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Socioeconomic and demographic disparities in breast cancer stage at presentation and survival: a Swiss population-based study

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Authors: Anita Feller, MSc[1,2]; Kurt Schmidlin, DMD, MPH[1]; Andrea Bordoni, MD[3]; Christine Bouchardy, MD[4]; Jean-Luc Bulliard, MD[5]; Bertrand Camey, MD[6]; Isabelle Konzelmann, MD[7]; Manuela Maspoli, MD[8]; Miriam Wanner, DSc.[9]; Kerri M. Clough-Gorr, DSc, MPH[1,10], for the SNC and the NICER working group

Affiliations:
(1) Institute of Social and Preventive Medicine (ISPM), University of Bern, Finkenhubelweg 11, CH-3012 Bern, Switzerland
(2) National Institute for Cancer Epidemiology and Registration (NICER), Seilergraben 49, 8001 Zürich, Switzerland
(3) Ticino Cancer Registry, Instituto cantonale di patologia, Via in Selva 24, 6601 Locarno 1
(4) Geneva Cancer Registry, Institute of Global Health, University of Geneva, Bd de la Cluse 55, 1205 Geneva, Switzerland
(5) Vaud Cancer Registry, University Institute of Social and Preventive Medicine (IUMSP), Route de la Corniche 10, Bâtiment Biopôle 2, 1010 Lausanne
(6) Fribourg Cancer Registry, St. Nicolas de Flüe 2, 1705 Fribourg
(7) Valais Cancer Registry, Health Observatory Valais, Avenue Grand-Champsec 86, 1950 Sion, Switzerland
(8) Neuchâtel and Jura Cancer Registry. Rue du Plan 30, 2000 Neuchâtel
(9) Cancer Registry Zurich and Zug, Institute of Pathology and Molecular Pathology, University Hospital Zurich and Epidemiology, Biostatistics and Prevention Institute, University Zurich, Vogelsangstrasse 10, 8091, Zurich, Switzerland
(10) Section of Geriatrics, Boston University Medical Center, 88 East Newton Street, Boston, MA 02118, USA

Corresponding author: Anita Feller, MSc, Email: anita.feller@ispm.unibe.ch
Institute of Social and Preventive Medicine (ISPM), Finkelhubelweg 11, 3012 Bern
Phone: +41 31 631 56 75, FAX: +41 31 631 35 20

Novelty and Impact (max. 75 words):
Switzerland has universal health insurance coverage, high health expenditures, and one of the highest life expectancies in the world. Despite that, this study describes high-risk groups for later-stage breast cancer (BC) diagnosis and higher BC specific mortality in Switzerland. Women of lower socioeconomic position were more likely to present with later-stage BC and showed poorer disease-specific survival. Notably, survival inequalities could not be explained by socioeconomic differences in stage at presentation and/or other sociodemographic factors.

Key words: health inequalities, breast cancer, incidence, survival, socioeconomic position

Abbreviations

Percentage of death certificate only cases	%DCO
95% confidence interval	95%CI
Federal Statistical Office	FSO
International statistical classification of diseases and related health problems	ICD-10
National Institute for Cancer Epidemiology and Registration	NICER
Odds ratio	OR
Person-years	PY
Surveillance, Epidemiology and End Results Program	SEER
Socioeconomic position	SEP
Sub-hazard ratio	SHR
Swiss National Cohort	SNC
Tumour, node and metastasis staging information	TNM

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Abstract

We explored socioeconomic and demographic disparities in breast cancer (BC) stage at presentation and survival in a Swiss population-based sample of female BC patients linked to the census-based Swiss National Cohort. Tumour stage was classified according to Surveillance, Epidemiology and End Results (SEER) Program summary stage (in situ/localized/regional/distant). We used highest education level attained to estimate SEP (low/middle/high). Further demographic characteristics of interest were age at presentation (30-49/50-69/70-84 years), living in a canton with organized screening (yes/no), urbanity of residence (urban/peri-urban/rural), civil status (single/married/widowed/divorced) and nationality (Swiss/non-Swiss). We used ordered logistic regression models to analyse factors associated with BC stage at presentation and competing risk regression models for factors associated with survival. Odds of later-stage BC were significantly increased for low SEP women (odds ratio (OR) 1.19, 95%CI 1.06-1.34) compared to women of high SEP. Further, women living in a canton without organized screening programme, women diagnosed outside the targeted screening age and single/widowed/divorced women were more often diagnosed at later stages. Women of low SEP experienced an increased risk of dying from BC (sub-hazard ratio 1.22, 95%CI 1.05-1.43) compared to women of high SEP. Notably, these survival inequalities could not be explained by socioeconomic differences in stage at presentation and/or other sociodemographic factors. It is concerning that these social gradients have been observed in a country with universal health insurance coverage, high health expenditures and one of the highest life expectancies in the world.

Background

Breast cancer (BC) is the most common cancer in Swiss women. In Switzerland, each year approximately 5,700 women are newly diagnosed with BC and the lifetime risk of developing BC is almost 13%.[1] Although mortality has fallen consistently over the last 30 years, BC is the leading cause of cancer death in Swiss women with approximately 1,400 women dying each year of this disease.[1] Tumour stage at presentation remains one of the major prognostics factors and women with early-stage BC are expected to have excellent survival rates. In a recent Swiss study, age-standardized 10-year relative survival varied from 9.3% (Stage IV) to 94.5% (Stage I) depending on stage at presentation.[2]

Several studies outside of Switzerland have reported negative associations between socioeconomic position (SEP) and BC stage at presentation as well as socioeconomic inequalities in survival after BC diagnosis.[3] Socioeconomic and demographic factors may influence access to health care[4], cancer awareness[5] and woman's attitudes towards preventive methods such as mammography screening, clinical breast examination and breast self-examination.[6]

In Switzerland, health care is organized at the cantonal level, resulting in regional differences in provision of cancer prevention and management services.[7] A Swiss BC pattern of care study, for example, reported considerable regional variations in early BC detection and treatment.[7] In western Switzerland (French-speaking part of the country), organized BC screening programmes have gradually been implemented since 1999 for women aged 50 to 69 years, whereas in most other regions (German and Italian-speaking parts of Switzerland) only opportunistic screening is available.[8] Consequently, screening uptake varies by canton and region. The Swiss Health Survey 2012 reports that in 2010-2011, cantons with organized mammography screening had a 68% mammogram coverage of women in the recommended screening age (50-69 years), compared to 37% in cantons without an organized programme.[9] Organized BC screening may reduce social inequalities in screening uptake[10, 11], although this has not been consistently observed across countries.[12]

