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Original article

# Breast cancer in younger women in Switzerland 1996–2009: A longitudinal population-based study

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ABSTRACT

*Background:* Breast cancer (BC) is the most commonly diagnosed cancer and a leading cause of death in younger women.
*Methods:* We analysed incidence, mortality and relative survival (RS) in women with BC aged 20–49 years at diagnosis, between 1996 and 2009 in Switzerland. Trends are reported as estimated annual percentage changes (EAPC).
*Results:* Our findings confirm a slight increase in the incidence of BC in younger Swiss women during the period 1996–2009. The increase was largest in women aged 20–39 years (EAPC 1.8%). Mortality decreased in both age groups with similar EAPCs. Survival was lowest among women 20–39 years (10-year RS 73.4%). We observed no notable differences in stage of disease at diagnosis that might explain these differences.
*Conclusions:* The increased incidence and lower survival in younger women diagnosed with BC in Switzerland indicates possible differences in risk factors, tumour biology and treatment characteristics that require additional examination.



## Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women, although it is relatively rare in younger women. More than 5000 cases of newly diagnosed BCs occur in Switzerland annually [1]. Approximately 20% of these cases are in women under 50 years old while less than 7% are younger than 40 years [1,2]. Nevertheless, BC is the most common cancer in younger women (more than 40% of all cancers) and a leading cause of cancer death (25% of all cancer deaths) in women under 40 years [2,3].

The overall incidence of BC in Switzerland and other developed countries has decreased by around 2% since around 2003, after

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decades of increase among women 50 years and older [1,4–6]. This phenomenon was observed solely among post-menopausal women and has been attributed to the dramatic reduction in the use of hormonal replacement therapy [7,8]. In contrast, an increase in the incidence of BC in younger Swiss women has been reported albeit inconsistently. Bouchardy et al. found a substantial rise in BC incidence among women aged 25–39 years in Geneva, Switzerland during the period 2002-2004 [9]. However, these findings were based on a small number of cases from a single canton cancer registry (CR) and were not confirmed by data from two other Swiss CRs [10]. International studies reporting over similar timeframes found annual increases of 1%–3% in BC incidence in younger European and American women [11–13].

Mortality from BC has been decreasing in Switzerland and across Europe since 1990. Changes in mortality are highly variable across countries and appear age-specific [14,15]. In Switzerland a decrease in mortality of 25% was observed between 1983 and 2007, mainly among women aged 50 years and older [1,10].

Data on BC survival in younger women have been mixed. Fredholm et al.examined BC survival in Swedish women between 1992 and 2005 using population-based CR data [16]. They found that five-year relative survival (RS) improved with increasing age. Similar findings are reported in the United States (US), the United Kingdom and other European countries [17–19]. Age also remained an independent risk factor for death in younger Swedish women after adjustment for BC and treatment characteristics [16]. A Swiss study investigating cause-specific BC survival found no survival differences between younger and older women. Although in this study younger Swiss women, consistent with other international studies, were diagnosed with more advanced and aggressive tumours [20].

BC has a substantial public health impact and continues to be widely studied. Because of the lower incidence in younger women population-based studies with larger sample sizes are best suited though none exist for Switzerland. The aim of this study was to comprehensively evaluate recent trends in BC among younger women in Switzerland, using nationally representative population-based CR data.

## Methods

### *Data sources and inclusion criteria*

Data on BC cases were obtained from the Swiss CRs of Basel (BS/BL), Fribourg (FR), Geneva (GE), Graubünden/Glarus (GR/GL), Jura (JU), Neuchâtel (NE), St. Gallen-Appenzell (SG/AR/AI), Ticino (TI), Valais (VS), Vaud (VD) and Zurich (ZH) for the incidence years 1996–2009 or 1996–2008 (CR BS/BL). The listed CRs cover around 60% of the Swiss population with permanent residency. Vital status follow-up was provided by all CRs with the exception of the CR of JU. Vital status information was collected by passive (linkage with federal mortality data) and active follow up (verification of vital status with the cantonal registration offices). Tumour, node and metastasis staging information (TNM) were provided by CRs listed above with the exception of JU and ZH. Depending on incidence year and CR, TNM codes were based on the fourth to sixth edition.

