

Effects of age and stage on breast cancer survival in Switzerland

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INTRODUCTION

Breast cancer is a public health priority in Switzerland as it represents the most common cancer in women. Each year, about 5'250 women develop breast cancer and 1'350 die from it¹. After increasing for several decades, the incidence rate became stable, and since 2003-2007, started to decrease as in other European countries and in the USA. With screening generalization and the progress made in treatment, the mortality has been constantly declining and survival improving. Switzerland ranks among the European countries with the best breast cancer prognosis².

Several factors are linked to breast cancer survival. Screening by mammography increases the precocity of diagnosis, thus improving the prognostic of the disease. The screening bias linked notably to an early diagnosis can also artificially increase survival. Stage and age at diagnosis are two major prognostics factors. The effects of stage at diagnosis on survival could differ according to age, and vice versa the impact of age on survival could depend on the stage of the disease. The two factors can also have different effects on short- and long-term (≥ 10 years) survival.

This study aims, for the first time in Switzerland, to assess concomitantly the effects of age and stage on short- and long-term relative survival rates using data from the Swiss population-based cancer registries.

METHODS

This study is based on cancer data of the National Core Dataset (NCD) managed by the National Institute for Cancer Epidemiology and Registration (NICER) for the purpose of national cancer monitoring in Switzerland³.

For this report, we used data from seven registries: Basel-Stadt and Basel-Landschaft (BS/BL), Fribourg (FR), Geneva (GE), Graubünden and Glarus (GR/GL), Ticino (TI), Valais (VS), and Zurich (ZH). Data from other cantons were not included if they did not provide survival data (Neuchâtel, Jura and Vaud), or information on tumour extent before 2009 (Appenzell Ausserrhoden, Appenzell Innerrhoden, and St. Gallen), or if they started cancer registration after 2008 (Lucerne, Nidwalden, Obwalden, Uri, Zug, and Thurgau).

Cases included in the study were all incident invasive primary breast cancers (International classification of disease in Oncology [ICDO] code: C50) diagnosed in women between 2003 and 2012, resident in the population covered by the seven cancer registries. The cantons BL, BS, and FR covered this time period only partially. The vital status was actively and/or passively followed-up until the end of the year 2012. We excluded all cases diagnosed at death (N=20) or with a death certificate as the only source of information (N=135). Case finding via death certificates was infrequent, <1% in each cancer registry. Patients with multiple primary tumours (16%) were included. Excluded were 258 cases because no active follow-up has been performed. Recent active follow-up was lacking for 5'137 cases (i.e. last date of follow-up <12.2012 with vital status alive). The vital status of these cases was set lost to follow-up using the date of last contact. Because we did not assume survival up to 31.12.2012 in the absence of reported death (i.e. based on passive follow-up), our survival estimates will be conservative. Using the assumption of survival in the absence of reported death could overestimate survival due to incomplete registration of deaths. The final study included 22'976 cases representing 98% of all breast cancer patients. Completeness of case ascertainment for breast cancer was estimated with the mortality-incidence ratio (MIR).

The stage of breast cancer was classified according to the Tumour Node Metastasis [TNM] classification based on pathological, and when absent, on clinical information⁴. We regrouped stages in five groups: stage I, II, III, IV, and unknown. When no information was available for metastasis, we assumed that there was none.

For survival analysis, we selected all 21'721 patients who had a follow-up between 2008 and 2012⁵. The relative survival (RS) was derived for consecutive time intervals of increasing length after diagnosis during which the mortality hazard ratios were assumed to remain constant. Temporal divisions were 0.05, 0.2, 0.4, 0.6, 1, 2, 3, 4, 5, 6, 8, and 10 years. RS was calculated as the ratio of the observed survival of cancer cases and the expected survival of persons in the general popula-

tion after matching for age, sex, calendar year of death, and cantonal pool⁶. Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables for the cantons combined⁷. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated and smoothed using the Elandt-Johnson formula⁸. RS ratios were estimated using the «strs» command (version 1.4.0) written for the Stata Statistical Software^{9,10}. RS estimates were age-standardized using the International Cancer Survival Standards (ICSS) weights for breast cancer 11. Confidence intervals at 95% (95% CI) were estimated by applying the delta method to a transformation of the cumulative hazard. For age-standardized RS, 95% CI were estimated as described¹¹.

