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# BMJ Open

## Breast cancer mortality reduction predominantly driven by progress in management

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## TITLE

Breast cancer mortality reduction predominantly driven by progress in management

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## 19 ABSTRACT

20 **Objectives:** In the past decades, mortality due to breast cancer importantly declined in  
21 Switzerland and other developed countries. The reasons for the decline remain controversial as  
22 several factors including important advances in treatment approaches, breast cancer awareness and  
23 the introduction of mammography screening programs in many European countries occurred almost  
24 simultaneously. In Switzerland, mammography programs exist in some regions for over 20 years,  
25 while in others do not exist yet, thus offering the possibility to analyse its effects with modern spatio-  
26 temporal methodology.

27 **Setting:** Switzerland

28 **Participants:** The study covers breast cancer deaths of the female population of Switzerland in  
29 the period 1969-2012. Data were retrieved from the Swiss Federal Statistical office (FSO) aggregated  
30 on small-area level.

31 **Design:** We fitted Bayesian hierarchical spatio-temporal models on death rates indirectly  
32 standardized by national references. We used linguistic region, degree of urbanisation, duration of  
33 population based screening programmes and socio-economic index as covariates.

34 **Results:** In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and  
35 declined strongly thereafter. Until 2009-2012, the standardized mortality ratio (SMR) declined to 57%  
36 (95% CI 54% to 60%) of the 1969-1972 value. None of the other coefficients of the spatial regressions  
37 had a significant effect on breast cancer mortality. In 2009-2012, no region had significantly elevated  
38 or reduced breast cancer mortality at 95% CI (Credible Interval) level compared to the national mean.

39 **Conclusion:** There was a strong reduction of breast cancer mortality from the 90s on. No  
40 important spatial disparities were observed. The moderate geographical differences we found are  
41 within credible intervals using modern Bayesian techniques. The factors studied (urbanisation,



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3 42 language, duration of population based screening programme and socioeconomic characteristics) did  
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5 43 not seem to have an influence on them.  
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## 9 44 **ARTICLE SUMMARY**

### 10 45 **What is already known on the subject?**

11  
12  
13  
14 46 Breast cancer mortality declined in the past decades, and we showed geographical disparities in  
15  
16  
17 47 a previous study in Switzerland. But it was not clear what the impact of mammography screening  
18  
19 48 programmes was, especially after implementation of more effective therapies since the first studies  
20  
21 49 on screening effectiveness.  
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### 23 50 **What does this study add?**

24  
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26  
27 51 On population level, the current duration of mammography screening programmes have no  
28  
29 52 significant impact on mortality differences in Switzerland. Also any other investigated factors were  
30  
31 53 outweighed by the overall mortality trend mainly driven by progress in cancer management.  
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### 33 54 **Strengths and limitations**

- 34  
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37 55 • Strengths of Bayesian spatial models are their improvement of estimation of an unstable rate  
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39 56 by “borrowing” strength from its neighbours,  
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41 57 • And they can also assess the significance of risk factors taking into account the geographical  
42  
43 58 correlation  
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45 59 • A limitation of the study is that data on the geographical differences in opportunistic  
46  
47 60 screening use and overall screening participation are not available,  
48  
49  
50 61 • the ecological study design does not allow assessing the combined impact of participation in  
51  
52 62 and type (program vs. opportunistic) of mammography screening,  
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54 63 • and we had to group into 0-4 and 5+ years of screening in order to avoid overfitting issues.  
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## 64 INTRODUCTION

65 In Switzerland, breast cancer is the most frequently diagnosed cancer in women[1], the leading  
66 cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. In the past  
67 decades, mortality due to breast cancer importantly declined in Switzerland and other developed  
68 countries[4]. The reasons for the decline remain controversial as several factors including important  
69 advances in treatment approaches, breast cancer awareness and the introduction of mammography  
70 screening programs in many European countries occurred almost simultaneously.

71 Some randomized controlled studies[5] have demonstrated a breast cancer mortality reduction  
72 of 20% for women invited to breast cancer screening. However, they were conducted in the 1970-80s  
73 and since then many advances in therapies have been made, so that some authors doubt that the  
74 difference would persist under present conditions. Therefore, often used historical prescreening  
75 control groups are not best suited to disentangle these effects. Autier et al [6] compared countries in  
76 Europe but a criticism was, that different countries may have different health systems. Kalager et  
77 al[7] used comparison groups in Norway and showed that only a third of total mortality reduction  
78 could be attributed to mammography screening, but used a short observation period. Also, in a  
79 setting, where voluntary screening is assumed to be high, it is unknown what the effect of an  
80 organised screening program would be for the population as a whole.

81 In Switzerland with its homogenous health system these pitfalls can be avoided. Switzerland is a  
82 small confederation of 26 relatively autonomous states called cantons with somewhat low  
83 inequalities[8] and high health and cancer related resources.[9-11] However, some health care  
84 policies are developed at cantonal level; in particular, the decision to initiate a population based  
85 mammography-screening programme. These programmes were implemented in Switzerland at  
86 different time points over the past two decades. The first Swiss mammography pilot programme was  
87 established in 1993 within the French-speaking canton of Vaud but it was only in 2010 that the first  
88 organised programme in a German-speaking canton (St. Gallen) started.

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3 89 In breast cancer incidence cantonal differences are well known and have been attributed to  
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5 90 differential use of opportunistic or organized mammography screening[12]. In addition, considerable  
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7 91 differences in health and health related behaviour –affecting the risk of breast cancer– have been  
8  
9 92 reported for the Swiss language regions including alcohol intake, smoking and healthy diet[13 14].  
10  
11 93 Differences in access to mammography screening and in lifestyle may be reflected in spatio-temporal  
12  
13 94 differences of both, breast cancer incidence and mortality, whereas only the latter will reflect the  
14  
15 95 management of breast cancer.

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17  
18 96 In contrast, breast cancer mortality studies in Switzerland showed contradictory results. Bulliard  
19  
20 97 et al[15] observed a steeper decrease in 1980-2002 in 55-74 year olds in French-speaking regions  
21  
22 98 where population based mammography screening started earlier. In a recent study[16] we presented  
23  
24 99 the spatio-temporal trends of female gender related cancer mortality in Switzerland by age group.  
25  
26  
27 100 The geographical differences found were small. We observed a differential decline in breast cancer  
28  
29 101 mortality by age. Decline was highest in women younger than 50 and lower in women 75 or older. A  
30  
31 102 similar pattern was observed in other European countries[4] and attributed to early detection with  
32  
33 103 mammography and to improved treatment [17-19]. However, it was not clear to which extent  
34  
35 104 improvements in survival could have effected the age of death, and the influence of screening  
36  
37 105 programmes were difficult to evaluate due to using fixed age groups rather than cohorts.

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39  
40 106 In the present study we aimed asses the spatio-temporal patterns in breast cancer mortality and  
41  
42 107 specifically the effect of population based mammography screening programmes on it. We corrected  
43  
44 108 for urbanisation for which a mortality gradient was described[20] and additionally for area-based  
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46 109 socio economic factors, which may have influenced results in the previous study.

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## 112 **METHODS**

### 113 **Data sources**

114 The Swiss Federal Statistical office (FSO) provided data on female breast cancer mortality,  
115 electronically available for the period 1969-2012. The anonymized data included gender, age, year of  
116 birth and death for each individual, nationality, municipality of residence, the cause of death and co-  
117 morbidities. The cause of death and co-morbidities were coded centrally from death certificates  
118 using until 1994 the 8th revision of the International Classification of Diseases (ICD) and afterwards  
119 the 10th revision. The transition to the 10th revision of the ICD-10 was accompanied by changes in  
120 death certificate coding practices (priority rules). We used age- and cancer site-specific correction  
121 factors as proposed by Lutz et al[21] for the death counts. We included all cases coded with main  
122 causes of death being cancer of the female breast (ICD-10 C50.0-C50.9). According to federal  
123 regulations, mortality data excluding person identifying information can be used in epidemiological  
124 studies without additional ethics committee approval.

125 The administrative borders of Swiss municipalities define the smallest geographical unit for  
126 which data were available. There are around 2'500 municipalities in the country with a median  
127 population of 740 inhabitants in 1970 and 1,150 in 2010.

128 Aggregated population data by age and area unit were extracted from the census that takes  
129 place in Switzerland every 10 years and the last one was conducted in 2010. Due to missing detailed  
130 intercensal population data, we aggregated the mortality data in five 4-year periods around the  
131 census years, i.e. 1969-1972, 1979-1982, 1989-1992, 1999-2002 and 2009-2012, in which population  
132 was assumed to be constant and identical to census year.

133 From the same source, we retrieved data on language region (German, French and Italian and  
134 Romansh) and urbanisation (rural/urban). We obtained information on population based screening  
135 programmes from the Swiss federation of cancer screening programmes[22], grouping into duration

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3 136 of the programmes at census years (no programme/ 0-4 years, 5+ years). Data on socio-economic  
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5 137 position (SEP) by municipality was provided by the Swiss National cohort[23] based on census data of  
6  
7 138 2000.  
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## 10 139 **Statistical methods**

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13 140 As small area geographical unit, we used the municipality borders as of 2012. We used  
14  
15 141 municipality transition protocols from the FSO to align all data to this structure.  
16

17  
18 142 We investigated mortality for all ages combined in a spatial and a non-spatial model, for the 5  
19  
20 143 time periods from 1969 to 2012 in order to assess possible non-linear time trends, and only for the  
21  
22 144 period 2009-2012.  
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24  
25 145 For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model  
26  
27 146 formulations as described in Herrmann et al 2015[16], fitted on the number of deaths aggregated by  
28  
29 147 small area and year with the mean being equal to the product of the expected death count and age  
30  
31 148 standardised mortality rate. The indirect standardisation used 5 years age intervals. Expected  
32  
33 149 mortality counts for each small area and year were obtained from the study population using  
34  
35 150 nationwide age-specific mortality rates for all periods, and only for the period 2009-2012  
36  
37 151 respectively. The small-area-specific random effects were modelled via conditional autoregressive  
38  
39 152 (CAR) models to filter out the noise and highlight the observed patterns.  
40  
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42

43 153 Differences influenced by linguistic region, life in rural or urban areas, screening programme  
44  
45 154 duration and socio-economic position were accounted for. These analyses will indicate whether  
46  
47 155 there are significant differences in the cancer mortality for each one of the above covariates,  
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49 156 assessed by 95% Bayesian Credible Intervals (CI).  
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## 51 157 **Patient involvement**

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54 158 No patients were involved in this study.  
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## 159 RESULTS

160 In total in Switzerland more than 61'000 women died from breast cancer from 1969 to 2012.

161 Table 1 presents the results of the regressions including all time periods and time trends. In

162 Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and declined

163 strongly since. Until the most recent period 2009-2012, the SMR reduced to 57% of the 1969-1972

164 value both in the non-spatial and the spatial model. The trends and geographical differences are

165 visualized in figure 1.

166

167

168 **Table 1** Spatio-temporal model estimates of age specific breast cancer mortality in Switzerland from

169 1969-1972 to 2009-2012. Bold values denote Age-Standardized Mortality-Ratio (SMR) Ratios

170 significantly different from 1. Spatial variation (standard deviation of spatial random effects): a value

171 of 0 means that there is no spatial correlation.

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
<b>Period</b>				
1969-1972	1.00		1.00	
1979-1982	1.01	(0.97;1.05)	1.01	(0.97;1.05)
1989-1992	<b>1.04</b>	(1.00;1.09)	<b>1.05</b>	(1.01;1.09)
1999-2002	<b>0.81</b>	(0.78;0.84)	<b>0.81</b>	(0.78;0.85)
2009-2012	<b>0.57</b>	(0.54;0.59)	<b>0.57</b>	(0.54;0.60)
<b>Language</b>				
German	1.00		1.00	
French	0.99	(0.95;1.02)	1.02	(0.92;1.14)
Italian/Roman.	1.01	(0.96;1.08)	0.99	(0.83;1.16)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	<b>1.05</b>	(1.01;1.08)	1.03	(0.98;1.08)
<b>Years of population based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.88;1.03)	0.95	(0.88;1.04)
<b>Socioeconomic index</b>				
per 10 point increase	1.02	(0.99;1.04)	1.02	(0.98;1.05)
<b>Spatial variation</b>			0.21	(0.18;0.24)

172 From the covariates studied, only year of death and the urbanisation level in the non-spatial  
 173 model had a significant impact when investigating all periods. An urban environment was associated  
 174 with a 5% elevated SMR (3% in the spatial model) compared to a rural environment.

175 Limiting the analysis to the period 2009-2012 none of the regression factors had a significant  
 176 effect on breast cancer mortality. (table 2)

177

178 **Table 2** Spatio-temporal model estimates of age specific breast cancer mortality in Switzerland  
 179 within 2009-2012. Bold values denote Age-Standardized Mortality-Ratio (SMR) Ratios significantly  
 180 different from 1.

	SMR Ratios (95% CI)		Spatial	
	Non-spatial			
<b>Language</b>				
German	1.00		1.00	
French	1.00	(0.86;1.15)	1.03	(0.81;1.33)
Italian/Roman.	1.01	(0.87;1.16)	1.00	(0.68;1.37)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
<b>Years of population based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
<b>Socioeconomic index</b>				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
<b>Spatial variation</b>			0.29	(0.24;0.35)

181

182

183 Most SMR ratios of the non-spatial and the spatial model showed nearly identical values. The  
 184 length of screening programme and French language region showed slightly higher values, but the  
 185 differences were not significantly different.

186 In 2009-2012, no region had significantly elevated or reduced breast cancer mortality at 95% CI  
187 level compared to the national mean. (figure 2) A map with covariate-adjusted smoothed SMR values  
188 is not shown due to no information gain. The covariates are not significant and the geographical  
189 patterns are the same as for the smoothed SMR values.

190 The socio-economic index value for the municipalities ranged from 28 to 85, with 25% of  
191 municipalities being below 55 and 25% being above 66.

## 192 DISCUSSION

193 In the past decades, breast cancer mortality nearly halved in Switzerland when considering all  
194 ages together. This trend, including the shift from increasing to decreasing rates around the period  
195 1989-1992, has been observed in several other European countries[4]. Although significant spatial  
196 differences in breast cancer incidence are well described for Switzerland, we have not found any  
197 significant differences in breast cancer mortality in any of the periods studied. We have not observed  
198 general significant differences between regions classified by duration of screening programmes,  
199 urbanisation, language and socio-economic position. Also when limiting the analysis to the most  
200 recent period 2009-2012 none of the factors is significant. In fact, at 95% CI level none of the regions  
201 had a significantly elevated or reduced breast cancer mortality compared to the national mean.

202 There are several factors, why the significant differences in incidence do not translate into  
203 corresponding mortality differences. Most importantly, risk factors such as health and health related  
204 behaviour reported to be different for the language regions[14] affect incidence but are not  
205 necessarily linked to mortality[24]. Accordingly, the French language region, despite earlier  
206 implementation of mammography screening programmes, did not show any benefit on breast cancer  
207 mortality in our study.

208 Since screening has been identified as a potential source of mortality reduction[18], we also  
209 included data on population based screening programme duration. However, our study did not show



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3 210 a significant effect on mortality on population level. The reasons for this are probably manifold and  
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5 211 may include the fact that screen detected cancers are mainly of low grade, many women have not  
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7 212 participated in the screening programmes or chose to undergo opportunistic screening, and the  
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9 213 effect of advances in diagnosis and therapy on mortality is quite strong and may have outweighed  
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11 214 benefits from population based screening programmes, as suggested by Autier et al.[25]. Moreover,  
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13 215 the level of opportunistic screening in Switzerland have been described to be quite high[26], but data  
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15 216 on the geographical differences in opportunistic screening use and overall screening participation are  
16  
17 217 not available. The ecological study design does not allow assessing the combined impact of  
18  
19 218 participation in and type (program vs. opportunistic) of mammography screening as well as stage of  
20  
21 219 tumor diagnosis at the level of cancer occurrence and mortality at the level of individuals. For the  
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23 220 above reasons, and because follow up is yet too short since the start of the programmes to fully take  
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25 221 effect[27], the interpretability with regard to screening is limited. In addition, we had to group into 0-  
26  
27 222 4 and 5+ years of screening in order to avoid overfitting issues. There are only few and nearby  
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29 223 regions with 10+ years of screening in 2009-2012 only (figure 1).

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33 224 The presented study is an in-depth analysis from our previous study[16], focussing on breast  
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35 225 cancer mortality using an additional year of more recent data. We were also interested in the effects  
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37 226 on population level as a whole. The applied methodology of age standardisation suits this by taking  
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39 227 advantage of the actual age structure rather than a standard population.

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42 228 The non-significant fixed effect of socio-economic position is in line with the results of Panczak et  
43  
44 229 al[28]. The additional correction served the disentanglement of affluence from the urbanisation  
45  
46 230 parameter –which is connected with access to medical services– and further possible distortions.[29]

47  
48  
49 231 A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an  
50  
51 232 unstable rate by “borrowing” strength from its neighbours[30]. They can also assess the significance  
52  
53 233 of risk factors taking into account the geographical correlation, and are able to show spatial patterns  
54  
55 234 after adjusting for geographical differences in certain risk factors. By adding a time dimension,

235 Bayesian spatio-temporal models indicate changes of geographical patterns over time and determine  
236 how the disease evolves over time in different regions and different groups of the population (age,  
237 language or affluence groups). These models provide the state-of-art modelling approach over the  
238 last fifteen years for assessing spatio-temporal patterns and trends. We have not observed that  
239 coefficients in our analysis are shrunk towards zero as hypothesised by Hodges and Reich[31] when  
240 including geographical correlation. In fact, in the spatial model for 2009-2012 the impact of the  
241 French language region is 1.03 in comparison to 1.00 in the non-spatial model. However, we have  
242 included the results of the non-spatial models as well.

## 243 **Conclusion**

244 Geographical differences in breast cancer mortality are present in Switzerland, but at a moderate  
245 level with no significant differences from the overall mean and not explained by the duration of  
246 population based screening programme, socio-economic position, urbanisation and language region.

247 There was a strong reduction of breast cancer mortality from the 90s on; geographical  
248 differences in the reduction were present but also small. The geographical differences will need to be  
249 re-evaluated when the running time of mammography screening programmes in Switzerland are  
250 sufficiently long for any effect of mortality to become visible.

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255 manuscript.

## 258 **COMPETING INTERESTS**

259 All authors have completed the ICMJE uniform disclosure form at  
260 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
261 work; no financial relationships with any organisations that might have an interest in the submitted  
262 work in the previous three years; no other relationships or activities that could appear to have  
263 influenced the submitted work.

## 264 **CONTRIBUTIONS**

265 PV, SE conceived of the study. CH carried out the analysis and data acquisition. CH, SE, PV  
266 contributed to the analysis of the data and the writing of the manuscript. All authors contributed to  
267 interpretation of the findings and critically revised the manuscript. All authors read and approved the  
268 final manuscript.

## 269 **TRANSPARENCY DECLARATION**

270 The lead author affirms that this manuscript is an honest, accurate, and transparent account of  
271 the study being reported; that no important aspects of the study have been omitted; and that any  
272 discrepancies from the study as planned (and, if relevant, registered) have been explained.

## 273 **ETHICAL APPROVAL**

274 Ethical approval was not required as this study is an analysis of publically available, anonymous  
275 and previously collected data.

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## 289 DATA SHARING STATEMENT

290 All data are publically available from the sources stated in the methods section. Statistical code is  
291 available from the corresponding author.