Several studies have identified stage at presentation as an important factor in survival differences between socioeconomic groups.[13] In most studies, however, disparities remained after adjustment for stage and other tumour and demographic characteristics.[13] Remaining disparities have been associated with treatment disparities, variations in comorbidities and/or additional factors like variations in psychosocial well-being and patients' support.[13] In Geneva, women with lower SEP were diagnosed with more advanced BC, received more often suboptimal

treatment and showed lower cause-specific and overall survival.[14] A later study in Geneva, observed substantial social inequalities in BC management including diagnostic procedures and primary treatment.[15]

A major goal of health care systems is to equally improve the health in all groups of the population they serve.[16] Despite this aim, socioeconomic and -demographic health inequalities in BC detection and survival have been observed all over the world[13], including countries with tax-funded health care systems designed to provide equal access to care.[17, 18]

Swiss data on socioeconomic health inequalities in stage at presentation and survival of BC in women is very limited. Therefore, the present study aimed to evaluate socioeconomic and demographic disparities in BC stage at presentation and survival in a Swiss population-based sample of female BC patients diagnosed between 2001 and 2008.

Materials and Methods

Data sources and inclusion criteria

This study is based on data from the SNC-NICER Cancer Epidemiology Study. The SNC-NICER Cancer Epidemiology Study took advantage of the Swiss National Cohort (SNC) and the National Institute for Cancer Epidemiology and Registration (NICER) cancer registry network to build a comprehensive historical cohort, allowing epidemiologic analysis of factors associated with cancer incidence, mortality and survival in Switzerland.

A detailed description of the SNC can be found elsewhere.[19] Briefly, 1990 and 2000 census records were probabilistically linked to cause-specific mortality or emigration records from 1991-2013 provided by the Federal Statistical Office (FSO). The Swiss census is mandatory and virtually complete with a 2000 census estimated coverage of 98.6%.[19] This study used SNC sociodemographic information on sex, education level, marital status, place of residence and nationality at census date. The coding of the underlying cause of death is federally standardised by the FSO. Since 1995, the 10th revision of the international classification of diseases and related health problems (ICD-10) has been used following international standards.

In Switzerland, cancer registration is primarily organized at the cantonal level. The earliest cancer registry (CR) data is available from Geneva dating back to 1970, followed by Vaud and Neuchâtel (1974), Zurich (1980), St. Gallen-Appenzell (1980), Basel-Stadt and Basel-Landschaft (1981), Valais (1989), Graubünden (1989), Glarus (1992), Ticino (1996), Jura (2005) and Fribourg (2006). More recently, cancer registration has been introduced in Lucerne (2010), Nidwalden,

Obwalden, Uri, Zug (2011), Thurgau (2012), Aargau (2013) and Bern (2014). All CRs implemented before 2008 have been requested to participate in the SNC-NICER Cancer Epidemiology Study. Seven out of eleven CRs eligible for the study, agreed to participate and provided incidence data to the pooled dataset: Fribourg, Geneva, Neuchâtel, Ticino, Valais, Vaud and Zurich. Data from these CRs were probabilistically linked to the SNC, including all incident cases starting from the date of the census 1990 (or from the implementation of cantonal cancer registration if later) through the end of 2008. In 2008, these cantons covered 46.1% of the Swiss population. To assess sample representativeness, we compared frequency distributions (age, civil status, education, urbanity of residence and nationality) between female residents of participating cantons and whole of Switzerland using census 2000 information. Compared to total Switzerland, the participating cantons showed distinctly higher proportions of women with tertiary education (16.8% versus 11.1%), women living in urban and peri-urban areas (35.3% versus 24.7% and 48.8% versus 41.2%, respectively), and women with foreign nationality (22.7% vs.15.5%). Cancer registration data used in this study included sex, date of birth, date of cancer diagnosis, basis of diagnosis, topography, morphology and behaviour of the tumour, and Tumour, Node and Metastasis staging information (TNM).

The current study population included 17,298 female BC cases (carcinoma in situ and invasive BC) first diagnosed between Census 2000 (5th of December 2000) and 31st of December 2008. TNM codes were based on the fifth and sixth TNM editions. The Census 2000 was used as starting point as for previous time periods, the proportion of missing stage information was high (up to >25%) in two cantons. Education was used as a proxy for SEP so young women (< 30 years of age at diagnosis, N=46) and women with missing education information (N=147) were excluded from the study population. In addition, women diagnosed at 85 years of age or older were excluded (N=936) because data quality (percentage of death certificate only cases [%DCO] 8.2%, histologically verified cases 78.4%) and completeness of stage information (60.1%) was low in this age group. The study population showed %DCO of 0.4% indicating high completeness of case ascertainment with 98.3% of the cases histologically verified and 94.8% with sufficient TNM information to classify tumour stage.

Stage at presentation analyses were based on data from a subset of cantonal cancer registries (Geneva, Valais, Zurich) that provided breast carcinoma in situ cases (N=10,915). In a supplemental analysis, stage at presentation calculations were repeated and limited to invasive BCs to enable the inclusion of all participating cancer registries (Suppl. Table 1). The

supplemental analysis followed survival analyses were based on invasive cancers including all participating cancer registries (16,296).

Analytic methods

Surveillance, Epidemiology and End Results (SEER) Program summary stage was calculated based on the TNM classification system following the algorithm for mapping stage at diagnosis from TNM to SEER summary stage as described by Walters et al.[20] We used SEER summary stage instead of the more detailed TNM staging system due to extensive and significant revision in BC staging between the fifth and sixth TNM edition.

We prioritized pathological T and N over clinical T and N. Missing M or Mx were assumed to be equivalent to M0. If clinical and pathological M was available, any indication of metastasis was prioritized. Pathological and clinical T and N information was available in 84.1% and 46.0% of all invasive BC cases, respectively. The proportion of cases with missing M or Mx was 26.4%. Overall, tumour stage could be calculated for 94.9% of all invasive BC cases. Carcinoma in situ cases have been identified based on the ICD-O-3 behaviour code.