RESULTS

The cohort included 22'976 breast cancer patients recorded between 2003 and 2012 by seven population-based registries which covered approximately 45% of the Swiss population. Table 1 presents the distribution of breast cancer patients by stage according to period of diagnosis, age and cancer registry. The registry of ZH, the largest in Switzerland, accounted for 40% of breast cancer patients. The median age at diagnosis was 63 years. It remained relatively stable during the study period. The age

at diagnosis was slightly lower (60-62 years) in French-speaking cantons (GE, FR, VS) than among the German and Italian-speaking ones (63-65 years). The median age at diagnosis increased with stage: 61 years for stage I, 63 years for stage II, 64 years for stage III, and 68 years for stage IV breast cancer (Table 1). Also, patients with missing stage (median age 81) were much older than patients with known disease extent.

Overall, 39% of women presented a stage I breast cancer, 35% a stage II, 15% a stage III, and 6% a stage IV. The proportion of women with a missing stage was low overall (5%), and varied between registries from 3.3% in GE to 7.5% in BS/BL. Stage distributions were generally more favourable for women aged 50-69 years (the 'screened age group'), who presented the largest proportion of stage I disease (46%). Older women were more likely to have metastatic disease than younger women (8% for age 70+ years versus 4% for age 0-49 years). We observed a slight increase over time for age-standardized rates of stage I disease (36 per 100'000 in 2003 to 43 per 100'000 in 2012) and a slight decrease of stage III (17 per 100'000 in 2003 to 10 per 100'000 in 2012) and unknown stage (5 per 100'000 in 2003 to 3 per 100'000 in 2012). The stage I breast cancers were more frequently observed in French-speaking cantons than in the German and Italian-speaking ones: 45% - 48% for GE, VS, FR versus 31% - 40% for ZH, BS/BL, TI, GR/GL.

Table 1: Distribution of primary malignant breast cancer patients by year of diagnosis, age at diagnosis, Swiss cantonal cancer registry, and stage.

	Stage I				Stage II				Stage III				Stage IV				Stage missing				All patients			
	Median age	N	%	rate*	Median age	N	%	rate*	Median age	N	%	rate*	Median age	N	%	rate*	Median age	N	%	rate*	Median age	N	%	
Year of diagnosis																								
2003	60.9	747	35.3	36.3	62.5	750	35.4	34.9	62.4	373	17.6	17.0	66.5	99	4.7	4.3	81.1	148	7.0	4.7	62.7	2117	9.2	
2004	60.8	826	38.7	39.6	61.5	757	35.4	35.0	62.5	331	15.5	14.6	68.2	107	5.0	4.4	80.5	116	5.4	3.8	62.2	2137	9.3	
2005	60.7	820	38.5	38.4	62.3	760	35.6	33.8	65.3	318	14.9	13.4	67.9	112	5.3	4.7	82.4	122	5.7	3.5	62.9	2132	9.3	
2006	60.4	907	38.9	39.7	62.8	766	32.8	31.6	63.5	365	15.6	14.5	64.1	132	5.7	5.3	79.6	164	7.0	4.8	62.9	2334	10.2	
2007	61.2	941	40.2	40.6	63.2	782	33.4	31.2	64.1	362	15.5	14.0	66.5	147	6.3	5.5	82.0	111	4.7	3.0	63.2	2343	10.2	
2008	62.3	927	37.3	38.5	62.5	914	36.7	36.9	64.7	405	16.3	15.7	70.2	120	4.8	4.3	82.1	122	4.9	3.2	63.7	2488	10.8	
2009	61.1	898	38.1	37.2	63.3	891	37.8	34.4	65.4	327	13.9	12.1	67.0	150	6.4	5.5	81.0	93	3.9	2.7	63.3	2359	10.3	
2010	61.1	1003	38.8	41.4	62.9	947	36.6	36.8	63.5	340	13.2	12.8	68.5	167	6.5	5.9	80.8	127	4.9	3.5	62.8	2584	11.2	
2011	62.4	936	41.7	41.1	63.3	779	34.7	32.7	63.4	293	13.0	12.3	69.4	139	6.2	5.4	82.1	99	4.4	2.9	63.5	2246	9.8	
2012	62.6	995	44.5	43.0	62.5	758	33.9	31.6	65.5	256	11.4	10.2	69.8	145	6.5	5.5	76.4	82	3.7	2.6	63.9	2236	9.7	
Age at diagnosis																								
0-49	45.1	1954	40.6		44.6	1826	37.9		44.3	738	15.3		44.7	193	4.0		42.9	106	2.2		44.7	4817	21.0	
50-69	61.0	4928	45.5		60.9	3710	34.2		60.9	1420	13.1		61.6	546	5.0		62.5	238	2.2		61.1	10842	47.2	
70+	75.9	2118	28.9		77.6	2568	35.1		79.3	1212	16.6		78.7	579	7.9		84.4	840	11.5		78.1	7317	31.8	
Cantonal cancer registry (Years of diagnosis)																								
ZH (2003-2012)	61.3	3239	35.6		62.9	3377	37.1		62.8	1526	16.8		67.4	500	5.5		80.4	457	5.0		63.1	9099	39.6	
GE (2003-2012)	61.2	1735	48.2		62.6	1155	32.1		62.3	404	11.2		66.7	186	5.2		80.5	120	3.3		62.3	3600	15.7	
BS/BL (2003-2010)	63.0	735	30.6		63.9	976	40.6		65.6	378	15.7		67.2	133	5.5		80.6	181	7.5		64.7	2403	10.5	
TI (2003-2012)	62.8	1119	39.9		63.8	971	34.6		65.5	351	12.5		68.6	193	6.9		78.1	174	6.2		64.4	2808	12.2	
VS (2003-2012)	61.0	963	44.8		60.3	709	33.0		65.6	286	13.3		72.4	93	4.3		83.3	100	4.6		62.2	2151	9.4	
GR/GL (2003-2012)	60.5	572	37.0		63.5	481	31.1		65.0	269	17.4		68.5	140	9.0		83.5	85	5.5		64.2	1547	6.7	
FR (2006-2012)	58.6	637	46.6		60.2	435	31.8		63.4	156	11.4		65.6	73	5.3		82.8	67	4.9		60.3	1368	6.0	
All patients	61.3	9000	39.2		62.7	8104	35.3		63.8	3370	14.7		67.5	1318	5.7		81.1	1184	5.2		63.1	22976	100	

