed with breast cancer in three healthcare regions of Sweden from 1992 to 2012. The loss in expectation of life and life years lost due to breast cancer were estimated using flexible parametric relative survival models by education group and age at diagnosis. The potential gain in life years and postponable deaths were calculated by applying the 1) stage distribution, 2) stage-specific relative survival, and 3) both stage distribution and stage-specific relative survival of the high education group to the low and medium education groups. For a cohort of around 3500 women diagnosed with breast cancer residing in three Swedish healthcare regions in a typical calendar year, we estimated that removing stage differences would postpone an additional 25 deaths at five years after diagnosis, and result in a gain of approximately 573 life years. Alternatively, if stage-specific breast cancer survival could be equated, approximately 692 life years could be saved and an additional 26 deaths could be postponed five years after diagnosis. Results such as these can help guide decisions on interventions intended to minimise socioeconomic differences in breast cancer outcomes.

1. Introduction

Breast cancer is the most common female cancer worldwide; in the EU alone an estimated 494 000 women were diagnosed with breast cancer in 2012 [1]. Although breast cancer survival in Sweden is generally high [2], outcomes have been shown to vary between sociodemographic groups [3–6]. Socioeconomic status (SES) is one of many factors that have been found to be associated with breast cancer survival [7], which is generally higher in women in high compared to low SES. Several studies have concluded that stage at diagnosis, among other factors, contributes to observed gradients in survival [6–8]. Quantifying differences in cancer survival between SES groups is of interest, but to improve understanding of the effect of factors such as stage at time of diagnosis, it is of importance to study the potential impact of eliminating these differences.

Measures such as the total gain in life years, or postponable deaths can be calculated to understand the potential impact of removing differences in prognostic factors in a population [9]. These can be estimated using a measure called the loss in expectation of life [10]. Such measures are useful because of their simple interpretation and that they focus on the effect of cancer in the population via absolute effects. In comparison to the commonly

Abbreviations: SES, Socioeconomic status; BCBaSe, Breast Cancer Data Base Sweden; FPM, flexible parametric models; LEL, loss in expectation of life; CI, confidence interval.

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https://doi.org/10.1016/j.breast.2019.03.005
0960-9776/

used relative survival, or cause-specific survival, these measures provide information about real world risk.

Even with sophisticated statistical measures, quantifying SES differences in survival can be challenging since data for SES or stage are often unavailable, or have large proportions of missing information. Although routine population-based cancer registries are powerful tools for research, information on clinical factors is generally limited.

Using information from a Swedish breast cancer research database (BCBaSe) generated by cross linkage between clinical registers and other register resources, we aimed to quantify the gain in life years and the number of postponable deaths if differences in the stage distribution and stage-specific survival between educational groups could be removed. A secondary aim was to determine whether removing differences in stage at diagnosis, or stage-specific survival between education groups has a larger impact.

2. Materials and methods

2.1. Data

Data on women diagnosed with invasive breast cancer between 1992 and 2012 were obtained from the Breast Cancer Data Base Sweden (BCBaSe). This research database contains information from Breast Cancer Quality Registers from the Stockholm/Gotland, Uppsala/Örebro and North healthcare regions of Sweden that have been linked to several national demographic and healthcare registers. BCBaSe contains clinical information on around 99% of women diagnosed in the specified regions [11], which represent approximately 60% of the Swedish population. BCBaSe also contains a randomly selected comparison cohort of breast-cancer free women matched in a ratio of 1:5 based on birth year and county of residence. Information on highest achieved educational level was obtained by individual level record linkage with the Longitudinal Integration Database for Health Insurance and Labour Market Systems database held by Statistics Sweden [12]. Educational level was categorised into low (compulsory education less than or up to nine years), medium (up to three years of non-compulsory secondary education) and high (post-secondary education). Highest achieved education was chosen as a measure of socioeconomic status since this is known to be stable for the majority of the population after adulthood [13]. The women were followed-up until date of death, date of emigration, or end of follow-up (31st December 2013), whichever occurred first. Data on clinical and pathological stage available in BCBaSe were used alongside the UICC stage classification to create the stage variable used in the analyses [14]; further details on this can be found in the supplementary materials.