We used highest education level attained by the woman to estimate SEP (compulsory education or less: low SEP, secondary education: middle SEP, tertiary education: high SEP).

We descriptively investigated stage at presentation by SEP, age-group (30-49, 50-69, 70-84 years) and residence (canton with or without organized screening). Ordered logistic regression models examined the association between cancer stage at presentation and SEP. We calculated three models using the following variables as predictors for stage at presentation: (model 1) SEP; (model 2) model 1 plus age at presentation (30-49, 50-69, 70-84 years), civil status (30-49, 50-69, 70-84 years) and nationality (Swiss, non-Swiss); (model 3) model 2 plus urbanity of residence and canton with or without organized screening programme. The third model has been additionally adjusted for canton of residence. No significant interactions were observed, therefore, we only included main effects in the final model.

For women within the recommended screening age, we conducted a sub-analysis of Valais and Geneva, the only two cantons which both, offered organized screening during the study period and provided carcinoma in situ cases to the study population. We examined the association between being diagnosed within or outside the organized programme and SEP using logistic regression including civil status and nationality and canton of residence as covariates.

Survival was analysed using competing risk regressions based on Fine and Gray's proportional hazard model.[21] All underlying causes of death other than BC were classified as competing risks. Four models have been calculated using the following variables as predictors: (model 1) SEP; (model 2) model 1 plus age at presentation, civil status and nationality; (model 3) model 2 plus stage at presentation; and (model 4) model 3 plus urbanity of residenc and canton with or without organized screening programme. Results of survival analyses are reported as sub-hazard ratios of death due to BC (SHRs) with 95% confidence intervals (95%CI).

Both final models (stage at presentation and survival analyses) have been additionally adjusted for canton of residence to account for unmeasured canton characteristics associated with SEP distribution and stage at diagnosis/survival.

All analyses were performed using the statistical software package Stata, version 13.1 for Windows (StataCorp, College Station, Texas).

Results

Patient characteristics by SEP cases included in stage at presentation and survival analyses are listed in Table 1. Incident breast carcinoma cases (N_{total}=10,915, N_{staged}=10,362) by cancer registry included in stage at presentation analyses is shown in Suppl. Table 2. Incident BC cases (N_{total}=16,296; N_{staged}=15,462) and person-years (PY) (PYs_{total}=127,040; PY_{staged}=121,553) by cancer registry included in survival analyses is shown in Suppl. Table 3.

BC stage at presentation

In the unadjusted model, odds ratios (ORs) of later stage at BC diagnosis were significantly increased for women of middle (OR 1.18, 95%CI 1.07-1.31) and low SEP (OR 1.30, 95%CI 1.16-1.46) compared to women of high SEP (Table 2). After adjustment for demographic factors (model 2) and area of living (urbanity of residence, canton with/without organized screening, canton of living) (model 3), ORs for middle SEP women and low SEP women decreased to 1.09 (95%CI 0.99-1.21) and 1.19 (95%CI 1.06-1.34), respectively. In the final model, women living in a canton without an organized screening programme were also more likely to have their BC diagnosed at a later stage (OR 1.42, 95%CI 1.30-1.55). Further, women outside the targeted screening age (30-49 years: OR 1.22, 95%CI 1.11-1.33; 70-84 years OR: 1.31, 95%CI 1.19-1.45) and single/widowed/divorced women showed elevated risks for later stages at diagnosis (OR 1.12 (95%CI 0.99-1.27) - 1.14 (95%CI 1.02-1.27)).

We observed higher proportions of early stage BC (carcinoma in situ and localized cancers) in cantons with organized BC screening compared to the canton without organized screening (Figure 1). In the recommended screening age-group (50-69 years), the observed proportion of early stage BC (carcinoma in situ and localized BC) was 64.7% vs. 51.9% (low SEP), 65.0% vs. 57.0% (middle SEP), and 69.4% vs. 56.6% (high SEP). A similar tendency towards higher proportions of early stage BC in cantons with organized screening (regardless of SEP) was also observed in the age-group 70-84 years. However, due to comparably high number of cases without stage information, i.e. in the canton without organized screening, figures for this age-group are difficult to interpret. In women aged 30-49 years, early stage detection in women varied across SEPs between 56.9% (middle SEP) and 59.5% (high SEP) in cantons with organized screening and 50.0% (middle SEP) and 53.3% (high SEP) in the canton without organized screening.

When looking at carcinoma in situ cases in women in the recommended screening age-group, only women living in a canton with organized screening programme showed a social gradient with 9.3%, 11.9% and 15.0% of carcinoma in situ cases for low, middle and high SEP women, respectively. In the canton without organized screening, the proportion of carcinoma in situ cases were fairly stable with 8.5% (low SEP), 9.8% (middle SEP) and 8.2% (high SEP).In cantons with organized programmes, 16% (canton Geneva) and 32% (canton Valais) of diagnosed BC cases in the age-group eligible for organized BC screening were detected within the framework of an organized programme. Compared to women with high SEP, women with middle (OR 1.25, 95%CI 1.03-1.53) and low SEP (OR 1.39, 95%CI 1.11-1.73) were more likely to be diagnosed outside of the organized screening programme.

BC survival

Stage information was lacking in 5.1% (Table 1). Of the 16,296 incident cases included in the survival analyses, 3,713 cases died before the end of follow-up (22.8%) and 229 (1.4%) were lost-to-follow-up.

In all models, diagnosed women with low SEP were more likely to die of BC compared to women with high SEP (Table 3). SHRs of low SEP women gradually decreased from 1.60 (95%CI 1.40-1.83, model 1) to 1.22 (95% CI 1.05-1.43, model 4) after adjustment for further demographic factors (model 2), stage at presentation (model 3) and area of living (canton with/without organized screening, canton of living, model 4). In the fully adjusted model (model 4), later stage at presentation was strongly associated with an increased risk of BC death (regional stage: SHR

4.12, 95%CI 3.66-4.63; distant stage: SHR 27.27, 95%CI 23.67-31.41). Compared to women diagnosed in the recommended screening age (50-69 years), women aged 70-84 years showed an elevated risk of BC death (SHR 1.34, 95%CI 1.19-1.50). For women aged 30-49 years, a reduced risk was observed (SHR 0.76, 95%CI 0.66-0.86). Living in a canton without an organized screening was associated with an increased SHR (SHR 1.44, 95%CI 1.23-1.68) even after adjustment for stage at diagnosis. Further, living in a non-urban region was associated with an increased risk of BC death with SHRs of 1.13 (95%CI 1.02-1.26) (peri-urban region) and 1.21 (95%CI 1.03-1.41) (rural region). Residents of foreign nationality were at lower risk of dying from their BC (SHR 0.84, 95%CI 0.73-0.98). We observed no statistically significant effects for civil status in the fully adjusted model (Table 3).