*: Age-standardized rate (EU-Standard population) per 100'000

Years since diagnosis	Age at diagnosis	Stage I			Stage II			Stage III			Stage IV			Stage missing			All patients		
		Relative survival [%]	95% CI		Relative survival [%]	95% CI		Relative survival [%]	95% CI		Relative survival [%]	95% CI		Relative survival [%]	95% CI		Relative survival [%]	95% CI	
1 5 10	Age-standardized	100.4	100.1	100.6	99.8	98.2	100.0	95.9	94.5	96.9	76.3	73.0	79.2	90.2	86.3	93.0	97.1	96.6	97.5
		99.1	98.3	99.8	91.1	89.5	92.5	72.5	69.8	75.0	27.3	23.6	31.1	65.6	60.0	70.7	85.6	84.6	86.5
		94.5	82.3	98.4	75.8	70.2	80.5	42.7	36.1	49.2	9.3	5.0	15.4	49.6	41.4	57.3	69.6	66.6	72.4
1	0-49	99.9	99.3	100.0	99.9	99.3	100.0	99.0	97.1	99.7	89.2	81.3	93.9	98.1	86.5	99.8	99.3	98.9	99.6
	50-69	100.1	99.8	100.3	99.7	99.1	100.0	97.6	96.0	98.6	80.3	75.1	84.5	93.1	86.2	96.7	98.5	98.1	98.8
	70+	101.4	100.5	102.0	99.8	98.5	100.7	92.4	89.5	94.9	66.6	60.9	71.7	84.7	79.7	89.0	94.7	93.7	95.6
5	0-49	98.6	97.5	99.3	94.3	92.4	95.8	78.9	74.2	82.9	38.7	28.6	48.7	88.5	73.9	95.3	91.4	90.1	92.5
	50-69	97.9	96.9	98.7	93.7	92.2	95.0	77.5	73.9	80.6	32.0	26.3	37.9	67.9	58.0	76.0	89.7	88.7	90.6
	70+	102.5	99.8	104.9	87.6	84.3	90.7	63.9	58.8	68.8	20.1	14.9	26.1	58.7	51.6	65.9	79.4	77.4	81.4
10	0-49	95.6	91.6	98.0	88.8	84.7	92.0	55.7	44.4	65.6	13.3	6.0	23.7	80.2	60.5	91.1	82.3	79.0	85.2
	50-69	95.4	92.5	97.7	78.0	72.5	82.8	51.4	42.8	59.5	8.3	2.7	18.1	63.0	51.9	72.6	77.9	75.1	80.5
	70+	89.2	78.6	98.9	71.1	61.4	80.5	29.5	19.3	41.5	14.0	7.4	23.2	21.3	10.4	37.3	58.6	53.1	64.0

