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Socioeconomic differences in survival among breast cancer patients in the Netherlands not explained by tumor size

E. Bastiaannet^{1,2}, A.J.M. de Craen², P.J.K. Kuppen¹, M.J. Aarts³, L.G.M. van der Geest⁴,
C.J.H. van de Velde¹, R.G.J. Westendorp², G.J. Liefers¹

¹Surgery (Leiden University Medical Centre), ²Gerontology & Geriatrics (Leiden University Medical Centre), ³Comprehensive Cancer Centre South Eindhoven. ⁴Comprehensive Cancer Centre West Leiden

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Corresponding author:

G.J. Liefers, MD PhD

Department of Surgery

Leiden University Medical Centre

P.O. Box 9600

2300 RC Leiden

Tel: 0031 71 5269111

Email: g.j.liefers@lumc.nl

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ABSTRACT

Background. There seem to be socioeconomically differences in survival for females with breast cancer, usually associated with a higher stage of disease. However, differences within tumor size have not been studied. Aim of this study was to assess differences in survival according to socioeconomic status (SES), stratified for tumor size and stage at diagnosis, for females with breast cancer in the Netherlands.

Methods. All females diagnosed with breast cancer (1995-2005) were selected from the Netherlands Cancer Registry. Patients were linked to a SES database according to postal code. A multivariable logistic regression was used to assess factors associated with SES. Overall Survival (OS) and Relative Survival (RS) were calculated.

Results. Overall, 127599 patients were included. Higher SES was associated with lower T-stage ($p < 0.0001$). A decreased survival (OS and RS) was found for patients with a lower SES. Also within different size groups, relative survival was different. Overall, 10-years OS for the high SES group was 65% and 58% for the low SES group (Hazard Ratio 1.1, $p < 0.001$) and RS was 79% versus 74% (Relative Excess Risk (RER) 1.2; $p < 0.001$). The socioeconomic differences remained statistically significant ($p < 0.001$) after adjustment for age, year of diagnosis, grade, TNM stage and treatment. For the lowest SES group 777 deaths could be avoided.

Conclusion. Socioeconomic differences in survival of breast cancer patients were observed in the Netherlands. Higher stage at diagnosis of patients with a lower SES only partly explains the decreased survival. Policies aimed at the reduction of socioeconomic health inequalities might be important to improve survival of breast cancer.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among females in developed countries. In the Netherlands, more than 12000 new cases of breast cancer are diagnosed each year and incidence is still increasing. Breast cancer is one of the few cancers that is more common in affluent women.[1] However, women with a lower socioeconomic status seem to have a decreased survival.[1-5] Socioeconomic differences in incidence have typically been attributed to life-style, particularly differences in distribution of known risk factors such as age at menarche, age at menopause, age at first pregnancy and use of hormone replacement therapy.[6-8] Social gradients in survival have also been reported which appear to persist after adjustment for stage, suggesting an inequality regarding awareness of the disease, access to early detection, treatment or other yet unknown factors.[6]

Overall, survival of cancer is influenced by factors which can be classified into three groups: tumor biological characteristics, patient characteristics and treatment.[9;10] Consequently, SES differences in survival must originate from an unequal socioeconomic distribution of some of these factors.[10] Until now, the reasons for social disparities in breast cancer prognosis are not completely known. Various studies have shown that reasons are probably multi-factorial, with possible explanations including health service factors, late stage at diagnosis, different tumor biology, treatment and levels of comorbidity.[2;5;11-14] Socio-economic differences in tumor size may be related to the length of delay between the occurrence of the first symptoms and the time of diagnosis, which is shorter for women of higher classes.[15] Besides, women from lower socio-economic strata are less likely to attend population screening programs and are also more likely to present with unfavorable stage at diagnosis, although not all studies confirm this.[4;16-18]

In the Netherlands an equal-access health care system is provided; all residents have compulsory health insurance and for those who have insufficient income, an extra

government allowance is paid to ensure overall coverage. A study from Wojcik et al showed that the type of health care system significantly affects disease outcome.[19] African-American women with breast cancer treated in the military health care facilities from the U.S. department of defense had a better survival rate than African-American women represented in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.[19] This suggests that ready access to medical facilities and the full complement of treatment options improves survival rates.

