

ORIGINAL ARTICLE

Long-term inequalities in breast cancer survival – a ten year follow-up study of patients managed within a National Health Care System (Sweden)

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Abstract

Introduction. Converging epidemiological evidence based on studies of different designs in a variety of populations and settings show that cancer survival tends to be poorer in low compared to high socioeconomic groups. In an extension of an earlier register-based study, we examined the influence of socioeconomic factors on long-term survival in women with a first diagnosis of invasive breast cancer in 1993 in Sweden, a country with a policy of providing equal access to health care to all at nominal cost within a National Health Care System. **Material and methods.** The study was based on data set generated by record linkages between the Swedish Cancer Register, Census databases and the Cause of Death Register. Four different categorical variables were used as indicators of socioeconomic standing. Cox proportional hazard regression models were used to estimate the effects of socioeconomic status on risk of death. **Results.** Of 4 645 eligible women with breast cancer, 1 016 had died from breast cancer at the end of follow-up on December 31, 2003. After adjustment for tumour size and age at diagnosis, risk of death was 19% lower among women belonging to a household of high compared to low socioeconomic status (HR high versus low 0.81; 95% CI: 0.67–0.97). **Discussion.** These findings indicate that social inequalities in breast cancer survival persist at least up to ten years after an initial diagnosis. While social gradients detected shortly after diagnosis may mainly reflect an influence of socioeconomic differences in overall health status and frailty, differentials persisting beyond five years rather point to a long-term influence of disparities in management of both primary tumours and recurrences. Further studies are needed to explore whether the present findings reflect amendable inequalities in access to state-of-the-art treatment. For all calendar periods, observed survival in the most privileged groups sets the goal for what is achievable for all breast cancer patients.

Converging epidemiological evidence based on studies of different designs in a variety of populations and settings show that cancer survival tends to be poorer in low compared to high socioeconomic groups [1–5]. These gradients appear to be most pronounced in cancers with good prognoses, such as breast cancer for which tumour stage at diagnosis is an important prognostic factor [4,6].

We have previously found evidence of socioeconomic inequalities in 5-year survival in breast cancer in Sweden [7], a country with a policy of providing equal access to health care to all at nominal cost within a National Health Care System. Outreach

mammography screening programs were established in Sweden in the late 1980s, while the management of breast cancer has been guided by regional consensus guidelines.

Using an expanded and updated version of a dataset used in our earlier study, the aim of the present investigation was to examine whether the previously observed social differences in survival remain detectable long-term. While five-year survival is a commonly used measure of cancer outcome, assessment of ten-year survival has become increasingly relevant as prognosis continues to improve over time for many malignancies. Also, extended follow-up

allows more precise estimates of risk of death, based on a larger number of events. The majority of studies to date exploring social disparities in breast cancer survival have been based on assessments of outcome five years following diagnosis.

Material and methods

The materials and methods have previously been described in detail [7]. In short, our study was based on a data set generated by record linkages between the Swedish Cancer Register, five Regional Cancer Registers, the 1980, 1985 and 1990 Census databases, the Fertility Register, the Migration Register, and the Cause of Death Register. Record linkages were made possible by an individually unique National Registration Number (NRN) assigned to each resident in Sweden.

Patients and their follow-up

A total of 5853 breast cancers (in 5649 women) diagnosed from January 1 to December 31, 1993 were identified in the Swedish Cancer Register. We restricted the analyses to women with no diagnoses of invasive cancers prior to 1993, and to women with adenocarcinoma of the breast to minimize the influence of differences in tumour biology. Additional diagnoses recorded more than one month after the first diagnosis in 1993 were considered as new tumours ($n=171$, of which 85 were breast cancers). Cases first diagnosed at autopsy ($n=10$) were included in the analyses as having zero survival. The final study population consisted of 4645 women. Patients were followed up regarding emigration and death through record linkages to the Migration Register and the Cause of Death Register until December 31, 2003. Following a manual review of death certificates retrieved from the Cause of Death Register, one case initially registered as having died from another cause was recoded as dead from breast cancer.

The study was approved by the Research Ethics Committee at Karolinska Institute.

Prognostic factors

Age at diagnosis was studied both in continuous and in categorical (<50 , 50–59, 60–69, 70–79, >80) form. Information on tumour characteristics at diagnosis (tumour size and nodal involvement classified according to the TNM system, and oestrogen receptor status) was obtained from five of the six Regional Cancer Registers, covering 80.4% of the female population in Sweden.