Table 2: Age-standardized and age-specific relative survival estimates for breast cancer in women, with 95% confidence intervals, stratified by years since diagnosis, and stage. Cases were selected by time of death or survival between 2008 and 2012 and pooled from seven cancer registries.

The survival analyses were based on 21'721 breast cancer patients representing 64'938 patient-years. The mean follow-up time was 1'625 days or 4.4 years (range 1 to 4'430 days). Overall, 5'350 patients were set lost to follow-up (which includes cases with incomplete active follow-up; see Methods) and 4'360 deaths were observed during the survival study period. The Table II presents the RS according to time since diagnosis, age, and stage. The RS of breast cancer patients was strongly associated to both stage and age at diagnosis. This is illustrated in Figure 1. The overall age-adjusted RS was 97% after 1 year (short-term survival), 86% after 5 years (medium-term survival), and 70% after 10 years (long-term survival).

The effect of stage

For non-metastatic breast cancer, stage had not a strong effect on 1-year RS. For stage I to III and age < 70 years, the 1-year RS was close to 100%. After 5 years, the effect of stage became more apparent. RS remained high and relatively close for stage I and II diseases (around 95%), but dropped to 78% for stage III disease. At 10 years, the difference by stage was even more evident. RS remained relatively close for stage I and II breast cancers (at least for women before the age of 70 years). Stage III breast cancer showed distinctly lower survival pattern (Table 2, Figure 1). For metastatic breast cancer the age-standardized RS was 76% at 1 year, 27% at 5 years, and 9% at 10 years. For missing stage, the RS curve was close to what observed for stage III breast cancer.

The effect of age

The relevance of age at diagnosis on survival was very clear when considering the difference in RS between age 0-49 years and 70 years and more. The age related differences become wider with increasing the follow-up time: the absolute difference of RS (all patients) between the oldest and the youngest age-groups was 4% at 1 year, 11% at 5 years, and 22% at 10 years survival. Also the RS differences by age increased with advancing stage: for the 5-year-RS the difference between the oldest and the youngest age groups was 4% for stage I, 7% for stage II, 15% for stage III, and 19% for stage IV.

The effect of age on RS was small for stage I breast cancer at 1, 5, and 10 years after diagnosis. For stage II the effect of age was observed mainly on long term RS, while for stage III, age affected short-, medium- and long-term RS. For metastatic breast cancer, the effect of age was evident for 1 and 5 years-RS with no clear pattern at 10 years. For missing stage the effect of age was observed whatever the delay after diagnosis, with 59% age-related survival gap at 10 years after diagnosis (Table 2).

RS among young women aged < 50 years was very close and even better to that observed for women aged 50-69 years whatever the stage and the delay since diagnosis (Table 2).

Elderly patients clearly experienced worse RS. This was true for stage I long-term RS, for stage II medium- and long-term RS, for stage III short-, medium-, and long-term RS, and for metastatic BC short- and medium-RS with no clear pattern for long-term RS.

For missing stage, RS was close to that observed for stage III breast cancer except among women < 50 years for whom RS of missing stage was between stage II and stage III breast cancer (Table 2, Figure 1).