The aim of this study was to analyze socioeconomic differences in breast cancer outcome in the Netherlands where treatment is guided by strict guidelines for all, without any financial restrictions.

METHODS

Patient selection

Adult female patients with their first primary breast cancer (invasive and in situ) diagnosed between 1995 and 2005 were selected from the Netherlands Cancer Registry (NCR). Patients with other tumors before their breast cancer were excluded. The nationwide Dutch network and registry of histo- and cytopathology, regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. Stage was divided according to TNM classification at the year of diagnosis. Pathological T, N and M stage was used; clinical stage was used if pathology was missing. Vital status was established either directly from the patient's medical record or through linkage of cancer registry data with the municipal population registries (follow-up until January 1st, 2008) which record information on their inhabitant's vital status.

Socioeconomic status was assigned to each individual using an area-based measure according to place of residence at the time of diagnosis. The area-based SES was provided by the Netherlands Institute for Social Research and consists of data concerning income, employment and education. These data are provided to the institute by a private organization which collects information by telephone calls with one person per 6-digit postal code area; this person is seen as representative for his or her area. Next, numbers are aggregated to 4 digit postal code areas. Validation studies indicate that numbers at aggregated level approach the true situation.[20] The range of SES in the cohort was from -3.60 to 5.01, with a higher score representing a high social deprivation (low SES) and a low score representing little social deprivation and consequently a high SES. Scores were divided in quintiles.

Statistical analysis

The association between stage (both T-stage and combined TNM stage) and socio-economic status was assessed. Overall Survival (OS) was calculated using standard survival analysis with multivariable Cox Proportional Hazard Analysis, with death due to any cause defined as event. Relative survival was calculated by the Hakulinen method as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age and year) general population. National life tables were used to estimate expected survival. Relative Survival (10-years) was stratified according to stage and calculated for each socio-economic group. Relative Excess Risks of death (RER) with p-value were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Finally, the number of avoidable deaths for each SES group relative to the highest SES group was calculated by: avoidable deaths within 5 years = total number of patients x expected survival x difference in relative survival between deprivation category and most affluent category.

RESULTS

Overall, 127599 breast cancer patients were included in this study. As shown in Table 1, most of the patients had breast cancer with ductal histology (70.0%), usually T1c (33.3%) or T2 (32.4%); N-stage was almost equally divided (N0 47.7% and N1-2 46.8%) and most of the patients had no distant metastases (M0 67.1%).

Figure 1 shows the distribution of tumor size according to the SES groups. For in situ tumors the percentage of patients decreased as SES decreased: 7.9% for patients with a low SES versus 8.9% for patients with a very high SES ($p < 0.001$). For T1 there was no statistically significant decrease ($p = 0.3$). For the stage T2, T3 and T4 there was a clear increase in the percentage of patients as SES became lower (all $p < 0.001$). For T2 the percentage of patients increased from 33.1% for patients with a very high SES to 35.1% in the very low SES; also for T4 this increase was shown (4.9% to 6.9%). SES was also significantly associated with grade, N-stage and M-stage. After adjusting for these factors, SES was still associated with tumor size; patients presented with larger tumors for lower SES groups ($p < 0.001$).

As shown in Table 2, relative survival per T-stage of disease was statistically different in almost all stages. With the exception of in situ tumors, patients with a very low SES had a decreased survival as compared to the other SES groups. After adjustment for age, year of diagnosis, histology, grade, N-stage, M-stage and treatment there remained a statistically significant difference for most stages, especially the lower stages. Also, for the combined stage at diagnosis (stage I, II, III and IV), socioeconomic differences were shown. After adjustment for potential confounders, socioeconomic differences were no longer apparent in stage III and IV.

