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TITLE

Breast cancer mortality reduction predominantly driven by progress in management

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KEYWORDS

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

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ABSTRACT

Objectives: In the past decades, mortality due to breast cancer importantly declined in Switzerland and other developed countries. The reasons for the decline remain controversial as several factors including important advances in treatment approaches, breast cancer awareness and the introduction of mammography screening programs in many European countries occurred almost simultaneously. In Switzerland, mammography programs exist in some regions for over 20 years, while in others do not exist yet, 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 in the period 1969-2012. Data were retrieved from the Swiss Federal Statistical office (FSO) aggregated on 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 was 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,

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

ARTICLE SUMMARY

What is already known on the subject?

Breast cancer mortality declined in the past decades, and we showed geographical disparities in a previous study in Switzerland. But it was not clear what the impact of mammography screening programmes was, especially after implementation of more effective therapies since the first studies on screening effectiveness.

What does this study add?

On population level, the current duration of mammography screening programmes have no significant impact on mortality differences in Switzerland. Also any other investigated factors where outweighed by the overall mortality trend mainly driven by progress in cancer management.

Strengths and limitations

- Strengths of Bayesian spatial models are their improvement of estimation of an unstable rate by "borrowing" strength from its neighbours,
- And they can also assess the significance of risk factors taking into account the geographical correlation
- A limitation of the study is that data on the geographical differences in opportunistic screening use and overall screening participation are not available,
- the ecological study design does not allow assessing the combined impact of participation in and type (program vs. opportunistic) of mammography screening,
- and we had to group into 0-4 and 5+ years of screening in order to avoid overfitting issues.

INTRODUCTION

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

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

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

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

In contrast, breast cancer mortality studies in Switzerland showed contradictory results. Bulliard et al[15] observed a steeper decrease in 1980-2002 in 55-74 year olds in French-speaking regions where population based mammography screening started earlier. In a recent study[16] we presented the spatio-temporal trends of female gender related cancer mortality in Switzerland by age group. The geographical differences found were small. We observed a differential decline in breast cancer mortality by age. Decline was highest in women younger than 50 and lower in women 75 or older. A similar pattern was observed in other European countries[4] and attributed to early detection with mammography and to improved treatment [17-19]. However, it was not clear to which extent improvements in survival could have effected the age of death, and the influence of screening programmes were difficult to evaluate due to using fixed age groups rather than cohorts.

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

METHODS

Data sources

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

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

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

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

of the programmes at census years (no programme/ 0-4 years, 5+ years). Data on socio-economic position (SEP) by municipality was provided by the Swiss National cohort[23] based on census data of 2000.

Statistical methods

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

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

For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model formulations as described in Herrmann et al 2015[16], fitted on the number of deaths aggregated by small area and year with the mean being equal to the product of the expected death count and age standardised mortality rate. The indirect standardisation used 5 years age intervals. Expected mortality counts for each small area and year were obtained from the study population using nationwide age-specific mortality rates for all periods, and only for the period 2009-2012 respectively. The small-area-specific random effects were modelled via conditional autoregressive (CAR) models to filter out the noise and highlight the observed patterns.

Differences influenced by linguistic region, life in rural or urban areas, screening programme duration and socio-economic position were accounted for. These analyses will indicate whether there are significant differences in the cancer mortality for each one of the above covariates, assessed by 95% Bayesian Credible Intervals (CI).

Patient involvement

No patients were involved in this study.

RESULTS

In total in Switzerland more than 61'000 women died from breast cancer from 1969 to 2012. Table 1 presents the results of the regressions including all time periods and time trends. In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and declined strongly since. Until the most recent period 2009-2012, the SMR reduced to 57% of the 1969-1972 value both in the non-spatial and the spatial model. The trends and geographical differences are visualized in figure 1.

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

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

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

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

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

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
Language				
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)
Urbanisation level				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
Years of population based screening				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
Socioeconomic index				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
Spatial variation			0.29	(0.24;0.35)

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

Conclusion

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

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

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTIONS

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

TRANSPARENCY DECLARATION

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

ETHICAL APPROVAL

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

LICENSE

DATA SHARING STATEMENT

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

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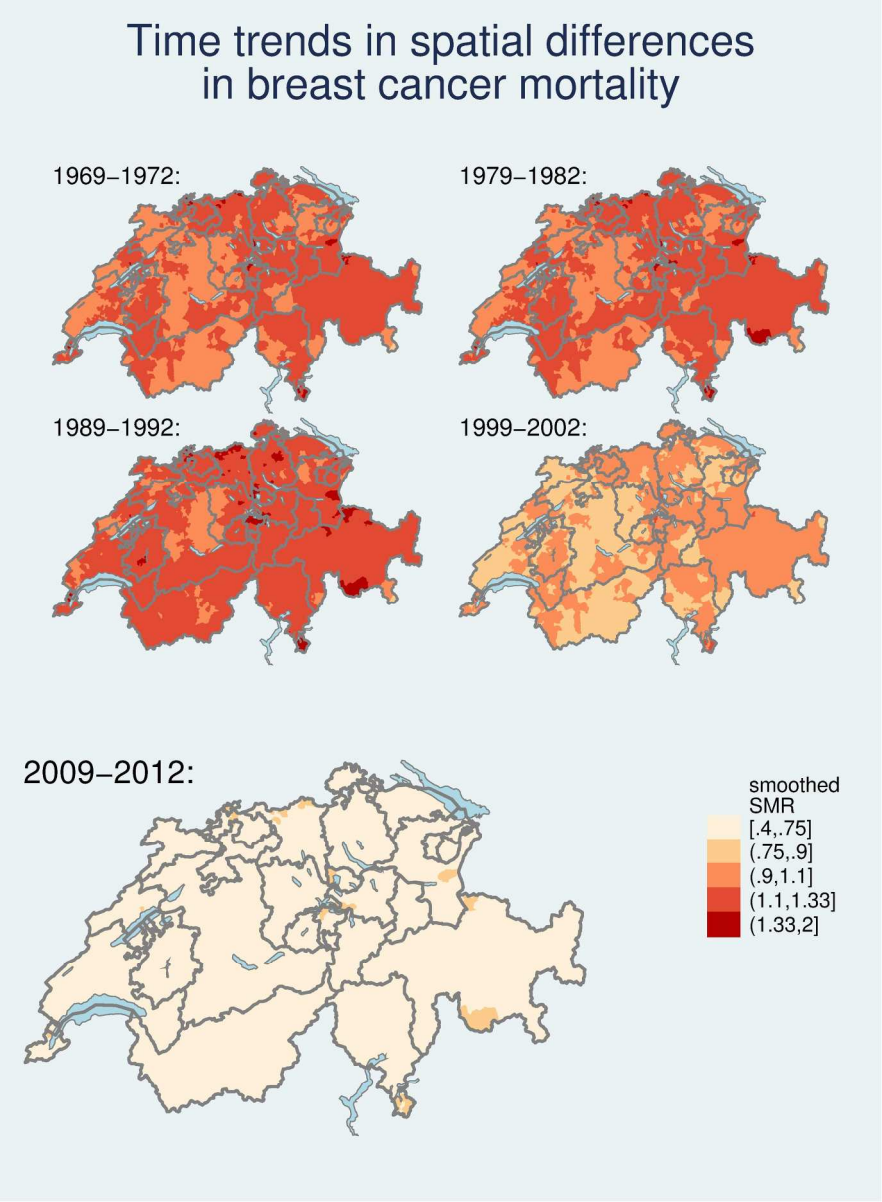
FIGURES

Fig. 1 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.

Fig. 2 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.