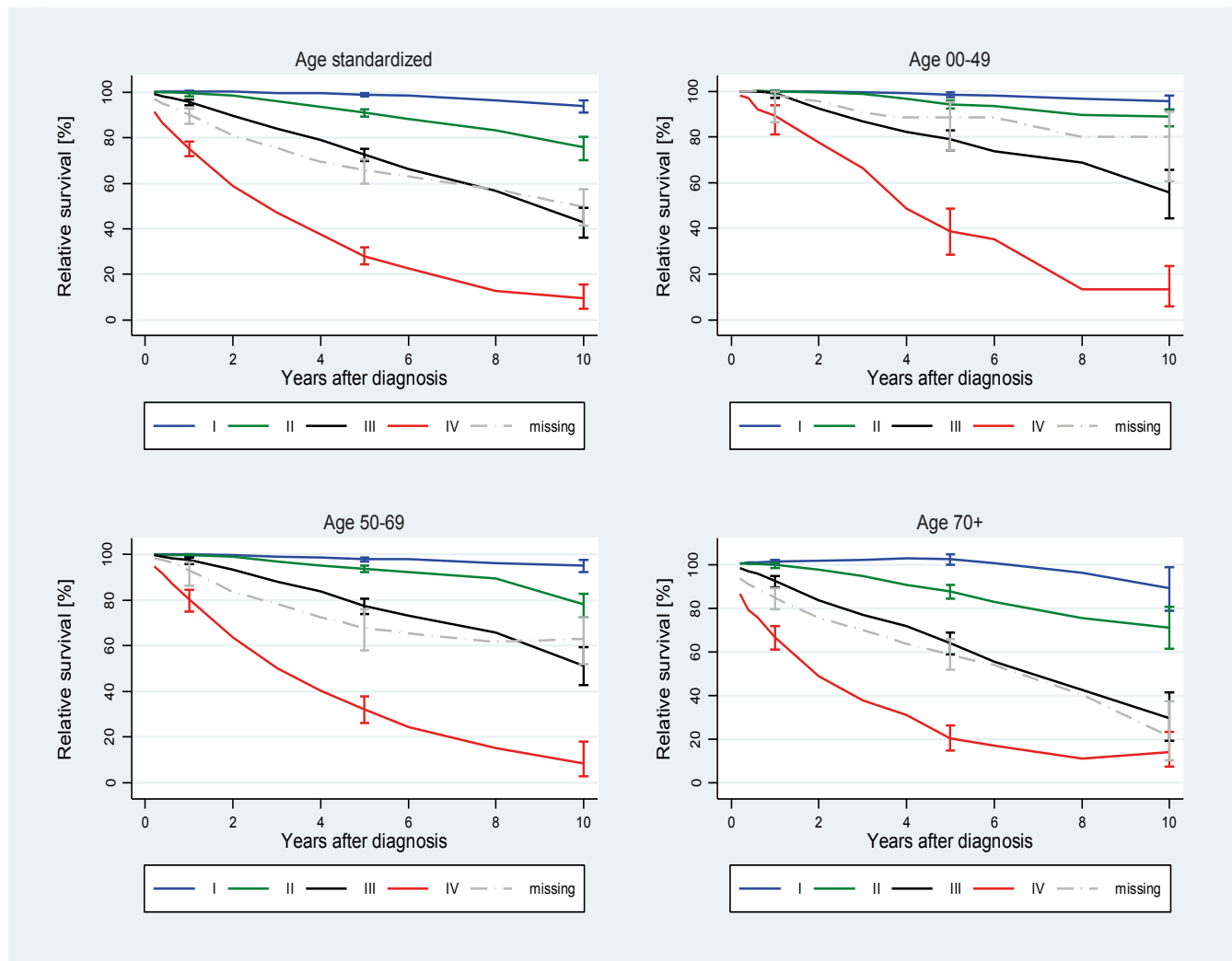
DISCUSSION

This Swiss population-based study on invasive breast cancer shows the effects of age and stage on short-, medium-, and long-term RS after invasive breast cancer. We found that overall 40% of patients were diagnosed at stage I disease. This proportion was higher in the French-speaking cantons which have all implemented mammography screening and where mammography screening coverage is higher than in the German and Italian-speaking cantons¹². Stage I breast cancer shows excellent survival even at long term and in each age-group studied. The survival for stage II breast cancer, although lower, is relatively close to that observed for stage I. In counterpart, patients diagnosed with stage III and IV disease have clearly worse prognosis whatever the age at diagnosis. In addition to stage, age has also an important effect on RS. We observed that survival in young women (<50 years) is now similar and often better than among women aged 50-69 years. In contrary and as ex-

pected, the elderly patients present poorer survival in particular for advanced stage and long-term follow-up.