Sociodemographic factors

For the purpose of the present study, four different categorical variables were used as indicators of socioeconomic standing.

A *socioeconomic index* variable, a commonly used indicator for socioeconomic status (SES) in Sweden based on occupational group [8], was stratified into six levels; unskilled blue-collar workers, skilled blue collar workers, low, intermediate and high level white collar workers and self-employed (including entrepreneurs and farmers). SES was also categorised into two levels; low (including blue collar workers and low level white collar workers) and high (intermediate and high level white collar workers and self-employed). Women classified as not gainfully employed included unemployed, housewives and pensioners. Information on SES was available for the woman as well as for the household, in which case level of SES was based on the person in the household who had the highest SES. If information on SES was missing or the woman was not gainfully employed in the 1990 Census, information from the Census databases on 1985 or 1980 was used, if providing useful additional data.

Educational level was classified into low (mandatory school <9 years), medium (high school 10–12 years) and high (college and university, >12 years). Individual disposable income and household disposable income were stratified into quartiles. Household income includes earnings from the index person and all other household members. Home ownership was divided into renting and owning.

Additional sociodemographic factors considered in the analyses included cohabitation (categorized as no or yes, where yes included married women), parity (nulliparous and parous), total number of people living in the household (including the woman) categorized into two groups (1, >1), country of origin (Sweden, Nordic countries and non-Nordic countries), geographical region of residence at time of diagnosis according to the coverage of six Regional Cancer Registers (Göteborg, Linköping, Lund, Norrland, Uppsala and Stockholm), and access to an outreach mammography screening program as yes or no.

Statistical methods

Time to event techniques were used: the Kaplan-Meier method was used to estimate the cause-specific survival distribution of time from diagnosis of breast cancer to death. Women contributed to person-time until they died, emigrated or were alive at the end of follow-up. Log-rank based tests were used to assess the crude effect of socioeconomic status on breast cancer survival and Cox proportional

hazards regression models were fitted to the survival data to estimate the effect of socioeconomic status (both women and household), while adjusting for the possible confounding effects of relevant demographic and clinical variables. Parameter estimates and 95% confidence intervals (CI) were obtained by maximizing the partial log likelihood. Model fitting and residual analyses were based on graphical and statistical tests, using Schoenfeld and cumulative Martingales residuals. The statistical software STATA 9 was used to carry out the analyses.

Results

During the study period there was a total of 1 937 deaths, of which 1 016 were due to breast cancer, corresponding to an overall 10 year cause-specific survival proportion of 78.1%.

Tumour stage, lymph node involvement and oestrogen receptor status were factors that all had strong prognostic impact. Women with small size tumours (0–20 mm) at diagnosis had a ten-year cause-specific survival proportion of 87.7% compared to 43.1% in women with large tumours (>50 mm) (Table I).

Women aged 50–59 years at diagnosis had a survival proportion of 80.8% ten years later, while the corresponding estimate in women 80 years or older was 74.6%. In the youngest age group (<50 years), the cause specific survival proportion was 76.1%.

Kaplan-Meier survival curves for a maximum of ten years of follow-up stratified by SES group are shown in Figure 1. In the group of low SES women, the cause-specific survival at ten years was 78%, compared to 82% in women of high SES. Similarly, the survival proportions were lower in the groups of low household SES, low income and no home ownership, compared to more privileged groups (Table I). Educational level and a more detailed classification of socioeconomic status based on occupation were also associated with survival. The best survival was observed in women with middle level education, while no difference was seen between patients with high and low levels of education. For socioeconomic status, the poorest survival proportion was observed in the group not employed (76%) which was slightly lower than the estimate for the unskilled blue collar workers (77.3%).

In the second part of the analysis, risk of death due to breast cancer was computed and adjusted for age and tumour size at diagnosis. A similar pattern was seen for almost all socioeconomic indicators following adjustment for age, with hazard ratios (HR) being lower among women with high compared to low socioeconomic status, albeit not always statistically

significant (Table II). However, following adjustment also for tumour size, the only socioeconomic indicator that remained significantly associated with risk of death was household SES (HR=0.81; 95% CI: 0.67–0.97). In the group of high SES women, a significant gradient became more pronounced following exclusion of the self-employed (HR=0.78; 95% CI: 0.61–0.98) (data not shown).