Mortality data, mid-year population estimates and canton-specific death rates for the time period under investigation were supplied by the Swiss Federal Statistical Office (SFSO), referring to all persons with permanent residence status in Switzerland. The mortality information is based on civil registries and on SFSO standardized death certificates indicating the causes of death. The coding of death certificates is carried out by the SFSO using the 10th revision of the International statistical classification of diseases and related health problems (ICD-10) for the entire country following international standards [21].

Incidence analyses were based on all recorded women with primary invasive BC, age at incidence 20 to <50 years, diagnosed in the time period 1996–2009. Survival analyses were restricted to women with first primary invasive BC. Cases diagnosed at death were excluded in survival analyses. All stage specific analyses were restricted to the data of CRs providing TNM-information to the pooled dataset.

### *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. [22] 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 [22]. Recoding of M status was done at two CRs (CR of VD and NE) as standard practice without documentation before we received their data. In the pooled dataset of the remaining CRs, stage calculation was based on recoded M status in 9.1% ($N = 383$) of all cases included in stage stratified analyses.

Annual incidence and mortality rates and corresponding 95% confidence intervals (95% CIs) were calculated as crude and age-standardized rates per 100,000 person-years (PYs) for the age groups 20–39, 40–49 and 20–49 years. Based on the internationally accepted International Association of Cancer Registries (IACR) method, incidence was calculated by counting all primary BC tumours rather than the number of patients with a first primary BC [23]. Age-standardized rates were calculated using the direct method (European standard) [24]. Annual percentage changes (EAPC) were estimated by fitting a regression line to the natural logarithm of the age-standardized rates using calendar year as continuous predictor variable. In addition, a sensitivity analysis was conducted excluding the two CRs with late entry (FR and JU). Relative survival (RS) was estimated by dividing the observed survival after diagnosis by the survival as expected in the general female population of corresponding age and calendar year. Observed survival (OS) was estimated based on transformation of the cumulative hazards. For estimating expected survival, the Ederer II method was used [25]. The expected survival probabilities are based on extrapolated and smoothed age-, calendar year- and canton-specific death rates of the female population.

Crude survival was age standardized using the age-distribution of newly diagnosed cases in 2006–2009 as reference population [25]. Confidence intervals for standardized estimates were calculated according to the method described by Corazziari et al. [26] Follow-up information was available up to the end of 2011. Living cases with last available follow-up date before December 31st 2011 were considered to be lost to follow-up.

RS was estimated using complete analyses including all incidence cases of the pooled dataset and follow-up information from 1996 to 2011 [25]. Age-standardized OS and RS probabilities were calculated for consecutive time intervals up to 10 years after diagnosis for all stages combined and stratified by stage (age groups 20–39, 40–49 and 20–49 years).

## Results

### *Breast cancer incidence*

The contribution of incident BC cases by CR is shown in Table 1. The pooled dataset included 8842 female breast cancer cases, 2065

**Table 1**
Contribution of breast cancer cases to the pooled incidence dataset from eleven Swiss cancer registries.

| CR | Diagnosis period | Cases (*N*) | % Of pooled data |
|---|---|---|---|
| BS/BL | 1996–2008 | 674 | 7.6 |
| FR | 2006–2009 | 191 | 2.2 |
| GE | 1996–2009 | 1075 | 12.2 |
| GR/GL | 1996–2009 | 386 | 4.4 |
| JU | 2005–2009 | 43 | 0.5 |
| NE | 1996–2009 | 358 | 4.0 |
| SG/AR/AI | 1996–2009 | 800 | 9.0 |
| TI | 1996–2009 | 702 | 7.9 |
| VD | 1996–2009 | 1517 | 17.2 |
| VS | 1996–2009 | 569 | 6.4 |
| ZH | 1996–2009 | 2527 | 28.6 |

(23.4%) were women aged 20–39 years and 6777 (76.6%) women aged 40–49 years. Changes in stage distribution at time of diagnosis for the time period 1996–2009 (grouped by 3–5 incidence years) are shown in Fig. 1. Trends in age-standardized BC incidence rates (ASIRs) are presented in Fig. 2 and corresponding EAPCs in Table 2.