2.2. Statistical methods

We modelled relative survival using flexible parametric models (FPM) [15,16]. Relative survival is defined as the all-cause survival in the cancer patients divided by their expected survival had they not had cancer [17]. Life tables containing expected survival were created using information from Statistics Sweden on a reference population for the three regions included in BCBaSe. These were then stratified by education group using methods described elsewhere [18]. The FPM included effects of age, stage at diagnosis and education. Interactions between age and other variables, and time-dependent effects of all variables were included in the model. A period analysis approach with a window between 2008 and 2012 was used. This approach utilizes patient information who are at risk within the period window and has been shown to make more accurate predictions for the future than the traditional cohort approach [19,20]. Missing values for stage and education were imputed using multiple imputation [21,22]. More detailed information about multiple imputation and modelling can be found in the supplementary materials.

The FPM was used to predict the loss in expectation of life (LEL) [10] for each education group and stage. Estimates of stage-standardised LEL for each education group and age were also calculated. This standardised LEL estimate used weights calculated by dividing the number of people at risk in the study population for each age (categorised into <40, 40–49, 50–59, 60–69, 70–79, and 80 + years), education and stage group, by the number of people at risk in each education and age group.

The potential gain in life years were quantified for the following:

- Scenario A: Removal of differences in the stage distribution. Stage-standardised age-specific LEL estimates for all education groups were calculated using the age group-specific stage distribution of the high education group without changing the stage-specific relative survival; see scenario A in Fig. 1 for an illustration.
- Scenario B: Removal of differences in stage-specific breast cancer survival. Stage-standardised age-specific LEL estimates for all education groups were calculated using the age group-specific relative survival of the high education group without changing the stage distribution of each education group; see scenario B in Fig. 1 for an illustration.
- Scenario C: Removal of differences in both the stage distribution and stage-specific relative survival. Stage-standardised LEL estimates were calculated using the stage distribution and relative survival of the high education group; see scenario C in Fig. 1 for an illustration.

Using scenarios A, B and C, we estimated the number of postponable deaths, i.e., how many deaths could be postponed for women with breast cancer using a cohort which represented the number of diagnoses in a typical calendar year. The number of postponable deaths are calculated as the number of deaths at a certain time point minus the number of deaths that would be expected at the same time point under one of the described scenarios. To put the number of postponable deaths into perspective, we also calculated the observed number of deaths within five years for women diagnosed with breast cancer in 2008. The postponable deaths measure is highly time-dependent since deaths cannot be postponed indefinitely. Subsequently, we also estimated the total gain in life years if differences between education groups in terms of stage distribution, or relative survival, were removed.

On the population level, the total gain in life years and postponable deaths are calculated for diagnoses in a 'typical calendar year'. This refers to the average sized cohort of women diagnosed with breast cancer from 2008 to 2012 by age at diagnosis and education group; this resulted in a total cohort of size 3483. We also estimated the total life years lost and postponable deaths in the whole of Sweden. To do this we assumed that our cohort of 3483 was approximately 43% of the total number of breast cancer diagnoses recorded in Sweden for one year [23] and that the characteristics of the population under study were representative of the whole country.

Bootstrapping was used to calculate 95% confidence intervals for standardised estimates. Further information on how total life years lost and postponable deaths were calculated is presented in the supplementary materials.

Breast cancer	Stage-specific relative survival according to education group. Proportion of stage given within parentheses		
	Low	Medium	High
Stage 1	0.97 (0.44)	0.98 (0.47)	0.98 (0.48)
Stage 2	0.92 (0.38)	0.93 (0.37)	0.94 (0.38)
Stage 3	0.75 (0.14)	0.77 (0.13)	0.79 (0.12)
Stage 4	0.25 (0.04)	0.30 (0.03)	0.33 (0.02)
Stage-standardised estimate of relative survival	0.891*	0.914	0.929