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## 21 380 **FIGURES**

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23 381 **Fig. 1** Development of age standardized breast cancer mortality (SMR) and spatial differences  
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25 382 therein among time. Values are calculated and smoothed in relation to the all-period combined  
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27 383 mortality. Darker colours represent a higher mortality for the specific age structure and population in  
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29 384 that area and time period.

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32 385 **Fig. 2** Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.

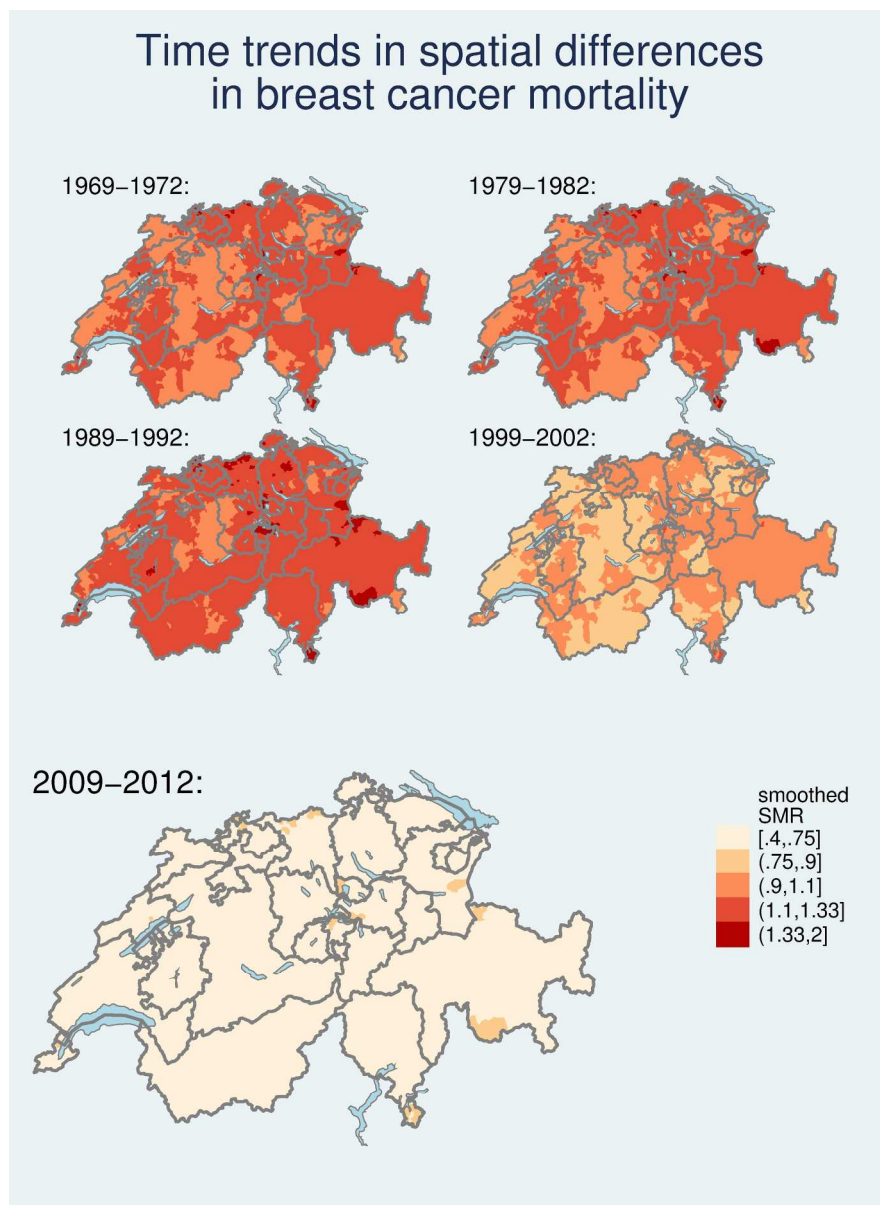
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## 39 387 **ADDITIONAL MATERIAL**

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41 388 A1. Figures depicting urbanization classification, language regions Screening duration and Swiss  
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43 389 Socio-Economic Position (SEP) in Switzerland.  
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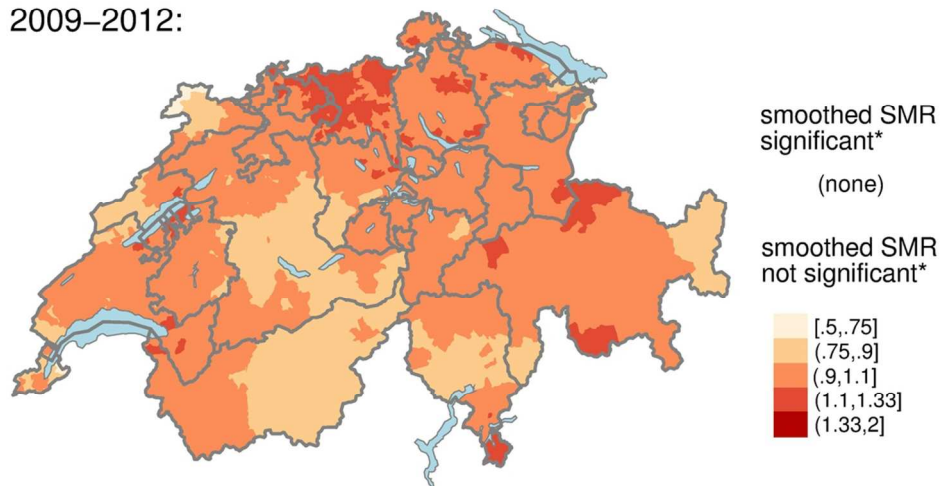
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Development of age standardized breast cancer mortality (SMR) and spatial differences therein among time. Values are calculated and smoothed in relation to the all-period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period.

190x259mm (300 x 300 DPI)

2009–2012:



Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.  
 \*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

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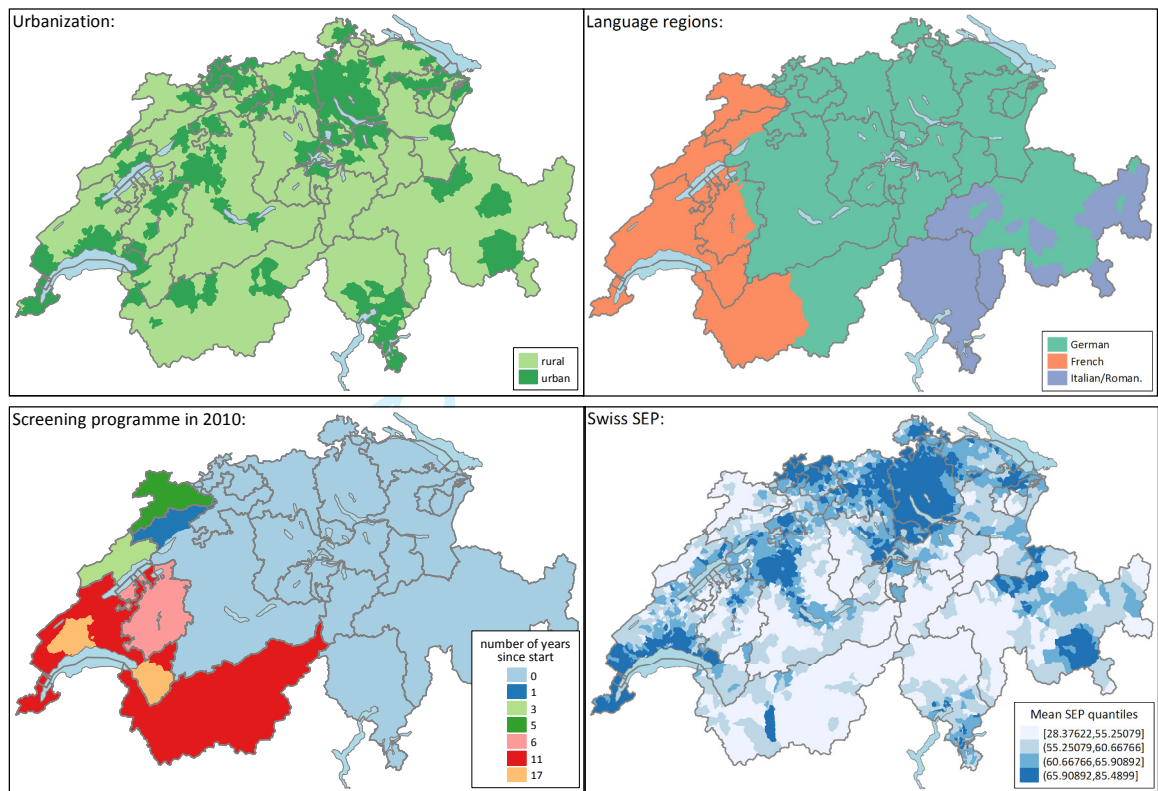
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## Additional material

**Figure A1:** Urbanization classification, language regions Screening duration and Swiss Socio-Economic Position (SEP) in Switzerland.



## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA (Ecological study)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, lines 85-88
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods page 5, Introduction 3-4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (c) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, page 5, lines 91-101
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5
Bias	9	Describe any efforts to address potential sources of bias	Methods page 6, Introduction page 4, Discussion page 9-10
Study size	10	Explain how the study size was arrived at	Ecological study, Methods page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods page 4-6
		(b) Describe any methods used to examine subgroups and interactions	Methods page 6
		(c) Explain how missing data were addressed	No missing data, ecological study
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	Pages 6-8

Continued on next page

<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results page 6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA, page 6
		(b) Indicate number of participants with missing data for each variable of interest	No missing data (ecological study)
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7-8
		(b) Report category boundaries when continuous variables were categorized	Page 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-8
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-11
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 11

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Spatio-temporal modelling of breast cancer mortality in a country with different regional screening policies

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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Oncology, Public health
Keywords:	Switzerland, Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY, mortality, Bayesian disease mapping

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## TITLE

Spatio-temporal modelling of breast cancer mortality in a country with different regional screening policies

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## KEYWORDS

Neoplasm, Breast cancer, Switzerland, Bayesian disease mapping, mortality

## WORD COUNT

2373 words, excluding title page, abstract, references, figures and tables.

## ABSTRACT

**Objectives:** In the past decades, mortality due to breast cancer has declined considerably in Switzerland and other developed countries. The reasons for this decline remain controversial as several factors including important advances in treatment approaches, breast cancer awareness and the introduction of mammography screening programmes in many European countries occurred almost simultaneously. In Switzerland, mammography programmes have existed in some regions for over 20 years, while in others do not yet exist, thus offering the possibility to analyse its effects with modern spatio-temporal methodology.

**Setting:** Switzerland

**Participants:** The study covers breast cancer deaths of the female population of Switzerland during the period 1969-2012. Data were retrieved from the Swiss Federal Statistical office (FSO) aggregated on a small-area level.

**Design:** We fitted Bayesian hierarchical spatio-temporal models on death rates indirectly standardized by national references. We used linguistic region, degree of urbanisation, duration of population based screening programmes and socio-economic index as covariates.

**Results:** In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and declined strongly thereafter. Until 2009-2012, the standardized mortality ratio (SMR) declined to 57% (95% CI 54% to 60%) of the 1969-1972 value. None of the other coefficients of the spatial regressions had a significant effect on breast cancer mortality. In 2009-2012 no region had significantly elevated or reduced breast cancer mortality at 95% CI (Credible Interval) level compared to the national mean.

**Conclusion:** There has been a strong reduction of breast cancer mortality from the 90s on. No important spatial disparities were observed. The moderate geographical differences we found are within credible intervals using modern Bayesian techniques. The factors studied (urbanisation,

43 language, duration of population based screening programme and socioeconomic characteristics) did  
44 not seem to have an influence on them.

## 45 **ARTICLE SUMMARY**

### 46 **Strengths and limitations**

- 47 • Modern Bayesian spatial model were used to improve estimation of an unstable rate by  
48 “borrowing” strength from its neighbours.
- 49 • The used model is capable to assess the significance of risk factors taking into account the  
50 geographical correlation.
- 51 • Switzerland with its homogeneous health system and different regional screening policies  
52 provides an ideal setting for assessing the impact of population based mammography  
53 screening programmes.
- 54 • Data on the geographical differences in opportunistic screening use and therefore overall  
55 screening participation are not available,
- 56 • The ecological study design does not allow an assessment of the combined impact of  
57 participation in and type (programme vs. opportunistic) of mammography screening.
- 58 •

## 59 **INTRODUCTION**

60 In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the  
61 leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. In the past  
62 decades mortality due to breast cancer has declined considerably in Switzerland and other developed  
63 countries[4]. The reasons for the decline remain controversial as several factors including important  
64 advances in treatment approaches, breast cancer awareness and the introduction of mammography  
65 screening programmes in many European countries occurred almost simultaneously.



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3 66 Some randomized controlled studies[5] have demonstrated a breast cancer mortality reduction  
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5 67 of 20% for women invited to breast cancer screening. However, they were conducted in the 1970-80s  
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7 68 and since then many advances in therapies have been made and adopted[6], so that some authors  
8  
9 69 doubt that the difference would persist under present conditions. Therefore, often used historical  
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11 70 pre-screening control groups are not best suited to disentangle these effects. Autier et al [7]  
12  
13 71 compared countries in Europe but a criticism was, that different countries may have different health  
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15 72 systems. Kalager et al[8] used comparison groups in Norway and showed that only a third of total  
16  
17 73 mortality reduction could be attributed to mammography screening, but used a short observation  
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19 74 period. Also, in a setting, where voluntary screening is assumed to be high, it is unknown what the  
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21 75 effect of an organised screening programme would be for the population as a whole.  
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25 76 In Switzerland with its homogenous health system these pitfalls can be avoided. Switzerland is a  
26  
27 77 small confederation of 26 relatively autonomous states called cantons with somewhat low  
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29 78 inequalities[9] and high health and cancer related resources.[10-12] Although the health care system  
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31 79 is homogenous in its provision of universal and rapid access and use of almost unlimited health care  
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33 80 resources, some health care policies are developed at cantonal level; in particular, the decision to  
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35 81 initiate a population based mammography-screening programme. These programmes were  
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37 82 implemented in Switzerland at different time points over the past two decades. The first Swiss  
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39 83 mammography pilot programme was established in 1993 in the French speaking canton of Vaud but  
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41 84 it was only in 2010 that the first organised programme in a German speaking canton (St. Gallen)  
42  
43 85 started.  
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47 86 In breast cancer incidence cantonal differences are well known and have been attributed to  
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49 87 differential use of opportunistic or organised mammography screening[13]. In addition, considerable  
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51 88 differences in health and health related behaviour –affecting the risk of breast cancer– have been  
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53 89 reported for the Swiss language regions including alcohol intake and a healthy diet[14 15], and  
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55 90 differences in the age at first birth and number of children[16]. Differences in access to  
56  
57 91 mammography screening and in lifestyle may be reflected in spatio-temporal differences of both  
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3 92 breast cancer incidence and mortality, whereas only the latter will reflect the management of breast  
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5 93 cancer.

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8 94 In contrast, breast cancer mortality studies in Switzerland showed contradictory results. Bulliard  
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10 95 et al[17] observed a steeper decrease in 1980-2002 in 55-74 year olds in French-speaking regions  
11  
12 96 where population based mammography screening started earlier. In a recent study[18] we presented  
13  
14 97 the spatio-temporal trends of female gender related cancer mortality in Switzerland by age group.  
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16 98 The geographical differences found were small. We observed a differential decline in breast cancer  
17  
18 99 mortality by age. Decline was highest in women younger than 50 and lower in women 75 or older. A  
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20 100 similar pattern was observed in other European countries[4] and attributed to early detection by  
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22 101 mammography and to improved treatment [19-21]. However, it was not clear to which extent  
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24 102 improvements in survival could have affected the age at death, i.e. a shift of deaths into the next  
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26 103 higher age group, and the influence of screening programmes were difficult to evaluate due to using  
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28 104 fixed age groups rather than cohorts.

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32 105 In the present study we aimed to assess the spatio-temporal patterns in breast cancer mortality  
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34 106 and specifically the effect of population based mammography screening programmes on it. We  
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36 107 corrected for urbanisation for which a mortality gradient was described[22] and additionally for area-  
37  
38 108 based socio economic factors, which may have influenced results in the previous study.

## 109 **METHODS**

### 110 **Data sources**

111 The Swiss Federal Statistical office (FSO) provided data on female breast cancer mortality,  
112 electronically available for the period 1969-2012. The anonymized data included gender, age, year of  
113 birth and death for each individual, nationality, municipality of residence, the cause of death and co-  
114 morbidities. The cause of death and co-morbidities were coded centrally from death certificates

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3 115 using until 1994 the 8th revision of the International Classification of Diseases (ICD) and afterwards  
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5 116 the 10th revision. The transition to the 10th revision of the ICD-10 was accompanied by changes in  
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7 117 death certificate coding practices (priority rules). We used age- and cancer site-specific correction  
8  
9 118 factors as proposed by Lutz et al[23] for the death counts. We included all cases coded with main  
10  
11 119 causes of death being cancer of the female breast (ICD-10 C50.0-C50.9). According to federal  
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13 120 regulations, mortality data excluding person identifying information can be used in epidemiological  
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15 121 studies without additional ethics committee approval.

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18 122 The administrative borders of Swiss municipalities define the smallest geographical unit for  
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20 123 which data were available. There are around 2'500 municipalities in the country with a median  
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22 124 population of 740 inhabitants in 1970 and 1,150 in 2010.

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25 125 Aggregated population data by age and area unit were extracted from the census that takes  
26  
27 126 place in Switzerland every 10 years. The last one was conducted in 2010. Due to missing detailed  
28  
29 127 intercensal population data, we aggregated the mortality data in five 4-year periods around the  
30  
31 128 census years, i.e. 1969-1972, 1979-1982, 1989-1992, 1999-2002 and 2009-2012, in which population  
32  
33 129 was assumed to be constant and identical to census year.

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37 130 From the same source we retrieved data on language region (German, French and Italian and  
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39 131 Romansh) and urbanisation (rural/urban). We obtained information on population based screening  
40  
41 132 programmes from the Swiss federation of cancer screening programmes[24], grouping into duration  
42  
43 133 of the programmes in census years (no programme/ 0-4 years, 5+ years). Data on socio-economic  
44  
45 134 position (SEP) by municipality was provided by the Swiss National cohort[25] based on census data of  
46  
47 135 2000.

## 50 51 136 **Statistical methods**

52  
53 137 As a small area geographical unit, we used the municipality borders as of 2012. We used  
54  
55 138 municipality transition protocols from the FSO to align all data to this structure.

