

# BMJ Open Adult children's socioeconomic resources and mothers' survival after a breast cancer diagnosis: a Swedish population-based cohort study

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## ABSTRACT

**Objectives:** Socioeconomic inequalities in survival after breast cancer persist worldwide. We aim to determine whether adult offspring's socioeconomic resources contribute to inequalities in mothers' survival after breast cancer.

**Methods:** 14 231 women, aged 65–79 years, with a child aged  $\geq 30$  years and a first primary diagnosis of breast cancer in the National Cancer Register between 2001 and 2010 were followed until death, 10 years after diagnosis, or end of study (December 2015). Relative survival proportions and excess mortality within 10 years of diagnosis by strata of offspring's education level and disposable income were estimated using flexible parametric models accounting for measures of mothers' socioeconomic position and expected mortality in the general population.

**Results:** 4292 women died during 102 236 person-years of follow-up. Crude 10-year relative survival proportions for mothers of children with  $>14$ , 12–14 and  $<12$  years of education were 0.89 (0.87 to 0.91), 0.87 (0.85 to 0.89) and 0.79 (0.76 to 0.81), respectively. Compared with mothers of children with  $>14$  years of education, mothers of children with  $<12$  or 12–14 years of education had substantially higher excess mortality (excess HR 1.69 (1.38 to 2.07) and 1.22 (1.00 to 1.48), respectively). Higher mortality did not differ between tertiles of offspring's disposable income.

**Conclusions:** Adult offspring's education level may contribute to inequalities in mothers' survival after breast cancer. Clinicians should be aware of the educational context beyond the individual and women with less educated offsprings may require extra support. This should be considered in future research, policy frameworks and interventions aimed at reducing survival inequalities.

## INTRODUCTION

Breast cancer is a leading contributor to the burden of disease in women;<sup>1</sup> in 2012, it killed 522 000 women globally.<sup>2</sup> However,

## Strengths and limitations of this study

- Using excess mortality as the main outcome allowed us to separate cancer-specific and cancer-consequent deaths from the deaths expected in the general population.
- Using population-based national registers of high quality and validity reduced the possibility of exposure misclassification, recall bias and selection bias compared with smaller studies with self-reported data.
- Information on clinical stage at diagnosis was only available in a subgroup of women.
- Despite differences in prognosis and treatment of patients diagnosed in stage 4 compared with patients diagnosed in earlier clinical stages, it was necessary to pool women in stages 3 and 4 for analysis since only 245 women were diagnosed in stage 4.
- Information on occupation was not available for the whole follow-up period, consequently this was not included in our analyses.

inequalities in survival after breast cancer persist worldwide.<sup>3–6</sup> Even in Sweden where there is universal access to free education and healthcare, survival after breast cancer is considerably lower among women of lower socioeconomic position.<sup>7</sup> Better survival among women with higher socioeconomic position may be due, in part, to better health awareness, more frequent attendance of screening programmes, earlier tumour detection, higher rates of diagnostic activity and a lower comorbidity burden.<sup>6–10</sup> Survival post-cancer is also influenced by the socioeconomic position of close relatives.<sup>11–15</sup> However, although many older individuals have adult children who can support their ageing parents, few studies have examined whether the socioeconomic resources of adult children are associated with parental health outcomes.<sup>16–19</sup> Existing studies

indicate a lower mortality risk (all-cause and cause-specific) among parents of children with higher socioeconomic position, but they do not separate differences in disease occurrence from differences in survival after a disease has occurred.<sup>16–19</sup> To the best of our knowledge, no study has yet examined whether parental survival after a cancer diagnosis is a function of offspring's socioeconomic position.

In line with the association between mothers own socioeconomic position and survival after breast cancer, we hypothesise that having a child with lower socioeconomic position may be associated with higher excess mortality (ie, poorer survival) after a breast cancer diagnosis, independent of mothers' own socioeconomic position. Associations may be stronger among mothers with low socioeconomic position, since mothers with higher socioeconomic position may have greater ability to maximise their own survival. Associations may also be stronger among those diagnosed at an earlier clinical stage, as the poor prognosis of later stage diagnoses may limit the opportunities for offspring to influence survival.<sup>20</sup> Children of higher socioeconomic position may facilitate an earlier diagnosis, as such, we also hypothesise that stage at diagnosis may, at least partly, mediate potential associations between offspring's socioeconomic position and mothers' survival after breast cancer.