In women aged 20–49 years, ASIRs increased from 57.4 (95% CI 52.5–62.5) per 100,000 PYs in 1996 to 68.3 (95% CI 63.4–73.6) per 100,000 PYs in 2009, corresponding to an EAPC of 0.8% (95% CI 0.3–1.2, $p < 0.01$). There were statistically significant increases in both age groups, but the largest increase occurred in the age group 20–39 years (EAPC 1.8%, 95% CI 0.6–2.9, $p < 0.001$). Exclusion of the two CRs with late entry (CR FR and JU) led to almost identical results in incidence trends.

Analyses by age-group and stage revealed no significant differences in stage distribution between women aged 20–39 years and 40–49 years ($p > 0.05$). Respectively, stage by age-group was 46.0% versus 50.2% local, 44.2% versus 40.7% regional, 2.5% versus 4.2% distant and 7.3% versus 4.9% for cases without stage information. Furthermore, we detected no time trends in incidence proportions by stage, within age-groups, or for age-groups combined.

*Breast cancer mortality*

Trends in BC mortality by age group are shown in Fig. 3 and corresponding EAPCs in Table 3.

Between 1996 and 2009, 393 (21.2%) breast cancer deaths were observed in women aged 20–39 years and 1463 (78.8%)in women aged 40–49 years resulting in a total of 1856 deaths. Age-standardized mortality rates (ASMRs) in the study population decreased since 1996, falling from 10.2 (95% CI 8.6–11.9) to 6.2 (95% CI 5.1–7.4) per 100,000 PYs in 2009 with an EAPC of 3.5% (95% CI −4.5 to 2.5, $p < 0.001$). The decreases in BC mortality were consistent across age groups.

*Breast cancer survival*

The contribution of BC cases by CR for survival analyses are listed in Table 4. Fig. 4 illustrates differences in RS by follow-up period and age group (all stages combined). Stage-stratified

**Table 2**
Annual percentage changes in breast cancer incidence, time period 1996–2009, age-groups 20–39, 40–49 and 20–49 years.

| Age groups in years | ASIRs per 100,000 PYs (95% CI) | | EAPC [95% CI] | *p*-value |
|---|---|---|---|---|
| | 1996 | 2009 | | |
| 20–39 | 17.3 [14.3; 20.8] | 24.6 [21.0–28.8] | 1.8 [0.6; 2.9] | <0.001 |
| 40–49 | 137.4 [124.4; 151.4] | 155.7 [143.0–169.6] | 0.5 [0.0; 0.9] | 0.042 |
| 20–49 | 57.4 [52.5; 62.5] | 68.3 [63.4–73.6] | 0.8 [0.3; 1.2] | 0.003 |