Compared to small tumours, the hazard ratio for large tumours was 7.00 (95% CI 5.34–9.17). There was evidence of a better prognosis for women living in the Linköping region compared to women residing in other administrative regions. Women living in areas with outreach mammography were at significantly lower risk of death from breast cancer (HR=0.70; 95% CI: 0.50–0.97).

The socioeconomic difference in survival was most pronounced in women younger than 50 years at diagnosis (HR=0.57; 95% CI: 0.53–0.87) (Table III). In women older than 80 years at diagnosis, the pattern was reversed with some evidence of a higher risk of death among women in high SES households.

In a final step, all variables that were significant (*p*-value <0.20) in univariate analyses were considered as potential candidates in a multivariate proportional hazards model in which age in continuous form was kept independently of its significance. The models were stratified both by tumour stage and lymph node status due to their highly non-proportional hazards. Thus, the final model presented in Table IV shows the hazard ratio estimate of the socioeconomic standing adjusted by parity and cohabitation, confirming the protective effect of high versus low social status (HR=0.73; 95% CI: 0.56–0.96).

In a separate step, all analyses were repeated with all-cause mortality as an outcome. With this approach, the overall pattern was similar showing a social gradient in survival (data not shown).

Discussion

Our finding of a social gradient in survival remaining up to ten years after diagnosis confirms the pattern observed in our earlier study based on fewer deaths during a five-year follow-up [7]. Not only did the main pattern remain long-term, but the results for subgroups were also almost identical. Irrespective of measure used to represent social status, the survival tended to be worse in lower socioeconomic groups, although the differences did not always reach formal statistical significance. The observed disparities, however, were for the most part rather modest which may reflect that social inequalities remain relatively small in the Swedish society. A study comparing breast cancer survival between socioeconomic

Table I. Characteristics of 4 645 women diagnosed with invasive breast cancer (BC) in 1993. Distribution of demographic and cancer-related variables by survival status on December 31, 2003.

Variable	Total n = 4 645	Alive n = 2 708		Dead (all causes) n = 1 937	
	n	n	%	n	%
Socioeconomic status, woman					
Un-skilled blue collar	950	627	66.0	323	34.0
Skilled blue collar	194	135	69.6	59	30.4
Low level white collar	708	504	71.2	204	28.8
Intermediate level white collar	518	407	78.6	111	21.4
High level white collar	258	199	77.1	59	22.9
Self employed	212	141	66.5	71	33.5
Not employed	1 603	568	35.4	1035	64.6
Missing data	202	127	62.9	75	37.1
Socioeconomic status, woman					
Low	1 852	1 266	68.4	586	31.6
High	988	747	75.6	241	24.4
Not employed	1,603	568	35.4	1035	64.6
Missing data	202	127	62.9	75	37.1
Socioeconomic status, household					
Low	1 775	1 143	64.4	632	35.6
High	1 639	1 192	72.7	447	27.3
Not employed	1 074	281	26.2	793	73.8
Missing data	157	92	58.6	65	41.4
Education					
Low	2 735	1 698	62.1	1 037	37.9
Middle	547	355	64.9	192	35.1
High	766	557	72.7	209	27.3
Missing data	597	98	16.4	499	83.6
Income (100 SEK), woman					
0–558	1 167	479	41.1	688	58.9
559–961	1 164	607	52.2	557	47.8
962–1420	1 134	736	64.9	398	35.1
1421–50000	1 152	867	75.3	285	24.7
Missing data	28	19	67.9	9	32.1
Income (100 SEK), household					
0–1118	1 136	396	34.9	740	65.1
1119–1993	1 096	608	55.5	488	44.5
1994–3087	1 149	788	68.6	361	31.4
3088–47865	1 098	838	76.3	260	23.7
Missing data	166	78	47.0	88	53.0
Home ownership					
No	1 608	781	48.6	827	51.4
Yes	2 836	1832	64.6	1 004	35.4
Missing Data	201	95	47.3	106	52.7
Parity					
Nulliparous	387	277	71.6	110	28.4
1	547	387	70.8	160	29.2
>2	1 781	1 332	74.8	449	25.2
Missing data	1 930	712	36.9	1 218	63.1
Number in people in the household					
1	1 457	615	42.2	842	57.8
>1	3 022	2 015	66.7	1 007	33.3
Missing data	166	78	47.0	88	53.0
Cohabitation					
No	1 798	821	45.7	977	54.3
Yes	2 681	1 809	67.5	872	32.5
Tumour size (mm)					
0–20	1 934	1 369	70.8	565	29.2
21–50	1 150	567	49.3	583	50.7
>50	123	40	32.5	83	67.5