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3 139 We investigated mortality for all ages combined in a spatial and a non-spatial model, on the one  
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5 140 hand for the 5 time periods from 1969 to 2012 in order to assess possible non-linear time trends, and  
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7 141 an the other hand only for the period 2009-2012.  
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10 142 For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model  
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12 143 formulations as described in Herrmann et al 2015[18], fitted on the number of deaths aggregated by  
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14 144 small area and year with the mean being equal to the product of the expected death count and age  
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16 145 standardised mortality rate. The indirect standardisation used 5 years age intervals. Expected  
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18 146 mortality counts for each small area and year were obtained from the study population using  
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20 147 nationwide age-specific mortality rates for all periods, and only for the period 2009-2012  
21  
22 148 respectively. The small-area-specific random effects were modelled via conditional autoregressive  
23  
24 149 (CAR) models to filter out the noise and highlight the observed patterns.  
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27  
28 150 Differences influenced by linguistic region, life in rural or urban areas, screening programme  
29  
30 151 duration and socio-economic position were accounted for. These analyses will indicate whether  
31  
32 152 there are significant differences in cancer mortality for each one of the above covariates, assessed by  
33  
34 153 95% Bayesian Credible Intervals (CI).  
35  
36

## 37 154 **Patient involvement**

38  
39 155 No patients were involved in this study.  
40  
41  
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43

## 44 156 **RESULTS**

45  
46  
47 157 In total in Switzerland more than 61'000 women died from breast cancer between 1969 and  
48  
49 158 2012. Table 1 presents the results of the regressions including all time periods and time trends. In  
50  
51 159 Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and has declined  
52  
53 160 strongly since. Until the most recent period 2009-2012, the SMR has fallen to 57% of the 1969-1972  
54  
55 161 value both in the non-spatial and the spatial model. The trends and geographical differences are  
56  
57 162 visualized in figure 1.  
58  
59

163

164

165 **Table 1** Spatio-temporal model estimates of age specific breast cancer mortality in Switzerland from

166 1969-1972 to 2009-2012. Bold values denote Age-Standardised Mortality-Ratio (SMR) Ratios

167 significantly different from 1. Spatial variation (standard deviation of spatial random effects): a value

168 of 0 means that there is no spatial correlation.

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
<b>Period</b>				
1969-1972	1.00		1.00	
1979-1982	1.01	(0.97;1.05)	1.01	(0.97;1.05)
1989-1992	<b>1.04</b>	(1.00;1.09)	<b>1.05</b>	(1.01;1.09)
1999-2002	<b>0.81</b>	(0.78;0.84)	<b>0.81</b>	(0.78;0.85)
2009-2012	<b>0.57</b>	(0.54;0.59)	<b>0.57</b>	(0.54;0.60)
<b>Language</b>				
German	1.00		1.00	
French	0.99	(0.95;1.02)	1.02	(0.92;1.14)
Italian/Roman.	1.01	(0.96;1.08)	0.99	(0.83;1.16)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	<b>1.05</b>	(1.01;1.08)	1.03	(0.98;1.08)
<b>Years of population based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.88;1.03)	0.95	(0.88;1.04)
<b>Socioeconomic index</b>				
per 10 point increase	1.02	(0.99;1.04)	1.02	(0.98;1.05)
<b>Spatial variation</b>			0.21	(0.18;0.24)

169 From the covariates studied, only year of death and the urbanisation level in the non-spatial

170 model had a significant impact when investigating all periods. An urban environment was associated

171 with a 5% elevated SMR (3% in the spatial model) compared to a rural environment.

172 Limiting the analysis to the period 2009-2012 none of the regression factors had a significant

173 effect on breast cancer mortality. (table 2)

174

175 **Table 2** Spatio-temporal model estimates of age standardised breast cancer mortality in  
 176 Switzerland in 2009-2012. Bold values denote Age-Standardised Mortality-Ratio (SMR) Ratios  
 177 significantly different from 1.

	<b>SMR Ratios (95% CI)</b>			
	Non-spatial		Spatial	
<b>Language</b>				
German	1.00		1.00	
French	1.00	(0.86;1.15)	1.03	(0.81;1.33)
Italian/Roman.	1.01	(0.87;1.16)	1.00	(0.68;1.37)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
<b>Years of population based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
<b>Socioeconomic index</b>				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
<b>Spatial variation</b>			0.29	(0.24;0.35)

178

179

180 Most SMR ratios of the non-spatial and the spatial model showed nearly identical values. The  
 181 length of a screening programme and the French language region showed slightly higher values, but  
 182 the differences were not significant.

183 In 2009-2012, no region had a significantly higher or lower breast cancer mortality rate at 95% CI  
 184 level compared to the national mean. (figure 2) A map with covariate-adjusted smoothed SMR values  
 185 is not shown due to no information gain. The covariates are not significant and the geographical  
 186 patterns are the same as for the smoothed SMR values.

187 The socio-economic index value for the municipalities ranged from 28 to 85, with 25% of  
 188 municipalities being below 55 and 25% being above 66.

## 189 DISCUSSION

1  
2  
3 190 In the past decades, breast cancer mortality has nearly halved in Switzerland when considering  
4  
5 191 all ages together. This trend, including the shift from increasing to decreasing rates around the  
6  
7 192 period 1989-1992, has been observed in several other European countries[4]. Although significant  
8  
9 193 spatial differences in breast cancer incidence are well described for Switzerland, we have not found  
10  
11 194 any significant differences in breast cancer mortality in any of the periods studied. We have not  
12  
13 195 observed general significant differences between regions classified by duration of screening  
14  
15 196 programmes, urbanisation, language and socio-economic position. Also when limiting the analysis to  
16  
17 197 the most recent period 2009-2012 none of the factors are significant. In fact, at 95% CI level none of  
18  
19 198 the regions have a significantly elevated or reduced breast cancer mortality compared to the national  
20  
21 199 mean.

22  
23  
24  
25 200 There are several factors why the significant differences in incidence do not translate into  
26  
27 201 corresponding mortality differences. Most importantly, risk factors such as health and health related  
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29 202 behaviour reported to be different for the language regions[15] affect incidence but are not  
30  
31 203 necessarily linked to mortality[26]. I.e. while a temporary increase in the use of hormone  
32  
33 204 replacement therapy has led to an increase in breast cancer incidence, many of those tumours have  
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35 205 a favorable prognosis and might have influenced breast cancer mortality only marginally[27].  
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37 206 Accordingly, the French language region, despite earlier implementation of mammography screening  
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39 207 programmes, does not show a relevant impact on breast cancer mortality in our study.

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42 208 Since screening has been identified as a potential source of mortality reduction[20], we also  
43  
44 209 included data on population based screening programme duration. However, our study did not show  
45  
46 210 a significant effect on mortality on population level. The reasons for this are probably manifold and  
47  
48 211 may include the fact that screen detected cancers are mainly of low stage, many women have not  
49  
50 212 participated in the screening programmes or have chosen to undergo opportunistic screening. In  
51  
52 213 addition, the effect of advances in diagnosis and therapy on mortality is quite strong and may have  
53  
54 214 outweighed benefits from population based screening programmes, as suggested by Autier et al.[28].  
55  
56 215 Moreover, the level of opportunistic screening in Switzerland has been described to be quite

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2  
3 216 high[29], but data on the geographical differences in opportunistic screening use and therefore  
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5 217 overall screening participation are not available. Data on participation in population based screening  
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7 218 programmes are published in a national monitoring report showing that participation rates are  
8  
9 219 nearly identical across all programmes[30].The ecological study design does not allow the  
10  
11 220 assessment of the combined impact of participation in and type (programme vs. opportunistic) of  
12  
13 221 mammography screening as well as stage of tumour at diagnosis and mortality on individual level.  
14  
15 222 For the above reasons, and because follow up is yet too short since the start of the programmes to  
16  
17 223 fully take effect[31], the interpretability with regard to screening is limited. In addition, we had to  
18  
19 224 group into 0-4 and 5+ years of screening in order to avoid overfitting issues. There are only few  
20  
21 225 regions which are in close proximity to each other with 10+ years of screening in 2009-2012 only  
22  
23 226 (additional material, figure A1).

24  
25  
26  
27 227 The presented study is an in-depth analysis from our previous study[18], focusing on breast  
28  
29 228 cancer mortality using an additional year of more recent data. We were also interested in the effects  
30  
31 229 on population level as a whole. The applied methodology of age standardisation suits this by taking  
32  
33 230 advantage of the actual age structure rather than of a standard population.

34  
35  
36 231 The non-significant fixed effect of socio-economic position is in line with the results of Panczak et  
37  
38 232 al[32]. The additional correction served the disentanglement of affluence from the urbanisation  
39  
40 233 parameter –which is connected with access to medical services– and further possible distortions.[33]

41  
42  
43 234 A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an  
44  
45 235 unstable rate by “borrowing” strength from its neighbours[34]. They can also assess the significance  
46  
47 236 of risk factors taking into account the geographical correlation, and are able to show spatial patterns  
48  
49 237 after adjusting for geographical differences in certain risk factors. By adding a time dimension,  
50  
51 238 Bayesian spatio-temporal models indicate changes of geographical patterns over time and determine  
52  
53 239 how the disease evolves over time in different regions and different groups of the population (age,  
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55 240 language or affluence groups). These models provide a state-of-art modelling approach over the last  
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3 241 fifteen years for assessing spatio-temporal patterns and trends. We have not observed that  
4  
5 242 coefficients in our analysis have shrunk towards zero when including geographical correlation as  
6  
7 243 hypothesised by Hodges and Reich[35]. In fact, in the spatial model for 2009-2012 the impact of the  
8  
9 244 French language region is 1.03 in comparison to 1.00 in the non-spatial model. However, we have  
10  
11 245 included the results of the non-spatial models as well.

## 14 246 **Conclusion**

15  
16 247 Geographical differences in breast cancer mortality are present in Switzerland, but at a moderate  
17  
18 248 level with no significant differences from the overall mean and are not explained by the duration of  
19  
20 249 population based screening programmes, socio-economic position, urbanisation and language  
21  
22 250 region.

23  
24  
25  
26 251 There has been a strong reduction of breast cancer mortality from the 90s on; geographical  
27  
28 252 differences in the reduction are present but are also small. The geographical differences will need to  
29  
30 253 be re-evaluated when the running time of mammography screening programmes in Switzerland is  
31  
32 254 sufficiently long enough for any effect on mortality to become visible.

## 36 255 **FUNDING**

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38 256 CH was supported by the Cancer League Eastern Switzerland and CH and PV were supported by a  
39  
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41  
42 258 no role in the study design, data collection and analysis, decision to publish, or preparation of the  
43  
44 259 manuscript.

## 48 260 **COMPETING INTERESTS**

49  
50  
51 261 All authors have completed the ICMJE uniform disclosure form at  
52  
53 262 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
54  
55 263 work; no financial relationships with any organisations that might have an interest in the submitted  
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264 work in the previous three years; no other relationships or activities that could appear to have  
265 influenced the submitted work.

## 266 **CONTRIBUTIONS**

267 PV, SE conceived of the study. CH carried out the analysis and data acquisition. CH, SE, PV  
268 contributed to the analysis of the data and the writing of the manuscript. CH, PV, BT, NP, CR and SE  
269 contributed to interpretation of the findings and critically revised the manuscript. All authors read  
270 and approved the final manuscript.

## 271 **TRANSPARENCY DECLARATION**

272 The lead author affirms that this manuscript is an honest, accurate, and transparent account of  
273 the study being reported; that no important aspects of the study have been omitted; and that any  
274 discrepancies from the study as planned (and, if relevant, registered) have been explained.

## 275 **ETHICAL APPROVAL**

276 Ethical approval was not required as this study is an analysis of publically available, anonymous  
277 and previously collected data.

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## 291 DATA SHARING STATEMENT

292 All data are publically available from the sources stated in the methods section. Statistical code is  
 293 available from the corresponding author.

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## 393 FIGURES

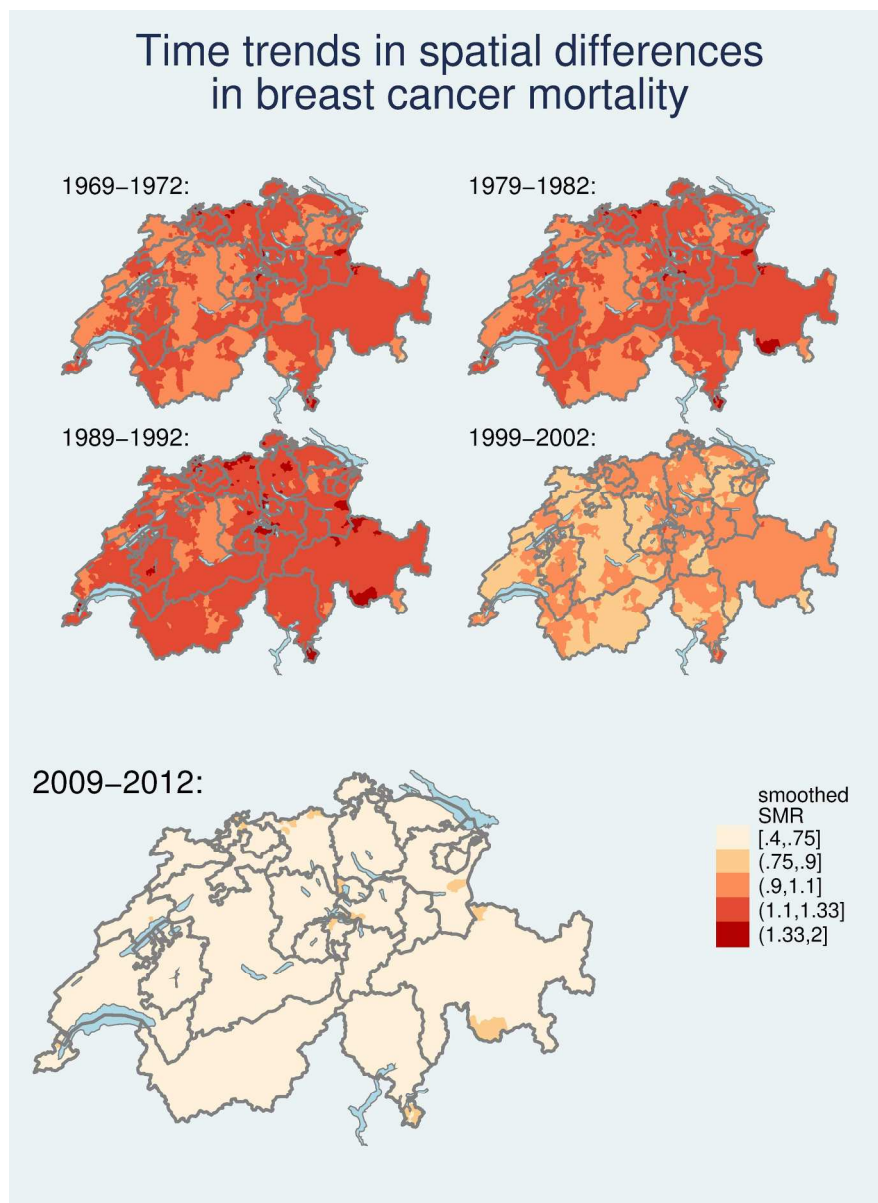
394 **Fig. 1** Development of age standardised breast cancer mortality (SMR) and spatial differences  
 395 therein among time. Values are calculated and smoothed in relation to the all-period combined  
 396 mortality. Darker colours represent a higher mortality for the specific age structure and population in  
 397 that area and time period.

398 **Fig. 2** Geographical differences in age standardised breast cancer mortality (SMR) in 2009-2012.

399 \*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

## 400 ADDITIONAL MATERIAL

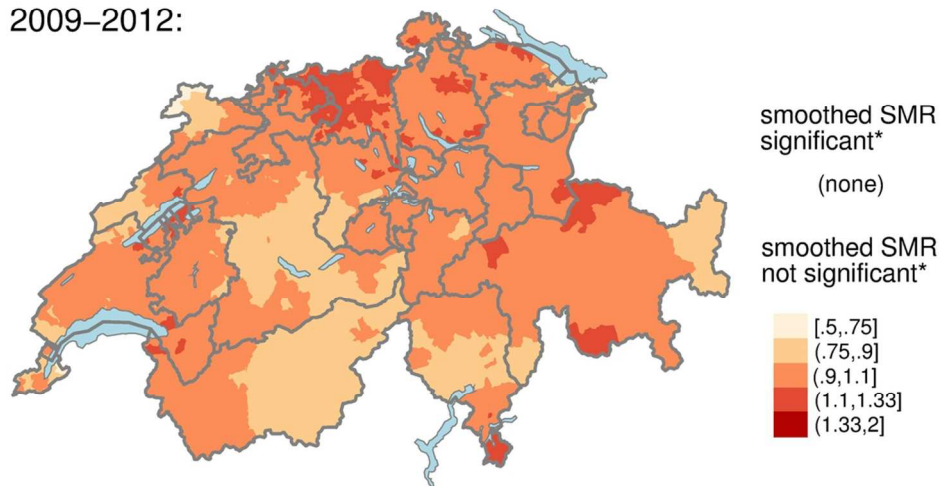
401 A1. Figures depicting urbanization classification, language regions Screening duration and Swiss  
 402 Socio-Economic Position (SEP) in Switzerland.



Development of age standardized breast cancer mortality (SMR) and spatial differences therein among time. Values are calculated and smoothed in relation to the all-period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period.

190x259mm (300 x 300 DPI)

2009–2012:



Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.  
 \*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

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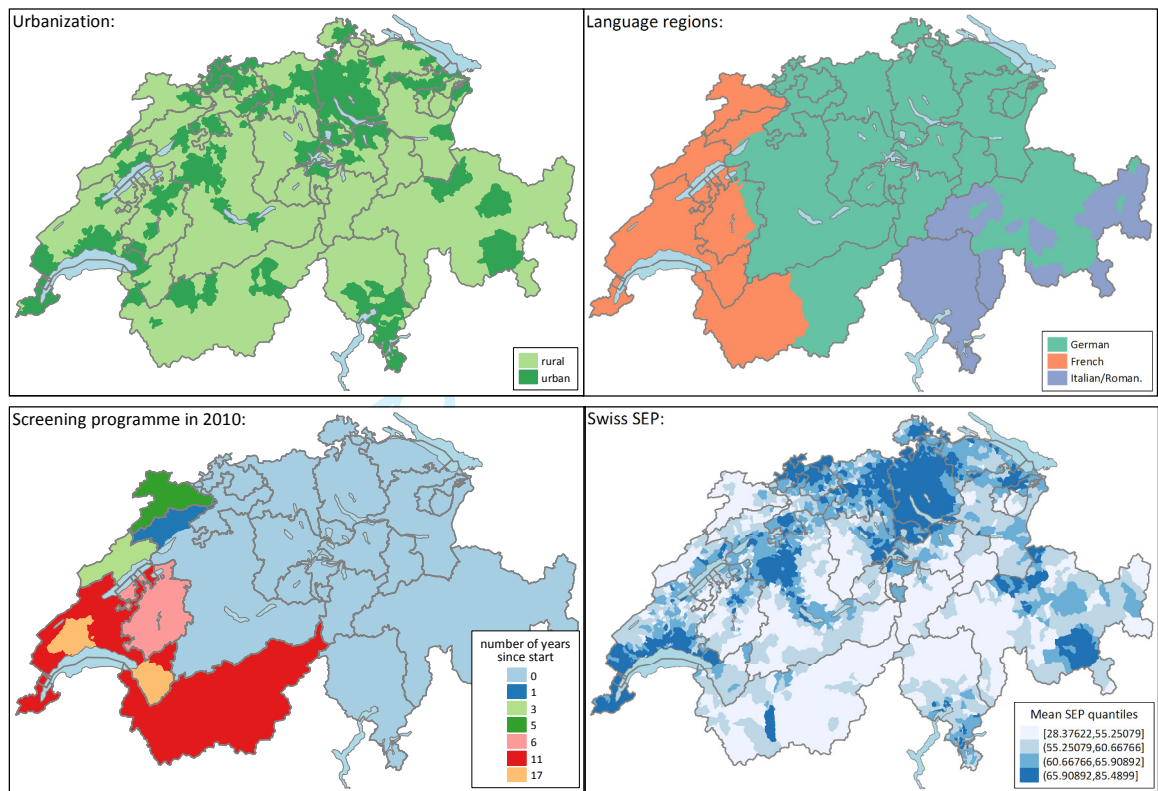
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## Additional material

**Figure A1:** Urbanization classification, language regions Screening duration and Swiss Socio-Economic Position (SEP) in Switzerland.



## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA (Ecological study)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, lines 85-88
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods page 5, Introduction 3-4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (c) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, page 5, lines 91-101
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5
Bias	9	Describe any efforts to address potential sources of bias	Methods page 6, Introduction page 4, Discussion page 9-10
Study size	10	Explain how the study size was arrived at	Ecological study, Methods page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods page 4-6
		(b) Describe any methods used to examine subgroups and interactions	Methods page 6
		(c) Explain how missing data were addressed	No missing data, ecological study
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	Pages 6-8

Continued on next page



<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results page 6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA, page 6
		(b) Indicate number of participants with missing data for each variable of interest	No missing data (ecological study)
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7-8
		(b) Report category boundaries when continuous variables were categorized	Page 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-8
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-11
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 11

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Spatio-temporal modelling of breast cancer mortality in a country with different regional screening policies

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## TITLE

Spatio-temporal modelling of breast cancer mortality in a country with different regional screening policies

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## KEYWORDS

Neoplasm, Breast cancer, Switzerland, Bayesian disease mapping, mortality

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2417 words, excluding title page, abstract, references, figures, and tables.

## ABSTRACT

**Objectives:** In the past decades, mortality due to breast cancer has declined considerably in Switzerland and other developed countries. The reasons for this decline remain controversial as several factors occurred almost simultaneously, including important advances in treatment approaches, breast cancer awareness, and the introduction of mammography screening programmes in many European countries. In Switzerland, mammography screening programmes have existed in some regions for over 20 years, but do not yet exist in others. This offers the possibility to analyse its effects with modern spatio-temporal methodology.

**Setting:** Switzerland

**Participants:** The study covers breast cancer deaths of the female population of Switzerland during the period 1969-2012. We retrieved data from the Swiss Federal Statistical Office (FSO) aggregated on a small-area level.

**Design:** We fitted Bayesian hierarchical spatio-temporal models on death rates indirectly standardised by national references. We used linguistic region, degree of urbanisation, duration of population-based screening programmes and socio-economic index as covariates.

**Results:** In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and declined strongly thereafter. Until 2009-2012, the standardised mortality ratio (SMR) declined to 57% (95% CI 54% to 60%) of the 1969-1972 value. None of the other coefficients of the spatial regressions had a significant effect on breast cancer mortality. In 2009-2012 no region had significantly elevated or reduced breast cancer mortality at 95% CI (Credible Interval) level compared to the national mean.

**Conclusion:** There has been a strong reduction of breast cancer mortality from the 90s on. No important spatial disparities were observed. The moderate geographical differences we found are within credible intervals using modern Bayesian techniques. The factors studied (urbanisation,

43 language, duration of population-based screening programme and socioeconomic characteristics) did  
44 not seem to have an influence on them.

## 45 **ARTICLE SUMMARY**

### 46 **Strengths and limitations**

- 47 • A modern Bayesian spatial model was used to improve estimation of an unstable rate by  
48 “borrowing” strength from its neighbours.
- 49 • The model is capable of assessing the significance of risk factors while also taking the  
50 geographical correlation into account.
- 51 • Switzerland with its homogeneous health system and different regional screening policies  
52 provides an ideal setting for assessing the impact of population-based mammography  
53 screening programmes.
- 54 • Data on the geographical differences in opportunistic screening use and therefore overall  
55 screening participation are not available,
- 56 • The ecological study design does not allow an assessment of the combined impact of  
57 participation in and type (programme vs. opportunistic) of mammography screening.
- 58 •

## 59 **INTRODUCTION**

60 In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the  
61 leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. Mortality  
62 due to breast cancer has declined considerably in the past decades in Switzerland and other  
63 developed countries[4]. The reasons for the decline remain controversial as several factors including  
64 important advances in treatment approaches, breast cancer awareness and the introduction of  
65 mammography screening programmes in many European countries occurred almost simultaneously.

1  
2  
3 66 Some randomised controlled studies[5] have demonstrated a breast cancer mortality reduction  
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5 67 of 20% for women invited for breast cancer screening. However, they were conducted in the 1970-  
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7 68 80s and since then many advances in therapies have been made and adopted[6] so that some  
8  
9 69 authors doubt that the difference would persist under present conditions. Therefore, often used  
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11 70 historical pre-screening control groups are not best suited to disentangle these effects. Autier et al  
12  
13 71 [7] compared countries in Europe but a criticism was, that different countries may have different  
14  
15 72 health systems. Kalager et al.[8] used comparison groups in Norway and showed that only a third of  
16  
17 73 total mortality reduction could be attributed to mammography screening, but used a short  
18  
19 74 observation period. Olsen et al.[9] confirmed these results in principle with the same data but with a  
20  
21 75 somewhat longer follow-up duration. Also, in a setting, where voluntary screening is assumed to be  
22  
23 76 high, it is unknown what the effect of an organised screening programme would be for the  
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25 77 population as a whole.

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29 78 In Switzerland, with its homogenous health system, these pitfalls can be avoided. Switzerland is a  
30  
31 79 small confederation of 26 relatively autonomous states called cantons with somewhat low  
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33 80 inequalities[10] and high health and cancer-related resources.[11-13] Although the health care  
34  
35 81 system is homogeneous in its provision of universal and rapid access and use of almost unlimited  
36  
37 82 health care resources, some health care policies are developed at cantonal level; in particular, the  
38  
39 83 decision to initiate a population-based mammography-screening programme. These programmes  
40  
41 84 were implemented in Switzerland at different time points over the past two decades. The first Swiss  
42  
43 85 mammography pilot programme was established in 1993 in the French-speaking canton of Vaud but  
44  
45 86 it was only in 2010 that the first organised programme in a German-speaking canton (St. Gallen)  
46  
47 87 started.

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50  
51 88 In breast cancer incidence cantonal differences are well known and have been attributed to the  
52  
53 89 differential use of opportunistic or organised mammography screening[14]. In addition, considerable  
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55 90 differences in health and health-related behaviour –affecting the risk of breast cancer– have been  
56  
57 91 reported for the Swiss language regions including alcohol intake and a healthy diet[15 16], and

1  
2  
3 92 differences in the age at first child birth and number of children[17]. Differences in access to  
4  
5 93 mammography screening and in lifestyle may be reflected in spatio-temporal differences in both  
6  
7 94 breast cancer incidence and mortality, whereas only the latter will reflect the management of breast  
8  
9 95 cancer.

10  
11  
12 96 In contrast, breast cancer mortality studies in Switzerland showed contradictory results. Bulliard  
13  
14 97 et al[18] observed a steeper decrease in 1980-2002 in 55-74-year-olds in French-speaking regions  
15  
16 98 where population-based mammography screening started earlier. In a recent study[19] we presented  
17  
18 99 the spatio-temporal trends of female gender related cancer mortality in Switzerland by age group.  
19  
20 100 The geographical differences found were small. We observed a differential decline in breast cancer  
21  
22 101 mortality by age. The decline was highest in women younger than 50 and lower in women 75 or  
23  
24 102 older. A similar pattern was observed in other European countries[4] and attributed to early  
25  
26 103 detection by mammography and to improved treatment [20-22]. However, it was not clear to which  
27  
28 104 extent improvements in survival could have affected the age at death. It was difficult to evaluate a  
29  
30 105 shift of deaths into the next higher age group, and the influence of screening programmes, due to  
31  
32 106 using fixed age groups rather than cohorts.

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35  
36 107 In the present study, we aimed to assess the spatio-temporal patterns in breast cancer mortality  
37  
38 108 and specifically the effect of population-based mammography screening programmes on it. We  
39  
40 109 corrected for urbanisation for which a mortality gradient was described[23] and additionally for area-  
41  
42 110 based socio-economic factors, which may have influenced results in the previous study.

## 43 44 45 46 47 111 **METHODS**

### 48 49 50 51 112 **Data sources**

52  
53  
54 113 The Swiss Federal Statistical Office (FSO) provided data on female breast cancer mortality,  
55  
56 114 electronically available for the period 1969-2012. The anonymised data included gender, age, year of

1  
2  
3 115 birth and death for each individual, nationality, municipality of residence, the cause of death and co-  
4  
5 116 morbidities. The cause of death and co-morbidities were coded centrally from death certificates  
6  
7 117 using until 1994 the 8th revision of the International Classification of Diseases (ICD) and afterwards  
8  
9 118 the 10th revision. The transition to the 10th revision of the ICD-10 was accompanied by changes in  
10  
11 119 death certificate coding practices (priority rules). We used age- and cancer site-specific correction  
12  
13 120 factors as proposed by Lutz et al[24] for the death counts. We included all cases coded with main  
14  
15 121 causes of death being cancer of the female breast (ICD-10 C50.0-C50.9). According to federal  
16  
17 122 regulations, mortality data excluding person identifying information can be used in epidemiological  
18  
19 123 studies without additional ethics committee approval.

21  
22  
23 124 The administrative borders of Swiss municipalities define the smallest geographical unit for  
24  
25 125 which data were available. There are around 2'500 municipalities in the country with a median  
26  
27 126 population of 740 inhabitants in 1970 and 1,150 in 2010.

28  
29  
30 127 Aggregated population data by age and area unit were extracted from the census that takes  
31  
32 128 place in Switzerland every 10 years. The last one was conducted in 2010. Due to missing detailed  
33  
34 129 intercensal population data, we aggregated the mortality data in five 4-year periods around the  
35  
36 130 census years, i.e. 1969-1972, 1979-1982, 1989-1992, 1999-2002 and 2009-2012, in which population  
37  
38 131 was assumed to be constant and identical to census year.

39  
40  
41 132 From the same source, we retrieved data on language region (German, French and Italian and  
42  
43 133 Romansh) and urbanisation (rural/urban). We obtained information on population-based screening  
44  
45 134 programmes from the Swiss federation of cancer screening programmes[25], and categorised their  
46  
47 135 duration in the census years into "no programme", "0-4 years" and "5+ years". Data on socio-  
48  
49 136 economic position (SEP) by municipality was provided by the Swiss National cohort[26] based on  
50  
51 137 census data of 2000.

52  
53  
54  
55 138 Table 1 shows the observed number of deaths and mortality rates for each of the co-variates.



139 **Table 1** Observed numbers of female breast cancer deaths and mortality rates per 100'000 PY by  
 140 period and municipality characteristics. The total numbers before 1994 include the correction  
 141 factors.

	Total no. of breast cancer deaths	%	yearly population (x1000)	crude rate	ASR	p-value for ASR homogeneity
<b>Period</b>						p<0.01
1969-1972	4'177	16%	3'180	32.8	32.0	
1979-1982	4'953	19%	3'251	38.1	32.5	
1989-1992	5'968	23%	3'483	42.8	32.6	
1999-2002	5'261	20%	3'720	35.4	25.4	
2009-2012	5'574	21%	3'993	34.9	22.3	
<b>Language</b>						p=0.56
German	18'613	72%	12'622	36.9	28.5	
French	5'915	23%	4'159	35.6	27.7	
Italian/Roman.	1'405	5%	847	41.5	28.9	
<b>Urbanisation level</b>						p=0.08
Rural	6'172	24%	4'491	34.4	26.9	
Urban	19'761	76%	13'137	37.6	28.8	
<b>Years of population based screening*</b>						p=0.53
no programme	4'246	76%	2'942	36.1	22.6	
1-4 years	169	3%	115	36.9	23.4	
5+ years	1'159	21%	936	31.0	21.2	
<b>Socioeconomic index quartiles</b>						p=0.24
Q1 (lowest)	1'999	8%	1'478	33.8	26.4	
Q2	4'313	17%	3'033	35.6	28.1	
Q3	5'864	23%	4'199	34.9	27.7	
Q4 (highest)	13'757	53%	8'919	38.6	29.0	

\*only for the period 2009-2012, length of screening refers to the year 2010

142

## 143 Statistical methods

144 As a small area geographical unit, we used the municipality borders as of 2012. We used  
 145 municipality transition protocols from the FSO to align all data to this structure.

146 We investigated mortality for all ages combined in a spatial and a non-spatial model, on the one  
 147 hand for the 5 time periods from 1969 to 2012 in order to assess possible non-linear time trends, and  
 148 on the other hand only for the period 2009-2012.

1  
2  
3 149 For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model  
4  
5 150 formulations as described in Herrmann et al 2015[19], fitted on the number of deaths aggregated by  
6  
7 151 small area and year with the mean being equal to the product of the expected death count and age-  
8  
9 152 standardised mortality rate. The indirect standardisation used 5 year age intervals. Expected  
10  
11 153 mortality counts for each small area and year were obtained from the study population using  
12  
13 154 nationwide age-specific mortality rates for all periods, and only for the period 2009-2012  
14  
15 155 respectively. The small-area-specific random effects were modelled via conditional autoregressive  
16  
17 156 (CAR) models to filter out the noise and highlight the observed patterns. The Deviance Information  
18  
19 157 Criterion (DIC) was used to select the regression model from Poisson/ zero-inflated Poisson and  
20  
21 158 Negative binomial regression models. The DIC was lowest with the Poisson regression model.

22  
23  
24  
25 159 We accounted for differences influenced by linguistic region, life in rural or urban areas,  
26  
27 160 screening programme duration, and socio-economic position. These analyses will indicate whether  
28  
29 161 there are significant differences in cancer mortality for each one of the above covariates, assessed by  
30  
31 162 95% Bayesian Credible Intervals (CI).

### 32 33 34 163 **Patient involvement**

35  
36 164 No patients were involved in this study.

## 37 38 39 40 41 165 **RESULTS**

42  
43  
44 166 In Switzerland, in total more than 61'000 women died from breast cancer between 1969 and  
45  
46 167 2012. Table 2 presents the results of the regressions including all time periods and time trends. In  
47  
48 168 Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and has declined  
49  
50 169 strongly since. Until the most recent period 2009-2012, the SMR has fallen to 57% of the 1969-1972  
51  
52 170 value both in the non-spatial and the spatial model. The trends and geographical differences are  
53  
54 171 visualised in figure 1.

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173

174 **Table 2** Spatio-temporal model estimates of age-specific breast cancer mortality in Switzerland from  
 175 1969-1972 to 2009-2012. Bold values denote Age-Standardised Mortality-Ratio (SMR) Ratios  
 176 significantly different from 1. Spatial variation (standard deviation of spatial random effects): a value  
 177 of 0 means that there is no spatial correlation.

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
<b>Period</b>				
1969-1972	1.00		1.00	
1979-1982	1.01	(0.97;1.05)	1.01	(0.97;1.05)
1989-1992	<b>1.04</b>	(1.00;1.09)	<b>1.05</b>	(1.01;1.09)
1999-2002	<b>0.81</b>	(0.78;0.84)	<b>0.81</b>	(0.78;0.85)
2009-2012	<b>0.57</b>	(0.54;0.59)	<b>0.57</b>	(0.54;0.60)
<b>Language</b>				
German	1.00		1.00	
French	0.99	(0.95;1.02)	1.02	(0.92;1.14)
Italian/Roman.	1.01	(0.96;1.08)	0.99	(0.83;1.16)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	<b>1.05</b>	(1.01;1.08)	1.03	(0.98;1.08)
<b>Years of population-based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.88;1.03)	0.95	(0.88;1.04)
<b>Socioeconomic index</b>				
per 10 point increase	1.02	(0.99;1.04)	1.02	(0.98;1.05)
<b>Spatial variation</b>			0.21	(0.18;0.24)

178

179 From the covariates studied, only the year of death and the urbanisation level in the non-spatial  
 180 model had a significant impact when investigating all periods. An urban environment was associated  
 181 with a 5% elevated SMR (3% in the spatial model) compared to a rural environment.

182 Limiting the analysis to the period 2009-2012 none of the regression factors had a significant  
 183 effect on breast cancer mortality. (table 3)

184

185 **Table 3** Spatio-temporal model estimates of age-standardised breast cancer mortality in  
 186 Switzerland in 2009-2012. Bold values denote Age-Standardised Mortality-Ratio (SMR) Ratios  
 187 significantly different from 1.

	<b>SMR Ratios (95% CI)</b>			
	Non-spatial		Spatial	
<b>Language</b>				
German	1.00		1.00	
French	1.00	(0.86;1.15)	1.03	(0.81;1.33)
Italian/Roman.	1.01	(0.87;1.16)	1.00	(0.68;1.37)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
<b>Years of population-based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
<b>Socioeconomic index</b>				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
<b>Spatial variation</b>			0.29	(0.24;0.35)

188

189 Most SMR ratios of the non-spatial and the spatial model showed nearly identical values. The  
 190 length of a screening programme and the French language region showed slightly higher values, but  
 191 the differences were not significant.

192 In 2009-2012, no region had a significantly higher or lower breast cancer mortality rate at 95% CI  
 193 level compared to the national mean. (figure 2) A map with covariate-adjusted smoothed SMR values  
 194 is not shown due to no information gain. The covariates are not significant and the geographical  
 195 patterns are the same as for the smoothed SMR values.

196 The socio-economic index value for the municipalities ranged from 28 to 85, where 25% of  
 197 municipalities were below 55 and 25% above 66.

198

## 199 **DISCUSSION**

200 In the past decades, breast cancer mortality has nearly halved in Switzerland when considering  
201 all ages together. This trend, including the shift from increasing to decreasing rates around the  
202 period 1989-1992, has been observed in several other European countries[4]. Although significant  
203 spatial differences in breast cancer incidence are well described for Switzerland, we have not found  
204 any significant differences in breast cancer mortality in any of the periods studied. We have not  
205 observed any general significant differences between regions classified by duration of screening  
206 programmes, urbanisation, language and socio-economic position. Also when limiting the analysis to  
207 the most recent period 2009-2012 none of the factors are significant. In fact, at 95% confidence level  
208 none of the regions have a significantly elevated or reduced breast cancer mortality compared to the  
209 national mean.

210 There are several factors why the significant differences in incidence do not translate into  
211 corresponding mortality differences. Most importantly, risk factors such as health and health-related  
212 behaviour reported to be different for the language regions[16] affect incidence but are not  
213 necessarily linked to mortality[27]. I.e. while a temporary increase in the use of hormone  
214 replacement therapy has led to an increase in breast cancer incidence, many of those tumours have  
215 a favourable prognosis and might have influenced breast cancer mortality only marginally[28].  
216 Accordingly, the French language region, despite earlier implementation of mammography screening  
217 programmes, does not show a relevant impact on breast cancer mortality in our study.