Table 3 shows the results of the multivariable survival analysis of both Overall Survival (death due to any cause) and Relative Survival. Adjusted for age, year of diagnosis,

histology, grade, T-stage, N-stage, M-stage and treatment, the SES score remained a significant independent prognostic factor for Overall Survival (HR 1.04 (SES as continuous factor); $p < 0.001$) and Relative Survival (RER 1.07; $p < 0.001$). Overall and Relative Survival were significantly lower in the lower socioeconomic groups.

Figure 2 shows Relative Survival according to SES; the 10-years RS was 74.0% for the lowest SES and 79.0% for the highest SES ($p < 0.001$). When stratified for age category, the difference in survival was most evident in the 61-75 years old patients with an RER of 1.26 (95%CI 1.14-1.40; $p < 0.001$). In all stages of disease there were treatment disparities for the different SES groups; patients from a very low SES received less surgery and less adjuvant treatment. Table 4 shows the number of avoidable deaths if relative survival in the lower SES groups was the same as the highest SES group. For the lowest SES group 777 deaths could be avoided if the survival was equally high as the highest SES group.

DISCUSSION

The present study shows that, in an 11-year nationwide study in breast cancer patients in the Netherlands (n=127599), a low SES is associated with worse survival, even stratified for tumor size or stage of disease. Also in an equal-access health care system SES should be considered as an independent prognostic factor for breast cancer survival. Health inequalities between social classes were already recognized several centuries ago, but one would expect that due to an improvement of working and living conditions these differences would have been reduced or even disappeared.[11] However, this is not the case for breast cancer patients in the Netherlands.

In the present study, an association between size of the tumor and SES was shown where larger tumors were associated with a lower SES. In the literature several conclusions concerning breast cancer stage and socio-economic status can be found. A study from the south Australian cancer registry compared diameters between 1980-1986 and 1997-2002 and analyzed socioeconomic predictors for large tumors in 1997-2002.[21] Their data showed an increase in smaller tumors over time, however indicated that earlier diagnosis is not evenly distributed among socioeconomic classes.[21] In the present study, we observed more in situ tumors (mostly screen detected) in patients from the higher SES, indicating that attendance for the screening program is higher in higher SES groups. A study from Stockholm (n=15021) showed significant differences in SES for clinical stage and survival.[6] However, in this study differences in survival were mostly the consequence of differences in non breast cancer mortality and no differences in stage-specific breast cancer mortality were seen, while in the present study differences in relative survival were seen.[6] Schrijvers et al reported the results of 29676 women in southeast England.[4] Remarkably, only in elderly women aged >65 years, the severity of deprivation related to the presence of advanced disease at time of diagnosis.[4] On the contrary, two other studies found no association between SES and tumor size.[2;15]

Regional small socioeconomic differences in breast cancer survival have been described before in the southeastern part of the Netherlands; Schrijvers et al studied patients diagnosed between 1980 and 1989 (n=3928) in this part of the country.[22] However, the differences could mostly be explained by differences in stage at diagnosis, while in the present study differences in Overall and Relative Survival remain significant after adjustment for stage differences. There are a number of individual patient and tumor characteristics that might affect survival and may vary across social groups, such as known risk behaviors as smoking and comorbidity.[23] The use of relative survival reflects disease-specific survival. Hence, results can not be explained by a higher rate of death due to other causes in the lower SES; although the presence of comorbidity may limit the treatment choices available to the patients.[24] Although scant research has been published, evidence shows that physician decisions may contribute to inequalities in cancer survival.[23] A prospective study showed that within breast cancer patients women with a lower level of education were administered lower doses of first-cycle chemotherapy.[25] Other studies have also found evidence for lower rates of breast conserving treatment, radiation therapy and adjuvant chemotherapy among women of lower socioeconomic status.[11;16;26]