Breast cancer survival in Switzerland is high as compared to the rest of Europe. The EURO CARE-5 study, which analysed survival of cancer patients diagnosed up to 2007 in 29 European countries/regions, estimated the mean 5-year RS for breast cancer to be 82%. Switzerland, whose data were based on six Swiss cancer registries, had a RS of 85%, the highest rate of all¹³. In the present study, which includes more patients in a more recent period of time (2008-2012), the age-standardized 5-year RS including all stages was 86%.

Figure 1. Relative survival curves with 95% confidence limits at 1, 5, and 10 years after the diagnosis of breast cancer by age- and stage-groups. Age standardized RS is based on age-specific weights for breast cancer defined by the International Cancer Survival Standards (ICSS).



Early detection of breast cancer is mainly due to the generalisation of breast cancer screening. In Switzerland there is a great disparity in mammographic screening use between the French-speaking and the German and Italian-speaking regions¹². In particular, since the beginning of the year 2000, the French-speaking cantons, have all implemented population breast cancer screening programs according to the international recommendations of quality and efficacy controls while few German and Swiss Italian cantons started screening programs only recently. In this study, the proportion of early stage (stage I) is higher in French speaking population. Despite marginal controversies on screening efficacy and adverse effects, mammography screening is still internationally recommended as effective at least for women aged 50 to 69 years¹⁴. Swiss disparities in diagnostic precocity should be avoided by national screening strategies of high quality.

In our study, we found that elderly women with breast cancer have particularly poor prognosis as compared with younger women. This has been already observed in Geneva, in Switzerland, as well as in numerous other countries in Europe and the USA¹⁵⁻¹⁷. This lower survival is attributed to late detection, incomplete investigation including staging assessment and a substantial under-use of optimal treatment. The proportion of both later stage at diagnosis and unknown stage were particularly high in elderly breast cancer patients. Among the reasons at the origin of under-treatment of elderly patients were the higher prevalence of comorbidities, the lowered life expectancy, the absence of data on treatment efficacy in clinical trials, and the increased adverse effects of treatment. But under-treatment among elderly patients were also linked to subjective beliefs such as putative lower benefits of treatment, a less aggressive nature of cancer, lower patient's compliance due to social marginalization, and physician's preference¹⁷. The under-treatment in older cancer patients is responsible of a non-negligible number of preventable cancer deaths. Treatments have to be adapted to the older patient's general health status, but should also offer the best chance of cure in Switzerland as well as in other countries.

Breast cancer in young women is thought to be more aggressive and to have worse prognosis but results from clinical research have been neither consistent nor definitive. In our study, we report that women younger than 50 years old have equal and even better survival than older women which confirms the results of a previous report from the Geneva Cancer Registry¹⁸. In this study young women were more likely to receive aggressive therapy, in particular chemotherapy. The study concluded that young age per se is not an independent prognostic factor when accounting for breast tumour characteristics and treatment.

This observational study on breast cancer survival has several limitations. First, it is based on seven cancer registries which have different facilities to access clinical information for staging and survival assessment. We regrouped all the cancers registries despite the fact that some heterogeneity certainly exists between cantons in terms of quality, access to screening, and optimal treatment and survival^{19,20}. We investigated the completeness of case ascertainment for breast cancer using the mortality-incidence ratio (MIRs). MIRs were determined for consecutive 5-year intervals from 1987 to 2011 for each cancer registry and provided no evidence for under-registration. We also observed that the proportion of unknown stage is low and quite similar between registries. But patients with missing stage show low RS estimates in the range of patients with stage III disease, indicating they are not randomly distributed across registries, age and stage. Patients with missing stage also showed large age-related survival gaps (59% in the case of 10-year RS), indicating that reasons for missing stage at different age at diagnoses might be very heterogeneous. It is thus likely, that stage-specific RS values are biased to a degree which is difficult to assess, though expected to be small because of the low proportion of such cases. Also, several factors could not be taken into account in our analysis in particular the way of detection (screening versus other), characteristics of tumour, treatment, comorbidities, and socioeconomic status which have all been shown to have a strong impact on breast cancer survival.

This analysis is a first step towards more detailed survival analyses of breast cancer survival in Switzerland. Further studies are needed to analyse in more detail the determinants of survival of breast cancer in Switzerland taking into account quality of cancer registration as well as other prognostic factors such way of discovery and treatments. Only then will it be possible to interpret the results more precisely in order to implement adequate public health actions.

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*For additional information on cancer in Switzerland, please see the NICER website at <http://nicer.org/>

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