*0.891 = 0.97*0.44 + 0.92*0.38 + 0.75*0.14 + 0.25*0.04

A

Stage distribution of high education group applied to low and medium education groups		
Low	Medium	High
0.97 **(0.48)**	0.98 **(0.48)**	0.98 (0.48)
0.92 **(0.38)**	0.93 **(0.38)**	0.94 (0.38)
0.75 **(0.12)**	0.77 **(0.12)**	0.79 (0.12)
0.25 **(0.02)**	0.30 **(0.02)**	0.33 (0.02)
0.910	0.922	0.929

B

Relative survival of high education group applied to the low and medium groups		
Low	Medium	High
0.98 (0.44)	**0.98** (0.47)	0.98 (0.48)
0.94 (0.38)	**0.94** (0.37)	0.94 (0.38)
0.79 (0.14)	**0.79** (0.13)	0.79 (0.12)
0.33 (0.04)	**0.34** (0.03)	0.33 (0.02)
0.912	0.921	0.929

C

Both stage distribution and relative survival of high education group applied to the low and medium groups		
Low	Medium	High
0.97 (0.46)	**0.97 (0.46)**	0.97 (0.46)
0.90 (0.34)	**0.90 (0.34)**	0.90 (0.34)
0.61 (0.18)	**0.61 (0.18)**	0.61 (0.18)
0.32 (0.02)	**0.32 (0.02)**	0.32 (0.02)
0.929	0.929	0.929

Fig. 1. Illustration of the three different scenarios where **A** shows how the standardisation changes when applying the stage-specific stage distribution of the high education group to all other groups, **B** shows the changes when applying the stage-specific relative survival of the high education group to the other groups, and **C** shows changes when combining both **A** and **B**. Bold values represent the changes made in each of the scenarios. Note that the figures presented here represent age and region-standardised five year relative survival estimated from a flexible parametric model assuming proportional hazards.

3. Results

Our analyses encompassed 62 121 women recorded in BCBaSe with a diagnosis of breast cancer between 1992 and 2012. Descriptive statistics of these women are shown in Table 1. The majority of women were diagnosed with stage I breast cancer (40.1%), 33.2%, 11.8% and 2.6% of women were diagnosed at stage II, stage III and stage IV, respectively. The stage distribution by education group is presented in Table 1. Stage information was missing for 12.4% of cases. Following multiple imputation, 45.3% of women had stage I breast cancer at diagnosis, 37.9% stage II disease, 13.6% stage III disease, and 3.3% stage IV breast cancer.

3.1. Loss in expectation of life

The expected remaining life years for the breast cancer patients and a matched healthy population are presented by age and education group in supplementary Table S1. For example, a cancer-free woman aged 45 between 2008 and 2012 in the medium education group would be expected to live for a remaining 40.8 years, whereas comparison women with a breast cancer diagnosis would be expected to live another 31.1 years; taking the difference of these two values gives the life years lost. Table 2 displays the life years lost and gained by education group and alternative scenarios for selected ages. The life years lost measure is highly dependent on

Table 1
Descriptive statistics of breast cancer patients in three regions of Sweden between 1992 and 2012.

	Low education N(%)	Medium education N(%)	High Education N(%)	Missing education N(%)	Total BCBaSe population N(%)
	N = 19 528	N = 23 482	N = 17 028	N = 2083	N = 62 121
Region					
Stockholm/Gotland	6563 (33.6)	9883 (42.1)	8821 (51.8)	1018 (48.9)	26 285 (42.3)
Örebro/Uppsala	9933 (50.9)	9458 (40.3)	5752 (33.8)	1019 (48.9)	26 162 (42.1)
North	3032 (15.5)	4141 (17.6)	2455 (14.4)	46 (2.2)	9674 (15.6)
Year of diagnosis					
1992–1995	3510 (18.0)	2967 (12.6)	1794 (10.5)	833 (40.0)	9104 (14.7)
1996–1999	4165 (21.3)	3938 (16.8)	2634 (15.5)	560 (26.9)	11 297 (18.2)
2000–2003	3811 (19.5)	4574 (19.5)	3151 (18.5)	280 (13.4)	11 816 (19.0)
2004–2007	3547 (18.2)	5009 (21.3)	3728 (21.9)	207 (9.9)	12 491 (20.1)
2008–2012	4495 (23.0)	6994 (29.8)	5721 (33.6)	203 (9.8)	17 413 (28.0)
Age of diagnosis					
Mean (SD)	69.3 (12.2)	59.7 (12.6)	56.7 (11.8)	85.9 (13.9)	62.4 (13.6)
Stage					
1	7174 (36.7)	9976 (42.5)	7454 (43.8)	306 (14.7)	24 910 (40.1)
2	6240 (32.0)	7935 (33.8)	5952 (35.0)	480 (23.0)	20 607 (33.2)
3	2364 (12.1)	2729 (11.6)	1954 (11.5)	253 (12.2)	7300 (11.8)
4	704 (3.6)	549 (2.3)	318 (1.9)	59 (2.8)	1630 (2.6)
.Missing	3046 (15.6)	2293 (9.8)	1350 (7.9)	985 (47.3)	7674 (12.4)