In the present study an indicator of socio-economic status based on the postal code of a residential area was used. This indicator was based on income, employment and education and collected by information of telephone calls with one person per 6-digit postal code area. This aggregate covers a relatively small geographical area, and thus probably represents a reliable approximation of individual SES status.[18] Dominguez and colleagues studied the association between health outcomes and several small-area-based socioeconomic measures and also with individual socioeconomic measures.[27] Results showed that, in general, the inequalities that were measured with the area-based measures were in the same range as those obtained with individual-based measures.[27] Besides, Hyndman et al studied the possible misclassification of social disadvantage when SES is based on postcode versus collector's district analyses and found that misclassification of

individuals to SES groups on the basis of postcode could lead to an underestimation of the true relationship between SES and health-related measures.[28] Ideally, individual-based measures of socioeconomic position would be used. Unfortunately, this information was not available as other information concerning several potential confounders such as comorbidity, receptor status and type and dose of the chemotherapy.

Possible explanations for the differences in survival according to SES include differences in access to early diagnosis (possibly through screening), tumor biology, and access to optimal treatment.[2;3;5;12-15] However, despite persistent publications on social and ethnic disparities in breast cancer outcome, we still do not know to which extent these factors explain social inequalities in breast cancer prognosis.[11] There is evidence that cancer presents with a more aggressive phenotype among patients from minority racial/ethnic groups in the US.[29] Social factors, however, seem to be more important than biological factors in explaining racial and ethnic cancer disparities, especially in the US where access to medical care is closely tied to economic status.[29] A recent study confirmed this: Yood et al showed ethnic differences in stage at diagnosis among women with similar medical care access.[30] That difference in distribution of stage had a major influence on differential African-American/European-American survival but does not fully explain it. However, adjustment for income, age, and marital status resulted in a negligible effect of race on survival.

Data from the Norwegian Women and Cancer Study showed an overall negative socioeconomic gradient in cancer survival.[9] Inclusion of stage modestly changed the risk difference, comorbidity did not alter the estimates, but further adjustment for smoking did change the estimates considerably. Other studies show that both patient and physician barriers to, expectation of, and communications about adjuvant therapy also contribute to the observed differences in survival.[31]

Just recently the year 2010 was marked as the European Year for Combating Poverty and Social Exclusion. Given its incidence, the number of cancer deaths in Europe that could potentially be avoided by reducing socioeconomic health inequalities appears particularly important for breast cancer. The present study shows that also in an equal-access health care system socioeconomic differences do exist in survival from breast cancer, even when adjusted for stage at diagnosis. This study suggests that health policies aimed at the reduction of social exclusion might be important to increase breast cancer specific survival.

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Table 1: Characteristics of study population (n=127599).

		Number	Percentage
Age (years)	≤40	7910	6.2
	41-50	23710	18.6
	51-60	33002	25.9
	61-70	26696	20.9
	71-80	22212	17.4
	≥81	14069	11.0
Histology	Ductal	89325	70.0
	Lobular	13629	10.7
	Other / combined	24645	19.3
Grade	1 / 2	53198	41.7
	3	34848	27.3
	Missing	39553	31.0
T-stage	In situ	10544	8.3
	T1a	2944	2.3
	T1b	13877	10.9
	T1c	42497	33.3
	T2	41322	32.4
	T3	4661	3.7
	T4	7060	5.5
	Missing	4694	3.7
N-stage	No lymph node metastases	60908	47.7
	Lymph node metastases	59773	46.8
	Missing	6918	5.4
M-stage	M0	85625	67.1
	M1	5894	4.6
	Missing	36080	28.3
Socioeconomic status	Very high	25496	20.0
	High	25538	20.0
	Intermediate	25524	20.0
	Low	25525	20.0
	Very low	25516	20.0

Table 2: Relative Survival (10-years RS) according to stage and SES.