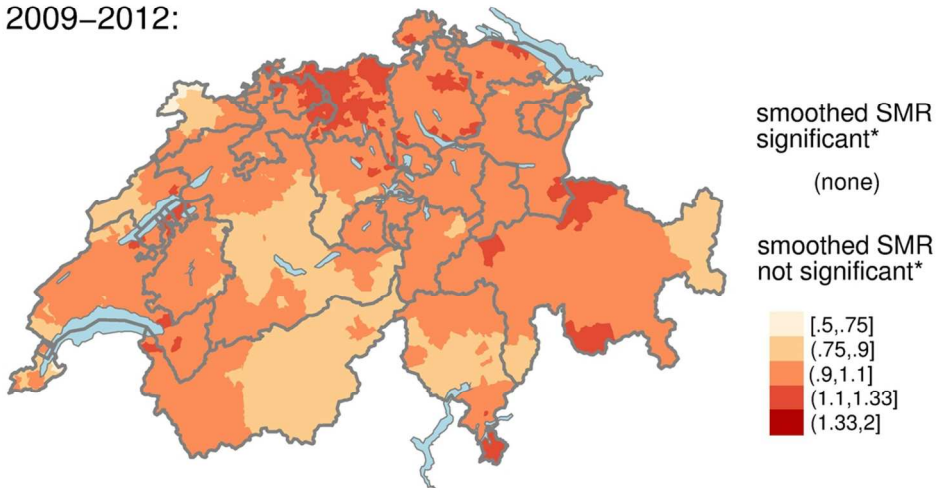
ADDITIONAL MATERIAL

A1. Figures depicting urbanization classification, language regions Screening duration and Swiss 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)

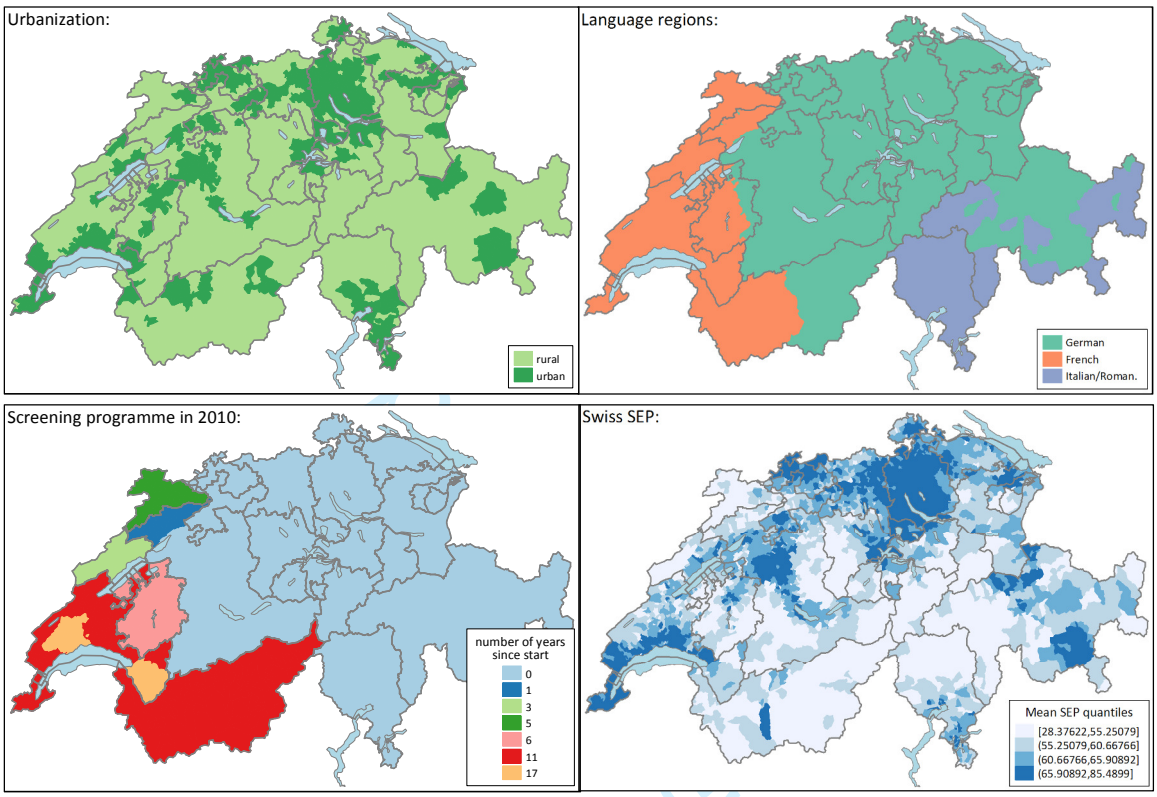


Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.
*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

101x68mm (300 x 300 DPI)

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Pages 6-8

Continued on next page

Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—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
Discussion			
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
Other information			
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.

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TITLE

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

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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,

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

ARTICLE SUMMARY

Strengths and limitations

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

INTRODUCTION

In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. In the past decades mortality due to breast cancer has declined considerably in Switzerland and other developed countries[4]. The reasons for the 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.

Some randomized controlled studies[5] have demonstrated a breast cancer mortality reduction of 20% for women invited to breast cancer screening. However, they were conducted in the 1970-80s and since then many advances in therapies have been made and adopted[6], so that some authors doubt that the difference would persist under present conditions. Therefore, often used historical pre-screening control groups are not best suited to disentangle these effects. Autier et al [7] compared countries in Europe but a criticism was, that different countries may have different health systems. Kalager et al[8] used comparison groups in Norway and showed that only a third of total mortality reduction could be attributed to mammography screening, but used a short observation period. Also, in a setting, where voluntary screening is assumed to be high, it is unknown what the effect of an organised screening programme would be for the population as a whole.

In Switzerland with its homogenous health system these pitfalls can be avoided. Switzerland is a small confederation of 26 relatively autonomous states called cantons with somewhat low inequalities[9] and high health and cancer related resources.[10-12] Although the health care system is homogenous in its provision of universal and rapid access and use of almost unlimited health care resources, some health care policies are developed at cantonal level; in particular, the decision to initiate a population based mammography-screening programme. These programmes were implemented in Switzerland at different time points over the past two decades. The first Swiss mammography pilot programme was established in 1993 in the French speaking canton of Vaud but it was only in 2010 that the first organised programme in a German speaking canton (St. Gallen) started.

In breast cancer incidence cantonal differences are well known and have been attributed to differential use of opportunistic or organised mammography screening[13]. In addition, considerable differences in health and health related behaviour –affecting the risk of breast cancer– have been reported for the Swiss language regions including alcohol intake and a healthy diet[14 15], and differences in the age at first birth and number of children[16]. Differences in access to mammography screening and in lifestyle may be reflected in spatio-temporal differences of both

breast cancer incidence and mortality, whereas only the latter will reflect the management of breast cancer.

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

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

METHODS

Data sources

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

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

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

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

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

Statistical methods

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

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

For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model formulations as described in Herrmann et al 2015[18], fitted on the number of deaths aggregated by small area and year with the mean being equal to the product of the expected death count and age standardised mortality rate. The indirect standardisation used 5 years age intervals. Expected mortality counts for each small area and year were obtained from the study population using nationwide age-specific mortality rates for all periods, and only for the period 2009-2012 respectively. The small-area-specific random effects were modelled via conditional autoregressive (CAR) models to filter out the noise and highlight the observed patterns.

Differences influenced by linguistic region, life in rural or urban areas, screening programme duration and socio-economic position were accounted for. These analyses will indicate whether there are significant differences in cancer mortality for each one of the above covariates, assessed by 95% Bayesian Credible Intervals (CI).

Patient involvement

No patients were involved in this study.

RESULTS

In total in Switzerland more than 61'000 women died from breast cancer between 1969 and 2012. Table 1 presents the results of the regressions including all time periods and time trends. In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and has declined strongly since. Until the most recent period 2009-2012, the SMR has fallen to 57% of the 1969-1972 value both in the non-spatial and the spatial model. The trends and geographical differences are visualized in figure 1.

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

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

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

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

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

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
Language				
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)
Urbanisation level				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
Years of population based screening				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
Socioeconomic index				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
Spatial variation			0.29	(0.24;0.35)

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.

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

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

DISCUSSION

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

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

Since screening has been identified as a potential source of mortality reduction[20], we also included data on population based screening programme duration. However, our study did not show a significant effect on mortality on population level. The reasons for this are probably manifold and may include the fact that screen detected cancers are mainly of low stage, many women have not participated in the screening programmes or have chosen to undergo opportunistic screening. In addition, the effect of advances in diagnosis and therapy on mortality is quite strong and may have outweighed benefits from population based screening programmes, as suggested by Autier et al.[28]. Moreover, the level of opportunistic screening in Switzerland has been described to be quite

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

The presented study is an in-depth analysis from our previous study[18], focusing on breast cancer mortality using an additional year of more recent data. We were also interested in the effects on population level as a whole. The applied methodology of age standardisation suits this by taking advantage of the actual age structure rather than of a standard population.