Table 2
Life years lost due to breast cancer when A removing differences in stage distribution between education groups, B removing differences in stage-specific relative survival between education groups, and C removing both differences in stage-distribution and stage-specific relative survival.

Age (years)	Education group	Life years lost (95% confidence interval)				Gain in life years (95% confidence interval)		
		Study population	Scenario A	Scenario B	Scenario C	Scenario A	Scenario B	Scenario C
45	Low	9.90 (8.46,11.33)	8.68 (7.27,10.09)	9.05 (8.15,9.94)	7.91 (7.05,8.77)	1.21 (1.13,1.30)	0.85 (−0.72,2.42)	1.98 (0.44,3.53)
	Medium	9.69 (8.76,10.62)	9.27 (8.34,10.21)	8.84 (7.90,9.78)	8.45 (7.52,9.38)	0.42 (0.38,0.46)	0.85 (−0.23,1.93)	1.24 (0.19,2.30)
	High	9.11 (8.10,10.13)						
55	Low	5.42 (4.85,5.99)	4.75 (4.18,5.32)	4.91 (4.47,5.34)	4.28 (3.85,4.70)	0.67 (0.64,0.71)	0.52 (−0.09,1.12)	1.15 (0.55,1.74)
	Medium	5.27 (4.78,5.76)	4.83 (4.35,5.31)	5.03 (4.56,5.50)	4.61 (4.15,5.07)	0.44 (0.40,0.47)	0.24 (−0.26,0.73)	0.66 (0.18,1.14)
	High	5.03 (4.52,5.54)						
65	Low	2.81 (2.53,3.08)	2.66 (2.38,2.93)	2.53 (2.27,2.79)	2.39 (2.13,2.65)	0.15 (0.14,0.17)	0.28 (−0.02,0.57)	0.42 (0.13,0.71)
	Medium	2.69 (2.44,2.93)	2.64 (2.40,2.89)	2.64 (2.36,2.92)	2.60 (2.31,2.88)	0.04 (0.03,0.05)	0.05 (−0.20,0.30)	0.09 (−0.15,0.34)
	High	2.86 (2.54,3.18)						
75	Low	2.28 (2.12,2.44)	1.93 (1.77,2.08)	2.07 (1.87,2.27)	1.75 (1.56,1.93)	0.35 (0.34,0.37)	0.21 (0.01,0.42)	0.54 (0.34,0.73)
	Medium	1.89 (1.74,2.05)	1.94 (1.78,2.10)	1.86 (1.67,2.06)	1.91 (1.71,2.11)	−0.04 (−0.06,-0.03)	0.03 (−0.17,0.23)	−0.01 (−0.22,0.19)
	High	2.11 (1.88,2.33)						

age at diagnosis, since older patients have fewer expected remaining life years to lose than younger patients. For example, women diagnosed with breast cancer at age 45 in the medium education group are predicted to lose, on average, 9.7 (95% CI: 8.8, 10.7) years of their remaining life, which is the difference between the previously presented life expectancy values. In contrast a woman diagnosed at age 75 is predicted to lose 1.9 (95% CI: 1.7, 2.1) years. Differences in the LEL between education groups can also be seen, although not as pronounced as for age. For example, a 55 year old woman in the low education group will on average lose 5.4 (95% CI: 4.9, 6.0) years of remaining life attributed to breast cancer, compared to 5.0 (95% CI: 4.5, 5.5) years in women in the high education group.