RS (95%CI)	Socio-economic status					p-value	Adjusted p-value
	Very high	High	Intermediate	Low	Very low		
In situ	99.8 (97.4-100)	99.6 (97.0-100)	98.2 (95.6-100)	96.6 (94.1-99.4)	100 (97.7-100)	<0.001	0.005
T1a (0.1-0.5 cm)	97.5 (92.7-100)	96.6 (91.2-100)	96.4 (90.1-100)	92.9 (87.0-97.7)	91.2 (85.0-96.4)	0.02	0.3
T1b (0.5-1.0 cm)	94.8 (92.3-97.0)	95.4 (92.9-97.7)	94.1 (91.6-96.4)	93.9 (91.4-96.2)	91.7 (88.9-94.2)	0.01	0.002
T1c (1.0-2.0 cm)	86.3 (84.8-87.8)	85.9 (84.3-87.5)	85.3 (83.7-86.9)	86.3 (84.6-87.9)	84.1 (82.3-85.8)	0.006	0.01
T2 (2.0-5.0 cm)	71.4 (69.6-73.2)	70.5 (68.6-72.4)	67.7 (65.8-69.6)	67.5 (65.6-69.3)	66.2 (64.3-68.1)	<0.001	<0.001
T3 (>5.0 cm)	46.0 (40.9-51.0)	49.5 (44.0-54.9)	47.6 (42.8-52.3)	42.7 (37.5-48.0)	44.2 (38.9-49.6)	0.04	0.3
T4	30.0 (26.0-34.2)	29.3 (25.3-33.5)	29.5 (25.7-33.4)	31.2 (27.2-35.4)	29.1 (25.6-32.8)	0.7	0.7
Stratified according to stage							
Stage I	92.9 (91.5-94.2)	93.3 (91.8-94.7)	92.2 (90.6-93.6)	92.7 (91.2-94.2)	89.9 (88.2-91.5)	0.02	0.01
Stage II	76.5 (75.0-77.9)	75.6 (74.0-77.1)	74.0 (72.4-75.5)	73.1 (71.5-74.7)	72.2 (70.6-73.9)	<0.001	<0.001
Stage III	44.7 (40.7-48.8)	45.2 (40.9-49.6)	45.5 (41.8-49.3)	44.9 (40.9-49.0)	44.0 (40.1-48.0)	0.04	0.4
Stage IV	9.1 (6.7-11.9)	9.9 (7.3-13.2)	6.8 (4.8-9.3)	7.1 (4.7-10.2)	7.6 (5.5-10.1)	0.01	0.1

Adjustment for year, age, histology, grade, N-stage, M-stage and treatment (surgery yes/no & adjuvant treatment yes/no)

Table 3: Results multivariable analysis Overall Survival and Relative Survival

		Multivariable analyses			Multivariable analyses		
		10-yr OS	HR (95% CI)	p-value	10-yr RS	RER (95% CI)	p-value
SES	Continuous		1.04 (1.03-1.05)	<0.001		1.07 (1.05-1.08)	<0.001
score							
Survival analysis according to SES groups							
SES	Very high	65.3	1	<0.001	79.0	1	<0.001
groups	High	64.9	1.04 (1.00-1.07)		78.6	1.06 (1.01-1.12)	
	Intermediate	62.4	1.06 (1.02-1.10)		76.7	1.11 (1.05-1.17)	
	Low	61.5	1.08 (1.04-1.11)		76.4	1.11 (1.06-1.17)	
	Very low	58.3	1.10 (1.06-1.13)		74.0	1.19 (1.13-1.25)	

Adjusted for age, year, histology, grade, T-stage, nodal status, distant metastases, surgery and adjuvant treatment