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

A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an unstable rate by “borrowing” strength from its neighbours[34]. They can also assess the significance of risk factors taking into account the geographical correlation, and are able to show spatial patterns after adjusting for geographical differences in certain risk factors. By adding a time dimension, Bayesian spatio-temporal models indicate changes of geographical patterns over time and determine how the disease evolves over time in different regions and different groups of the population (age, language or affluence groups). These models provide a state-of-art modelling approach over the last

fifteen years for assessing spatio-temporal patterns and trends. We have not observed that coefficients in our analysis have shrunk towards zero when including geographical correlation as hypothesised by Hodges and Reich[35]. In fact, in the spatial model for 2009-2012 the impact of the French language region is 1.03 in comparison to 1.00 in the non-spatial model. However, we have included the results of the non-spatial models as well.

Conclusion

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

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

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted

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

CONTRIBUTIONS

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

TRANSPARENCY DECLARATION

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

ETHICAL APPROVAL

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

LICENSE

DATA SHARING STATEMENT

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

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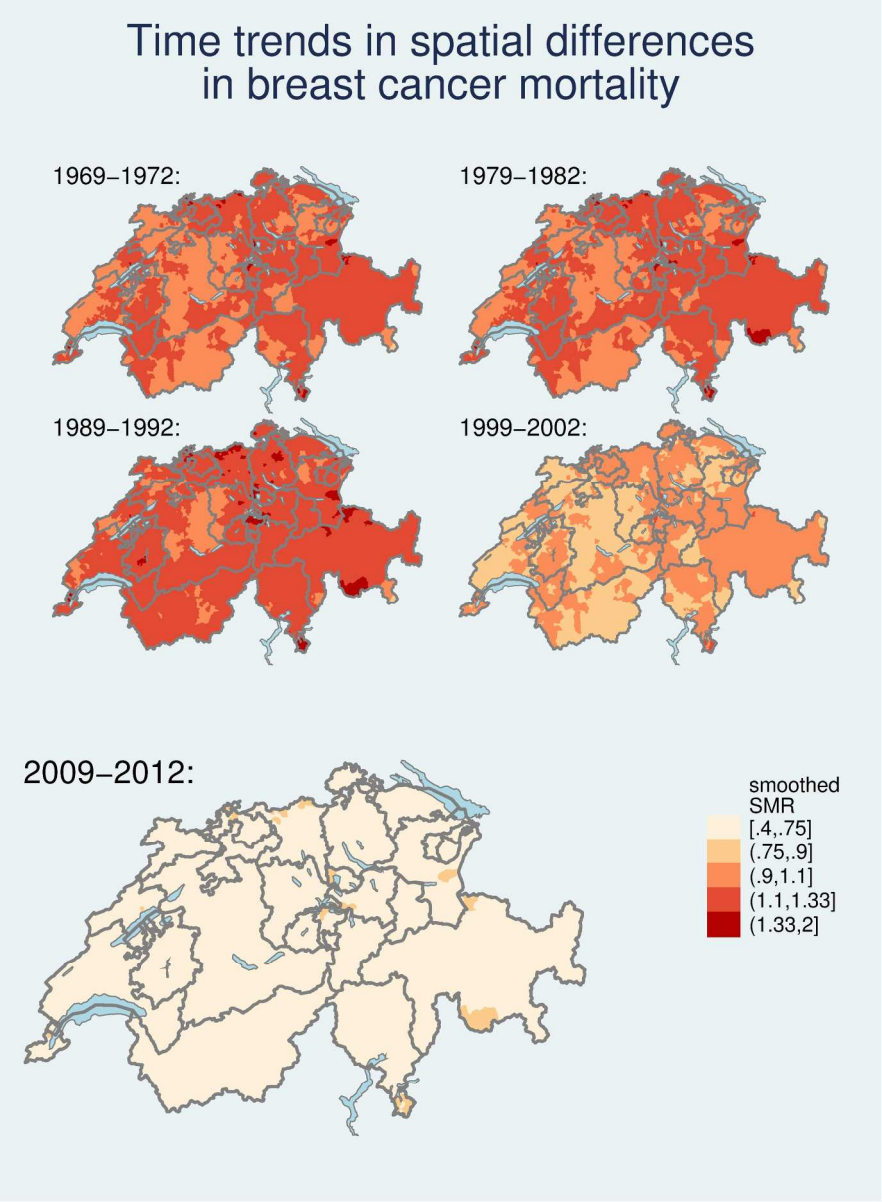
FIGURES

Fig. 1 Development of age standardised 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.

Fig. 2 Geographical differences in age standardised breast cancer mortality (SMR) in 2009-2012. *Significance is denoted as values significantly different at 95%CI from 1, the national mean.

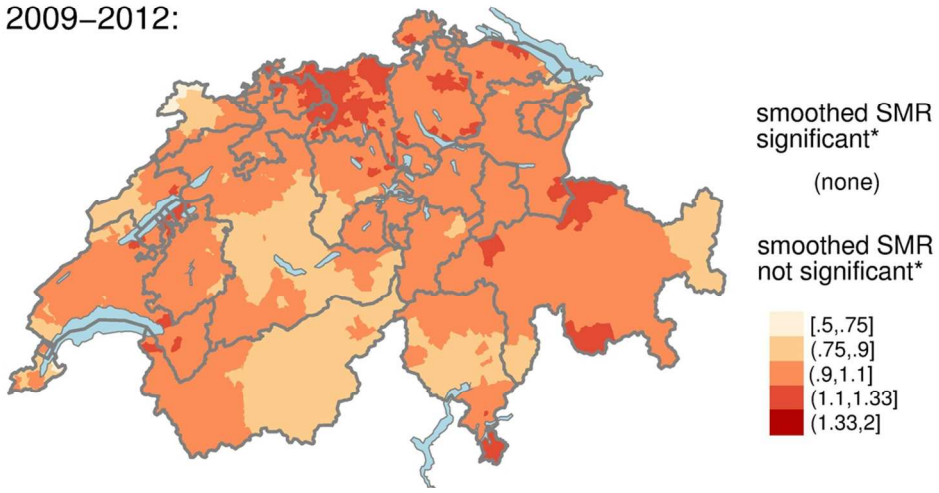
ADDITIONAL MATERIAL

A1. Figures depicting urbanization classification, language regions Screening duration and Swiss 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)

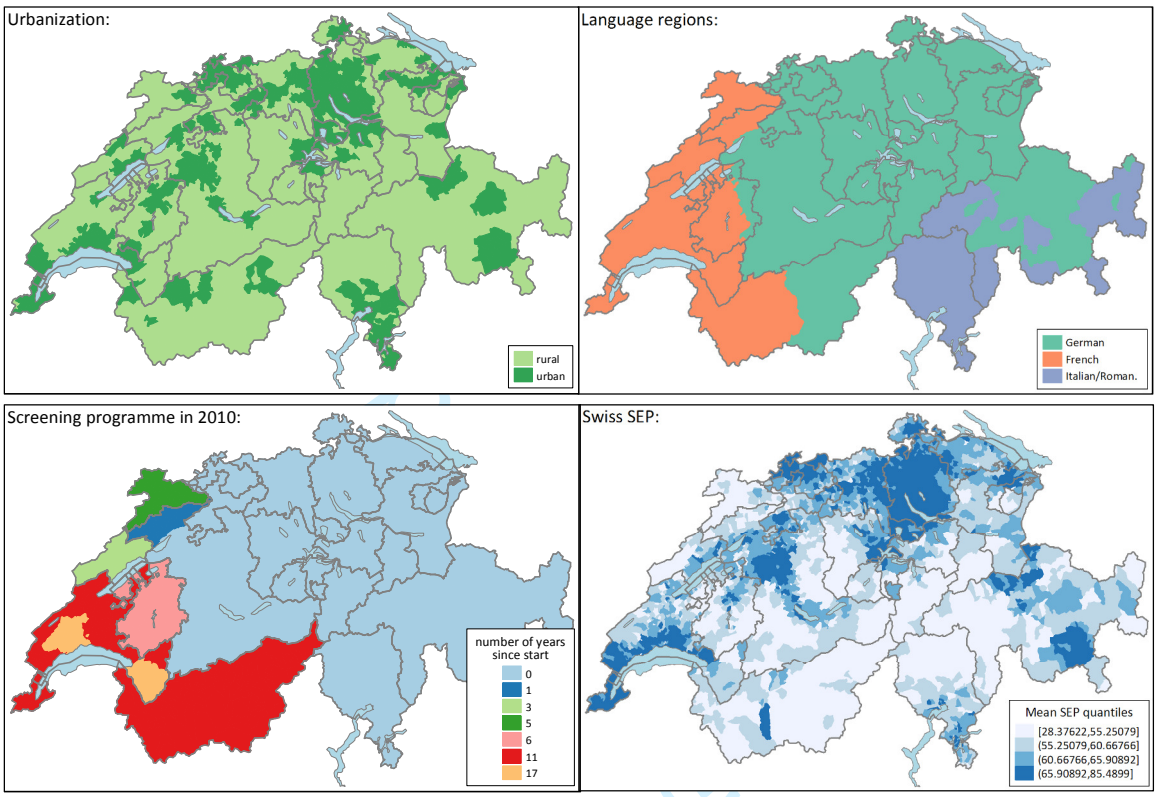


Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.
*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

101x68mm (300 x 300 DPI)

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Pages 6-8

Continued on next page

Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—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
Discussion			
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
Other information			
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.