218 Since screening has been identified as a potential source of mortality reduction[21], we also  
219 included data on population-based screening programme duration. However, our study did not show  
220 a significant effect on mortality on the population level. The reasons for this are probably manifold  
221 and may include the fact that screen-detected cancers are mainly of low stage, many women have  
222 not participated in the screening programmes or have chosen to undergo opportunistic screening. In  
223 addition, the effect of advances in diagnosis and therapy on mortality is quite strong and may have

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2  
3 224 outweighed benefits from population-based screening programmes, as suggested by Autier et  
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5 225 al.[29]. Moreover, the level of opportunistic screening in Switzerland has been described to be quite  
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7 226 high[30], but data on the geographical differences in opportunistic screening use and therefore  
8  
9 227 overall screening participation are not available. Data on participation in population-based screening  
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11 228 programmes are published in a national monitoring report showing that participation rates of the  
12  
13 229 programmes are close to the combined mean of 47.8% [31].The ecological study design does not  
14  
15 230 allow the assessment of the combined impact of participation in and type (programme vs.  
16  
17 231 opportunistic) of mammography screening, or the impact of stage of tumour at diagnosis, and  
18  
19 232 mortality on individual level. For the above reasons, the interpretability with regard to screening is  
20  
21 233 limited. In addition, we had to group into 0-4 and 5+ years of screening in order to avoid overfitting  
22  
23 234 issues. There are only a few regions which are in close proximity to each other with 10+ years of  
24  
25 235 screening in 2009-2012 only (additional material, figure A1).

26  
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28  
29 236 The presented study is an in-depth analysis of our previous study[19], focusing on breast cancer  
30  
31 237 mortality using an additional year of more recent data. We were also interested in the effects on the  
32  
33 238 population level as a whole. The applied methodology of age standardisation suits this by taking  
34  
35 239 advantage of the actual age structure rather than of a standard population.

36  
37  
38 240 The non-significant fixed effect of socio-economic position is in line with the results of Panczak et  
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40 241 al[32]. The additional correction served the disentanglement of affluence from the urbanisation  
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42 242 parameter –which is connected with access to medical services– and further possible distortions.[33]

43  
44  
45 243 A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an  
46  
47 244 unstable rate by “borrowing” strength from its neighbours[34]. They can also assess the significance  
48  
49 245 of risk factors taking into account the geographical correlation, and are able to show spatial patterns  
50  
51 246 after adjusting for geographical differences in certain risk factors. By adding a time dimension,  
52  
53 247 Bayesian spatio-temporal models indicate changes of geographical patterns over time and determine  
54  
55 248 how the disease evolves in different regions and different groups of the population (age, language or  
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60

249 affluence groups). These models provide a state-of-the-art modelling approach over the last fifteen  
250 years for assessing spatio-temporal patterns and trends. We have not observed that coefficients in  
251 our analysis have shrunk towards zero when including geographical correlation as hypothesised by  
252 Hodges and Reich[35]. In fact, in the spatial model for 2009-2012, the impact of the French language  
253 region is 1.03 in comparison to 1.00 in the non-spatial model. However, we have included the results  
254 of the non-spatial models as well.

## 255 **Conclusion**

256 Geographical differences in breast cancer mortality are present in Switzerland, but at a moderate  
257 level with no significant differences to the overall mean and are not explained by the duration of  
258 population-based screening programmes, socio-economic position, urbanisation and language  
259 region.

260 There has been a strong reduction of breast cancer mortality from the 90s on; geographical  
261 differences in the reduction are present but are also small. The geographical differences will need to  
262 be re-evaluated when the running time of mammography screening programmes in Switzerland is  
263 sufficiently long enough for any effect on mortality to become visible.

## 264 **FUNDING**

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267 no role in the study design, data collection, and analysis, decision to publish, or preparation of the  
268 manuscript.

## 269 **COMPETING INTERESTS**

270 All authors have completed the ICMJE uniform disclosure form at  
271 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted

1  
2  
3 272 work; no financial relationships with any organisations that might have an interest in the submitted  
4  
5 273 work in the previous three years; no other relationships or activities that could appear to have  
6  
7 274 influenced the submitted work.  
8  
9  
10

## 11 275 **CONTRIBUTIONS**

12 276 PV, SE conceived of the study. CH carried out the analysis and data acquisition. CH, SE, PV  
13  
14  
15 277 contributed to the analysis of the data and the writing of the manuscript. CH, PV, BT, NP, CR and SE  
16  
17 278 contributed to interpretation of the findings and critically revised the manuscript. All authors read  
18  
19 279 and approved the final manuscript.  
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22  
23

## 24 280 **TRANSPARENCY DECLARATION**

25 281 The lead author affirms that this manuscript is an honest, accurate, and transparent account of  
26  
27 282 the study being reported; that no important aspects of the study have been omitted; and that any  
28  
29 283 discrepancies from the study as planned (and, if relevant, registered) have been explained.  
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## 35 284 **ETHICAL APPROVAL**

36 285 Ethical approval was not required as this study is an analysis of publically available, anonymous  
37  
38 286 and previously collected data.  
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## 44 287 **LICENSE**

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## 300 DATA SHARING STATEMENT

301 All data are publically available from the sources stated in the methods section. The statistical  
302 code is available from the corresponding author.

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## 402 FIGURES

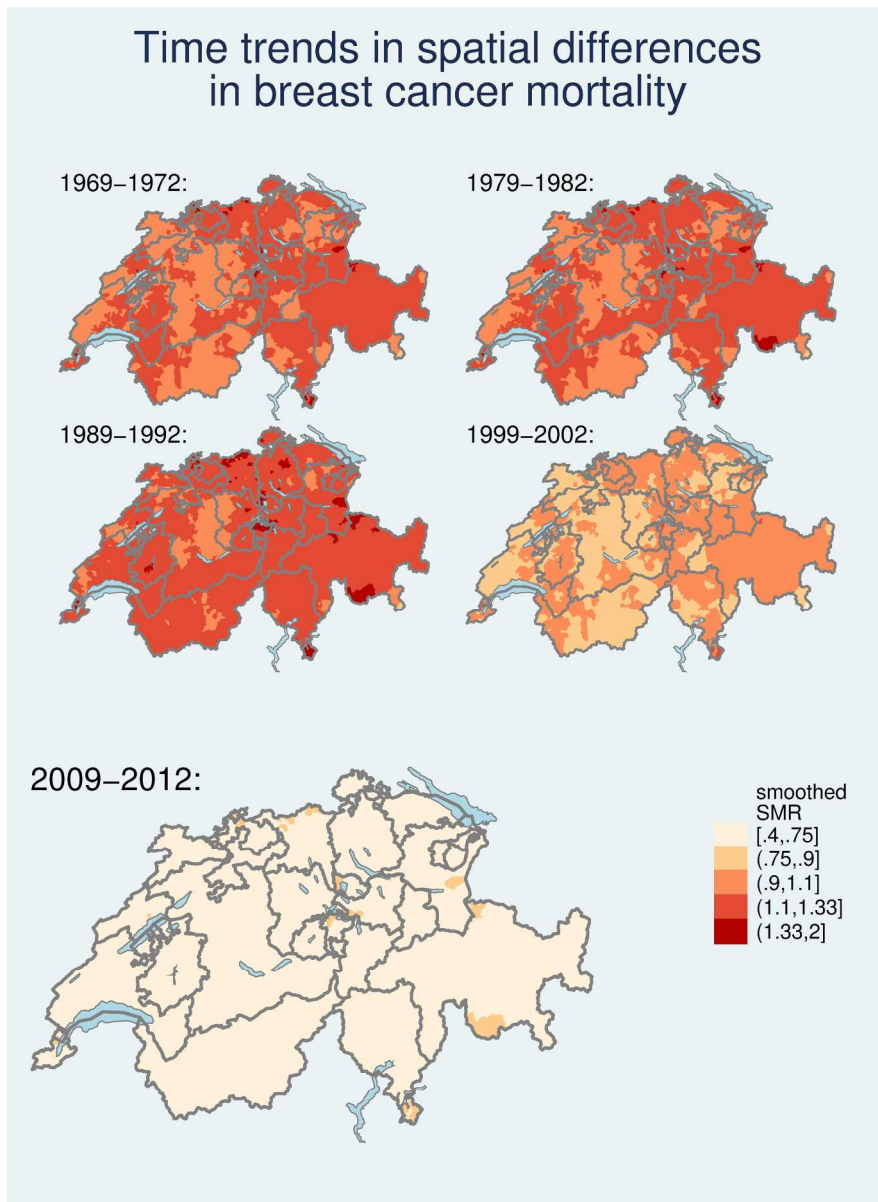
403 **Fig. 1** Development of age-standardised breast cancer mortality (SMR) and spatial differences  
404 therein among time. Values are calculated and smoothed in relation to the all-period combined  
405 mortality. Darker colours represent a higher mortality for the specific age structure and population in  
406 that area and time period.

407 **Fig. 2** Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012.

408 \*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

## 409 ADDITIONAL MATERIAL

410 A1. Figures depicting urbanization classification, language regions Screening duration and Swiss  
411 Socio-Economic Position (SEP) in Switzerland.

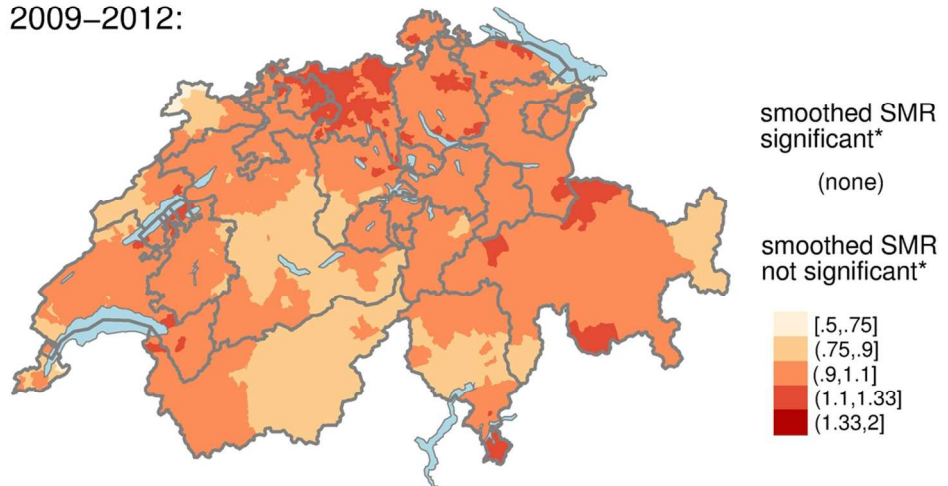


Development of age standardized breast cancer mortality (SMR) and spatial differences therein among time. Values are calculated and smoothed in relation to the all-period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period.

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Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.  
\*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

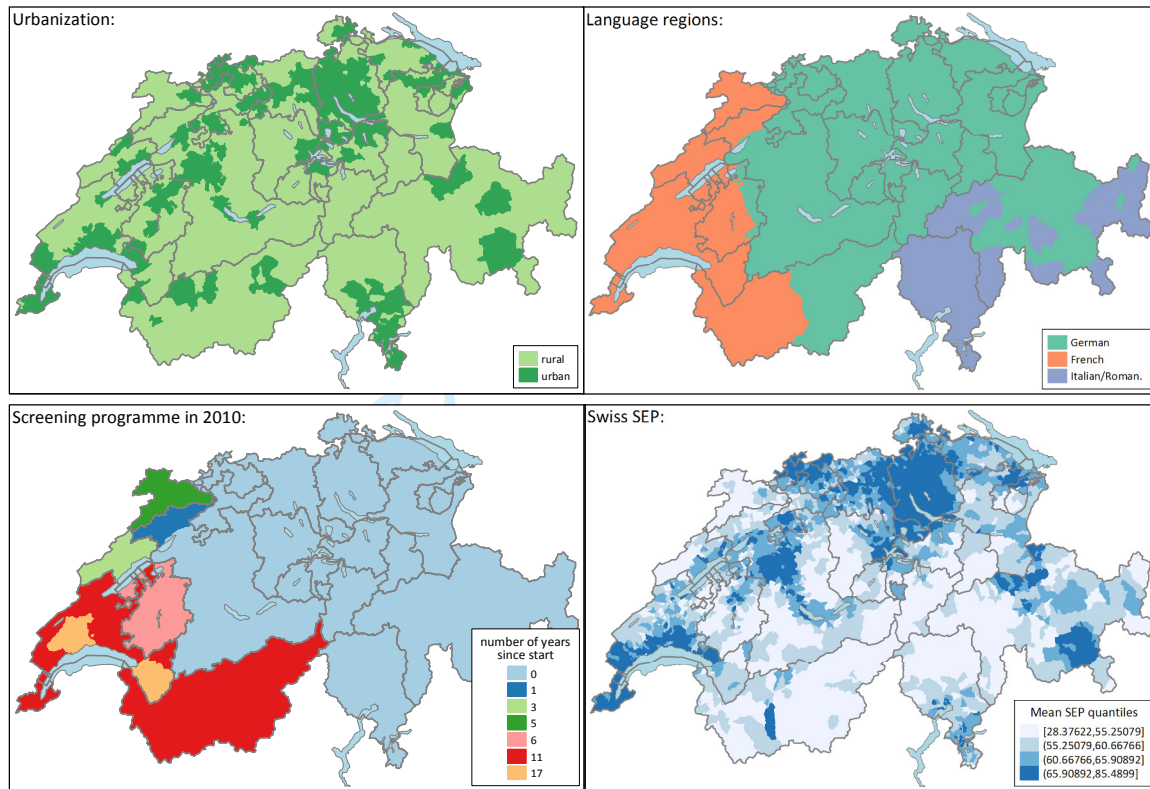
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**Additional material**

**Figure A1:** Urbanization classification, language regions Screening duration and Swiss Socio-Economic Position (SEP) in Switzerland.



## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA (Ecological study)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, lines 85-88
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods page 5, Introduction 3-4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (c) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, page 5, lines 91-101
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5
Bias	9	Describe any efforts to address potential sources of bias	Methods page 6, Introduction page 4, Discussion page 9-10
Study size	10	Explain how the study size was arrived at	Ecological study, Methods page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods page 4-6
		(b) Describe any methods used to examine subgroups and interactions	Methods page 6
		(c) Explain how missing data were addressed	No missing data, ecological study
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	Pages 6-8

Continued on next page

<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results page 6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA, page 6
		(b) Indicate number of participants with missing data for each variable of interest	No missing data (ecological study)
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7-8
		(b) Report category boundaries when continuous variables were categorized	Page 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-8
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-11
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 11

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



# BMJ Open

## Impact of mammography screening programmes on breast cancer mortality in Switzerland, a country with different regional screening policies

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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Oncology, Public health
Keywords:	Switzerland, Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY, mortality, Bayesian disease mapping

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## TITLE

Impact of mammography screening programmes on breast cancer mortality in Switzerland, a country with different regional screening policies

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## KEYWORDS

Neoplasm, Breast cancer, Switzerland, Bayesian disease mapping, mortality

## WORD COUNT

2450 words, excluding title page, abstract, references, figures, and tables.

## ABSTRACT

**Objectives:** In the past decades, mortality due to breast cancer has declined considerably in Switzerland and other developed countries. The reasons for this decline remain controversial as several factors occurred almost simultaneously, including important advances in treatment approaches, breast cancer awareness, and the introduction of mammography screening programmes in many European countries. In Switzerland, mammography screening programmes have existed in some regions for over 20 years, but do not yet exist in others. This offers the possibility to analyse its effects with modern spatio-temporal methodology.

**Setting:** Switzerland

**Participants:** The study covers breast cancer deaths of the female population of Switzerland during the period 1969-2012. We retrieved data from the Swiss Federal Statistical Office (FSO) aggregated on a small-area level.

**Design:** We fitted Bayesian hierarchical spatio-temporal models on death rates indirectly standardised by national references. We used linguistic region, degree of urbanisation, duration of population-based screening programmes and socio-economic index as covariates.

**Results:** In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and declined strongly thereafter. Until 2009-2012, the standardised mortality ratio (SMR) declined to 57% (95% CI 54% to 60%) of the 1969-1972 value. None of the other coefficients of the spatial regressions had a significant effect on breast cancer mortality. In 2009-2012 no region had significantly elevated or reduced breast cancer mortality at 95% CI (Credible Interval) level compared to the national mean.

**Conclusion:** There has been a strong reduction of breast cancer mortality from the 1990s onwards. No important spatial disparities were observed. The moderate geographical differences we found are within credible intervals using modern Bayesian techniques. The factors studied

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3 43 (urbanisation, language, duration of population-based screening programme and socioeconomic  
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5 44 characteristics) did not seem to have an influence on them.  
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## 9 45 **ARTICLE SUMMARY**

### 10 46 **Strengths and limitations**

- 11 47 • A modern Bayesian spatial model was used to improve estimation of an unstable rate by  
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16 48 “borrowing” strength from its neighbours.
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19 49 • The model is capable of assessing the significance of risk factors while also taking the  
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21 50 geographical correlation into account.
- 22  
23 51 • Switzerland with its homogeneous health system and different regional screening policies  
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25 52 provides an ideal setting for assessing the impact of population-based mammography  
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27 53 screening programmes.
- 28  
29 54 • Data on the geographical differences in opportunistic screening use and therefore overall  
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31 55 screening participation are not available,
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33 56 • The ecological study design does not allow an assessment of the combined impact of  
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35 57 participation in and type (programme vs. opportunistic) of mammography screening.
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## 39 40 41 42 59 **INTRODUCTION**

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45 60 In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the  
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47 61 leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. Mortality  
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49 62 due to breast cancer has declined considerably in the past decades in Switzerland and other  
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51 63 developed countries[4]. The reasons for the decline remain controversial because several factors  
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54 64 including important advances in treatment approaches, breast cancer awareness and the  
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3 65 introduction of mammography screening programmes in many European countries occurred almost  
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5 66 simultaneously.  
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8 67 Some randomised controlled studies[5] have demonstrated a breast cancer mortality reduction  
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10 68 of 20% for women invited for breast cancer screening. However, they were conducted in the 1970s  
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12 69 to 80s. Since then, many advances in therapies have been made and adopted[6] so that some  
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14 70 authors doubt that the difference would persist under present conditions. Therefore, often used  
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16 71 historical pre-screening control groups are not best suited to disentangle these effects. Autier et al  
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18 72 [7] compared countries in Europe but a criticism was that different countries may have different  
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20 73 health systems. Kalager et al.[8] used comparison groups in Norway and showed that only a third of  
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22 74 the total mortality reduction could be attributed to mammography screening. However, a short  
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24 75 observation period was used. Olsen et al.[9] confirmed these results in principle with the same data  
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26 76 but with a somewhat longer follow-up duration. In addition, in a setting where voluntary screening is  
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28 77 assumed to be high, it is unknown what the effect an organised screening programme would be for  
29  
30 78 the population as a whole.  
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34 79 In Switzerland, with its homogenous health system, these pitfalls can be avoided. Switzerland is a  
35  
36 80 small confederation of 26 relatively autonomous states called cantons with somewhat low  
37  
38 81 inequalities[10] and many health- and cancer-related resources.[11-13] Although the health care  
39  
40 82 system is homogeneous in providing universal and rapid access to and use of almost unlimited health  
41  
42 83 care resources, some health care policies are developed at the cantonal level; in particular, the  
43  
44 84 decision to initiate a population-based mammography-screening programme. These programmes  
45  
46 85 were implemented in Switzerland at different times over the past two decades. The first Swiss  
47  
48 86 mammography pilot programme was established in 1993 in the French-speaking canton of Vaud.  
49  
50 87 However, it was only in 2010 that the first organised programme in a German-speaking canton (St.  
51  
52 88 Gallen) started.  
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3 89 In breast cancer incidence, cantonal differences are well-known and have been attributed to the  
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5 90 differential use of opportunistic or organised mammography screening[14]. In addition, considerable  
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7 91 differences in health and health-related behaviour that affect the risk of breast cancer, including  
8  
9 92 alcohol intake and a healthy diet, have been reported for the Swiss language regions [15 16], as well  
10  
11 93 as differences in the age at first child birth and number of children born to a mother[17]. Differences  
12  
13 94 in access to mammography screening and in lifestyle may be reflected in spatio-temporal differences  
14  
15 95 in both breast cancer incidence and mortality, whereas only the latter will reflect the management of  
16  
17 96 breast cancer.