Table 4: Avoidable deaths within 5 years of diagnosis by deprivation category

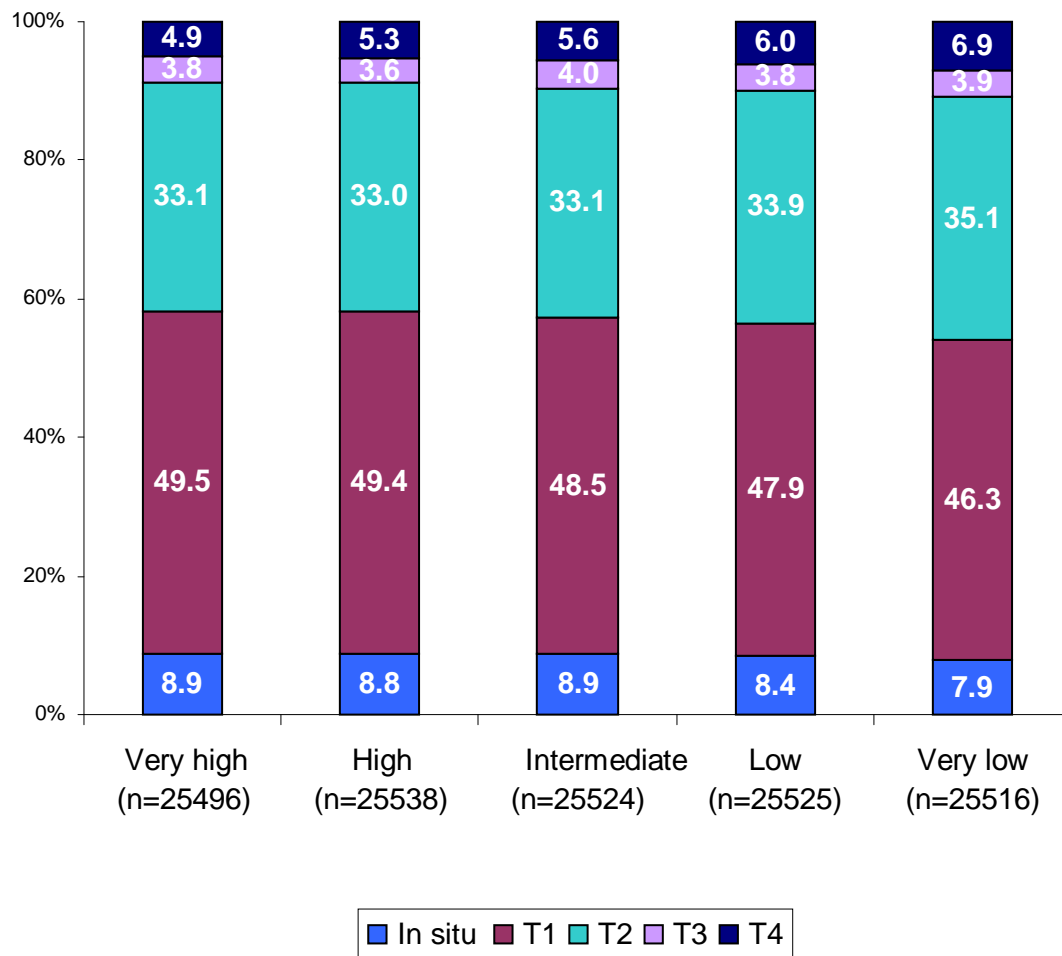
SES category	Number of patients	Deaths in 5 year		Avoidable deaths##	
		Total number	Excess deaths#	N	%
Very high	25496	4782	2962	0 (reference)	-
High	25538	4823	3066	119	3.9%
Intermediate	25524	5225	3341	374	11.2%
Low	25525	5477	3481	540	15.5%
Very low	25516	5922	3748	777	20.7%

#Excess deaths = observed deaths – expected deaths. ##Avoidable deaths within 5 years = total number of patients x expected survival x difference in relative survival between deprivation category and most affluent category

Figure 1: Distribution of T-stage according to socio-economic status.