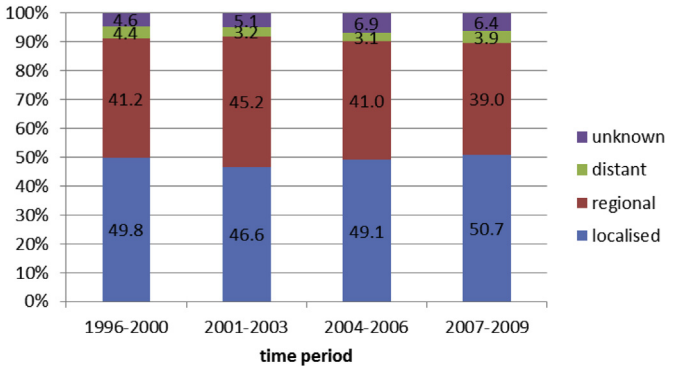


**Fig. 1.** Distribution of incident breast cancer cases by SEER summary stage by time period, age-group 20–49 years.

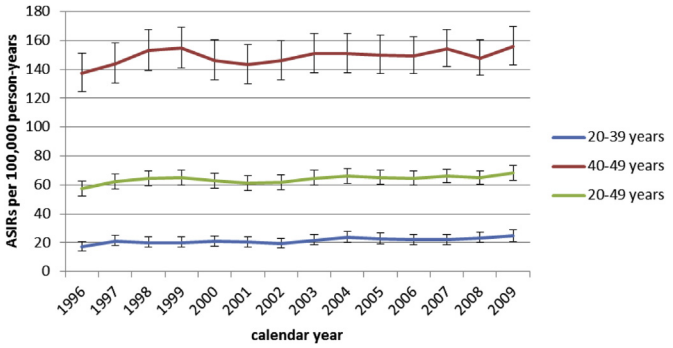


**Fig. 2.** Age-standardized incidence trends (ASIRs) in breast cancer, time period 1996–2009, age-groups 20–39, 40–49 and 20–49 years.

**Table 3**
Annual percentage changes in breast cancer mortality, time period 1996–2009, age-groups 20–39, 40–49 and 20–49 years.

| Age groups in years | ASMRs per 100,000 PYs [95% CI] | | EAPC (95% CI) | *p*-value |
|---|---|---|---|---|
| | 1996 | 2009 | | |
| 20–39 | 3.0 [1.9; 4.0] | 1.6 [0.9; 2.5] | −3.7 [−5.6;−1.7] | 0.001 |
| 40–49 | 24.8 [20.7; 29.6] | 15.3 [12.4; 18.7] | −3.5 [−4.8;−2.2] | <0.001 |
| 20–49 | 10.2 [8.6; 11.9] | 6.2 [5.1; 7.4] | −3.5 [−4.5;−2.5] | <0.001 |

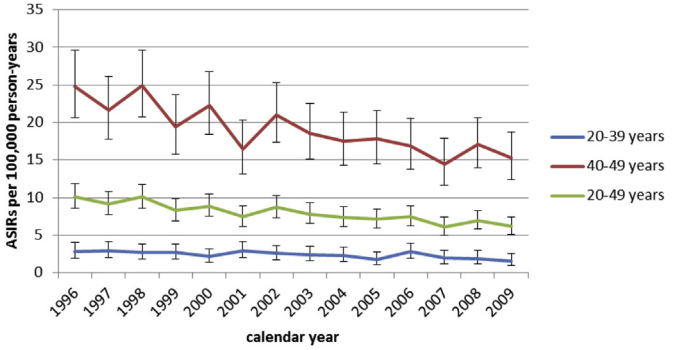


**Fig. 3.** Age-standardized mortality trends (ASMRs) in breast cancer, time period 1996–2009, age-groups 20–39, 40–49 and 20–49 years.

**Table 4**
Contribution of breast cancer cases to the pooled dataset from 11 Swiss CRs for survival analyses (all stages combined and stage-stratified analyses).

| CR | Diagnosis period | All stages | | | Stage-stratified (stage information available) | | |
|---|---|---|---|---|---|---|---|
| | | Cases (*N*) | Person-years (PY) | % Of pooled PY | Cases (*N*) | Person-years (PY) | % Of pooled PY |
| BS/BL | 1996–2008 | 650 | 4366 | 12.5 | 626 | 4258 | 12.8 |
| FR | 2006–2009 | 191 | 530 | 1.5 | 189 | 524 | 1.6 |
| GE | 1996–2009 | 1071 | 6751 | 19.4 | 1023 | 6497 | 19.5 |
| GR/GL | 1996–2009 | 384 | 2162 | 6.2 | 375 | 2119 | 6.4 |
| JU[a] | 2005–2009 | – | – | – | – | – | – |
| NE | 1996–2009 | 334 | 2377 | 6.8 | 279 | 2061 | 6.2 |
| SG/AR/AI | 1996–2009 | 794 | 5261 | 15.1 | 774 | 5119.5 | 15.3 |
| TI | 1996–2009 | 701 | 4247 | 12.2 | 683 | 4151 | 12.4 |
| VS | 1996–2009 | 567 | 3969 | 11.4 | 546 | 3807 | 11.4 |
| VD | 1996–2009 | 1482 | 5127 | 14.7 | 1370 | 4864 | 14.6 |
| ZH[b] | 1996–2009 | – | – | – | – | – | – |

[a] No vital status follow-up.
[b] No stage information, incomplete follow-up information.