Our primary aim is to determine whether offspring's education level and disposable income (as proxy measures of socioeconomic position) are associated with mothers' excess mortality after a breast cancer diagnosis, independent of mothers' own socioeconomic position. Second, we aim to assess evidence of effect modification by mothers' education, mothers' disposable income and clinical stage at diagnosis. Finally, we aim to examine whether clinical stage at diagnosis mediates any potential associations between measures of offspring's socioeconomic position and mothers' excess mortality.

## METHODS

### Study design

We conducted a population-based cohort study of all women aged 65–79 years, with a child aged  $\geq 30$  years, no previous cancer diagnosis and a first primary breast cancer diagnosis in Sweden between 2001 and 2010. Restricting the cohort based on offspring's age helped ensure that offspring had reached a stable education level. Information on exposures, outcomes and covariates relating to mothers, their offspring and partners was obtained from Swedish national registers. Registers were linked using the unique personal identity number assigned to all Swedish residents.<sup>21</sup> Patients with cancer were followed until death and censored on migration, surviving 10 years after diagnosis, or end of study period, that is, 31 December 2015.

### Data sources

The cohort was identified using the Swedish Cancer Register. Registration of all new primary malignancies is

statutory in Sweden and the completeness of the Cancer Register is estimated to be 98.6% for breast cancer.<sup>22</sup> Breast cancer diagnoses were defined using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), code C50: malignant neoplasm of breast. We used the Multi-Generation Register to identify the mothers' offspring (both biological and adopted).<sup>23</sup> Each mother's partner in the year prior to diagnosis was identified from the Total Population Register.<sup>24</sup> Information on education level, disposable income, age, sex, municipality of residence, marital status and country of birth were ascertained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies. We used information from each mother's most highly educated child aged  $\geq 30$  years living in Sweden in the year prior to cancer diagnosis. If a mother had multiple children aged  $\geq 30$  years with an equal education level, we used information from the oldest child.

### Outcome

Date of death was obtained from the Total Population Register.

### Exposures

Offspring's education level was categorised as:  $< 12$  years of education (ie, those with primary education and up to 2 years of secondary education (usually vocational)), 12–14 years of education (ie, those with 3 years of secondary education (usually academic) and  $< 3$  years of university education) and  $> 14$  years of education (ie, those with at least 3 years of university education). Offspring's disposable income was calculated as the sum of their household income after taxes and monetary social benefits, adjusted for household size and averaged across the 3 years prior to their mother's cancer diagnosis. Offspring's disposable income was grouped into tertiles for analysis.

### Covariates

Mothers' and partners' education level was categorised as: primary (ie,  $< 10$  years of education), secondary (ie, 10–12 years of education) and tertiary (ie, more than 12 years of education). These categories differ from the categories used for offspring's education level due to inflation of education over time. Among offspring, 4.3% had primary education (ie,  $< 10$  years of education), compared with 44.6% in mothers. Marital status was categorised as: 'married/cohabiting', 'single' (ie, divorced/separated/never married) and 'widowed'. Proximity of residence between mothers and their offspring was based on the distance between the mid-point of their respective municipality of residence and categorised as  $< 50$ , 50–150 and  $> 150$  km. Country of birth was categorised as: 'Sweden', 'Nordic countries' (Norway, Denmark, Finland and Iceland), 'Europe' (member states of the European Union before 2013) and 'outside Europe' (including individuals with an

unknown country of birth). Mothers' disposable income was calculated in the same way as offspring's disposable income (described above), and also grouped in tertiles for analysis. Clinical stage at diagnosis was defined using TNM criteria,<sup>25</sup> and categorised as stages 1, 2, and 3 and 4 combined.

### Exclusions

In total, we identified 14 514 women aged 65–79 years, with a child aged  $\geq 30$  years, no previous cancer diagnosis and a first primary breast cancer diagnosis in Sweden between 2001 and 2010. We excluded 283 mothers (2.0% of study population) with missing information about their own or their offspring's education level or income, leaving 14 231 women with complete data for analysis. Information on clinical stage at diagnosis was not recorded in the Swedish Cancer Register until 2004. As such, all analyses including stage at diagnosis were conducted in a subgroup of 8616 mothers diagnosed from 2004 to 2010.