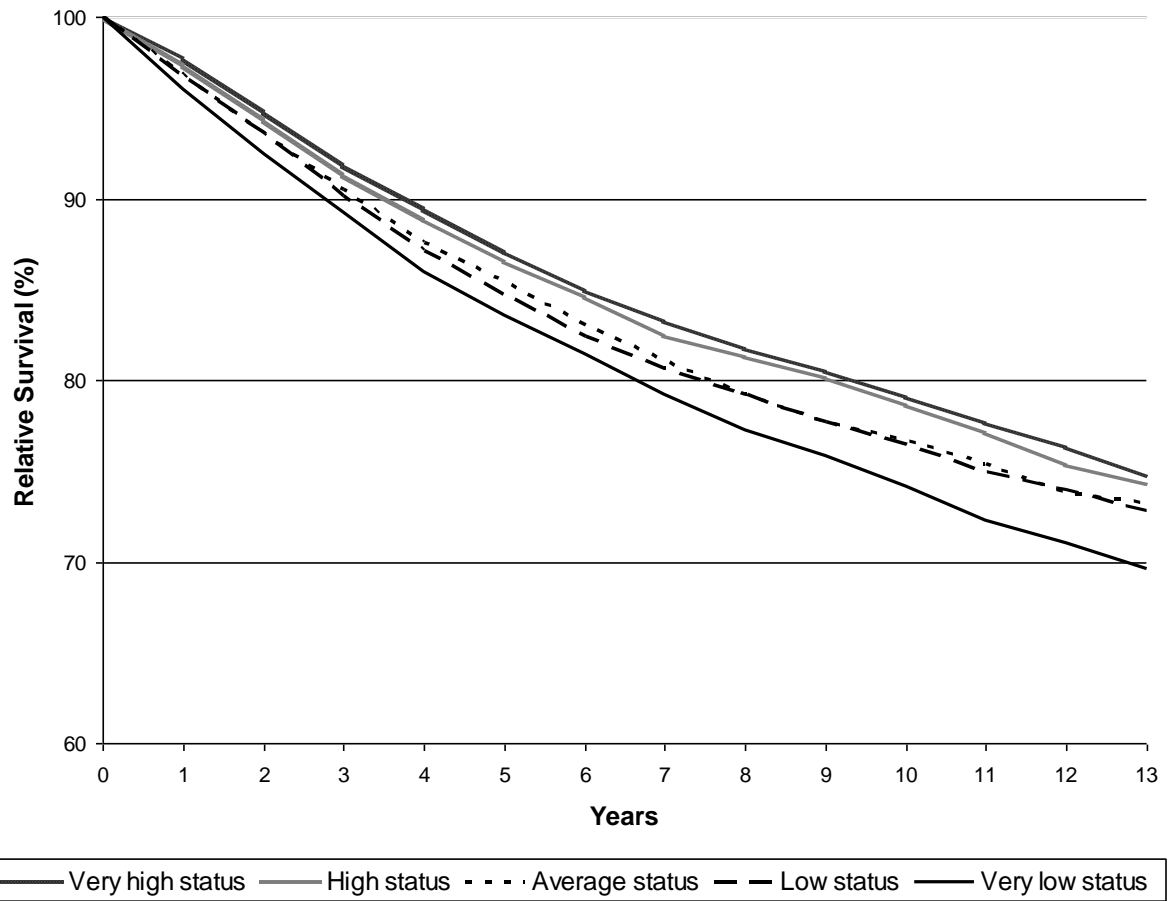
Figure 2: Relative Survival according to socioeconomic status.

Figure 1: Distribution of T-stage according to socio-economic status.



Association between T-stage and SES: $p < 0.001$, adjusted for histology, grade, nodal status and distant metastases.

Figure 2: Relative Survival according to socioeconomic status.



The 10-years Relative Survival was 79.0% for the highest SES and 74.0% for the lowest SES with a corresponding adjusted RER 1.2 ($p < 0.001$).