3.2. Gain in life years

Table 2 also presents the gain in life years that could be achieved if differences in the stage distribution, or stage-specific survival differences, between education groups were to be removed. Generally, larger gains in life years were seen in younger patients if differences in stage distributions could be removed. For example, in the low education group, 1.2 (95% CI: 1.1, 1.3) life years could be gained for a woman diagnosed at age 45, compared to 0.4 (95% CI: 0.3, 0.4) life years in a woman diagnosed at age 75. Interestingly, changing the stage distribution for those aged 75 years in the medium education group resulted in a negative gain of −0.04, indicating the stage distribution in this group was slightly better than in the high education group. When equating the stage-specific relative survival we estimated that 0.9 (95% CI: −0.7, 2.4) life years could be gained for women diagnosed at age 45 in the low education group. In contrast, a 75 year old woman in this education group was estimated to gain 0.2 (95% CI: 0.0, 0.4) life years. Our results indicate that removing differences between education groups results in fewer life years lost for the low and medium education groups. In addition, fewer years are lost for the low and medium groups in comparison to the high education group where changes in the stage distribution or stage-specific survival are not made by design, see Table 2. This is due to the expected remaining life years in the low and medium education groups being lower than the high education group (Table S1), and as a result have more potential years to gain.

3.3. Total gain in life years

Table 3 shows the total life years lost and the potential gain in life years for each of the scenarios for a cohort of 3483 women diagnosed in a typical calendar year. Without removing any differences between education groups, 15 856 life years would be lost for women in the Stockholm/Gotland, Uppsala/Örebro and North regions of Sweden due to breast cancer. If all differences between education groups could be removed, 14 627 (95% CI: 13 416, 15 838) life years would have been lost, i.e., a gain of 1230 (95% CI: 537,

Table 3
Total life years lost due to breast cancer and gain in life years in three regions of Sweden for a cohort of 3483 women diagnosed in a typical calendar year when removing A differences in stage distribution, B differences in stage-specific relative survival and, C both stage distribution and stage-specific relative survival differences between education groups.

	Study population	Population using scenario A	Population using scenario B	Population using scenario C
Total life years lost (95% CI)	15 856 (14 922, 16 790)	15 283 (14 347, 16 220)	15 165 (13 947, 16 382)	14 627 (13 416, 15 838)
Total gain in life years (95% CI)	–	573 (549, 597)	692 (−13, 1397)	1230 (537, 1 922)

1922) life years in the population under study. This approximately translates to a gain of 2878 life years for Sweden.

3.4. Postponable deaths

The number of observed deaths within five years from diagnosis in 2008 was 275, 158 and 106 for the low, medium and high education groups. Fig. 2 and supplementary Table S2 show the number of deaths that could be postponed if differences in stage distribution (Fig. 2, panel A), differences in stage-specific relative survival (Fig. 2, panel B), and differences in both stage distribution and stage-specific relative survival (Fig. 2, panel C) between education groups could be removed. Note that the height of the curve in Fig. 2 represents the number of avoidable deaths at the time represented on the x-axis. For a cohort of 3483 women diagnosed in a typical calendar year, an estimated 49 deaths could be postponed beyond five years from diagnosis if all differences between education groups were to be removed. If differences in stage at diagnosis were removed, approximately 25 deaths could be postponed, whereas approximately 26 deaths could be postponed beyond five years from diagnosis if differences in stage-specific relative survival were removed for the population under study. For the whole country, removing stage differences, stage-specific relative survival differences and both of these, would translate into approximately 59, 61, and 115 deaths postponed at five years.