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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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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,

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

ARTICLE SUMMARY

Strengths and limitations

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

INTRODUCTION

In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. Mortality due to breast cancer has declined considerably in the past decades in Switzerland and other developed countries[4]. The reasons for the 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.

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

In Switzerland, with its homogenous health system, these pitfalls can be avoided. Switzerland is a small confederation of 26 relatively autonomous states called cantons with somewhat low inequalities[10] and high health and cancer-related resources.[11-13] Although the health care system is homogeneous in its provision of universal and rapid access and use of almost unlimited health care resources, some health care policies are developed at cantonal level; in particular, the decision to initiate a population-based mammography-screening programme. These programmes were implemented in Switzerland at different time points over the past two decades. The first Swiss mammography pilot programme was established in 1993 in the French-speaking canton of Vaud but it was only in 2010 that the first organised programme in a German-speaking canton (St. Gallen) started.

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

differences in the age at first child birth and number of children[17]. Differences in access to mammography screening and in lifestyle may be reflected in spatio-temporal differences in both breast cancer incidence and mortality, whereas only the latter will reflect the management of breast cancer.

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

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

METHODS

Data sources

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

birth and death for each individual, nationality, municipality of residence, the cause of death and co-morbidities. The cause of death and co-morbidities were coded centrally from death certificates using until 1994the 8th revision of the International Classification of Diseases (ICD) and afterwards the 10th revision. The transition to the 10th revision of the ICD-10 was accompanied by changes in death certificate coding practices (priority rules). We used age- and cancer site-specific correction factors as proposed by Lutz et al[24] for the death counts. We included all cases coded with main causes of death being cancer of the female breast (ICD-10 C50.0-C50.9). According to federal regulations, mortality data excluding person identifying information can be used in epidemiological studies without additional ethics committee approval.

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

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

From the same source, we retrieved data on language region (German, French and Italian and Romansh) and urbanisation (rural/urban). We obtained information on population-based screening programmes from the Swiss federation of cancer screening programmes[25], and categorised their duration in the census years into "no programme", "0-4 years" and "5+ years". Data on socio-economic position (SEP) by municipality was provided by the Swiss National cohort[26] based on census data of 2000.

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

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

	Total no. of breast cancer deaths	%	yearly population (x1000)	crude rate	ASR	p-value for ASR homogeneity
Period						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	
Language						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	
Urbanisation level						p=0.08
Rural	6'172	24%	4'491	34.4	26.9	
Urban	19'761	76%	13'137	37.6	28.8	
Years of population based screening*						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	
Socioeconomic index quartiles						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

Statistical methods

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

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

For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model formulations as described in Herrmann et al 2015[19], fitted on the number of deaths aggregated by small area and year with the mean being equal to the product of the expected death count and age-standardised mortality rate. The indirect standardisation used 5 year age intervals. Expected mortality counts for each small area and year were obtained from the study population using nationwide age-specific mortality rates for all periods, and only for the period 2009-2012 respectively. The small-area-specific random effects were modelled via conditional autoregressive (CAR) models to filter out the noise and highlight the observed patterns. The Deviance Information Criterion (DIC) was used to select the regression model from Poisson/ zero-inflated Poisson and Negative binomial regression models. The DIC was lowest with the Poisson regression model.

We accounted for differences influenced by linguistic region, life in rural or urban areas, screening programme duration, and socio-economic position. These analyses will indicate whether there are significant differences in cancer mortality for each one of the above covariates, assessed by 95% Bayesian Credible Intervals (CI).

Patient involvement

No patients were involved in this study.

RESULTS

In Switzerland, in total more than 61'000 women died from breast cancer between 1969 and 2012. Table 2 presents the results of the regressions including all time periods and time trends. In Switzerland, breast cancer mortality in females slightly increased until 1989-1992 and has declined strongly since. Until the most recent period 2009-2012, the SMR has fallen to 57% of the 1969-1972 value both in the non-spatial and the spatial model. The trends and geographical differences are visualised in figure 1.

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

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

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

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

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

	SMR Ratios (95% CI)			
	Non-spatial		Spatial	
Language				
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)
Urbanisation level				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
Years of population-based screening				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
Socioeconomic index				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
Spatial variation			0.29	(0.24;0.35)

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.

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

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

DISCUSSION

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

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

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

outweighed benefits from population-based screening programmes, as suggested by Autier et al.[29]. Moreover, the level of opportunistic screening in Switzerland has been described to be quite high[30], but data on the geographical differences in opportunistic screening use and therefore overall screening participation are not available. Data on participation in population-based screening programmes are published in a national monitoring report showing that participation rates of the programmes are close to the combined mean of 47.8% [31].The ecological study design does not allow the assessment of the combined impact of participation in and type (programme vs. opportunistic) of mammography screening, or the impact of stage of tumour at diagnosis, and mortality on individual level. For the above reasons, the interpretability with regard to screening is limited. In addition, we had to group into 0-4 and 5+ years of screening in order to avoid overfitting issues. There are only a few regions which are in close proximity to each other with 10+ years of screening in 2009-2012 only (additional material, figure A1).

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

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

A strength of Bayesian spatial models is their “smoothing” or improvement of estimation of an unstable rate by “borrowing” strength from its neighbours[34]. They can also assess the significance of risk factors taking into account the geographical correlation, and are able to show spatial patterns after adjusting for geographical differences in certain risk factors. By adding a time dimension, Bayesian spatio-temporal models indicate changes of geographical patterns over time and determine how the disease evolves in different regions and different groups of the population (age, language or