19  
20 97 In contrast, breast cancer mortality studies in Switzerland showed contradictory results. Bulliard  
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22 98 et al[18] observed a steeper decrease from 1980 to 2002 in 55-74-year-olds in French-speaking  
23  
24 99 regions where population-based mammography screening started earlier. In a recent study[19] we  
25  
26 100 presented the spatio-temporal trends of female gender related cancer mortality in Switzerland by  
27  
28 101 age group. The geographical differences found were small. We observed a differential decline in  
29  
30 102 breast cancer mortality by age. The decline was highest in women younger than 50 and lower in  
31  
32 103 women 75 or older. A similar pattern was observed in other European countries[4] and attributed to  
33  
34 104 early detection by mammography and to improved treatment [20-22]. However, it was not clear to  
35  
36 105 what extent improvements in survival could have affected the age at death. It was difficult to  
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38 106 evaluate a shift of deaths into the next higher age group, and the influence of screening  
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40 107 programmes, based on using fixed age groups rather than cohorts.

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44 108 In the present study, we aimed to assess the spatio-temporal patterns in breast cancer mortality,  
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46 109 and specifically the effect of population-based mammography screening programmes on it. We  
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48 110 corrected for urbanisation for which a mortality gradient was described[23] and additionally for area-  
49  
50 111 based socio-economic factors, which may have influenced results in the previous study.

## 55 112 **METHODS**

## 113 **Data sources**

114 The Swiss Federal Statistical Office provided data on female breast cancer mortality,  
115 electronically available for the period of 1969-2012. The anonymised data included sex, age, year of  
116 birth and death for each individual, nationality, municipality of residence, the cause of death and co-  
117 morbidities. The cause of death and co-morbidities were coded centrally from death certificates  
118 using the 8th revision of the International Classification of Diseases (ICD) for deaths until 1994, and  
119 the 10th revision for deaths that occurred afterwards. The transition to the 10th revision of the ICD-  
120 10 was accompanied by changes in death certificate coding practices (priority rules). We used age-  
121 and cancer site-specific correction factors as proposed by Lutz et al[24] for the death counts. We  
122 included all cases coded with main causes of death being cancer of the female breast (ICD-10 C50.0-  
123 C50.9). According to federal regulations, mortality data excluding a person's identifying information  
124 can be used in epidemiological studies without additional ethics committee approval.

125 The administrative borders of Swiss municipalities define the smallest geographical unit for  
126 which data were available. There are around 2500 municipalities in the country with a median  
127 population of 740 inhabitants in 1970 and 1150 in 2010.

128 Aggregated population data by age and area unit were extracted from the census that takes  
129 place in Switzerland every 10 years. The last census was conducted in 2010. Because of missing  
130 detailed intercensal population data, we aggregated the mortality data in five 4-year periods around  
131 the census years, i.e. 1969-1972, 1979-1982, 1989-1992, 1999-2002 and 2009-2012, in which  
132 population was assumed to be constant and identical to the census year.

133 From the same source, we retrieved data on language region (German, French, and Italian and  
134 Romansh) and urbanisation (rural/urban). We obtained information on population-based screening  
135 programmes from the Swiss Federation of Cancer Screening Programmes[25], and categorised their  
136 duration in the census years into "no programme", "0-4 years" and "5+ years". Data on socio-



137 economic position (SEP) by municipality were provided by the Swiss National Cohort[26] based on  
138 the census data of 2000.

139 Table 1 shows the observed number of deaths and mortality rates for each of the co-variates.

140 **Table 1** Observed numbers of female breast cancer deaths and mortality rates per 100,000 PY by  
141 period and municipality characteristics. The total numbers before 1994 include the correction  
142 factors.

	Total no. of breast cancer deaths	%	yearly population (x1000)	crude rate	ASR	p-value for ASR homogeneity
<b>Period</b>						p<0.01
1969-1972	4,177	16%	3,180	32.8	32.0	
1979-1982	4,953	19%	3,251	38.1	32.5	
1989-1992	5,968	23%	3,483	42.8	32.6	
1999-2002	5,261	20%	3,720	35.4	25.4	
2009-2012	5,574	21%	3,993	34.9	22.3	
<b>Language</b>						p=0.56
German	18,613	72%	12,622	36.9	28.5	
French	5,915	23%	4,159	35.6	27.7	
Italian/Roman.	1,405	5%	847	41.5	28.9	
<b>Urbanisation level</b>						p=0.08
Rural	6,172	24%	4,491	34.4	26.9	
Urban	19,761	76%	13,137	37.6	28.8	
<b>Years of population based screening*</b>						p=0.53
no programme	4,246	76%	2,942	36.1	22.6	
1-4 years	169	3%	115	36.9	23.4	
5+ years	1,159	21%	936	31.0	21.2	
<b>Socioeconomic index quartiles</b>						p=0.24
Q1 (lowest)	1,999	8%	1,478	33.8	26.4	
Q2	4,313	17%	3,033	35.6	28.1	
Q3	5,864	23%	4,199	34.9	27.7	
Q4 (highest)	13,757	53%	8,919	38.6	29.0	

\*only for the period 2009-2012, length of screening refers to the year 2010

## 144 Statistical methods

145 As a small area geographical unit, we used the municipality borders as of 2012. We used  
146 municipality transition protocols from the Federal Statistical Office to align all data to this structure.

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2  
3 147 We investigated mortality for all ages combined in a spatial and a non-spatial model, one time  
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5 148 for the five time periods from 1969 to 2012 to assess possible non-linear time trends, and another  
6  
7 149 time only for the period of 2009-2012.  
8  
9

10 150 For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model  
11  
12 151 formulations as described in Herrmann et al 2015[19], fitted on the number of deaths aggregated by  
13  
14 152 small area and year, with the mean being equal to the product of the expected death count and age-  
15  
16 153 standardised mortality rate. The indirect standardisation used 5-year age intervals. Expected  
17  
18 154 mortality counts for each small area and year were obtained from the study population using  
19  
20 155 nationwide age-specific mortality rates, once for all periods and again only for the period of 2009-  
21  
22 156 2012. The small-area-specific random effects were modelled via conditional autoregressive (CAR)  
23  
24 157 models to filter out the noise and highlight the observed patterns. The deviance information criterion  
25  
26 158 (DIC) was used to select the regression model from Poisson, zero-inflated Poisson and Negative  
27  
28 159 Binomial regression models. The DIC was lowest with the Poisson regression model.  
29  
30

31  
32 160 We accounted for differences that were influenced by linguistic region, life in rural or urban  
33  
34 161 areas, screening programme duration, and socio-economic position. These analyses are used to  
35  
36 162 indicate whether there are significant differences in cancer mortality for each of the above  
37  
38 163 covariates, assessed by 95% Bayesian Credible Intervals (CI).  
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## 41 164 **Patient involvement**

42  
43 165 No patients were involved in this study.  
44  
45  
46  
47

## 48 166 **RESULTS**

49  
50  
51 167 In Switzerland, more than 61,000 women died from breast cancer between 1969 and 2012. Table  
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53 168 2 presents the results of the regressions including all time periods and time trends. In Switzerland,  
54  
55 169 breast cancer mortality in females slightly increased until the 1989-1992 period, and has declined  
56  
57 170 strongly since. Until the most recent period (2009-2012), the SMR has fallen to 57% of the 1969-1972  
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59

171 period's value, both in the non-spatial and the spatial models. The trends and geographical  
172 differences are visualised in Figure 1.

173

174

175 **Table 2** Spatio-temporal model estimates of age-specific breast cancer mortality in Switzerland from  
176 the 1969-1972 period to the 2009-2012 period. Bold values denote age-standardised mortality-ratio  
177 (SMR) ratios significantly different from 1. Spatial variation (standard deviation of spatial random  
178 effects): a value of 0 means that there is no spatial correlation.

Period	SMR Ratios (95% CI)		Spatial	
	Non-spatial			
1969-1972	1.00		1.00	
1979-1982	1.01	(0.97;1.05)	1.01	(0.97;1.05)
1989-1992	<b>1.04</b>	(1.00;1.09)	<b>1.05</b>	(1.01;1.09)
1999-2002	<b>0.81</b>	(0.78;0.84)	<b>0.81</b>	(0.78;0.85)
2009-2012	<b>0.57</b>	(0.54;0.59)	<b>0.57</b>	(0.54;0.60)
<b>Language</b>				
German	1.00		1.00	
French	0.99	(0.95;1.02)	1.02	(0.92;1.14)
Italian/Roman.	1.01	(0.96;1.08)	0.99	(0.83;1.16)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	<b>1.05</b>	(1.01;1.08)	1.03	(0.98;1.08)
<b>Years of population-based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.88;1.03)	0.95	(0.88;1.04)
<b>Socioeconomic index</b>				
per 10 point increase	1.02	(0.99;1.04)	1.02	(0.98;1.05)
<b>Spatial variation</b>			0.21	(0.18;0.24)

179

180 From the covariates studied, only the year of death and the urbanisation level in the non-spatial  
181 model had a significant impact when investigating all periods. An urban environment was associated  
182 with a 5% elevated SMR (3% in the spatial model) compared with a rural environment.

183 Limiting the analysis to the period of 2009-2012, none of the regression factors had a significant  
184 effect on breast cancer mortality. (Table 3)

185

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188

**Table 3** Spatio-temporal model estimates of age-standardised breast cancer mortality in

Switzerland in the 2009-2012 period. Bold values denote age-standardised mortality-ratio (SMR)

ratios significantly different from 1.

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
<b>Language</b>				
German	1.00		1.00	
French	1.00	(0.86;1.15)	1.03	(0.81;1.33)
Italian/Roman.	1.01	(0.87;1.16)	1.00	(0.68;1.37)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
<b>Years of population-based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
<b>Socioeconomic index</b>				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
<b>Spatial variation</b>			0.29	(0.24;0.35)

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Most SMR ratios of the non-spatial and the spatial model showed nearly identical values. The length of a screening programme and the French language region showed slightly higher values, but the differences were not significant.

193

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196

In the 2009-2012 period, no region had a significantly higher or lower breast cancer mortality rate at 95% CI level compared with the national mean. (Figure 2) A map with covariate-adjusted smoothed SMR values is not shown because there was no information gain. The covariates are not significant and the geographical patterns are the same as for the smoothed SMR values.

197

198

The socio-economic index value for the municipalities ranged from 28 to 85, where 25% of municipalities were below 55 and 25% above 66.

199

## 200 DISCUSSION

201 In the past decades, breast cancer mortality has nearly halved in Switzerland when considering  
202 all ages together. This trend, including the shift from increasing to decreasing rates around the  
203 period of 1989-1992, has been observed in several other European countries[4]. Although significant  
204 spatial differences in breast cancer incidence are well described for Switzerland, we have not found  
205 any significant differences in breast cancer mortality in any of the periods studied. We have not  
206 observed any general significant differences between regions classified by duration of screening  
207 programmes, urbanisation, language and socio-economic position. In addition, when limiting the  
208 analysis to the most recent period (2009-2012), none of the factors are significant. In fact, at 95%  
209 confidence level, none of the regions have a significantly elevated or reduced breast cancer mortality  
210 compared with the national mean.

211 There are several factors that explain why the significant differences in incidence do not translate  
212 into corresponding mortality differences. Most importantly, risk factors such as health and health-  
213 related behaviour that are reported to be different for the language regions[16] affect incidence but  
214 are not necessarily linked to mortality[27]. That is, while a temporary increase in the use of hormone  
215 replacement therapy has led to an increase in breast cancer incidence, many of those tumours have  
216 a favourable prognosis and might have influenced breast cancer mortality only marginally[28].  
217 Accordingly, the French language region, despite earlier implementation of mammography screening  
218 programmes, does not show a relevant impact on breast cancer mortality in our study.

219 Because screening has been identified as a potential source of mortality reduction[21], we also  
220 included data on population-based screening programme duration. However, our study did not show  
221 a significant effect on mortality on the population level. The reasons for this are probably manifold,  
222 and may include factors such as screen-detected cancers being mainly of low stage, many women  
223 having not participated in the screening programmes, or having chosen to undergo opportunistic  
224 screening. In addition, the effect of advances in diagnosis and therapy on mortality is quite strong

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2  
3 225 and may have outweighed benefits from population-based screening programmes, as suggested by  
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5 226 Autier et al.[29]. Moreover, the level of opportunistic screening in Switzerland has been described to  
6  
7 227 be quite high[30], but data on the geographical differences in opportunistic screening use, and  
8  
9 228 therefore overall screening participation, are not available. Data on participation in population-based  
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11 229 screening programmes are published in a national monitoring report showing that participation rates  
12  
13 230 of the programmes are close to the combined mean of 47.8% [31].The ecological study design does  
14  
15 231 not allow the assessment of the combined impact of participation in and type (programme vs.  
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17 232 opportunistic) of mammography screening, or the impact of stage of tumour at diagnosis, and  
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19 233 mortality at an individual level. For the above reasons, the interpretability with regard to screening is  
20  
21 234 limited. In addition, we had to group into 0-4 years and 5+ years of screening, which was done to  
22  
23 235 avoid overfitting issues. There are only a few regions that are in close proximity to each other with  
24  
25 236 10+ years of screening in the 2009-2012 period only (additional material, Figure A1).

27  
28  
29 237 The present study is an in-depth analysis of our previous study[19], focusing on breast cancer  
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31 238 mortality using an additional year of more recent data. We were also interested in the effects on the  
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33 239 population as a whole. The applied methodology of age standardisation suits this by taking  
34  
35 240 advantage of the actual age structure rather than of a standard population.

36  
37  
38 241 The non-significant fixed effect of socio-economic position is in line with the results of Panczak et  
39  
40 242 al[32]. The additional correction served the disentanglement of affluence from the urbanisation  
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42 243 parameter –which is connected with access to medical services– and further possible distortions.[33]

43  
44  
45 244 A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an  
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47 245 unstable rate by “borrowing” strength from its neighbours[34]. These models can also assess the  
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49 246 significance of risk factors, taking into account the geographical correlation, and are able to show  
50  
51 247 spatial patterns after adjusting for geographical differences in certain risk factors. By adding a time  
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53 248 dimension, Bayesian spatio-temporal models indicate changes of geographical patterns over time  
54  
55 249 and determine how a disease evolves in different regions and different groups of the population

250 (age, language or affluence groups). These models have provided a state-of-the-art modelling  
251 approach over the last 15 years for assessing spatio-temporal patterns and trends. We have not  
252 observed that coefficients in our analysis have shrunk towards zero when including geographical  
253 correlation as hypothesised by Hodges and Reich[35]. In fact, in the spatial model for the 2009-2012  
254 period, the impact of the French language region is 1.03 compared with 1.00 in the non-spatial  
255 model. However, we have included the results of the non-spatial models as well.

## 256 **Conclusion**

257 There has been a strong reduction of breast cancer mortality from the 1990s onwards.  
258 Geographical differences are present, but at a moderate level with no significant differences in the  
259 overall mean. In addition, they are not explained by the duration of population-based screening  
260 programmes, socio-economic position, urbanisation and language region. Low participation rates and  
261 opportunistic screening use may have contributed to the low impact of mammography screening  
262 programmes. Continuous evaluation of geographical patterns of breast cancer mortality using  
263 modern spatio-temporal methodology is necessary for evaluating the efficacy of programmes.

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## 269 **COMPETING INTERESTS**

270 All authors have completed the ICMJE uniform disclosure form at  
271 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
272 work; no financial relationships with any organisations that might have an interest in the submitted



273 work in the previous three years; no other relationships or activities that could appear to have  
274 influenced the submitted work.

## 275 **CONTRIBUTIONS**

276 PV, SE conceived of the study. CH carried out the analysis and data acquisition. CH, SE, PV  
277 contributed to the analysis of the data and the writing of the manuscript. CH, PV, BT, NP, CR and SE  
278 contributed to interpretation of the findings and critically revised the manuscript. All authors read  
279 and approved the final manuscript.

## 280 **TRANSPARENCY DECLARATION**

281 The lead author affirms that this manuscript is an honest, accurate, and transparent account of  
282 the study being reported; that no important aspects of the study have been omitted; and that any  
283 discrepancies from the study as planned (and, if relevant, registered) have been explained.

## 284 **ETHICAL APPROVAL**

285 Ethical approval was not required as this study is an analysis of publically available, anonymous  
286 and previously collected data.

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## 300 DATA SHARING STATEMENT

301 All data are publically available from the sources stated in the methods section. The statistical  
 302 code is available from the corresponding author.

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401

## 402 FIGURES

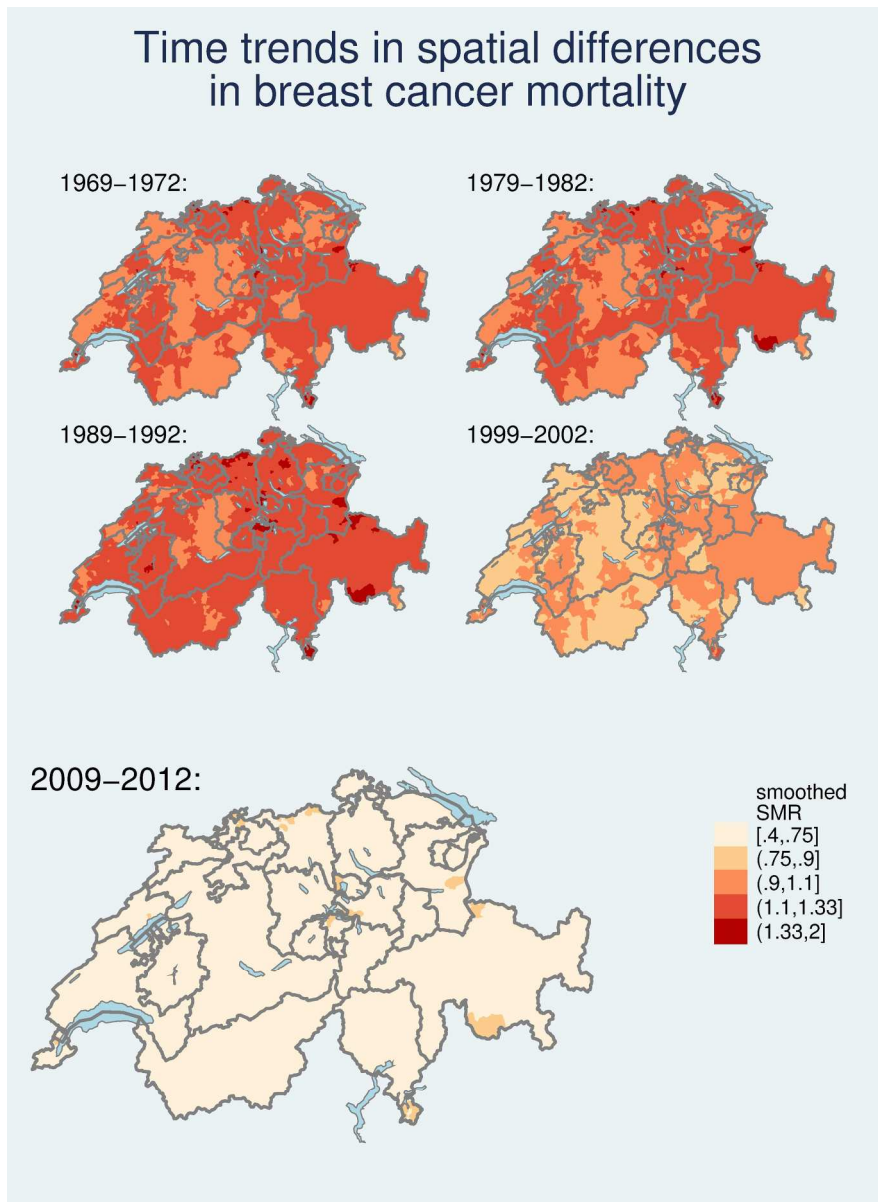
403 **Fig. 1** Development of age-standardised breast cancer mortality (SMR) and spatial differences  
404 therein among time. Values are calculated and smoothed in relation to the all-period combined  
405 mortality. Darker colours represent a higher mortality for the specific age structure and population in  
406 that area and time period.