Discussion

Summary of main findings

Despite universal health insurance coverage[22], high health expenditures[22], the highest average household net financial wealth worldwide[23] and one of the highest life expectancies in the world[24], high risk groups for later-stage BC and lower BC survival were identified in Switzerland. In our study, women of lower SEP, unmarried women, women below (<50 years) or above (>69 years) the recommended screening age, and women living in a canton with no organized BC screening programme showed an increased risk of being diagnosed with a later-stage BC. In addition, women of lower SEP experienced poorer disease-specific survival. Notably, these survival inequalities could not be explained by socioeconomic differences in stage at presentation and/or other sociodemographic factors such as age, nationality and civil status.

Discussion in the context of the literature

Our Swiss results are in line with international data, showing that lower SEP is associated with later-stage BC and shortened survival.[3] Much of the deprivation gap in survival can be attributed to inequalities in stage at presentation, the most important single predictor for BC survival.[13, 25] However, in most research socioeconomic survival gaps remained in stage-stratified analyses or after adjustment for stage at diagnosis.[13, 25] Further, socioeconomic inequalities for BC stage and survival were observed in various countries irrespective of the measurement used for SEP classification (e.g. education, occupation, income, area-based deprivation index).[13] Possible reasons for the delayed BC diagnosis in lower SEP women might be related to inequalities in health care access[4], cancer awareness[5] and/or attitudes towards cancer (e. g. cancer fatalism).[6]

All these factors might substantially contribute to observed disparities in BC screening uptake[11, 26], and/or cancer-related health behaviour such as health care seeking after detection of first symptoms (patient-mediated delay).[27] Essentially, equal access to health care goes beyond universal health insurance coverage and adequate provision of accessible health services (such as provision in proximity of the patient's residence).[28] Additional factors such as language barriers, uncovered costs (travel costs, childcare during consultation/treatment) or previous negative health care experiences might hamper health care access of individuals and specific social groups.[29] Disparities in cancer awareness might have also influenced the results. In a Danish study, for example, lower SEP was associated with less awareness of BC symptoms and risk factors.[5] Further, fatalistic attitudes towards cancer have been shown to be associated with lower SEP[6, 30], whereas cancer fatalism in turn was associated with being less positive about early detection and being more fearful about seeking help for suspicious symptoms.[30] In our study, we observed a social shift towards higher proportions of carcinoma in situ cases for women in the recommended screening age only in cantons offering organized screening. In the canton without organized screening, proportions of carcinoma in situ cases were fairly equal across SEP groups, similar to those observed in low SEP women in cantons with organized screening. As carcinoma in situ are rare in the symptomatic setting, observed variations were most likely caused by differences in mammography screening use (organized and/or opportunistic). In the canton without organized screening programme, social inequalities in early detection were mainly visible for localized BC indicating that in this canton other factors such as inequalities in cancer awareness/knowledge, health care access and /or help seeking behaviour after detection of symptoms might have led to the observed results.

In our study, socioeconomic inequalities in survival remained after adjusting for stage at presentation suggesting that further factors such as treatment disparities and/or variations in comorbidities might play a role. This assumption is supported by the findings in the canton of Geneva, where lower SEP women were more likely to receive suboptimal treatment compared to their more affluent counterparts.[14, 15]

In women aged 70-84 years, lower SEP was associated with an increased proportion of unstaged BCs. However, a clear social gradient was only apparent in the cantons with organized screening programmes. Women 85 years and older were excluded from the analyses because of the high proportion with missing stage information despite the fact that tumour stage should be investigated (at least clinically) in all women with BC.[31] However, a distinction must be made

between a true lack of stage information and a lack of reporting stage.[32] A true lack of staging might occur in patients with very limited life expectancy (severe comorbidities, high age)[32, 33] or due to patients' choice.[32, 34] In contrast, lack of reporting refers to cases where clinical and/or pathological stage has been investigated but has not been captured by the cancer registry. A study investigating the completeness of BC staging in the New Zealand Cancer Registry, found that 12% of staged BC cases were recorded as unknown stage in the cancer registry system.[32] Although observed socioeconomic inequalities in diagnostic assessment might be – at least partly – explained by the fact that comorbidities are more common in lower SEP women and in older women.[35]

Biennial mammography coverage in the recommended screening age was substantially higher in cantons with an organized programme (located in the western, French-speaking region of Switzerland) compared to cantons without organized programme.[9] However, the participation rate in the organized programmes varied substantially across cantons. In 2004, screening coverage in the organized programme of women aged 50-69 years was 23% in Geneva compared to 66% in Valais.[36] Importantly, opportunistic screening has widely been offered concomitantly to organized programmes in Switzerland.[36] A prospective study in Geneva reported that only 12% of women invited to screening were screened within the organized programme and 39% received screening outside of the framework of the organized programme.[10] Therefore, the lower participation rate in the Geneva programme likely reflects a higher prevalence of opportunistic screening rather than real differences in mammography coverage.[37]

In our analyses, the cantons with organized BC screening programmes showed a shift towards earlier stages in women aged 50 years and older compared to the canton without an implemented programme. A similar shift – albeit less pronounced – has been observed for younger women below the recommended screening age indicating that younger women in cantons with organised screening are more likely to undergo mammography screening than their counterparts in cantons without a programme.