### Statistical analysis

Excess mortality (or relative survival) was defined as the observed mortality among patients divided by the expected mortality in the general population by age, sex, calendar year and education level. Expected mortality in the general Swedish population was ascertained from the Human Mortality Database<sup>26</sup> adjusted for mothers' educational level in line with methods previously described.<sup>27</sup> We used flexible parametric models equivalent to Cox regression to estimate crude survival functions for overall survival and relative survival accounting for the expected survival in the general population.<sup>28</sup> To visually examine mothers' survival after a breast cancer diagnosis, we plotted smoothed survival curves, comparable to Kaplan-Meier curves, by strata of offspring's education level and tertiles of offspring's disposable income. Using flexible parametric models, we estimated excess HRs (EHRs) and 95% CIs of death within 10 years of diagnosis between strata of offspring's education level and tertiles of offspring's disposable income. EHRs can be interpreted as the risk of death, compared with the reference group, after accounting for the expected mortality in the general population. We present crude models and models adjusted for mothers' education level, disposable income, marital status, country of birth, age, number of children, proximity of residence to child, child's age and sex, partner's education level, and year of diagnosis.

Effect modification on the additive scale was examined by calculating the relative excess risk due to interaction.<sup>29</sup> In these analyses, variables were recoded to ensure that the stratum with the lowest risk, when the exposure and potential-modifying factor were jointly considered, was the reference category.<sup>30</sup> Effect modification on the multiplicative scale was examined by calculating ratios to relative risks (RRRs) between strata of

mothers' education, strata of mothers' disposable income and strata of clinical stage at diagnosis.<sup>31</sup>

We conducted a mediation analysis to assess the possibility that any statistically significant associations between measures of offspring's socioeconomic position and mothers' survival were mediated by cancer stage at diagnosis. Using a unified approach based within the causal inference literature, we calculated the direct effect of measures of offspring's socioeconomic position on mothers' cancer survival and the indirect effect of these via stage at diagnosis.<sup>32</sup>

Flexible parametric models did not converge when models included stage at diagnosis. As such, we used Cox regression to estimate HRs and 95% CIs of all-cause mortality, rather than excess mortality, for these analyses. Age was incorporated into all models as the time scale.

### PATIENT INVOLVEMENT

Patients were not involved in the design of the study.

## RESULTS

### Descriptive characteristics

Among the 14 231 mothers included in this study, 4292 women died during 102 236 person-years of time at risk (mean (SD) follow-up time, 7.2 (2.8) years). The mean (SD) age of mothers at diagnosis was 71 (4.3) years and age of offspring at mothers' diagnosis was 44.9 (6.3) years. Compared with mothers of children with  $>14$  years of education, a higher proportion of mothers of children with  $<12$  years of education had primary education (62% vs 30%), were in the lowest tertile of income (48% vs 28%), and lived within 50 km of their offspring (82% vs 57%), whereas a lower proportion were married/cohabiting (49% vs 61%; [table 1](#)). Similar patterns were observed when sociodemographic characteristics were stratified by offspring's income level (see online supplementary table S1) and among mothers with information available on clinical stage at diagnosis (see online supplementary table S2A and B).

### Mothers' survival by offspring's education level and disposable income

Crude survival curves stratified by offspring's education level indicated lower survival among mothers of children with  $<12$  or 12–14 years of education, than mothers of children with  $>14$  years of education for both overall survival ([figure 1A](#)) and relative survival accounting for the expected survival in the general population ([figure 1B](#)). However, differences in mothers' survival by offspring's disposable income were not apparent ([figure 1C, D](#)).

The results of the survival curves are reflected in analyses of excess mortality ([table 2](#)). In adjusted models, the excess hazard of death within 10 years of diagnosis was 69% higher among mothers of children with  $<12$  years of education and 22% higher among mothers of children with 12–14 years of education compared with the excess hazard of death among mothers of

**Table 1** Sociodemographic characteristics of the 14 231 women included in the main analysis, stratified by offspring's education level