Table I (Continued)

Variable	Total n = 4 645	Alive n = 2 708		Dead (all causes) n = 1 937	
	n	n	%	n	%
Tumour of any size with direct extension to chest wall or skin	56	10	17.9	46	82.1
Missing Data	1 382	722	52.2	660	47.8
Lymph node involvement					
No	1 879	1 395	74.2	484	25.8
Yes	1 058	521	49.2	537	50.8
Missing Data	1 708	792	46.4	916	53.6
Oestrogen receptor status					
Negative	959	570	59.4	389	40.6
Positive	1 596	1 025	64.2	571	35.8
Missing Data	2 090	1 113	53.3	977	46.7
Region					
Göteborg	816	456	55.9	360	44.1
Linköping	438	276	63.0	162	37.0
Lund	841	517	61.5	324	38.5
Norrland	392	249	63.5	143	36.5
Uppsala	958	563	58.8	395	41.2
Stockholm	1 200	647	53.9	553	46.1
Covered by screening program					
No	221	128	57.9	93	42.1
Yes	4 257	2 578	60.6	1 679	39.4
Missing Data	167	2	1.2	165	98.8
Age at diagnosis					
<50	1 002	735	73.4	267	26.6
50–59	896	696	77.7	200	22.3
60–69	1 078	734	68.1	344	31.9
70–79	944	441	46.7	503	53.3
>80	725	102	14.1	623	85.9
Country of origin					
Sweden	4042	2325	57.5	1 717	42.5
Nordic country	212	131	61.8	81	38.2
Non Nordic country	363	233	64.2	130	35.8
Missing data	28	19	67.9	9	32.1

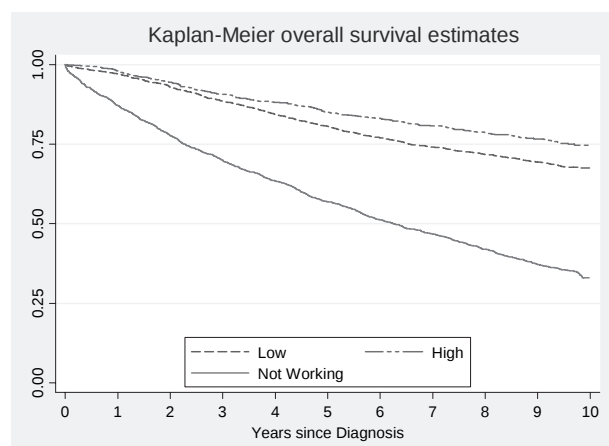


Figure 1. Kaplan-Meier stratified survival curves for a maximum of 10 years of follow-up. Women with a first diagnosis of invasive breast cancer in 1993. Follow-up to December 31, 2003.

groups in Canada and USA showed a poorer prognosis for low SES women with breast cancer in the USA compared to low SES breast cancer patients in Canada [9], a finding which may reflect the same phenomenon.

Survival differed between age groups. Older women generally had a worse prognosis compared to younger age groups, possibly reflecting an influence of a greater comorbidity burden and age-biased management resulting in undertreatment of elderly patients [10]. However, one of the poorest survival rates were found in premenopausal patients (<50 years) which may partly be explained by more aggressive tumour characteristics and possibly also detrimental influences of recent pregnancies in young women [11]. The social gradient also appeared to be strongest in the youngest age group, which could reflect that the management of breast cancer varies more in this numerically smaller and

Table II. Social factors and tumour characteristics and all-cause risk of death in women diagnosed with breast cancer in 1993. Hazard ratios for death, estimates adjusted for age at diagnosis* and for age in combination with tumour size at diagnosis.**