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

Conclusion

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

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

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted

work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

CONTRIBUTIONS

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

TRANSPARENCY DECLARATION

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

ETHICAL APPROVAL

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

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DATA SHARING STATEMENT

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

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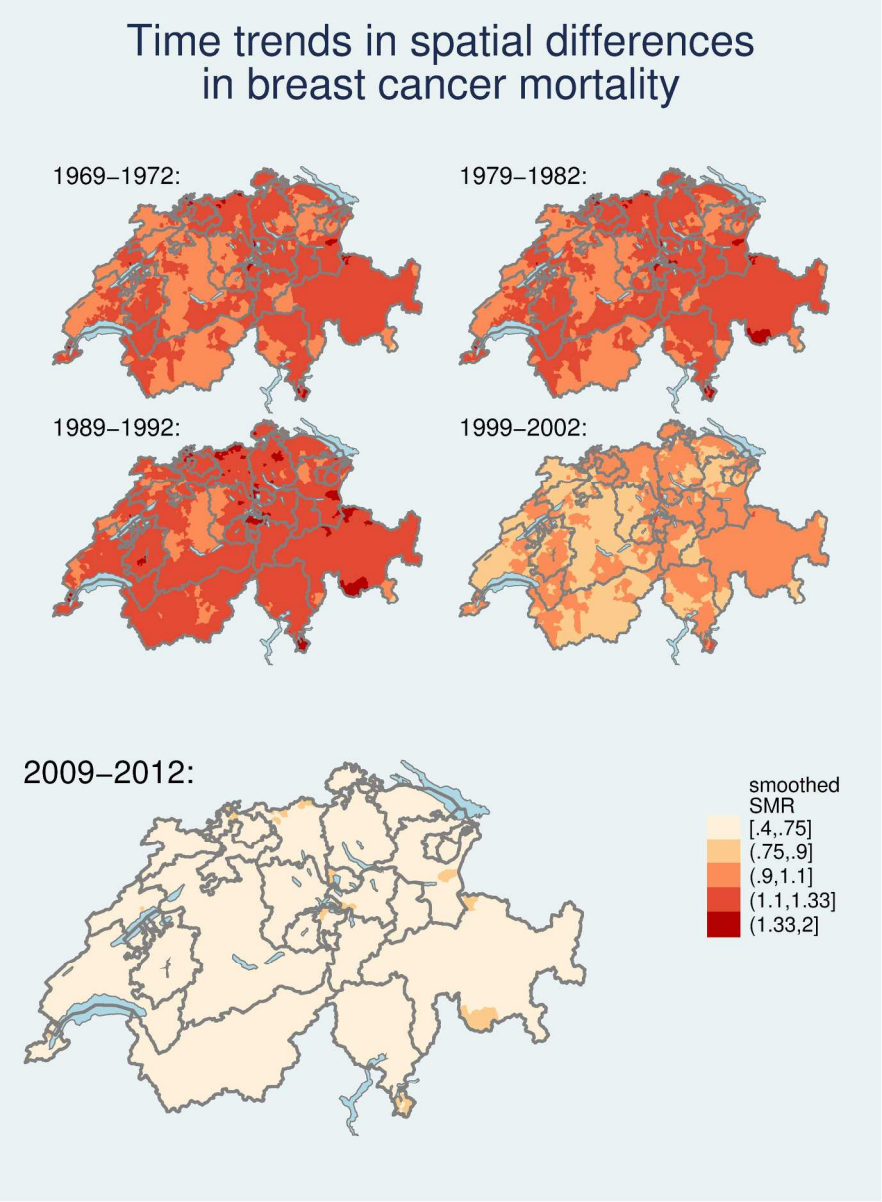
FIGURES

Fig. 1 Development of age-standardised 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.

Fig. 2 Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012. *Significance is denoted as values significantly different at 95%CI from 1, the national mean.

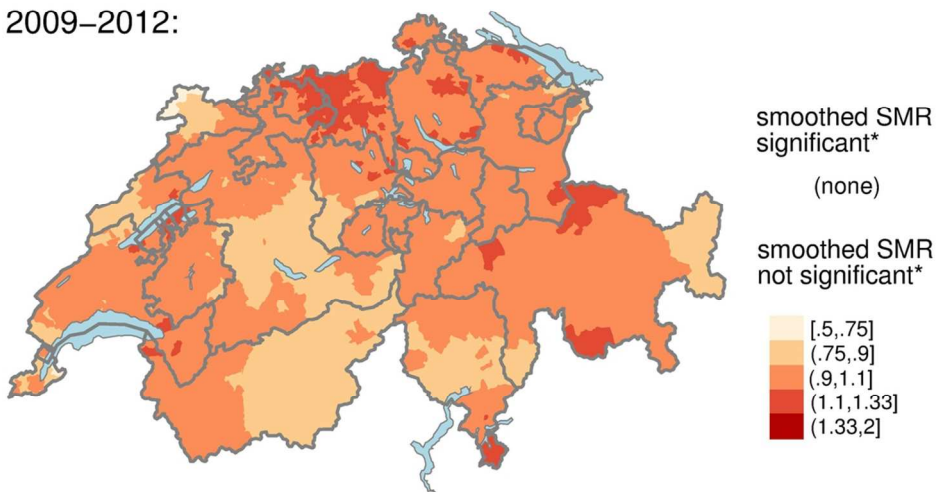
ADDITIONAL MATERIAL

A1. Figures depicting urbanization classification, language regions Screening duration and Swiss 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)

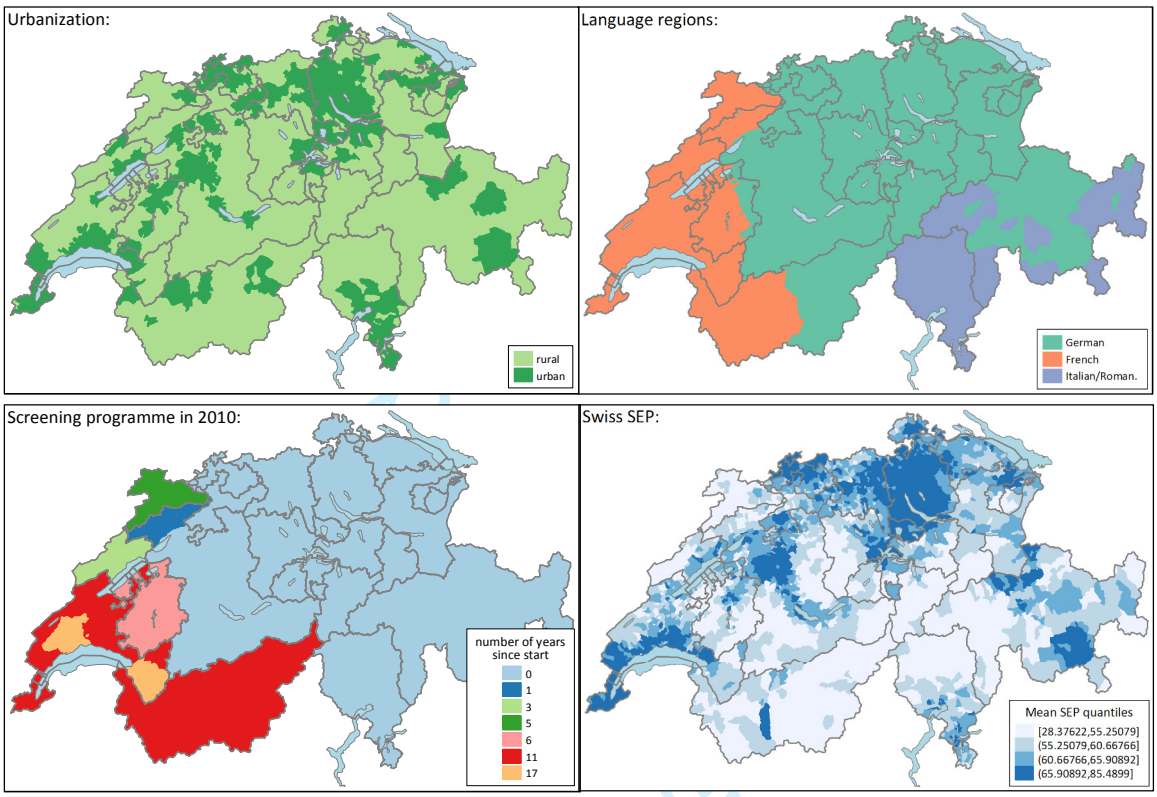


Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.
*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

101x68mm (300 x 300 DPI)

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Pages 6-8

Continued on next page

Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—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
Discussion			
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
Other information			
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.

BMJ Open

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

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

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

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

ARTICLE SUMMARY

Strengths and limitations

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

INTRODUCTION

In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. Mortality due to breast cancer has declined considerably in the past decades in Switzerland and other developed countries[4]. The reasons for the decline remain controversial because 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.

Some randomised controlled studies[5] have demonstrated a breast cancer mortality reduction of 20% for women invited for breast cancer screening. However, they were conducted in the 1970s to 80s. Since then, many advances in therapies have been made and adopted[6] so that some authors doubt that the difference would persist under present conditions. Therefore, often used historical pre-screening control groups are not best suited to disentangle these effects. Autier et al [7] compared countries in Europe but a criticism was that different countries may have different health systems. Kalager et al.[8] used comparison groups in Norway and showed that only a third of the total mortality reduction could be attributed to mammography screening. However, a short observation period was used. Olsen et al.[9] confirmed these results in principle with the same data but with a somewhat longer follow-up duration. In addition, in a setting where voluntary screening is assumed to be high, it is unknown what the effect an organised screening programme would be for the population as a whole.

In Switzerland, with its homogenous health system, these pitfalls can be avoided. Switzerland is a small confederation of 26 relatively autonomous states called cantons with somewhat low inequalities[10] and many health- and cancer-related resources.[11-13] Although the health care system is homogeneous in providing universal and rapid access to and use of almost unlimited health care resources, some health care policies are developed at the cantonal level; in particular, the decision to initiate a population-based mammography-screening programme. These programmes were implemented in Switzerland at different times over the past two decades. The first Swiss mammography pilot programme was established in 1993 in the French-speaking canton of Vaud. However, it was only in 2010 that the first organised programme in a German-speaking canton (St. Gallen) started.