	Mothers of children with >14 years of education			Mothers of children with 12–14 years of education				Mothers of children with <12 years of education				
	n	Per cent	Number of deaths	Person-years	n	Per cent	Number of deaths	Person-years	n	Per cent	Number of deaths	Person-years
	5030		1286	36 746	5284		1542	38 122	3917		1464	27 367
Offspring's disposable income tertile												
Highest	2142	43	554	16 017	1586	30	487	11 406	907	23	371	6314
Middle	1616	32	426	11 748	1809	34	529	13 122	1374	35	505	9553
Lowest	1272	25	306	8982	1889	36	526	13 594	1636	42	588	11 501
Mothers' education level												
Tertiary (>12 years)	1761	35	374	13 029	781	15	194	5733	221	6	58	1619
Secondary (10–12 years)	1779	35	453	13 029	2073	39	547	15 028	1275	33	421	9074
Primary (<10 years)	1490	30	459	10 688	2430	46	801	17 360	2421	62	985	16 674
Mothers' disposable income tertile												
Highest	2178	43	484	16 100	1528	29	322	11 252	733	19	199	5217
Middle	1464	29	389	10 686	1738	33	517	12 620	1305	33	487	9143
Lowest	1388	28	413	9961	2018	38	703	14 250	1879	48	778	13 007
Partners' education level												
Tertiary (>12 years)	1075	21	208	8077	478	9	113	3495	140	4	44	968
Secondary (10–12 years)	1119	22	259	8206	1153	22	262	8516	577	15	156	4272
Primary (<10 years)	816	16	231	5969	1328	25	385	9755	1169	30	395	8464
Missing	2020	40	588	14 495	2325	44	782	16 356	2031	52	869	13 663
Year of diagnosis												
2001	424	8	161	3404	488	9	161	4034	390	10	173	2928
2002	401	8	142	3328	481	9	163	3930	414	11	176	3207
2003	422	8	131	3541	467	9	162	3841	421	11	178	3284
2004	423	8	125	3576	551	10	203	4403	398	10	174	3048
2005	464	9	161	3824	506	10	180	4102	411	10	172	3160
2006	457	9	125	3755	497	9	162	3876	395	10	166	2910
2007	525	10	109	4059	519	10	152	3753	378	10	148	2565
2008	601	12	125	4039	540	10	126	3557	361	9	93	2362
2009	637	13	104	3793	553	10	110	3222	362	9	91	2052
2010	676	13	103	3427	682	13	123	3404	387	10	93	1851
Country of birth												
Sweden	4537	90	1162	33 180	4730	90	1379	34 149	3517	90	1309	24 516
Nordic countries	250	5	57	1809	348	7	107	2476	264	7	98	1897
Europe	174	3	46	1294	154	3	43	1110	89	2	40	624
Outside Europe	69	1	21	463	52	1	13	387	47	1	17	330
Marital status												
Married/cohabiting	3075	61	715	22 729	3030	57	794	22 268	1929	49	612	14 048
Single	867	17	226	6063	1012	19	308	7059	911	23	356	6154
Widowed	1088	22	345	7954	1242	24	440	8794	1077	27	496	7165
Number of children												
1	872	17	239	6303	1183	22	355	8559	1454	37	575	10 115
2	2410	48	597	17 634	2443	46	689	17 573	1565	40	552	10 946

Continued



Table 1 Continued

	Mothers of children with >14 years of education				Mothers of children with 12–14 years of education				Mothers of children with <12 years of education			
	n	Per cent	Number of deaths	Person-years	n	Per cent	Number of deaths	Person-years	n	Per cent	Number of deaths	Person-years
3+	1748	35	450	12 809	1658	31	498	11 990	898	23	337	6307
Sex of child												
Males	2309	46	595	16 924	2442	46	699	17 627	2064	53	774	14 271
Females	2721	54	691	19 823	2842	54	843	20 495	1853	47	690	13 097
Proximity of residence between mother and child												
<50 km	2854	57	723	20 646	3862	73	1130	27 844	3218	82	1181	22 607
50–150 km	854	17	212	6387	626	12	183	4511	353	9	143	2436
>150 km	1322	26	351	9713	796	15	229	5766	346	9	140	2324

children with >14 years of education. In adjusted models, we found no evidence of differences in excess hazard of death between tertiles of offspring's disposable income.

#### Effect modification by mothers' education level, disposable income and clinical stage at diagnosis

There was no evidence of effect modification by mothers own education level or disposable income on either the additive (see online supplementary table S3) or the multiplicative (see online supplementary table S4) scale, for the association of either measure of offspring's socioeconomic position with mothers' excess mortality.