	Adjusted for age*	Adjusted for age and size**
Woman, socioeconomic status		
Unskilled blue collar	1.00	1.00
Skilled blue collar	0.92	1.03
Low-level white collar	0.87	0.83
Intermediate white collar	0.62	0.70
High-level white collar	0.68	0.68
Self-employed	0.94	1.04
Unemployed	1.12	
Socioeconomic status, woman		
Low	1.00	1.00
High	0.75	0.82
Socioeconomic status, household		
Low	1.00	1.00
High	0.78	0.79
Education		
Low	1.00	1.00
Medium	0.84	0.88
High	0.89	0.95
Income (100 SEK), woman		
0-558	1.00	1.00
559-961	0.95	1.05
962-1420	0.89	0.93
1421-50000	0.68	0.79
Income (100 SEK), household		
0-1119	1.00	1.00
1120-1994	0.88	0.91
1995-3087	0.71	0.75
3088-47865	0.61	0.66
Home ownership		
Renting	1.00	1.00
Owning	0.83	0.82
Parity		
Nulliparous	1.00	1.00
Parous	0.92	1.23
Cohabitation		
No	1.00	1.00
Yes	0.79	0.83
Number of people in the household		
1	1.00	1.00
>1	0.82	0.86
Tumour size (mm)		
0-20	1.00	
21-50	1.80	
>50	3.46	
Tumour of any size with direct extension to chest wall or skin	4.30	
Lymph node involvement		
No	1.00	1.00
Yes	2.65	2.19
Oestrogen receptor status		
Negative	1.00	1.00
Positive	0.72	0.72

Table II (Continued)

	Adjusted for age*	Adjusted for age and size**
Region		
Göteborg	1.00	1.00
Linköping	0.85	0.74
Lund	0.86	0.88
Norrland	0.91	1.06
Uppsala	0.93	1.01
Stockholm	1.07	n/a
Covered by screening program		
No	1.00	1.00
Yes	0.91	0.88
Country of origin		
Sweden	1	1
Nordic country	1.25	1.54
Non Nordic country	0.94	1.08

clinically more heterogeneous group for whom treatment guidelines may be less strictly adhered to. Also, at the time of diagnosis of the patients in the present study, only a small proportion of women below the age of 50 were covered by an outreach mammography screening program. However, we found no difference in the distribution of tumour size at diagnosis between young and old breast cancer patients.

Possible underlying causes for reported socioeconomic differences in cancer survival can be attributed to factors related to the tumour, the patient, and the management of the disease [5,12].

The tumour: Early detection and tumour characteristics

In our study, the socioeconomic variation in survival remained following adjustment for tumour characteristics which corroborates findings in some earlier studies [7,13,14], indicating that observed gradients cannot be explained solely by differences in timing and stage at diagnosis [15,16]. In 1993, the year of diagnosis for all breast cancer cases in the present study, 95% of the female population 50 years or older was covered by screening programs. While we previously have been unable to detect pronounced socioeconomic differences in attendance in outreach mammography screening in central Sweden [17], other investigators have found evidence of socioeconomic gradients in utilization in an urban area in southern Sweden [18]. There is some evidence suggesting that tumour biology may differ between socioeconomic groups with negative oestrogen receptor status being more common among deprived women [19]. In our study, we did not find any such differences. In one study, histopathological tumour type could explain only 3% of the elevated risk of death among low socioeconomic groups [16], while

Table III. Socioeconomic standing (woman and household) and hazard ratios (high vs low) for all cause death by age group at diagnosis, and adjusted for tumour size.

Age group	SES woman	Adjusted for size	SES household	Adjusted for size
<50	0.65	0.76	0.59	0.64
50–59	0.76	0.70	0.71	0.66
60–69	0.68	0.72	0.75	0.79
70–79	1.07	1.26	0.89	0.94
>80	2.47	1.96	1.64	1.82

other investigators have found no associations between socioeconomic factors and tumour size, nodal status, oestrogen receptor status and histological grade [20].

The patient: Comorbidity, life-style, psychosocial factors, awareness and compliance

Burden of comorbidity may contribute to observed social gradients in cancer survival. Findings in an American study showed that a high comorbidity score was associated with higher overall mortality rates in breast cancer patients [21]. However, that study did not examine breast cancer specific mortality and the groups were compared based on ethnicity, and not socioeconomic standing. In a Dutch study, other chronic health conditions were more prevalent at the time of breast cancer diagnosis among low and medium SES women compared to high SES women [22]. In the present study, we found evidence of an all-cause higher risk of death in low socioeconomic groups across indicators of socioeconomic standing which may reflect burden of concomitant disease, which in turn could influence both management choices and how well the patient accepts, responds to and tolerates breast cancer therapy.