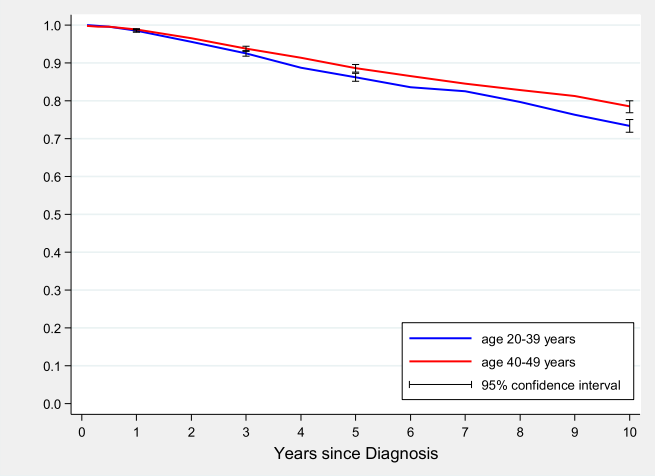


**Fig. 4.** Relative survival by age-group, time period 1996–2009, follow-up period 1996–2011 based on CRs providing vital status follow-up (10 out of 11 CRs).

survival figures in women aged 20–39, 40–49 and 20–49 years are presented in Table 5.

Among cases with follow-up within 5 years post-diagnosis, 82.1% were still alive, 12.4% had died and 5.5% were lost to follow-up. At 10 years post-diagnosis 62.5% were alive, 26.8% had died and 10.7% were lost to follow-up. For all stages combined, RS in women aged 20–49 years was 98.8% (95% CI 98.4–99.0) after one year, 93.5% (95% CI 92.8–94.2) after three years, 88.1% (95% CI 87.1–89.0) after five years and 77.3% (95% CI 75.7–78.9) after ten years since diagnosis. Overall, 10-year RS was lower among women aged 20–39 years (73.4%; 95% CI 71.1–75.0) than women aged 40–49 years (78.5%; 95% CI 76.9–80.1).

Ten years after diagnosis, RS by stage was 89.8% (95% CI 87.9–91.4) for the localized stage, 70.6% (95% CI 67.8–72.2) for the regional stage and 19.6% (95% CI 12.8–27.5) for the distant stage. Cases with unknown stage had showed a 10-year RS of 60.3% (95% CI 50.4–68.8).

Analyses by age-group and stage revealed lower survival for women aged 20–39 years than women aged 40–49 years for all stages. Respectively, 10-year RS by stage was 86.1% (95% CI 83.9–88.1) versus 90.7 (95% CI 88.8–92.3) local, 65.1% (95% CI 62.1–67.9) versus 72.7% (95% CI 69.8–75.4) regional and 14.1 [95% CI 3.8-30.9] versus 21.2 [14.2-29.2] distant. However, cases without stage information showed reversed results with RS of 73.1% (95% CI 66.7–78.4) in women aged 20–39 years versus 56.1% (95% CI 44.8–66.0) in women aged 40–49 years.