In breast cancer incidence, cantonal differences are well-known and have been attributed to the differential use of opportunistic or organised mammography screening[14]. In addition, considerable differences in health and health-related behaviour that affect the risk of breast cancer, including alcohol intake and a healthy diet, have been reported for the Swiss language regions [15 16], as well as differences in the age at first child birth and number of children born to a mother[17]. Differences in access to mammography screening and in lifestyle may be reflected in spatio-temporal differences in both breast cancer incidence and mortality, whereas only the latter will reflect the management of breast cancer.

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

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

METHODS

Data sources

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

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

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

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

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

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

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

	Total no. of breast cancer deaths	%	yearly population (x1000)	crude rate	ASR	p-value for ASR homogeneity
Period						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	
Language						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	
Urbanisation level						p=0.08
Rural	6,172	24%	4,491	34.4	26.9	
Urban	19,761	76%	13,137	37.6	28.8	
Years of population based screening*						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	
Socioeconomic index quartiles						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

Statistical methods

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

We investigated mortality for all ages combined in a spatial and a non-spatial model, one time for the five time periods from 1969 to 2012 to assess possible non-linear time trends, and another time only for the period of 2009-2012.

For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model formulations as described in Herrmann et al 2015[19], fitted on the number of deaths aggregated by small area and year, with the mean being equal to the product of the expected death count and age-standardised mortality rate. The indirect standardisation used 5-year age intervals. Expected mortality counts for each small area and year were obtained from the study population using nationwide age-specific mortality rates, once for all periods and again only for the period of 2009-2012. The small-area-specific random effects were modelled via conditional autoregressive (CAR) models to filter out the noise and highlight the observed patterns. The deviance information criterion (DIC) was used to select the regression model from Poisson, zero-inflated Poisson and Negative Binomial regression models. The DIC was lowest with the Poisson regression model.

We accounted for differences that were influenced by linguistic region, life in rural or urban areas, screening programme duration, and socio-economic position. These analyses are used to indicate whether there are significant differences in cancer mortality for each of the above covariates, assessed by 95% Bayesian Credible Intervals (CI).

Patient involvement

No patients were involved in this study.

RESULTS

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

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

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

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

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

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

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	
Language				
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)
Urbanisation level				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
Years of population-based screening				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
Socioeconomic index				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
Spatial variation			0.29	(0.24;0.35)

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.

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.

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

DISCUSSION

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

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

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

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

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

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

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

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

Conclusion

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

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted

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

CONTRIBUTIONS

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

TRANSPARENCY DECLARATION

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

ETHICAL APPROVAL

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

LICENSE

DATA SHARING STATEMENT

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

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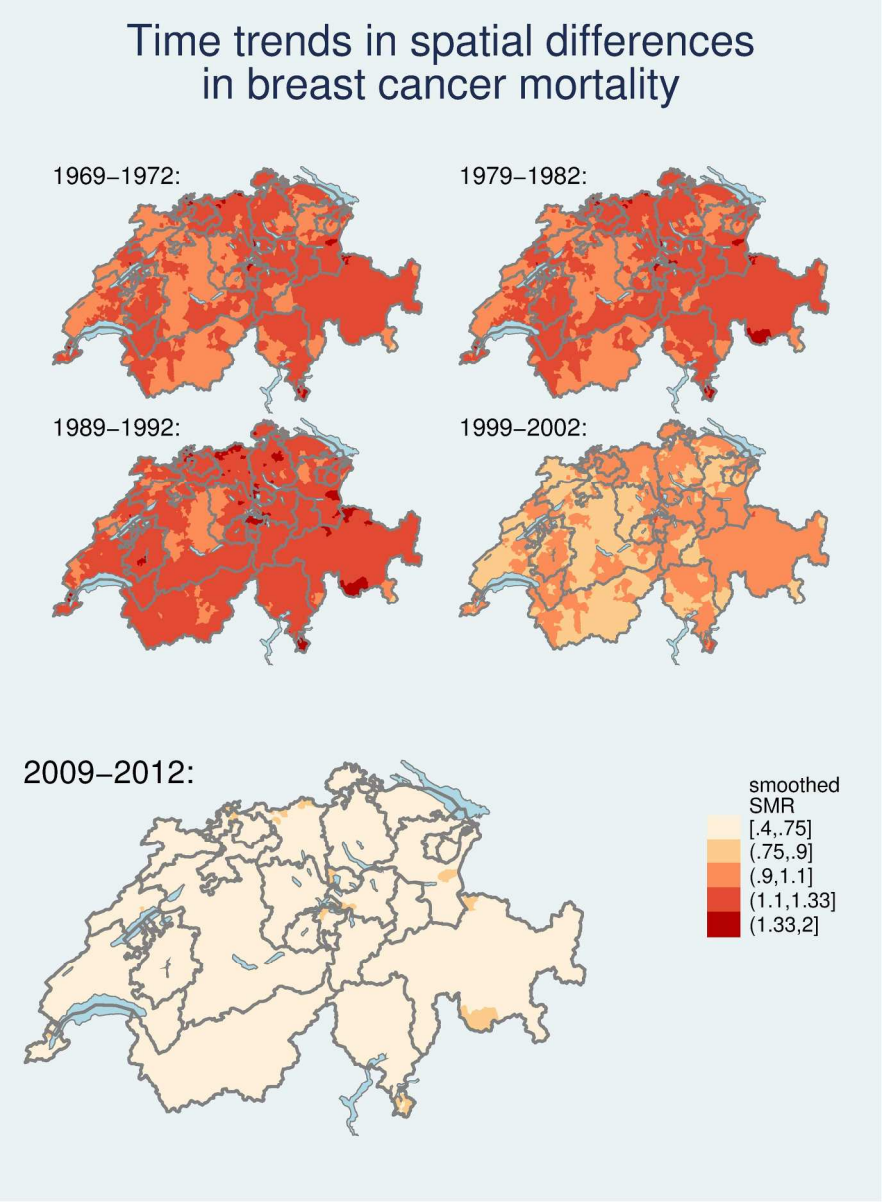
FIGURES

Fig. 1 Development of age-standardised 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.

Fig. 2 Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012. *Significance is denoted as values significantly different at 95%CI from 1, the national mean.

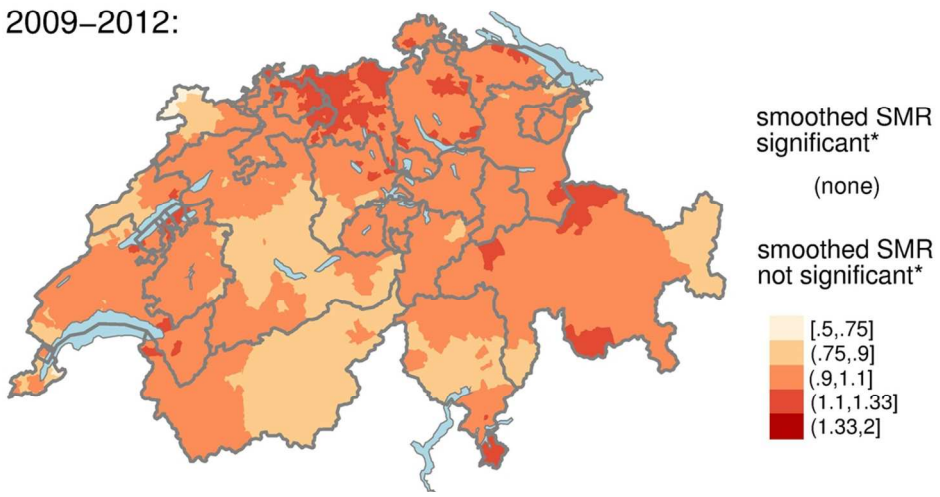
ADDITIONAL MATERIAL

A1. Figures depicting urbanization classification, language regions Screening duration and Swiss 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)