Lifestyle factors such as smoking and overweight, which are known to be over-represented in groups of low socioeconomic status [23,24], may negatively influence breast cancer prognosis [21,25] not only

directly, but also indirectly by inducing comorbidity that could affect treatment and tumour progression. There is also some epidemiological evidence indicating that psychosocial factors could influence progression and survival in breast cancer [26,27]. Results from a recent animal study showed that exposure to chronic behavioural stress resulted in higher levels of catecholamines, greater tumour burden and more invasive growth of ovarian carcinoma cells in a mouse model. Tumours in stressed animals showed increased vascularisation, pointing towards the effects of stress on tumour growth being mediated by angiogenic processes [28]. It remains unclear, however, if and to what extent psychosocial factors correlate with socioeconomic status or if they are mainly influenced by individual circumstances. More recently, increasing attention has been given to disparities in the awareness of the disease such as health care seeking behaviours and knowledge about breast cancer and its treatment which could influence patient compliance [29].

Management of the disease

Socioeconomic differences in management and access to state-of-the-art treatment may play a central role for inequalities in survival. In a US setting, it has been shown that affluent women are more likely to receive both breast conservative surgery and endocrine therapy compared to more deprived women [19]. However, in at least one earlier report, differences in survival outcome between socioeconomic groups remained after adjustment for treatment [15]. In another study, stage-specific management did not differ between women of different SES groups [30]. Findings from a recent US-based study showed that black women were more likely to stop treatment prematurely and that early termination was associated with poorer survival. However, the association between SES and ethnicity is complex [21].

Strengths of the present study include the prospective, population-based design and the ability to assess the influence of a series of different measures of socioeconomic status which were determined on the individual or household level. The influence of changing treatment practices over time was

Table IV. Social factors and tumour characteristics and the risk of death (all causes). Multivariate proportional hazard model.

Variable	Hazard ratio (95%CI)
Socioeconomic status (woman)	
Low	1 (Reference)
High	0.81
Age at diagnosis (linear term)	1.02
Cohabitation	
No	1 (Reference)
Yes	0.66
Parity	
Nulliparous	1 (Reference)
Parous	1.48

minimized by focusing on breast cancer cases diagnosed during one calendar year. All tumours had been classified histopathologically, and only adenocarcinomas were included in the analyses. Non-random misclassification was not an issue, since information on outcome was collected independently of information on tumour characteristics and socioeconomic indicators. In a validation of breast cancer recorded as an underlying cause of death in the Swedish Cause of Death Register, less than 2% of deaths were judged to be in disagreement with the conclusions of an end point committee that reviewed medical information case by case [31]. In this setting, with high quality data available on cause of death, cause-specific survival proportion estimates provide an acceptable alternative to computing survival proportions (relative survival) using social class-specific death rates to estimate expected survival [32].

A weakness of our study was the absence of data on treatment and the inclusion of women classified as not employed, a heterogeneous group including pensioners, unemployed and housewives which both had the highest overall mortality, and the highest cause-specific mortality. The majority of women in this group were pensioners with 78% of the patients being older than 70 years of age at diagnosis. Also, women with missing data probably represent a selected group and had a low overall survival. Similarly, women classified as self-employed are likely to belong to a heterogeneous group. For that reason analyses were made with and without this group in the high SES category. The relatively large number of missing data on parity and educational level reflects the age distribution, and data on these factors was not available for the oldest birth cohorts. Further, it cannot be excluded that educational level was misclassified in some older women due to changes over time in the Swedish school system.

In conclusion, we found that social inequalities in breast cancer survival persist up to ten years following diagnosis. A socioeconomic gradient detected shortly after diagnosis may mainly reflect adverse influences on the likelihood of survival mediated by socioeconomic differences in overall health status and frailty, while disparities persisting beyond five years rather would point to a long-term influence of suboptimal management and treatment of primary tumours or recurrences. To improve the understanding of the origins of the observed disparities, further studies are needed to explore in detail not only the role of breast cancer management and treatment by social group, but also comorbidity, lifestyle and psychosocial factors. Furthermore, to our knowledge, no study to date has investigated the genetic properties of breast cancer tumours in relation to socioeconomic factors. Social differences

in cancer survival are of public health importance since identification of factors amenable to intervention can help prevent unnecessary premature deaths and save human lives. For all calendar periods, observed survival in the most privileged groups sets the goal for what is achievable in all breast cancer patients.

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