## Discussion

### *Summary of main findings*

Our findings confirm a slight increase in the incidence of invasive BC in younger Swiss women during the period 1996–2009. The

**Table 5**
Observed (OS) and relative survival (RS) by stage (complete analyses), incidence years 1996–2009, follow-up period 1996–2011.

| | *N*[a] | 1-year survival | | 3-year survival | | 5-year survival | | 10-year survival | |
|---|---|---|---|---|---|---|---|---|---|
| | | OS% | RS%[a] [95% CI] | OS%[a] | RS%[a] [95% CI] | OS% | RS%[a] [95% CI] | OS%[a] | RS%[a] [95% CI] |
| Age 20–39 | | | | | | | | | |
| Localized | 669 | 99.8 | 99.9 [99.5; 100.0] | 96.7 | 96.9 [96.0; 97.6] | 93.2 | 93.5 [92.3; 94.6] | 85.5 | 86.1 [83.9; 88.1] |
| Regional | 646 | 98.4 | 98.4 [97.8; 98.9] | 90.7 | 90.9 [89.6; 92.0] | 83.1 | 83.4 [81.6; 85.0] | 64.7 | 65.1 [62.1; 67.9] |
| Distant | 36 | 83.5 | 83.5 [76.0; 88.9] | 48.5 | 48.5 [39.4; 57.1] | 18.6 | 18.7 [6.4; 36.0] | 14.0 | 14.1 [3.8; 30.9] |
| Unknown | 97 | 96.7 | 96.7 [94.3; 98.1] | 88.8 | 88.9 [85.1; 91.9] | 80.4 | 80.6 [75.5; 84.7] | 72.6 | 73.1 [66.7; 78.4] |
| Age 40–49 | | | | | | | | | |
| Localized | 2384 | 99.6 | 99.8 [99.4; 99.9] | 97.6 | 98.0 [97.2; 98.5] | 94.3 | 95.0 [93.9; 96.0] | 89.0 | 90.7 [88.8; 92.3] |
| Regional | 1932 | 99.2 | 99.3 [98.8; 99.6] | 92.9 | 93.3 [92.1; 94.4] | 86.6 | 87.3 [85.5; 88.8] | 71.4 | 72.7 [69.8; 75.4] |
| Distant | 198 | 85.8 | 85.9 [80.5; 89.9] | 55.8 | 56.0 [48.4; 63.0] | 40.1 | 40.4 [32.7; 48.0] | 20.7 | 21.2 [14.2; 29.2] |
| Unknown | 212 | 94.8 | 95.0 [91.1; 97.2] | 85.9 | 86.3 [80.4; 90.5] | 71.6 | 72.1 [64.2; 78.6] | 55.1 | 56.1 [44.8; 66.0] |
| Age 20–49 | | | | | | | | | |
| Localized | 3053 | 99.7 | 99.8 [99.4; 99.9] | 97.4 | 97.8 [97.1; 98.4] | 94.3 | 94.9 [93.8; 95.8] | 88.3 | 89.8 [87.9; 91.4] |
| Regional | 2578 | 99.1 | 99.2 [98.7; 99.5] | 92.7 | 93.1 [91.9; 94.1] | 86.1 | 86.7 [85.0; 88.2] | 69.4 | 70.6 [67.8; 72.2] |
| Distant | 234 | 85.4 | 85.5 [80.0; 89.5] | 55.5 | 55.7 [48.6; 62.2] | 35.1 | 35.3 [28.4; 42.4] | 19.2 | 19.6 [12.8; 27.5] |
| Unknown | 309 | 95.3 | 95.4 [92.0; 97.4] | 86.9 | 87.2 [82.0; 90.0] | 73.7 | 74.2 [67.2; 80.0] | 59.4 | 60.3 [50.4; 68.8] |

[a] Based on CRs providing stage information (9 out of 11 CRs).

increase was primarily in women aged 20–39 years. Survival among women diagnosed with BC aged 20–39 years was lower than survival among women aged 40–49 years. Despite this fact, mortality decreased in both age groups with similar EAPCs between 1996 and 2009. We observed no notable differences in stage of disease at diagnosis by time period that might explain these differences in mortality. The increased incidence and lower survival in the youngest women diagnosed with BC in Switzerland indicates possible differences in risk factors, tumour biology and treatment characteristics that require additional examination. Although the overall number of women affected by BC at an early age is considerably less than those in later years, the impact is certainly not less in the context of potential years lost.