Women outside the recommended screening age showed an increased risk of being diagnosed at later stages. For the time period under investigation, the recommended screening age in Switzerland was 50-69 years. The age-cut was based on the fact that at this time the most convincing evidence for a beneficial effect available from randomized controlled trials existed for women aged 50-69 years. However, women older than 69 years were allowed to continue screening within the organized program if desired and if no major comorbidities existed.[36]

Diagnosing BC by mammography is more difficult in younger women because their breast tissue is denser making it hard to detect anomalies - the main reason why mammography screening is not recommended for younger women.[36] BC in younger women has been shown to be more aggressive[38] and have a less favourable prognosis[39], although the latter has not been consistently observed.[40] In our study, we observed an increased survival for women below the age of 50 years compared to their older counterparts (overall and adjusted for stage at presentation). An earlier Swiss study found that women with BC diagnosed below the age of 40 years had substantially lower survival than women diagnosed between the age of 40-49 years.[39] Due to the small number of cases below the age of 40 years we categorised younger women as < 50 years thus potential survival disadvantages in the very young women could not be examined in this study.

Several studies outside of Switzerland observed beneficial impacts of being married in regard to BC stage at presentation and survival after BC[13, 41], indicating that social support might have a significant impact on cancer detection, treatment and survival.[41] A study in the United States observed that unmarried women were at higher risk of being diagnosed with metastatic cancer, under-treatment and death resulting from their cancer.[41] In our study, we observed an increased risk for unmarried women for being diagnosed with later stage BC (albeit not reaching significance for widowed women). For survival after BC, we observed a significantly lower survival only in single women and only if not adjusted for stage at diagnosis. In this study marital status was obtained from the census and with increasing time between date of census and end of follow-up, marital status might have changed leading to misclassification when referring to the time of or after diagnosis.

In our study, women living in non-urban regions showed lower survival compared to their urban counterparts. Factors that may mediate these disparities may include inequalities in tumour characteristics (i.e. stage at presentation), patients' treatment preferences and adherence, and/or access to and quality of care received. However, in our study we did not observe significant disparities in stage at presentation between the rural and urban population suggesting that differences in early-detection played a minor role.

Compared to women with Swiss nationality, our results suggest that women of foreign nationality have an overall and stage-specific survival benefit. A potential explanation for these differences is the so-called "healthy migrant effect". The healthy migrant effect describes an empirically observed mortality advantage of migrants relative to the population in the host

country due to self-selection of migrants who tend to differ from their fellow countrymen in respect to education, risk exposure or health, leading to better health outcomes despite potential social inequalities and discrimination in the host country. However, data quality issues might have affected the results in this study. Death records of non-Swiss residents showed an increased probability of not being linked to census data compared to death records of Swiss nationals[19] and (undocumented) out-migration may have led to incomplete mortality follow-up, especially in semi-skilled or unskilled migrant workers, who tend to leave the home country when they are sick or disabled.[42] Additionally, it is difficult to draw conclusions for the non-Swiss population because it is a highly heterogeneous group. Non-Swiss have different countries of origin, migration status (first, second or third generation immigrants), type of residence permit, level of education, employment and income, to name a few. Hence, this topic should be investigated further in future studies.

Strengths and Limitations

This is the first Swiss study investigating socioeconomic inequalities of BC stage at presentation and survival, combining data from multiple Swiss cantons and from a national census. Overall, the study population had less than 0.5% DCO cases indicating a high completeness of case ascertainment. In the age-group under investigation, stage information was available for 95% of all cases.

Our study has some limitations. First, the meaning and consequences of educational attainment might vary by birth cohort.[43] However, there is considerable international evidence that education is strongly associated with health, health behaviour and preventive service use and that a substantial share of these effects are of causal origin.[44] In addition, individual education is generally stable beyond early adulthood whereas civil status and living conditions are more likely to change over time and individual education level was virtually complete (>99%) in the study population. In a preceeding analysis, we compared three indicators of SEP in relation to stage at presentation: (1) education woman - highest education level attained by the woman (compulsory or less, upper-secondary, upper-tertiary education), (2) education couple – if married, highest education level attained by the woman or spouse, and (3) quintiles of the Swiss neighbourhood index (Swiss-SEP), a composite area-level SEP measure based on income, education, occupation and housing conditions.[45] Regardless of SEP indicator used, we observed comparable patterns and effects for SEP and the covariates included in the models[46], although importantly, each indicator of SEP measures different aspects of socioeconomic stratification.[43]

Overall, only 7 out of 26 Swiss cantons participated in the study covering around 46% of the population. Further, stage at presentation analyses were restricted to cantonal cancer registries providing carcinoma in situ cases diminishing population coverage for these analyses to 27%. The resulting study sample was not representative for the female Swiss population with respect to SEP, urbanity or residence and nationality. Importantly, there may be also other unmeasured cantonal/regional characteristics associated with stage at presentation and/or survival that could impact the results. Therefore, we additionally adjusted for canton of residence in the final models. Generalisability of these finding, although better than previous publications, remains limited by the lack of cantonal cancer registry participation and should be made with caution.

Another weakness of the study is the lack of more detailed tumour characteristics ((morphologic subtype, grade, oestrogen receptor (ER) status, progesterone-receptor (PR) status, human epidermal growth factor receptor 2 (HER2/neu) and other prognostic factors such as comorbidities and cancer treatment. From studies outside of Switzerland, it is known that morphological type of BC and ER status might vary between social groups.[13] A Swiss study conducted in Geneva reported variations depending on SEP for stage at presentation and morphological BC type, but not for grade, tumour size and ER status.[14] Substantial treatment differences between social groups have been also been reported for this canton.[14, 15] Additional analysis of morphological type by SEP (not presented) suggests that morphological differences reported from Geneva might be largely the result of varying proportions of cases with unknown morphological type (classified as other morphological type in their analyses) rather than reflecting real morphological differences between social groups. Further, stage at presentation has been consistently shown to be a major predictor of BC survival and other tumour characteristics contributed much less to the explanation of the observed survival experience.[13]

Comorbidities are more common in lower SEP women and may have an adverse impact on cancer survival.[35] Comorbidities might be associated with less complete diagnostic assessment including biopsy for staging[32, 33], limited treatment options, and a decreased likelihood to receive treatment with curative intent[47]. Further, SEP might influence patients treatment choice[48] and/or adherence to treatment[49]. However, studies in the canton of Geneva suggest that observed survival inequalities after BC are – at least partly – caused by differences in care management depending on SEP.[14, 15] Unfortunately, information on comorbidities were not available for this study.