On an additive scale, there was no statistically significant evidence of effect modification by clinical stage at diagnosis for associations of either measure of offspring's socioeconomic position with mothers' mortality (see online supplementary table S5). However, evaluation of effect modification on a multiplicative scale indicated that the association of offspring's education level with mothers' mortality was stronger among women diagnosed in stage 1 than among women diagnosed in stage 2 or 3 and 4 combined (see online supplementary table S6). RRRs (95% CIs) between stages were <1 for mothers of children with <12 years of education compared with mothers of children with >14 years of education. However, for mothers of children with 12–14 years of education compared with mothers of children with >14 years of education, RRRs between stages were <1, but 95% CIs overlapped with 1.

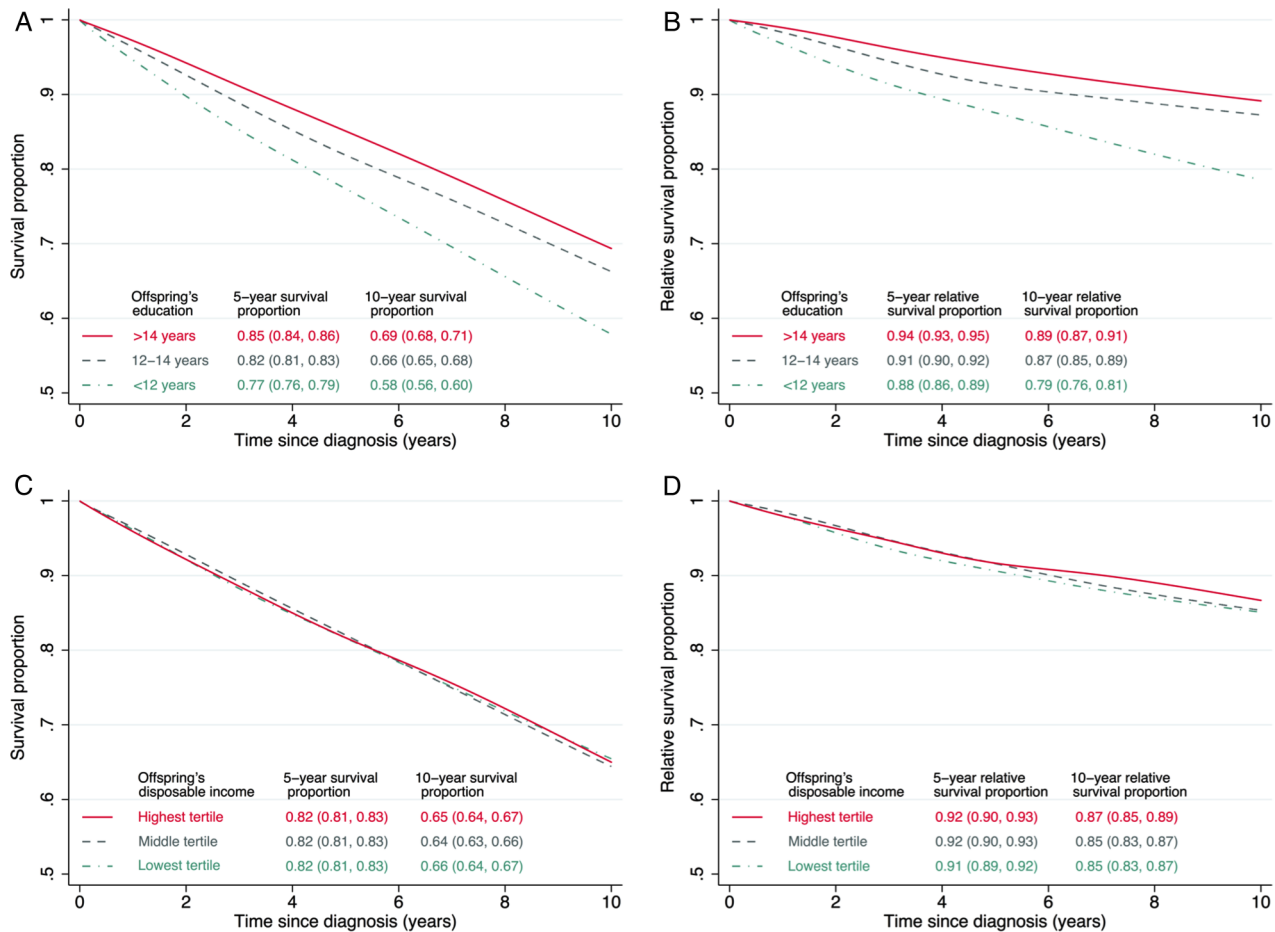
#### Mediation by clinical stage at diagnosis

Mediation analysis indicated a significant direct effect of offspring's education level on mothers' excess mortality after a breast cancer diagnosis. However, there was no significant indirect effect of offspring's education level on mothers' excess mortality acting through clinical stage at diagnosis (see online supplementary table S7).