4. Discussion

We quantified the gain in life years and postponable deaths for women diagnosed with breast cancer in three Swedish healthcare regions when removing differences in 1) stage at diagnosis and 2) stage-specific survival between education groups. We estimated that for a cohort of 3843 women diagnosed in a typical calendar year in these regions, removing differences in the stage distribution would result in postponing 25 deaths beyond five years from diagnosis, compared to a postponement of 26 deaths when removing differences in stage-specific survival. When considering the whole life-span of women with breast cancer, 573 life years could be gained if differences in stage at diagnosis were eliminated, in comparison to 692 life years when removing stage-specific survival. Our results indicate that removing both stage and survival differences between education groups could produce a gain in life years of 8%.

Other studies undertaken in Sweden have found increased mortality in breast cancer patients of low SES in comparison to high SES, both in terms of highest educational achievement [7] and occupation [24]. Studies in Sweden and Norway have also reported no statistical significant differences in mortality between education groups [4,25]. Eaker et al. reported both a difference in mortality and in the five-year relative survival of Swedish breast cancer patients diagnosed between 1993 and 2005 [5]. Our results echo these differences in outcomes of breast cancer patients between socioeconomic groups via different methodology. Several previous studies using similar methods have focused on postponable deaths when equating the relative survival of cancer patients between education groups, social class or socioeconomic groups in the Nordic countries, Finland, and in England and Wales [26–28]. Rutherford et al. considered the effect of stage on the postponable deaths between deprivation groups for women with breast cancer residing in the East of England [9]. To our knowledge, this is the first study in Sweden quantifies the effect of breast cancer stage and survival on education group using the avoidable deaths and gain in life year measures. These encourage further understanding of the reasons behind the differences and quantify the potential impact of the differences on a population level.

The underlying reasons for differences between socioeconomic groups are multifactorial and are in practice difficult to eliminate. Differences in stage at diagnosis could reflect timeliness of diagnosis, knowledge and screening attendance. Health-seeking behaviour could also play a role; for example, patients from a higher socioeconomic background are generally more health-aware, more likely able to navigate the health care system and push for a diagnosis. Factors that could contribute to observed differences in stage-specific survival include lifestyle, social support, access to and quality of treatment and comorbidity burden [7]. For example, compared to patients from a higher socioeconomic background, patients from lower socioeconomic groups generally have higher rates of concomitant conditions and mortality. If interventions were introduced to reduce differences between educational group, then improvements would likely not be limited to the low and medium education groups, i.e., those with high education group would benefit to some extent; it is important to note we have not accounted for this in our study. Identifying and removing all differences represents a challenge, particularly in a country where healthcare, including outreach invitational mammography, is available to all residents at low out-of-pocket costs.

A major strength of our study was the use of high-quality population-based quality registry data that provided an opportunity to quantify cancer survival by variables other than those traditionally used such as age, sex and year. The methodology used to calculate the loss in expectation of life relies on extrapolation of expected and relative survival curves into the future. While the future is unknown, previous assessments of these methods indicate that the method works well [10]. At the same time, the period approach was utilised since this has been shown to make more accurate predictions for the future than the traditional cohort approach [19,20]. Also, since breast cancer survival has been improving over time [29], the present results may not be accurate for future cohorts of women with breast cancer. An additional consideration is that educational achievement was used as proxy for SES even though it does not capture all aspects of socioeconomic status, and can vary depending on the age cohort. However, there is evidence that the choice of socioeconomic indicator does not have a large impact when comparing patterns of cancer survival between socioeconomic groups [30]. Information on stage was missing for 12% of included women. However, the main analysis results remained largely unchanged when different multiple imputation