Since the introduction of BC screening programmes, the usefulness of mammography screening has been questioned. Critics argue that screening-induced over-diagnosis and its consequences outbalance potential mortality benefits.[50] Consequently, our analyses might be affected by higher proportions of over-diagnosis in the cantons with implemented screening programme resulting in higher mammography screening coverage.

Finally, we used the SEER basic summary staging because substantial TNM classification changes over the investigated time period prevented the use of the more detailed TNM-staging. A more detailed staging system might have shown stronger effects.

Conclusions

Characteristics associated with later stage BC diagnosis in Switzerland were lower SEP, being unmarried, being outside of the recommended screening age and living in a canton without an organized BC screening programme. In addition, women of lower SEP experienced poorer disease-specific survival. Notably, these survival inequalities could not be explained by socioeconomic differences at stage of presentation and/or other sociodemographic factors such as age, nationality and civil status. Appropriate intervention strategies are needed to reduce socioeconomic and demographic health inequalities in women with BC.

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Table 1: Patient characteristics by socioeconomic position (SEP). (1) Carcinoma in situ and invasive breast cancer cases from three Swiss cancer registries (CRs) for stage at presentation analyses. (2) Invasive breast cancer cases from seven Swiss cancer registries (CRs) for survival analyses.

Analysis of SEP and stage at presentation	Low SEP N	Low SEP column %	Middle SEP N	Middle SEP column %	High SEP N	High SEP column %	Total N	Total column %
(1) Stage at presentation analyses (N=10,915)								
Stage at presentation								
in situ	217	7.3	574	9.6	211	11.0	1,002	9.2
Local	1,382	46.3	2,780	46.3	951	49.4	5,113	46.8
Regional	1,036	34.7	2,139	35.6	625	32.5	3,800	34.8
distant	142	4.8	239	4.0	66	3.4	447	4.1
unknown stage	206	6.9	275	4.6	72	3.7	553	5.1
Age at presentation								
<50 years	435	14.6	1,340	22.3	590	30.7	2,365	21.7
50-69 years	1,433	48.0	3,296	54.9	1,090	56.6	5,819	53.3
69-84 years	1,115	37.4	1,371	22.8	245	12.7	2,731	25.0
Civil status								
single	242	8.1	750	12.5	388	20.2	1,380	12.6
married	1,766	59.2	3,785	63.0	1,146	59.5	6,697	61.4
widowed	638	21.4	632	10.5	115	6.0	1,385	12.7
divorced	337	11.3	840	14.0	276	14.3	1,453	13.3
Nationality								
Swiss	2,270	76.1	5,455	90.8	1,548	90.8	9,273	85.0
non-Swiss	713	23.9	552	9.2	377	9.2	1,642	15.0
Urbanity of residence								
urban	1,225	41.1	2,157	35.9	840	43.6	4,222	38.7
peri-urban	1,326	44.5	3,417	56.9	1,015	52.7	5,758	52.8
rural	432	14.5	433	7.2	70	8.6	935	8.6
Living in an region with organized breast cancer screening								
Yes[1]	1,457	48.8	1,990	33.1	994	51.6	4,441	40.7
No[2]	1,526	51.2	4,017	66.9	931	48.4	6,474	59.3
Total N row %	**2,983**	**27.3**	**6,007**	**55.0**	**1,925**	**17.6**	**10,915**	**100.0**
(2) Survival analysis (N=16,296)								
Stage at presentation								
Local	2,507	51.4	4,633	53.4	1,535	56.1	8,675	53.2
regional	1,778	36.5	3,254	37.5	982	36.0	6,014	36.9
Distant	267	5.5	396	4.6	110	4.0	773	4.7
unknown stage	326	6.7	400	4.6	108	4.0	834	5.1
Age at presentation								
<50 years	608	12.5	1,958	22.6	818	29.9	3,384	20.8
50-69 years	2,252	46.2	4710	54.2	1,566	57.3	8,528	52.3
70-84 years	2,018	41.4	2,015	23.2	351	12.8	4,384	26.9
Civil status								
Single	387	7.9	1,115	12.8	527	19.3	2,029	12.5
Married	2,838	58.2	5,483	63.2	1,659	60.6	9,980	61.2
widowed	1,106	22.7	918	10.6	175	6.4	2,199	13.5
divorced	547	11.2	1,167	13.4	374	13.7	2,088	12.8
Nationality								
Swiss	3,788	77.7	7,878	90.7	2,211	80.8	13,877	85.2
non-Swiss	1,090	22.4	805	9.3	524	19.2	2,419	14.8
Urbanity of residence								
urban	1,852	38.0	2,949	34.0	1,059	38.7	5,860	36.0
peri-urban	2,088	42.8	4,731	54.5	1,435	52.5	8,254	50.7
rural	938	19.2	1,003	11.6	241	8.8	2,182	13.4

Living in a canton with organized breast cancer screening								
Yes[3]	2,600	53.3	3,828	44.1	1,588	58.1	8,016	49.2
No[4]	2,278	47.7	4,855	55.9	1,147	41.9	8,280	50.8
Vital status at end of follow-up								
Alive	3,277	67.2	6,819	78.5	2,258	82.6	12,354	75.8
Dead	1,510	31.0	1,780	20.5	423	15.5	3,713	22.8
lost-to-follow-up	91	1.9	84	1.0	54	2.0	229	1.4
Total N row %	**4,878**	**29.9**	**8,683**	**53.3**	**2,735**	**16.8**	**16,296**	**100,0**

Note: For stage analyses, 92 cases (0.8%) out of originally 11,007 cases have been excluded due to missing SEP information. For survival analyses 147 cases (0.9%) out of originally 16,516 cases have been excluded due to missing SEP information. From the remaining dataset, 73 additional cases were excluded due to zero survival time (death certificate only cases or cases first diagnosed at autopsy).

[1]Geneva, Valais; [2]Zurich; [3]Fribourg, Geneva, Valais, Vaud; [4]Neuchâtel, Ticino, Zurich. In Neuchâtel, an organized screening programme was implemented in 2007. Incident cases of the years 2007 and 2008 were excluded from analyses.