## DISCUSSION

In this large population-based study, having offspring with a lower education level was associated with higher excess mortality (ie, poorer survival) in mothers after a breast cancer diagnosis, independent of mothers' own education level and disposable income. The association was stronger among women diagnosed at an earlier clinical stage. These findings were in line with our hypotheses. However, in contrast to our hypotheses, we found no evidence of effect modification by mothers' own education level or disposable income, and the association was not mediated by clinical stage at diagnosis.

The strengths of our study include using excess mortality as the main outcome. This allowed us to separate cancer-specific and cancer-consequent deaths from the deaths expected in the general population.<sup>33</sup> Using population-based national registers of high quality and validity reduced the possibility of exposure



**Figure 1** Crude overall and relative survival proportions by strata of offspring's education and disposable income. (A) Overall survival by strata of offspring's education. (B) Relative survival accounting for the expected survival in the general population by strata of offspring's education. (C) Overall survival by tertiles of offspring's disposable income. (D) Relative survival accounting for the expected survival in the general population by tertiles of offspring's disposable income.

**Table 2** EHRs\* of death within 10 years of a breast cancer diagnosis, by offspring's education level and disposable income

	Crude models		Adjusted models†	
	Offspring's education and income in separate models EHR (95% CI)	Offspring's education and income in mutually adjusted models EHR (95% CI)	Offspring's education and income in separate models EHR (95% CI)	Offspring's education and income in mutually adjusted models EHR (95% CI)
Offspring's education level (years)				
>14	Reference	Reference	Reference	Reference
12-14	1.27 (1.05 to 1.53)	1.26 (1.05 to 1.52)	1.23 (1.01 to 1.48)	1.22 (1.00 to 1.48)
<12	2.06 (1.73 to 2.45)	2.04 (1.71 to 2.44)	1.71 (1.40 to 2.08)	1.69 (1.38 to 2.07)
Offspring's disposable income tertile				
Highest	Reference	Reference	Reference	Reference
Middle	1.11 (0.94 to 1.33)	1.01 (0.85 to 1.20)	1.06 (0.90 to 1.26)	1.01 (0.85 to 1.19)
Lowest	1.19 (1.01 to 1.42)	1.04 (0.88 to 1.23)	1.15 (0.97 to 1.37)	1.06 (0.89 to 1.26)

\*Ratio of excess hazard of death accounting for the expected survival in the general population by age, sex, calendar year and education level.

†Adjusted for mothers' education level, mothers' income (tertile), partners' education level, year of diagnosis, country of birth, marital status, number of children, sex of child, age of child in year prior to mother's diagnosis, proximity of residence between mother and child. EHR, excess HR.

misclassification, recall bias and selection bias compared with smaller studies with self-reported data. One limitation was that the information on clinical stage at diagnosis was only available in a subgroup of women. However,

excluding women without stage at diagnosis for some analyses is not likely to have resulted in a biased sample since the reason for excluding these women (ie, diagnosis before 2004) was not associated with the exposure or

the outcome. Despite differences in prognosis and treatment of patients diagnosed in stage 4 compared with patients diagnosed in earlier clinical stages, it was necessary to pool women in stages 3 and 4 for analysis since only 245 women were diagnosed in stage 4. However, the main finding from the analyses stratified by stage was that the strongest association was among women diagnosed in stage 1, this message is likely to be similar whether or not women diagnosed in stages 3 and 4 were pooled. In addition, occupation is considered a key measure of socioeconomic position. However, information on occupation was not available for the whole follow-up period; consequently, this was not included in our analyses. Although mothers may have several children providing support, we only account for the most highly educated child aged 30 years or over. Nonetheless, alternative measures of offspring's education level, such as the proportion of all children with tertiary education, have been tested previously and found to be analogous.<sup>16</sup> There has been inflation in education over time; however, there remains a gradient of education level across society. As such, we believe that education is still a suitable proxy measure for socioeconomic position. In this study, we report relative survival as an estimate of net survival. One alternative method for addressing our research question would have been to calculate net survival using the method proposed by Perme *et al.*<sup>34</sup> However, the bias introduced by calculating relative survival as an estimate of net survival is considered small.<sup>35</sup> As such, these methods would have produced similar results and overarching conclusions.