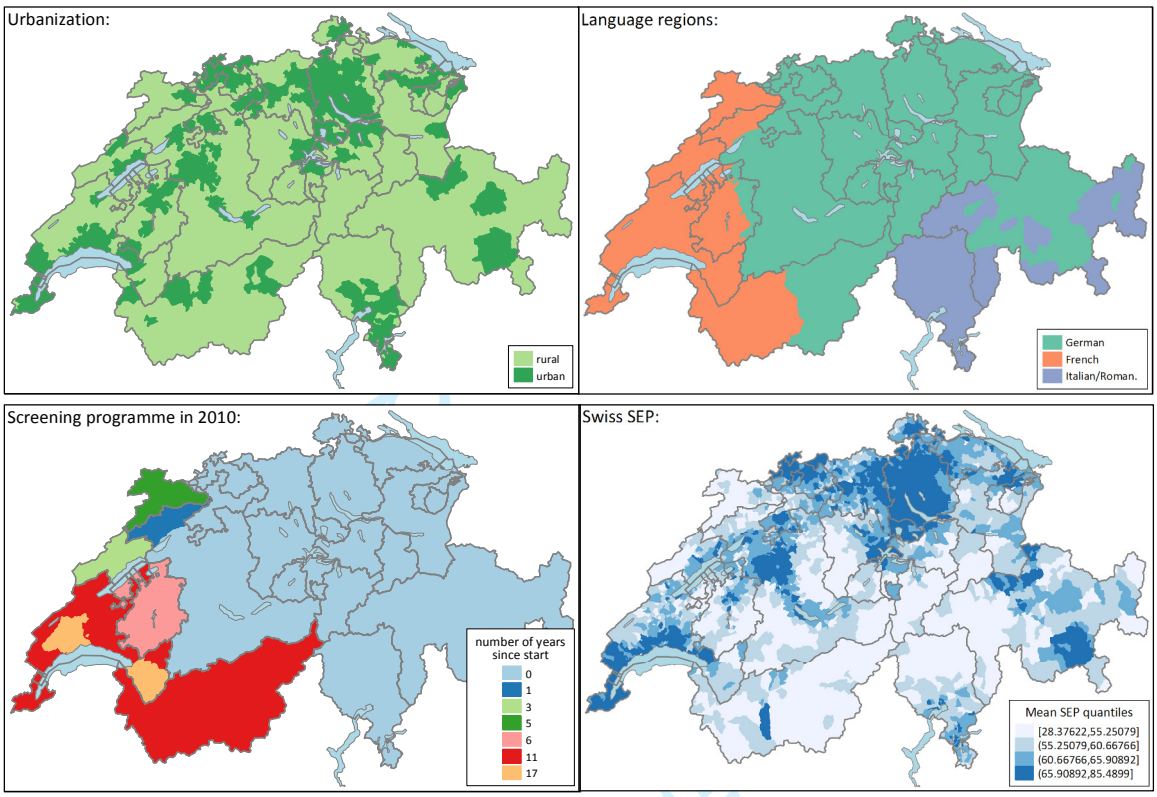


Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.
*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

101x68mm (300 x 300 DPI)

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Pages 6-8

Continued on next page

Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—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
Discussion			
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
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*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.

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

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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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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

have an influence on them. Low participation rates and opportunistic screening use may have contributed to the low impact of MSPs.

ARTICLE SUMMARY

Strengths and limitations

- A modern Bayesian spatial model was used to improve estimation of an unstable rate by "borrowing" strength from its neighbours.
- The model is capable of assessing the significance of risk factors while also taking the geographical correlation into account.
- Switzerland with its homogeneous health system and different regional screening policies provides an ideal setting for assessing the impact of population-based mammography screening programmes.
- Data on the geographical differences in opportunistic screening use and therefore overall screening participation are not available, where opportunistic screening use is estimated to be high and programme participation less than 50%.
- The ecological study design does not allow an assessment of the combined impact of participation in and type (programme vs. opportunistic) of mammography screening.
-

INTRODUCTION

In Switzerland breast cancer is the most frequently diagnosed cancer in women[1], it is the leading cause of cancer-related deaths[2] and of premature mortality for Swiss women[3]. Mortality due to breast cancer has declined considerably in the past decades in Switzerland and other developed countries[4]. The reasons for the decline remain controversial because 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.

Some randomised controlled studies[5] have demonstrated a breast cancer mortality reduction of 20% for women invited for breast cancer screening. However, they were conducted in the 1970s to 80s. Since then, many advances in therapies have been made and adopted[6] so that some authors doubt that the difference would persist under present conditions. Therefore, often used historical pre-screening control groups are not best suited to disentangle these effects. Autier et al [7] compared countries in Europe but a criticism was that different countries may have different health systems. Kalager et al.[8] used comparison groups in Norway and showed that only a third of the total mortality reduction could be attributed to mammography screening. However, a short observation period was used. Olsen et al.[9] confirmed these results in principle with the same data but with a somewhat longer follow-up duration. In addition, in a setting where voluntary screening is assumed to be high, it is unknown what the effect an organised screening programme would be for the population as a whole.

In Switzerland, with its homogenous health system, these pitfalls can be avoided. Switzerland is a small confederation of 26 relatively autonomous states called cantons with somewhat low inequalities[10] and many health- and cancer-related resources.[11-13] Although the health care system is homogeneous in providing universal and rapid access to and use of almost unlimited health care resources, some health care policies are developed at the cantonal level; in particular, the decision to initiate a population-based mammography-screening programme. These programmes were implemented in Switzerland at different times over the past two decades. The first Swiss mammography pilot programme was established in 1993 in the French-speaking canton of Vaud. However, it was only in 2010 that the first organised programme in a German-speaking canton (St. Gallen) started.

In breast cancer incidence, cantonal differences are well-known and have been attributed to the differential use of opportunistic or organised mammography screening[14]. In addition, considerable differences in health and health-related behaviour that affect the risk of breast cancer, including alcohol intake and a healthy diet, have been reported for the Swiss language regions [15 16], as well as differences in the age at first child birth and number of children born to a mother[17]. Differences in access to mammography screening and in lifestyle may be reflected in spatio-temporal differences in both breast cancer incidence and mortality, whereas only the latter will reflect the management of breast cancer.

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

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

METHODS

Data sources

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

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

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

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

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

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

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

	Total no. of breast cancer deaths	%	yearly population (x1000)	crude rate	ASR	p-value for ASR homogeneity
Period						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	
Language						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	
Urbanisation level						p=0.08
Rural	6,172	24%	4,491	34.4	26.9	
Urban	19,761	76%	13,137	37.6	28.8	
Years of population based screening*						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	
Socioeconomic index quartiles						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

Statistical methods

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

We investigated mortality for all ages combined in a spatial and a non-spatial model, one time for the five time periods from 1969 to 2012 to assess possible non-linear time trends, and another time only for the period of 2009-2012.

For the spatial model, we used the Bayesian hierarchical spatio-temporal Poisson model formulations as described in Herrmann et al 2015[19], fitted on the number of deaths aggregated by small area and year, with the mean being equal to the product of the expected death count and age-standardised mortality rate. The indirect standardisation used 5-year age intervals. Expected mortality counts for each small area and year were obtained from the study population using nationwide age-specific mortality rates, once for all periods and again only for the period of 2009-2012. The small-area-specific random effects were modelled via conditional autoregressive (CAR) models to filter out the noise and highlight the observed patterns. The deviance information criterion (DIC) was used to select the regression model from Poisson, zero-inflated Poisson and Negative Binomial regression models. The DIC was lowest with the Poisson regression model.

We accounted for differences that were influenced by linguistic region, life in rural or urban areas, screening programme duration, and socio-economic position. These analyses are used to indicate whether there are significant differences in cancer mortality for each of the above covariates, assessed by 95% Bayesian Credible Intervals (CI).

Patient involvement

No patients were involved in this study.

RESULTS

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

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

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

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

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

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

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	
Language				
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)
Urbanisation level				
Rural	1.00		1.00	
Urban	0.97	(0.89;1.06)	0.97	(0.89;1.07)
Years of population-based screening				
0, 1-4 years	1.00		1.00	
5+ years	0.95	(0.82;1.11)	0.99	(0.78;1.23)
Socioeconomic index				
per 10 point increase	1.03	(0.97;1.09)	1.03	(0.95;1.10)
Spatial variation			0.29	(0.24;0.35)

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.

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.