407 **Fig. 2** Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012.

408 \*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

## 409 ADDITIONAL MATERIAL

410 A1. Figures depicting urbanization classification, language regions Screening duration and Swiss  
411 Socio-Economic Position (SEP) in Switzerland.

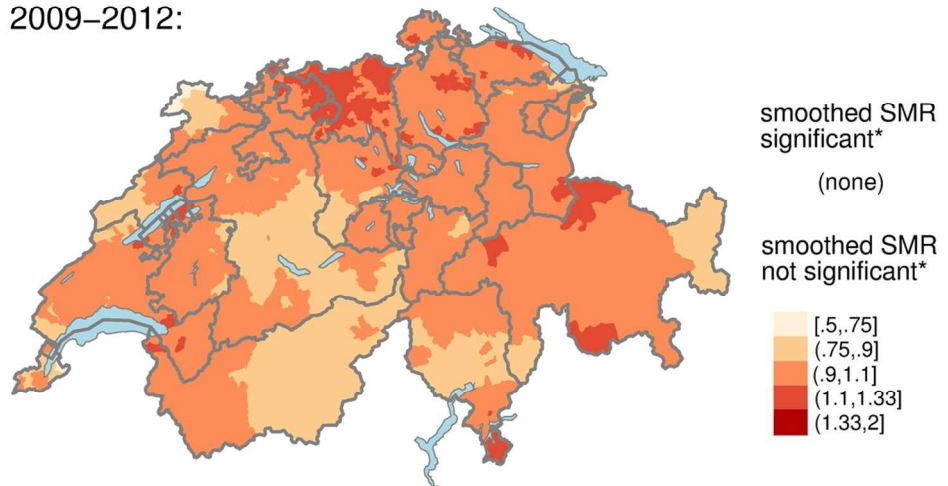


Development of age standardized breast cancer mortality (SMR) and spatial differences therein among time. Values are calculated and smoothed in relation to the all-period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period.

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2009–2012:



Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.  
\*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

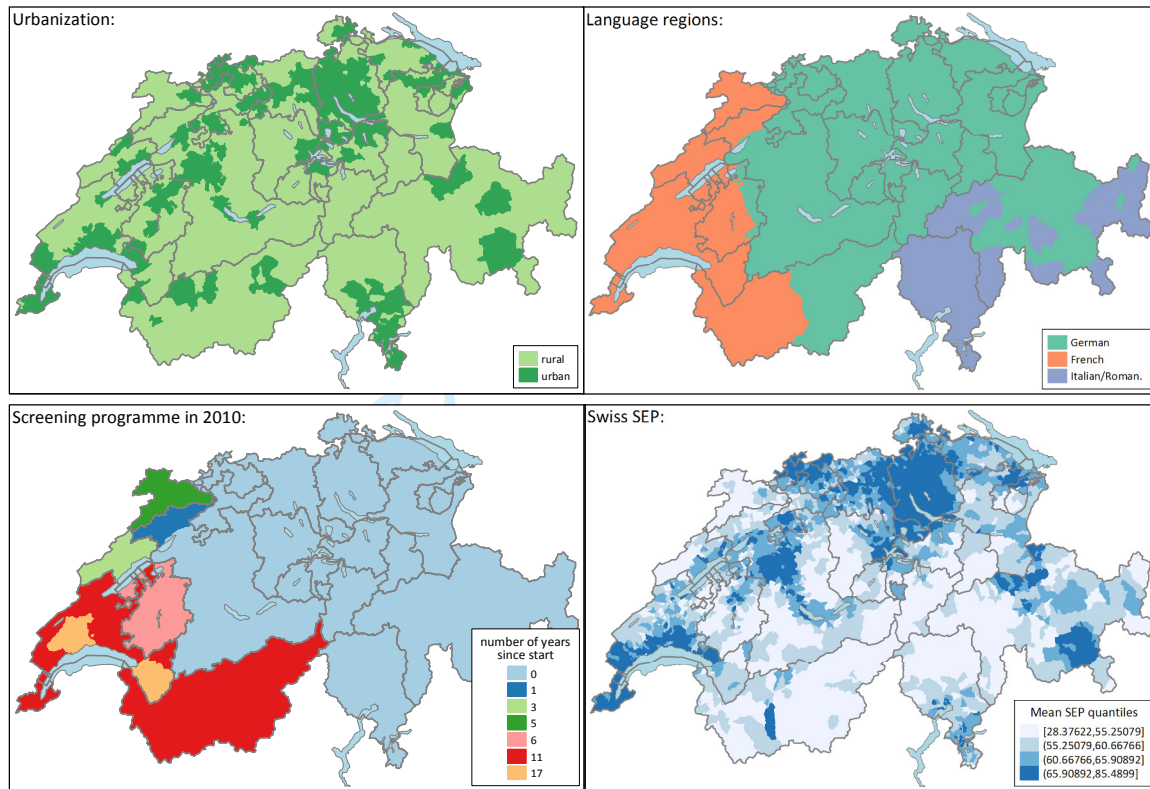
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**Additional material**

**Figure A1:** Urbanization classification, language regions Screening duration and Swiss Socio-Economic Position (SEP) in Switzerland.





## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA (Ecological study)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, lines 85-88
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods page 5, Introduction 3-4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (c) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, page 5, lines 91-101
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5
Bias	9	Describe any efforts to address potential sources of bias	Methods page 6, Introduction page 4, Discussion page 9-10
Study size	10	Explain how the study size was arrived at	Ecological study, Methods page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods page 4-6
		(b) Describe any methods used to examine subgroups and interactions	Methods page 6
		(c) Explain how missing data were addressed	No missing data, ecological study
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	Pages 6-8

Continued on next page

<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results page 6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA, page 6
		(b) Indicate number of participants with missing data for each variable of interest	No missing data (ecological study)
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7-8
		(b) Report category boundaries when continuous variables were categorized	Page 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-8
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-11
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 11

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Impact of mammography screening programmes on breast cancer mortality in Switzerland, a country with different regional screening policies

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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Oncology, Public health
Keywords:	Switzerland, Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY, mortality, Bayesian disease mapping

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Manuscripts

## TITLE

Impact of mammography screening programmes on breast cancer mortality in Switzerland, a country with different regional screening policies

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## KEYWORDS

Neoplasm, Breast cancer, Switzerland, Bayesian disease mapping, mortality

## WORD COUNT

2450 words, excluding title page, abstract, references, figures, and tables.

## ABSTRACT

**Introduction:** In the past decades, mortality due to breast cancer has declined considerably in Switzerland and other developed countries. The reasons for this decline remain controversial as several factors occurred almost simultaneously, including important advances in treatment approaches, breast cancer awareness, and the introduction of mammography screening programmes in many European countries. In Switzerland, mammography screening programmes (MSPs) have existed in some regions for over 20 years, but do not yet exist in others. This offers the possibility to analyse its effects with modern spatio-temporal methodology. We aimed to assess the spatio-temporal patterns and the effect of MSPs on breast cancer mortality.

**Setting:** Switzerland

**Participants:** The study covers breast cancer deaths of the female population of Switzerland during the period 1969-2012. We retrieved data from the Swiss Federal Statistical Office (FSO) aggregated on a small-area level.

**Design:** We fitted Bayesian hierarchical spatio-temporal models on death rates indirectly standardised by national references. We used linguistic region, degree of urbanisation, duration of population-based screening programmes and socio-economic index as covariates.

**Results:** In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and declined strongly thereafter. Until 2009-2012, the standardised mortality ratio (SMR) declined to 57% (95% CI 54% to 60%) of the 1969-1972 value. None of the other coefficients of the spatial regressions had a significant effect on breast cancer mortality. In 2009-2012 no region had significantly elevated or reduced breast cancer mortality at 95% CI (Credible Interval) level compared to the national mean.

**Conclusion:** There has been a strong reduction of breast cancer mortality from the 1990s onwards. No important spatial disparities were observed. The factors studied (urbanisation, language, duration of population-based MSP and socioeconomic characteristics) did not seem to

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3 44 have an influence on them. Low participation rates and opportunistic screening use may have  
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5 45 contributed to the low impact of MSPs.  
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## 9 46 **ARTICLE SUMMARY**

### 10 47 **Strengths and limitations**

- 11  
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14 48 • A modern Bayesian spatial model was used to improve estimation of an unstable rate by  
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16 49 “borrowing” strength from its neighbours.  
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19 50 • The model is capable of assessing the significance of risk factors while also taking the  
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21 51 geographical correlation into account.  
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23 52 • Switzerland with its homogeneous health system and different regional screening policies  
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25 53 provides an ideal setting for assessing the impact of population-based mammography  
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27 54 screening programmes.  
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29 55 • Data on the geographical differences in opportunistic screening use and therefore overall  
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31 56 screening participation are not available, where opportunistic screening use is estimated to  
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33 57 be high and programme participation less than 50%.  
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36 58 • The ecological study design does not allow an assessment of the combined impact of  
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38 59 participation in and type (programme vs. opportunistic) of mammography screening.  
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## 45 61 **INTRODUCTION**

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47 62 In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the  
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49 63 leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. Mortality  
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51 64 due to breast cancer has declined considerably in the past decades in Switzerland and other  
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53 65 developed countries[4]. The reasons for the decline remain controversial because several factors  
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55 66 including important advances in treatment approaches, breast cancer awareness and the  
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3 67 introduction of mammography screening programmes in many European countries occurred almost  
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5 68 simultaneously.  
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8 69 Some randomised controlled studies[5] have demonstrated a breast cancer mortality reduction  
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10 70 of 20% for women invited for breast cancer screening. However, they were conducted in the 1970s  
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12 71 to 80s. Since then, many advances in therapies have been made and adopted[6] so that some  
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14 72 authors doubt that the difference would persist under present conditions. Therefore, often used  
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16 73 historical pre-screening control groups are not best suited to disentangle these effects. Autier et al  
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18 74 [7] compared countries in Europe but a criticism was that different countries may have different  
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20 75 health systems. Kalager et al.[8] used comparison groups in Norway and showed that only a third of  
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22 76 the total mortality reduction could be attributed to mammography screening. However, a short  
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24 77 observation period was used. Olsen et al.[9] confirmed these results in principle with the same data  
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26 78 but with a somewhat longer follow-up duration. In addition, in a setting where voluntary screening is  
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28 79 assumed to be high, it is unknown what the effect an organised screening programme would be for  
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30 80 the population as a whole.  
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34 81 In Switzerland, with its homogenous health system, these pitfalls can be avoided. Switzerland is a  
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36 82 small confederation of 26 relatively autonomous states called cantons with somewhat low  
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38 83 inequalities[10] and many health- and cancer-related resources.[11-13] Although the health care  
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40 84 system is homogeneous in providing universal and rapid access to and use of almost unlimited health  
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42 85 care resources, some health care policies are developed at the cantonal level; in particular, the  
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44 86 decision to initiate a population-based mammography-screening programme. These programmes  
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46 87 were implemented in Switzerland at different times over the past two decades. The first Swiss  
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48 88 mammography pilot programme was established in 1993 in the French-speaking canton of Vaud.  
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50 89 However, it was only in 2010 that the first organised programme in a German-speaking canton (St.  
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52 90 Gallen) started.  
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3 91 In breast cancer incidence, cantonal differences are well-known and have been attributed to the  
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5 92 differential use of opportunistic or organised mammography screening[14]. In addition, considerable  
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7 93 differences in health and health-related behaviour that affect the risk of breast cancer, including  
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9 94 alcohol intake and a healthy diet, have been reported for the Swiss language regions [15 16], as well  
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11 95 as differences in the age at first child birth and number of children born to a mother[17]. Differences  
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13 96 in access to mammography screening and in lifestyle may be reflected in spatio-temporal differences  
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15 97 in both breast cancer incidence and mortality, whereas only the latter will reflect the management of  
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17 98 breast cancer.

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20 99 In contrast, breast cancer mortality studies in Switzerland showed contradictory results. Bulliard  
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22 100 et al[18] observed a steeper decrease from 1980 to 2002 in 55-74-year-olds in French-speaking  
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24 101 regions where population-based mammography screening started earlier. In a recent study[19] we  
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26 102 presented the spatio-temporal trends of female gender related cancer mortality in Switzerland by  
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28 103 age group. The geographical differences found were small. We observed a differential decline in  
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30 104 breast cancer mortality by age. The decline was highest in women younger than 50 and lower in  
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32 105 women 75 or older. A similar pattern was observed in other European countries[4] and attributed to  
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34 106 early detection by mammography and to improved treatment [20-22]. However, it was not clear to  
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36 107 what extent improvements in survival could have affected the age at death. It was difficult to  
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38 108 evaluate a shift of deaths into the next higher age group, and the influence of screening  
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40 109 programmes, based on using fixed age groups rather than cohorts.

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44 110 In the present study, we aimed to assess the spatio-temporal patterns in breast cancer mortality,  
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46 111 and specifically the effect of population-based mammography screening programmes on it. We  
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48 112 corrected for urbanisation for which a mortality gradient was described[23] and additionally for area-  
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50 113 based socio-economic factors, which may have influenced results in the previous study.

## 55 114 **METHODS**

## 115 **Data sources**

116 The Swiss Federal Statistical Office provided data on female breast cancer mortality,  
117 electronically available for the period of 1969-2012. The anonymised data included sex, age, year of  
118 birth and death for each individual, nationality, municipality of residence, the cause of death and co-  
119 morbidities. The cause of death and co-morbidities were coded centrally from death certificates  
120 using the 8th revision of the International Classification of Diseases (ICD) for deaths until 1994, and  
121 the 10th revision for deaths that occurred afterwards. The transition to the 10th revision of the ICD-  
122 10 was accompanied by changes in death certificate coding practices (priority rules). We used age-  
123 and cancer site-specific correction factors as proposed by Lutz et al[24] for the death counts. We  
124 included all cases coded with main causes of death being cancer of the female breast (ICD-10 C50.0-  
125 C50.9). According to federal regulations, mortality data excluding a person's identifying information  
126 can be used in epidemiological studies without additional ethics committee approval.

127 The administrative borders of Swiss municipalities define the smallest geographical unit for  
128 which data were available. There are around 2500 municipalities in the country with a median  
129 population of 740 inhabitants in 1970 and 1150 in 2010.

130 Aggregated population data by age and area unit were extracted from the census that takes  
131 place in Switzerland every 10 years. The last census was conducted in 2010. Because of missing  
132 detailed intercensal population data, we aggregated the mortality data in five 4-year periods around  
133 the census years, i.e. 1969-1972, 1979-1982, 1989-1992, 1999-2002 and 2009-2012, in which  
134 population was assumed to be constant and identical to the census year.

135 From the same source, we retrieved data on language region (German, French, and Italian and  
136 Romansh) and urbanisation (rural/urban). We obtained information on population-based screening  
137 programmes from the Swiss Federation of Cancer Screening Programmes[25], and categorised their  
138 duration in the census years into "no programme", "0-4 years" and "5+ years". Data on socio-

139 economic position (SEP) by municipality were provided by the Swiss National Cohort[26] based on  
 140 the census data of 2000.

141 Table 1 shows the observed number of deaths and mortality rates for each of the co-variates.

142 **Table 1** Observed numbers of female breast cancer deaths and mortality rates per 100,000 PY by  
 143 period and municipality characteristics. The total numbers before 1994 include the correction  
 144 factors.

	Total no. of breast cancer deaths	%	yearly population (x1000)	crude rate	ASR	p-value for ASR homogeneity
<b>Period</b>						p<0.01
1969-1972	4,177	16%	3,180	32.8	32.0	
1979-1982	4,953	19%	3,251	38.1	32.5	
1989-1992	5,968	23%	3,483	42.8	32.6	
1999-2002	5,261	20%	3,720	35.4	25.4	
2009-2012	5,574	21%	3,993	34.9	22.3	
<b>Language</b>						p=0.56
German	18,613	72%	12,622	36.9	28.5	
French	5,915	23%	4,159	35.6	27.7	
Italian/Roman.	1,405	5%	847	41.5	28.9	
<b>Urbanisation level</b>						p=0.08
Rural	6,172	24%	4,491	34.4	26.9	
Urban	19,761	76%	13,137	37.6	28.8	
<b>Years of population based screening*</b>						p=0.53
no programme	4,246	76%	2,942	36.1	22.6	
1-4 years	169	3%	115	36.9	23.4	
5+ years	1,159	21%	936	31.0	21.2	
<b>Socioeconomic index quartiles</b>						p=0.24
Q1 (lowest)	1,999	8%	1,478	33.8	26.4	
Q2	4,313	17%	3,033	35.6	28.1	
Q3	5,864	23%	4,199	34.9	27.7	
Q4 (highest)	13,757	53%	8,919	38.6	29.0	

\*only for the period 2009-2012, length of screening refers to the year 2010

## 146 Statistical methods

147 As a small area geographical unit, we used the municipality borders as of 2012. We used  
 148 municipality transition protocols from the Federal Statistical Office to align all data to this structure.

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3 149 We investigated mortality for all ages combined in a spatial and a non-spatial model, one time  
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5 150 for the five time periods from 1969 to 2012 to assess possible non-linear time trends, and another  
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7 151 time only for the period of 2009-2012.  
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10 152 For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model  
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12 153 formulations as described in Herrmann et al 2015[19], fitted on the number of deaths aggregated by  
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14 154 small area and year, with the mean being equal to the product of the expected death count and age-  
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16 155 standardised mortality rate. The indirect standardisation used 5-year age intervals. Expected  
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18 156 mortality counts for each small area and year were obtained from the study population using  
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20 157 nationwide age-specific mortality rates, once for all periods and again only for the period of 2009-  
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22 158 2012. The small-area-specific random effects were modelled via conditional autoregressive (CAR)  
23  
24 159 models to filter out the noise and highlight the observed patterns. The deviance information criterion  
25  
26 160 (DIC) was used to select the regression model from Poisson, zero-inflated Poisson and Negative  
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28 161 Binomial regression models. The DIC was lowest with the Poisson regression model.  
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32 162 We accounted for differences that were influenced by linguistic region, life in rural or urban  
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34 163 areas, screening programme duration, and socio-economic position. These analyses are used to  
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36 164 indicate whether there are significant differences in cancer mortality for each of the above  
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38 165 covariates, assessed by 95% Bayesian Credible Intervals (CI).  
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## 41 166 **Patient involvement**

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43 167 No patients were involved in this study.  
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## 48 168 **RESULTS**

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51 169 In Switzerland, more than 61,000 women died from breast cancer between 1969 and 2012. Table  
52  
53 170 2 presents the results of the regressions including all time periods and time trends. In Switzerland,  
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55 171 breast cancer mortality in females slightly increased until the 1989-1992 period, and has declined  
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57 172 strongly since. Until the most recent period (2009-2012), the SMR has fallen to 57% of the 1969-1972  
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173 period's value, both in the non-spatial and the spatial models. The trends and geographical  
 174 differences are visualised in Figure 1.