*Findings in context with the literature*

These increased incidence findings among young Swiss women are consistent with data from other European and American CRs [11–13,27]. For example, a study based on SEER data from US found a comparable trend with an increase of 1.3% per year for the period 1992–2004, among white US women less than 40 years old [11]. The canton-specific data from Switzerland, however, has been less definitive. Our study is the first nationally representative population-based sample. The increase in incidence we found was considerably less than reported by Bouchardy et al. and more in line with findings from Levi et al. [9,10] Both previous studies indicated that detection bias may be contributing to Swiss increases although screening is seldom recommended for women less than 50 years old. Unfortunately, we were unable to investigate effects of screening on our findings because we had no information on detection methods.

This increase in BC incidence among younger women seems to be a relatively recent one. Earlier publications reported stable BC incidence. For example, Tarone et al. found no increase in BC incidence in US women under the age of 50 years between 1975 and 2002 [28]. This change in BC incidence may be, at least in part, attributable to increased BC awareness and detection in most developed countries over the past decade.

Women's risk of developing BC is multifactorial. It depends on genetic factors, family history, hormone exposures, reproductive history and lifestyle-related factors. Changes in the prevalence and characteristics of these risk factors over time may influence incidence rates within a society. For example, early age at menarche has been associated with an increased risk of BC [29]. Increasing incidence may also be the consequence of other reproductive factors like age at first birth, parity and breastfeeding. Data have shown that BC risk decreases with younger age at first birth, higher number of births and breastfeeding [30,31]. European countries have experienced a decline in the number of births per woman and a simultaneous increase in age at first birth [32]. Other risk factors like hormone exposures (e.g. earlier and more frequent use of hormone containing contraceptives) and lifestyle-related factors (e.g. increasing prevalence of alcohol consumption), to name a few, may also have contributed to the recent increase in BC incidence [33–35]. Unfortunately our study had no information on BC risk factors.

Despite the increase in incidence, BC mortality rates in Switzerland decreased in younger women. This is encouraging because other studies have shown that younger women are often diagnosed with tumours that have poorer prognostic features compared to their older counterparts (e.g. larger tumour sizes, advanced stage, lymph node involvement, poor differentiation, high proliferation rate, negative hormone receptor status, human epidermal growth factor receptor 2 [HER2]) [20,36–38]. Tumour biology and treatment characteristics are important factors that can influence BC mortality and survival. Further, access to more effective treatments and better tumour response have been shown to be associated with better BC outcomes specifically in younger women [39,40]. Similarly to a Swedish study conducted by Fredholm et al., we found lower survival in the youngest age group regardless of stage [16]. Fredholm et al. reported poor survival in women less than 35 years old diagnosed early and receiving intensive treatment, suggesting that tumour biology may play an important role in differences of BC prognoses among younger women. The current study did not have information on BC detection methods but found no evidence that findings were attributable to changes in stage distribution over the follow-up period. The lack of tumour and treatment information limited assessment of their potential contribution to our mortality and survival findings.

*Strengths and weaknesses*

The large population-based study sample allows generalizability of findings to the national level. The large study size also resulted in sufficient precision to analyse BC in the younger age groups with the lowest incidence.

A major weakness of this study is the lack of information on treatment and risk factors. Also importantly we were unable to identify if diagnoses had increased as a result of screening. SEER summary stage was the only staging system available in this study. It is the most basic way of categorizing how far cancer has spread from its point of origin. It is conceivable that a more detailed staging system and/or information on tumour biology could have led to different results. However, more detailed TNM-staging was not available. Completeness of case ascertainment over time was assessed based on percentages of death certificate only (DCO) cases. Overall, the study population had less than 1% DCO for all years under investigation. Nevertheless, in some CRs a complete and systematic follow-up for DCOs was not carried out for all calendar years [41].

## Conclusions

This study shows a slightly increasing incidence of BC in younger Swiss women despite decreasing mortality over the same period. Changes in incidence, mortality and survival can be indicators of important underlying public health issues. Further investigations are needed to study this rise in incidence and to identify specific risk factors that may be influencing BC in younger women.

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## Conflict of interest statement

None of the authors has a conflict of interest.

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