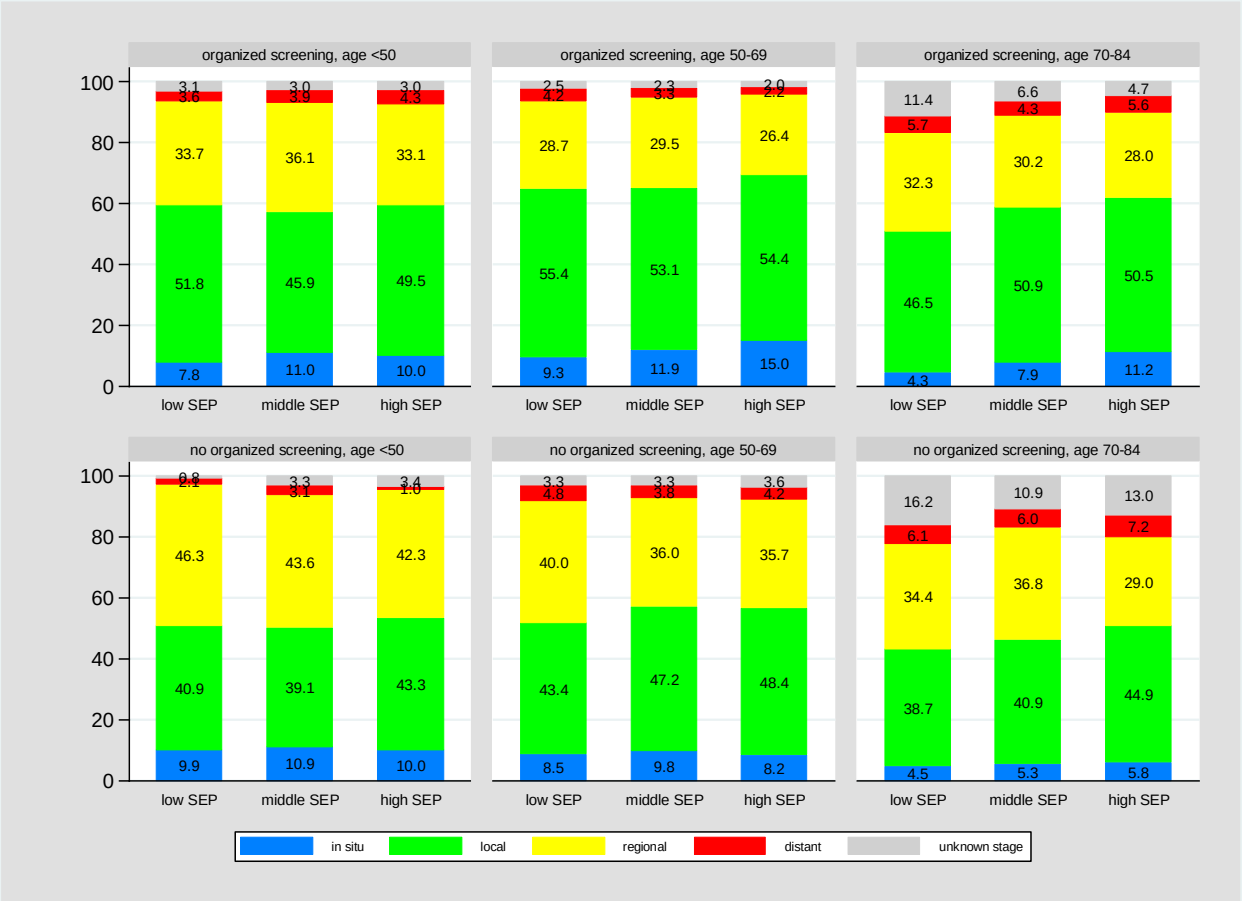

Figure 1: Distribution of breast cancer stage at presentation by socioeconomic position (SEP), age-group and canton of residence (canton with organized mammography screening: Geneva, Valais; canton without organized mammography screening: Zurich).

Table 2: Odds ratio (OR) of later stage at breast cancer at presentation: Carcinoma in situ and invasive breast cancer cases from three Swiss cancer registries (CRs)

	Model 1		Model 2		Model 3	
	OR	[95%CI]	OR	[95%CI]	OR	[95%CI]
SEP						
High SEP (ref.)						
Middle SEP	1.18	[1.07-1.31]	1.17	[1.05-1.29]	1.09	[0.99-1.21]
Low SEP	1.30	[1.16-1.46]	1.25	[1.12-1.41]	1.19	[1.06-1.34]
Age at presentation						
50-69 years (ref.)						
30-49 years			1.24	[1.13-1.36]	1.22	[1.11-1.33]
70-84 years			1.41	[1.27-1.55]	1.31	[1.19-1.45]
Civil status						
married (ref.)						
single			1.14	[1.01-1.27]	1.13	[1.01-1.27]
widowed			1.13	[1.00-1.28]	1.12	[0.99-1.27]
divorced			1.18	[1.06-1.32]	1.14	[1.02-1.27]
Nationality						
Swiss (ref.)						
Non-Swiss			0.97	[0.87-1.07]	0.97	[0.88-1.08]
Urbanity						
urban (ref.)						
peri-urban					0.93	[0.86-1.01]
rural					0.98	[0.84-1.14]
Organized screening[1]						
yes (ref.)						
no					1.42	[1.30-1.55]

Three models have been calculated using the following variables as predictors: (model 1) SEP; (model 2) model 1 plus age at presentation, civil status and nationality; (model 3) model 2 plus canton with or without organized screening programme and urbanity of residence. The third model has been additionally adjusted for canton of residence.

[1]Cantons with organized screening: Geneva, Valais; canton without organized screening: Zurich.