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176

177 **Table 2** Spatio-temporal model estimates of age-specific breast cancer mortality in Switzerland from  
 178 the 1969-1972 period to the 2009-2012 period. Bold values denote age-standardised mortality-ratio  
 179 (SMR) ratios significantly different from 1. Spatial variation (standard deviation of spatial random  
 180 effects): a value of 0 means that there is no spatial correlation.

Period	SMR Ratios (95% CI)		Spatial	
	Non-spatial			
1969-1972	1.00		1.00	
1979-1982	1.01	(0.97;1.05)	1.01	(0.97;1.05)
1989-1992	<b>1.04</b>	(1.00;1.09)	<b>1.05</b>	(1.01;1.09)
1999-2002	<b>0.81</b>	(0.78;0.84)	<b>0.81</b>	(0.78;0.85)
2009-2012	<b>0.57</b>	(0.54;0.59)	<b>0.57</b>	(0.54;0.60)
<b>Language</b>				
German	1.00		1.00	
French	0.99	(0.95;1.02)	1.02	(0.92;1.14)
Italian/Roman.	1.01	(0.96;1.08)	0.99	(0.83;1.16)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	<b>1.05</b>	(1.01;1.08)	1.03	(0.98;1.08)
<b>Years of population-based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.88;1.03)	0.95	(0.88;1.04)
<b>Socioeconomic index</b>				
per 10 point increase	1.02	(0.99;1.04)	1.02	(0.98;1.05)
<b>Spatial variation</b>			0.21	(0.18;0.24)

181

182 From the covariates studied, only the year of death and the urbanisation level in the non-spatial  
 183 model had a significant impact when investigating all periods. An urban environment was associated  
 184 with a 5% elevated SMR (3% in the spatial model) compared with a rural environment.

185 Limiting the analysis to the period of 2009-2012, none of the regression factors had a significant  
 186 effect on breast cancer mortality. (Table 3)

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**Table 3** Spatio-temporal model estimates of age-standardised breast cancer mortality in Switzerland in the 2009-2012 period. Bold values denote age-standardised mortality-ratio (SMR) ratios significantly different from 1.

	<b>SMR Ratios (95% CI)</b>			
	Non-spatial		Spatial	
<b>Language</b>				
German	1.00		1.00	
French	1.00	(0.86;1.15)	1.03	(0.81;1.33)
Italian/Roman.	1.01	(0.87;1.16)	1.00	(0.68;1.37)
<b>Urbanisation level</b>				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
<b>Years of population-based screening</b>				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
<b>Socioeconomic index</b>				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
<b>Spatial variation</b>			0.29	(0.24;0.35)

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Most SMR ratios of the non-spatial and the spatial model showed nearly identical values. The length of a screening programme and the French language region showed slightly higher values, but the differences were not significant.

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In the 2009-2012 period, no region had a significantly higher or lower breast cancer mortality rate at 95% CI level compared with the national mean. (Figure 2) A map with covariate-adjusted smoothed SMR values is not shown because there was no information gain. The covariates are not significant and the geographical patterns are the same as for the smoothed SMR values.

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200

The socio-economic index value for the municipalities ranged from 28 to 85, where 25% of municipalities were below 55 and 25% above 66.

201

## 202 DISCUSSION

203 In the past decades, breast cancer mortality has nearly halved in Switzerland when considering  
204 all ages together. This trend, including the shift from increasing to decreasing rates around the  
205 period of 1989-1992, has been observed in several other European countries[4]. Although significant  
206 spatial differences in breast cancer incidence are well described for Switzerland, we have not found  
207 any significant differences in breast cancer mortality in any of the periods studied. We have not  
208 observed any general significant differences between regions classified by duration of screening  
209 programmes, urbanisation, language and socio-economic position. In addition, when limiting the  
210 analysis to the most recent period (2009-2012), none of the factors are significant. In fact, at 95%  
211 confidence level, none of the regions have a significantly elevated or reduced breast cancer mortality  
212 compared with the national mean.

213 There are several factors that explain why the significant differences in incidence do not translate  
214 into corresponding mortality differences. Most importantly, risk factors such as health and health-  
215 related behaviour that are reported to be different for the language regions[16] affect incidence but  
216 are not necessarily linked to mortality[27]. That is, while a temporary increase in the use of hormone  
217 replacement therapy has led to an increase in breast cancer incidence, many of those tumours have  
218 a favourable prognosis and might have influenced breast cancer mortality only marginally[28].  
219 Accordingly, the French language region, despite earlier implementation of mammography screening  
220 programmes, does not show a relevant impact on breast cancer mortality in our study.

221 Because screening has been identified as a potential source of mortality reduction[21], we also  
222 included data on population-based screening programme duration. However, our study did not show  
223 a significant effect on mortality on the population level. The reasons for this are probably manifold,  
224 and may include factors such as screen-detected cancers being mainly of low stage, many women  
225 having not participated in the screening programmes, or having chosen to undergo opportunistic  
226 screening. In addition, the effect of advances in diagnosis and therapy on mortality is quite strong



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3 227 and may have outweighed benefits from population-based screening programmes, as suggested by  
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5 228 Autier et al.[29]. Moreover, the level of opportunistic screening in Switzerland has been described to  
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7 229 be quite high[30], but data on the geographical differences in opportunistic screening use, and  
8  
9 230 therefore overall screening participation, are not available. Data on participation in population-based  
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11 231 screening programmes are published in a national monitoring report showing that participation rates  
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13 232 of the programmes are close to the combined mean of 47.8% [31].The ecological study design does  
14  
15 233 not allow the assessment of the combined impact of participation in and type (programme vs.  
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17 234 opportunistic) of mammography screening, or the impact of stage of tumour at diagnosis, and  
18  
19 235 mortality at an individual level. For the above reasons, the interpretability with regard to screening is  
20  
21 236 limited. In addition, we had to group into 0-4 years and 5+ years of screening, which was done to  
22  
23 237 avoid overfitting issues. There are only a few regions that are in close proximity to each other with  
24  
25 238 10+ years of screening in the 2009-2012 period only (additional material, Figure A1).

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29 239 The present study is an in-depth analysis of our previous study[19], focusing on breast cancer  
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31 240 mortality using an additional year of more recent data. We were also interested in the effects on the  
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33 241 population as a whole. The applied methodology of age standardisation suits this by taking  
34  
35 242 advantage of the actual age structure rather than of a standard population.

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38 243 The non-significant fixed effect of socio-economic position is in line with the results of Panczak et  
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40 244 al[32]. The additional correction served the disentanglement of affluence from the urbanisation  
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42 245 parameter –which is connected with access to medical services– and further possible distortions.[33]

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45 246 A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an  
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47 247 unstable rate by “borrowing” strength from its neighbours[34]. These models can also assess the  
48  
49 248 significance of risk factors, taking into account the geographical correlation, and are able to show  
50  
51 249 spatial patterns after adjusting for geographical differences in certain risk factors. By adding a time  
52  
53 250 dimension, Bayesian spatio-temporal models indicate changes of geographical patterns over time  
54  
55 251 and determine how a disease evolves in different regions and different groups of the population

252 (age, language or affluence groups). These models have provided a state-of-the-art modelling  
253 approach over the last 15 years for assessing spatio-temporal patterns and trends. We have not  
254 observed that coefficients in our analysis have shrunk towards zero when including geographical  
255 correlation as hypothesised by Hodges and Reich[35]. In fact, in the spatial model for the 2009-2012  
256 period, the impact of the French language region is 1.03 compared with 1.00 in the non-spatial  
257 model. However, we have included the results of the non-spatial models as well.

## 258 **Conclusion**

259 There has been a strong reduction of breast cancer mortality from the 1990s onwards.  
260 Geographical differences are present, but at a moderate level with no significant differences in the  
261 overall mean. In addition, they are not explained by the duration of population-based screening  
262 programmes, socio-economic position, urbanisation and language region. Low participation rates and  
263 opportunistic screening use may have contributed to the low impact of mammography screening  
264 programmes. Continuous evaluation of geographical patterns of breast cancer mortality using  
265 modern spatio-temporal methodology is necessary for evaluating the efficacy of programmes.

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269 no role in the study design, data collection, and analysis, decision to publish, or preparation of the  
270 manuscript.

## 271 **COMPETING INTERESTS**

272 All authors have completed the ICMJE uniform disclosure form at  
273 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted  
274 work; no financial relationships with any organisations that might have an interest in the submitted

1  
2  
3 275 work in the previous three years; no other relationships or activities that could appear to have  
4  
5 276 influenced the submitted work.  
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8

## 9 277 **CONTRIBUTIONS**

10  
11 278 PV, SE conceived of the study. CH carried out the analysis and data acquisition. CH, SE, PV  
12  
13 279 contributed to the analysis of the data and the writing of the manuscript. CH, PV, BT, NP, CR and SE  
14  
15 280 contributed to interpretation of the findings and critically revised the manuscript. All authors read  
16  
17 281 and approved the final manuscript.  
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## 22 282 **TRANSPARENCY DECLARATION**

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24 283 The lead author affirms that this manuscript is an honest, accurate, and transparent account of  
25  
26 284 the study being reported; that no important aspects of the study have been omitted; and that any  
27  
28 285 discrepancies from the study as planned (and, if relevant, registered) have been explained.  
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## 33 286 **ETHICAL APPROVAL**

34  
35 287 Ethical approval was not required as this study is an analysis of publically available, anonymous  
36  
37 288 and previously collected data.  
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## 42 289 **LICENSE**

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## 16 302 **DATA SHARING STATEMENT**

17  
18 303 All data are publically available from the sources stated in the methods section. The statistical  
19  
20 304 code is available from the corresponding author.  
21  
22  
23

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403

## 404 FIGURES

405 **Fig. 1** Development of age-standardised breast cancer mortality (SMR) and spatial differences  
406 therein among time. Values are calculated and smoothed in relation to the all-period combined  
407 mortality. Darker colours represent a higher mortality for the specific age structure and population in  
408 that area and time period.

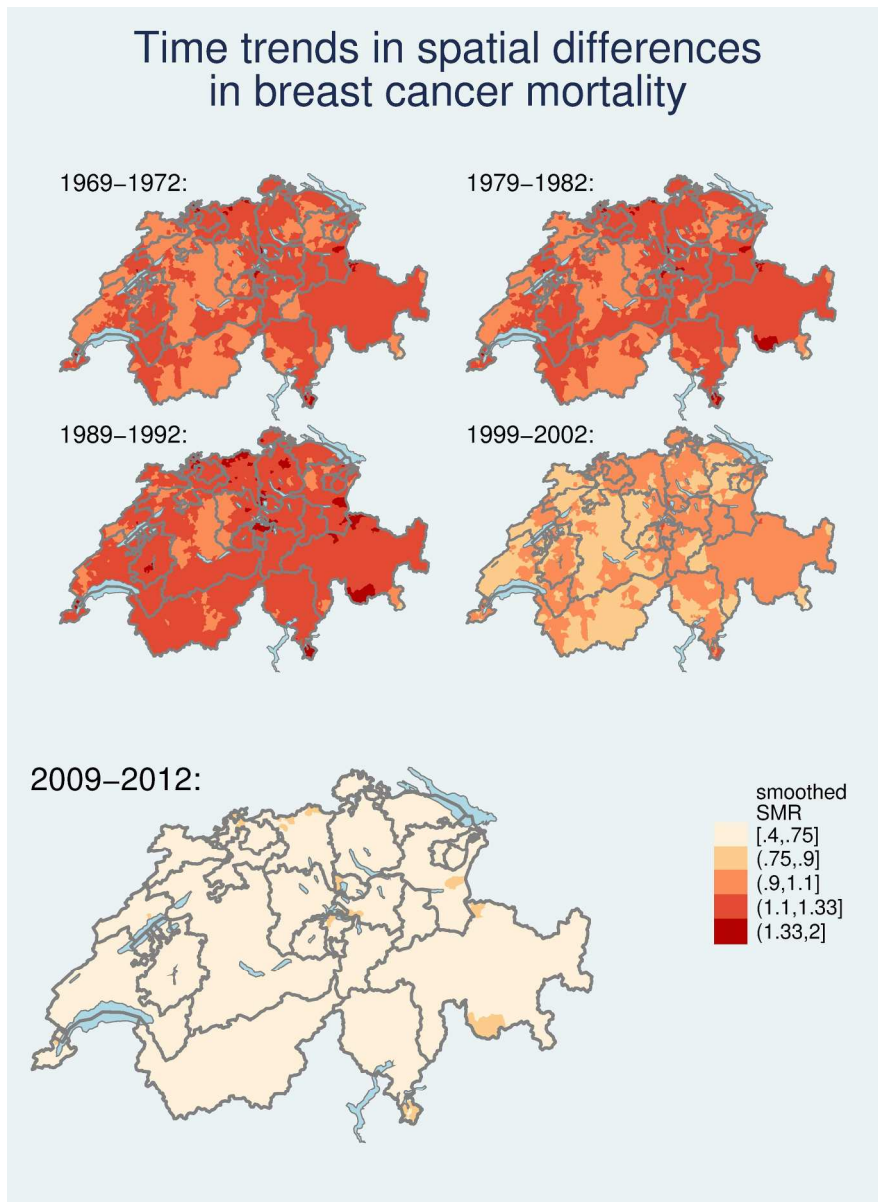
409 **Fig. 2** Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012.

410 \*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

## 411 ADDITIONAL MATERIAL

412 A1. Figures depicting urbanization classification, language regions Screening duration and Swiss  
413 Socio-Economic Position (SEP) in Switzerland.





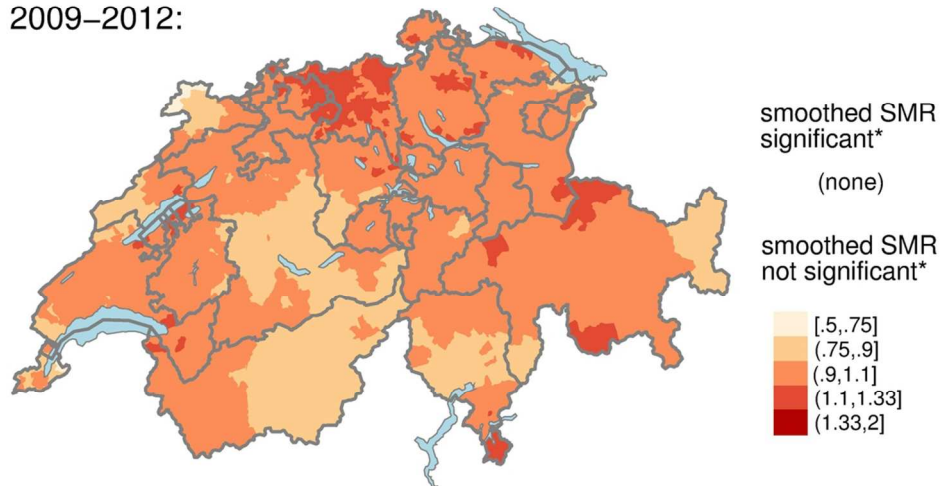
Development of age standardized breast cancer mortality (SMR) and spatial differences therein among time. Values are calculated and smoothed in relation to the all-period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period.

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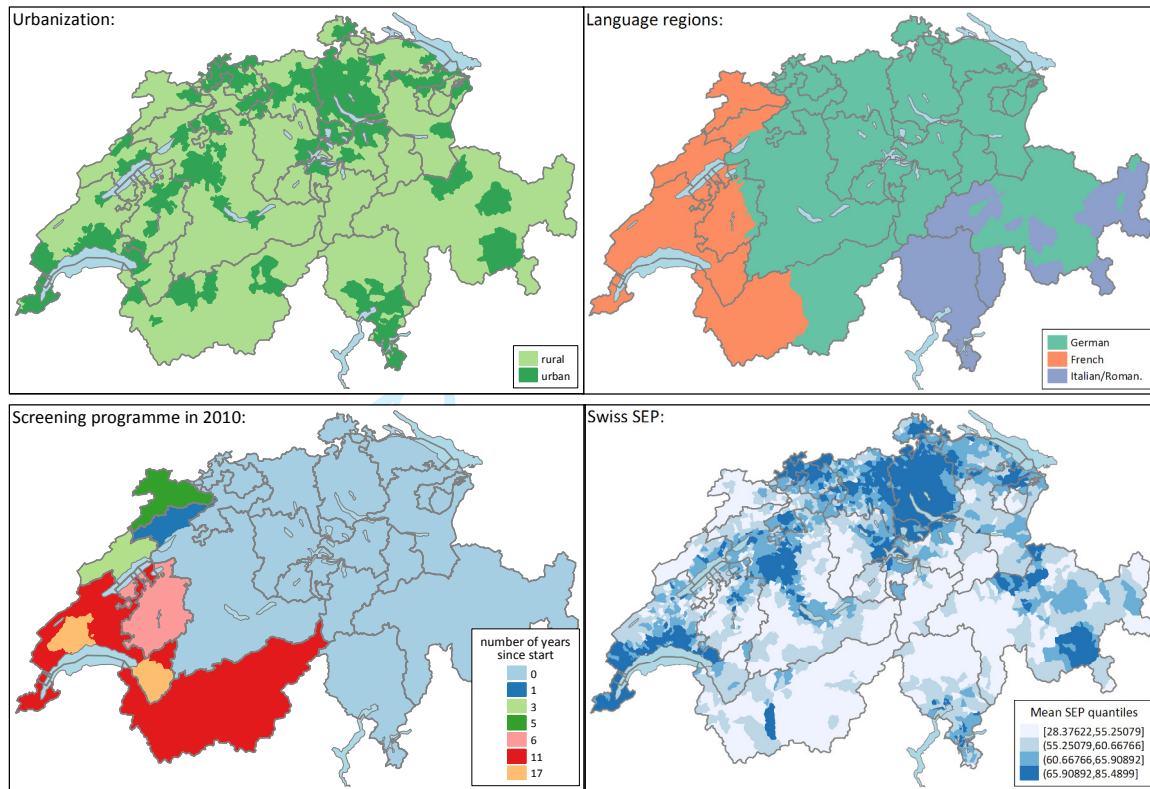
Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.  
\*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

101x68mm (300 x 300 DPI)

view only

**Additional material**

**Figure A1:** Urbanization classification, language regions Screening duration and Swiss Socio-Economic Position (SEP) in Switzerland.



## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA (Ecological study)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, lines 85-88
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Methods, pages 4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods page 5, Introduction 3-4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (c) <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Methods, page 5, lines 91-101
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, page 6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, page 5
Bias	9	Describe any efforts to address potential sources of bias	Methods page 6, Introduction page 4, Discussion page 9-10
Study size	10	Explain how the study size was arrived at	Ecological study, Methods page 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods page 4-6
		(b) Describe any methods used to examine subgroups and interactions	Methods page 6
		(c) Explain how missing data were addressed	No missing data, ecological study
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	Pages 6-8

Continued on next page

<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results page 6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA, page 6
		(b) Indicate number of participants with missing data for each variable of interest	No missing data (ecological study)
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	NA
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7-8
		(b) Report category boundaries when continuous variables were categorized	Page 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-8
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 9-11
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 11

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).