Previous studies indicate a lower mortality risk among parents of children with higher socioeconomic position, but they do not separate disease occurrence from disease survival.<sup>16–19</sup> We show for the first time that offspring's education level is associated with mothers' survival after a serious disease diagnosis. Our results support suggestions that factors linked specifically to offspring's education, such as health awareness or the ability to interpret information, rather than material resources, may be particularly important for parental health outcomes.<sup>17</sup> We found no evidence that associations between measures of offspring's socioeconomic position and mothers' excess mortality were stronger among mothers with low socioeconomic position. However, power to detect such effect modification is low, as such, it should be examined further in future studies.<sup>31</sup> In contrast, effect modification by clinical stage at diagnosis indicates that offspring's education level may be particularly important for mothers diagnosed with breast cancer at an early stage. Patients with cancer detected at an earlier stage have a better overall prognosis than those with disease detected at a later stage, this may create a greater opportunity for offspring to influence survival. It may be that the mechanisms through which offspring's education level is associated with mothers' survival act in the longer term. The association of offspring's education level with mothers'

mortality was not due to mothers with more educated children having their cancer diagnosed at an earlier clinical stage. As such, offspring's education level is likely to be associated with mothers' survival via mechanisms other than earlier detection. Several pathways through which offspring's socioeconomic position may influence parental survival have been proposed.<sup>16</sup> For example, offsprings may provide practical and emotional support, act as role models for positive health behaviours, help their parents navigate the healthcare system and act as personal advocates to ensure their parents obtain the most appropriate level of care. Other possible explanations for our results include confounding by unmeasured family norms, for example, families who value education might also be families who value health-enhancing behaviours. Nonetheless, we do not believe that this would fully explain our results. An alternative explanation is that parental ill health may affect offspring's education. However, as offspring were at least 30 years old at the time of their mothers' first breast cancer diagnosis, this is not a likely explanation.

The results of this study contribute to a better understanding of factors leading to inequalities in breast cancer survival. This work will help equip clinicians, researchers and policymakers to reduce and prevent disparities across society in the future and will thus reduce the burden of disease for individuals and society. Our results highlight the potential importance of actively involving family members in daily clinical practice. Women with less educated offspring may require more support from clinicians and other healthcare professionals than women with highly educated offspring and should be provided with equal treatment opportunities. The educational context beyond that of the individual should be considered in future research and policy frameworks. Moreover, interventions aimed at reducing survival inequalities should consider targeting women with less educated offspring as well as less educated women themselves, particularly when women have been diagnosed in an early clinical stage. Maintaining a well-educated population is beneficial for the economy and individual health outcomes, and may also have multigenerational consequences with potential to reduce the burden of the ageing population.

In Sweden, there is universal access to free education and healthcare. Moreover, monetary social benefits are included in our measure of disposable income. As such, our results may be amplified in other settings where access to education and healthcare has stronger social patterning or where wider economic disparities exist. This possibility should be examined in future studies. In addition, it is important to further examine the potential mechanisms through which offspring's education level is associated with parental survival. For example, future research may focus on understanding whether offspring's education is associated with parental rates of diagnostic activity, access to treatment and adherence to treatment. Finally, in order to establish whether health

behaviours may be confounding or mediating the association that we have found, it is important that our results are replicated in data with detailed information available on lifestyle factors.

**Contributors** RL and GRW were responsible for the conception of the study. All authors contributed to the study design. MF was responsible for acquiring the data. MT conducted data management and some statistical analyses. HLB carried out the statistical analyses and drafted the manuscript. All authors contributed to the interpretation of the results and contributed to critically revising the manuscript for important intellectual content and approved the final version for submission. RL was responsible for study supervision and is the guarantor for the study. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Competing interests** None declared.

**Ethics approval** Ethical approval for the study was granted by the Regional Ethical Review Board, Stockholm, Sweden (2011/634-31/4). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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**Data sharing statement** Researchers can, after ethical approval, apply for the data from Statistics Sweden and the Swedish National Board of Health and Welfare.

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