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

DISCUSSION

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

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

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

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

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

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

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

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

Conclusion

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

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted

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

CONTRIBUTIONS

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

TRANSPARENCY DECLARATION

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

ETHICAL APPROVAL

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

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DATA SHARING STATEMENT

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

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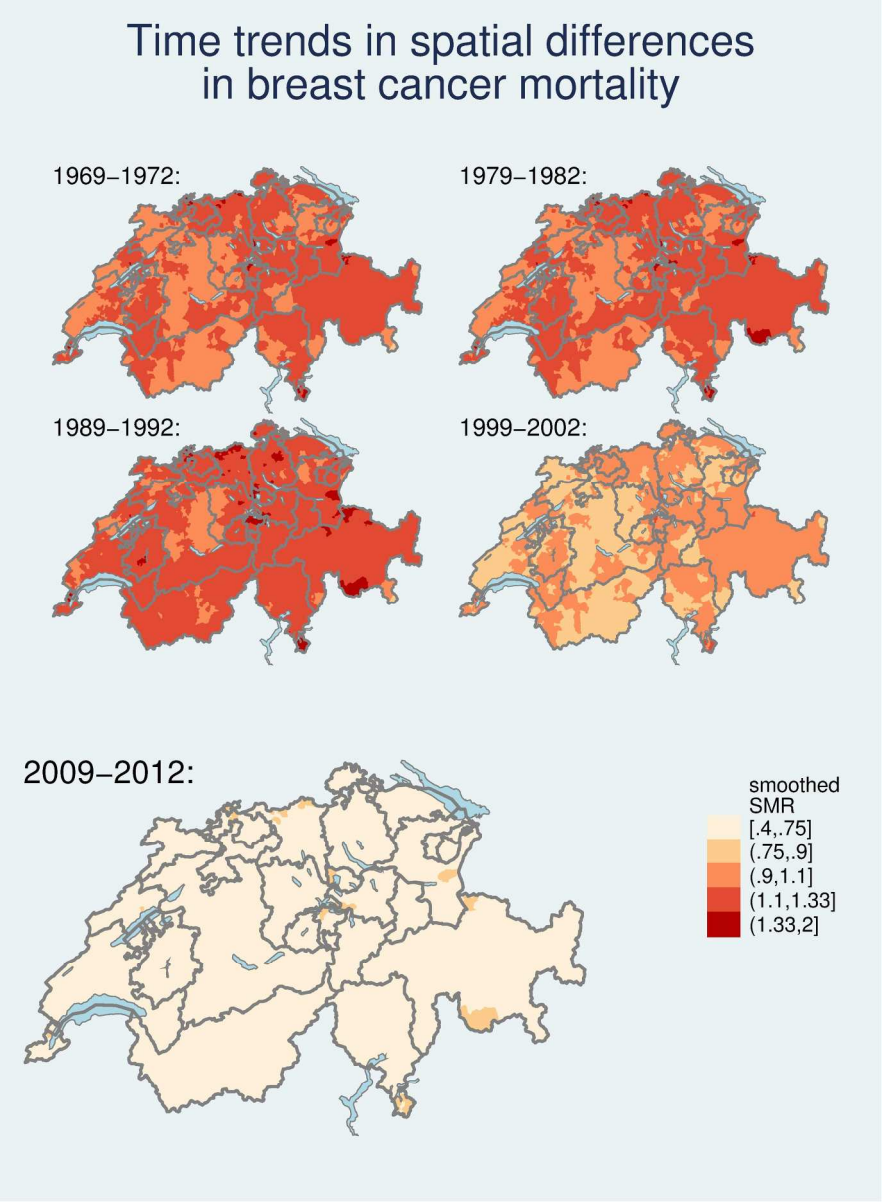
FIGURES

Fig. 1 Development of age-standardised 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.

Fig. 2 Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012. *Significance is denoted as values significantly different at 95%CI from 1, the national mean.

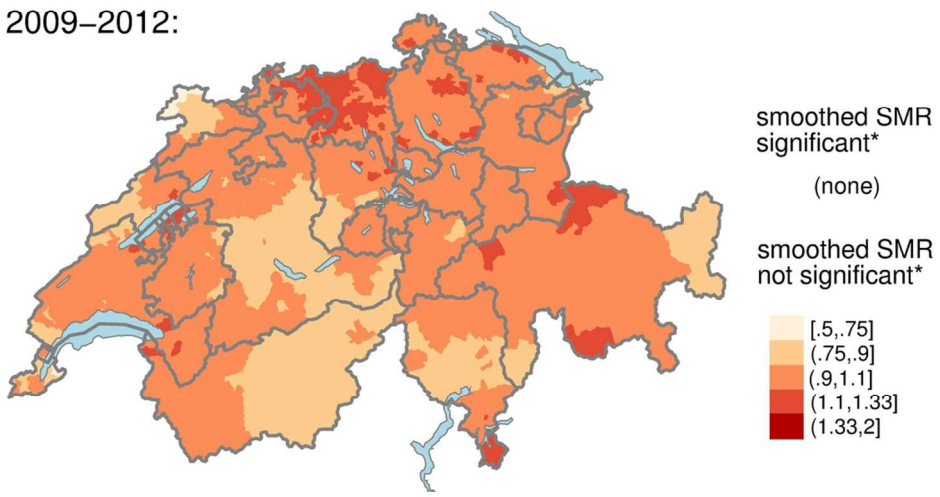
ADDITIONAL MATERIAL

A1. Figures depicting urbanization classification, language regions Screening duration and Swiss 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)

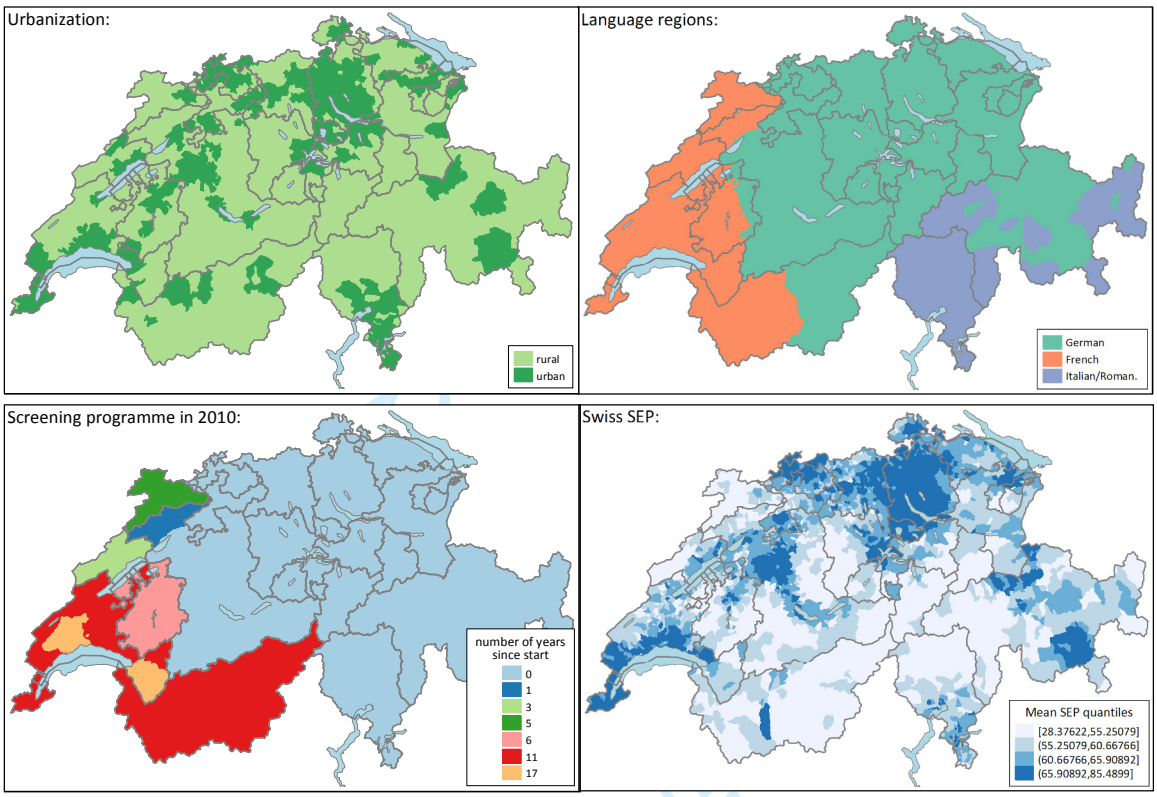


Geographical differences in age standardized breast cancer mortality (SMR) in 2009-2012.
*Significance is denoted as values significantly different at 95%CI from 1, the national mean.

101x68mm (300 x 300 DPI)

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
Title and abstract	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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	Pages 6-8

Continued on next page

Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—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
Discussion			
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
Other information			
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.