Table 3: Subhazard ratios and 95% confidence intervals (95%CI), competing risk survival after breast cancer in Swiss women

	Model 1		Model 2		Model 3		Model 4	
	SHR	[95%CI]	SHR	[95%CI]	SHR	[95%CI]	SHR	[95%CI]
SEP								
High SEP (ref.)								
Middle SEP	1.20	[1.06-1.37]	1.13	[0.99-1.29]	1.06	[0.92-1.22]	1.01	[0.88-1.16]
Low SEP	1.60	[1.40-1.83]	1.39	[1.21-1.61]	1.29	[1.11-1.50]	1.22	[1.05-1.43]
Age at presentation								
50-69 years (ref.)								
30-49 years			0.84	[0.74-0.95]	0.77	[0.67-0.87]	0.76	[0.66-0.86]
70-84 years			1.48	[1.33-1.64]	1.31	[1.17-1.47]	1.34	[1.19.1.50]
Civil status								
married (ref.)								
single			1.24	[1.09-1.42]	1.14	[0.99-1.31]	1.16	[1.00-1.33]
widowed			1.10	[0.97-1.25]	1.09	[0.95-1.26]	1.09	[0.94-1.26]
divorced			1.02	[0.89-1.17]	0.94	[0.82-1.09]	0.97	[0.83-1.12]
Nationality								
Swiss (ref.)								
Non-Swiss			0.82	[0.72-0.94]	0.80	[0.69-0.92]	0.84	[0.73-0.98]
Stage at presentation								
local (ref.)								
regional					4.21	[3.75-4.74]	4.12	[3.66-4.63]
distant					26.92	[23.39-30.98]]	27.27	[23.67-31.41]
Urbanity								
urban (ref.)								
peri-urban							1.13	[1.02-1.26]
rural							1.21	[1.03-1.41]
Organized screening								
yes (ref.)								
no							1.44	[1.23-1.68]

Survival was analysed using competing risk regressions based on Fine and Gray's proportional hazard model [21]. All underlying causes of death other than breast cancer were classified as competing risks. Four models have been calculated using the following variables as predictors: (model 1) SEP; (model 2) model 1 plus age at presentation, civil status and nationality; (model 3) model 2 plus stage at presentation; and (model 4) model 3 plus canton with or without organized screening programme and urbanity of residence. The fourth model has been additionally adjusted for canton of residence. Results are reported as sub-hazard ratios for breast cancer survival (SHRs) with 95% confidence intervals (95%CI).
[1]Cantons with organized screening: Fribourg, Geneva, Valais, Vaud; cantons without organized screening: Neuchâtel, Ticino, Zurich. In Neuchâtel, an organized screening programme was implemented in 2007. Incident cases of the years 2007 and 2008 were excluded from analyses.

Suppl. Table 1: Odds ratio (OR) of later breast cancer stage at at presentation: invasive breast cancer cases from seven Swiss cancer registries (CRs).

	Model 1		Model 2		Model 3	
	OR	[95%CI]	OR	[95%CI]	OR	[95%CI]
SEP						
High SEP (ref.)						
Middle SEP	1.11	[1.01-1.21]	1.11	[1.02-1.22]	1.07	[0.98-1.17]
Low SEP	1.16	[1.06-1.28]	1.17	[1.06-1.29]	1.15	[1.04-1.27]
Age at presentation						
50-69 years (ref.)						
30-49 years			1.32	[1.22-1.43]	1.31	[1.21-1.42]
70-84 years			1.20	[1.11-1.30]	1.21	[1.11-1.32]
Civil status						
married (ref.)						
single			1.10	[1.00-1.21]	1.08	[0.98-1.19]
widowed			1.03	[0.93-1.15]	1.02	[0.92-1.13]
divorced			1.07	[0.98-1.18]	1.06	[0.97-1.17]
Nationality						
Swiss (ref.)						
Non-Swiss			1.00	[0.91-1.09]	1.01	[0.93-1.11]
Urbanity						
urban (ref.)						
peri-urban					0.95	[0.89-1.02]
rural					1.06	[0.96-1.19]
Organized screening[1]						
yes (ref.)						
no					1.45	[1.31-1.60]

Three models have been calculated using the following variables as predictors: (model 1) SEP; (model 2) model 1 plus age at presentation, civil status and nationality; (model 3) model 2 plus canton with or without organized screening programme and urbanity of residence. The third model has been additionally adjusted for canton of residence.

[1]Cantons with organized screening: Fribourg, Geneva, Valais, Vaud; cantons without organized screening: Neuchâtel, Ticino, Zurich. In Neuchâtel, an organized screening programme was implemented in 2007. Incident cases of the years 2007 and 2008 were excluded from analyses

Suppl. Table 2: Contribution of carcinoma in situ and invasive breast cancer cases from three Swiss cancer registries (CRs) to the pooled dataset to investigate the association between socioeconomic position and stage at presentation, incidence period 05/12/2000 - 31/12/2008

CR	All cases		Cases with stage information	
	Cases (N)	% of pooled dataset	Cases (N)	% of pooled dataset
Geneva (a)	2,827	26.0	2,721	26.3
Valais (a)	1,614	14.8	1,547	14.9
Zurich (b)	6,474	59.3	6,094	58.8

Note: 92 cases (0.8%) out of originally 11,007 cases have been excluded due to missing SEP information.
(a) Canton with organized mammography screening.
(b) Canton without organized mammography screening.

Suppl. Table 3: Contribution of invasive breast cancer cases to the pooled dataset from seven Swiss cancer registries (CRs) to investigate the association of socioeconomic position and breast cancer survival, incidence period 05/12/2000 - 31/12/2008

CR	all stages			with stage information		
	Cases (N)	Person-years (PY)	% of pooled PY	Cases (N)	Person-years (PY)	% of pooled PY
Fribourg (a, c)	474	2,817	2.2	460	2,737	2.3
Geneva (a)	2,501	20,488	16.1	2,405	19,877	16.4
Neuchâtel (b, d)	707	5,871	4.6	620	5,318	4.4
Ticino (b)	1,773	13,856	10.9	1,712	13,174	10.8
Valais (a)	1,458	11,410	9.0	1,393	11,022	9.1
Vaud (a)	3,583	28,378	22.3	3,395	27,312	22.5
Zurich (b)	5,800	44,220	34.8	5,477	42,113	34.6

Note: 147 cases (0.9%) out of originally 16,516 cases have been excluded due to missing SEP information. From the remaining dataset, 73 additional cases were excluded due zero survival time (death certificate only cases or cases first diagnosed at autopsy).
(a) Canton with organized mammography screening for the time period under investigation.
(b) Canton without organized mammography screening for the time period under investigation.
(c) Fribourg contributed cases from 01/01/2006-31/12/2008 only.
(d) In Neuchâtel, mammography screening was implemented in 2007. Incident cases from the years 2007/2008 were excluded from analyses.