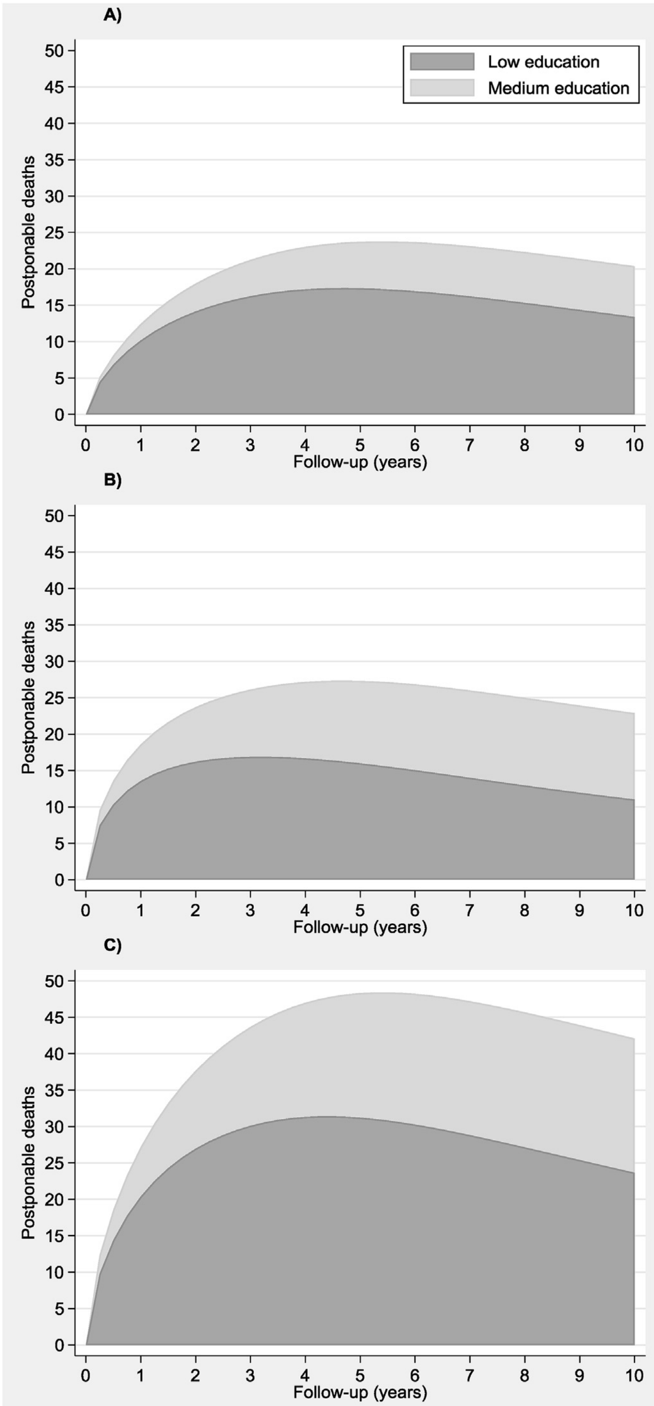

Fig. 2. Postponable deaths for a cohort of 3483 Swedish women diagnosed with breast cancer in a typical calendar year when applying. A) the same stage-distribution, B) the same stage-specific relative survival and C) both the same stage distribution and stage-specific relative survival for all education levels as the high education group. Note that the height of the curve in Fig. 2 represents the number of avoidable deaths at the time represented on the x-axis. For example, the postponable deaths at 5 years for the low education group in scenario A is approximately 18 years.

models were applied. The potential effect on the whole of Sweden is interesting, but could only be estimated crudely in this study. Consequently, results presented for Sweden as a whole should not be over-interpreted. However, dramatic differences from our presented results for the whole of Sweden are unlikely.

5. Conclusion

In this study we addressed questions such as "What would the impact be on life years and postponable deaths for breast cancer patients if stage and stage-specific survival differences between educational groups could be removed?". Our findings indicate that interventions directed in removing stage distribution and survival differences between education groups could result in improvements in the survival of women with breast cancer. Approximately 2800 life years could be gained for Swedish women diagnosed with breast cancer in one calendar year if these differences between education groups could be removed. Results such as these can help guide decisions on interventions intended to reduce socioeconomic differences in early breast cancer detection, management and survival.

Conflicts of interest

None declared.

Funding

This work was supported by grants from the Swedish Cancer Society and Swedish Research Council.

Acknowledgements

This work was funded by the Swedish Cancer Society [CAN 2015/583] the Swedish Research Council [2017-01591] and Cancer Research UK [C14183/A18262]. We would also like to thank the Breast Cancer Quality Register steering groups in Stockholm, Uppsala-Örebro and the Northern region for allowing the data to be used for this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2019.03.005.

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