Geographical disparities, trends and projections in female gender-related cancers in Switzerland

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Prof. Dr. Martin Spiess
Dekan

Meiner Familie gewidmet

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My heartfelt dedication goes to my family. My home is where you are!

Summary

Gender-related cancers have a deep impact on patients and on public health. The psychological and social consequences are further pronounced through their direct link with sexuality, reproduction and gender identity. This thesis focusses on the female cancers. Female gender cancers account for about 42% of all newly diagnosed cancer cases and 29% of all cancer-related deaths in women in Switzerland. Among female gender-related cancers, breast cancer is the predominant one accounting for more than three-quarters of new cases in this group.

This thesis aims to apply and further develop rigorous analytical methods on cancer data collected from cancer registries and the Federal Statistical Office (FSO) in order to quantify the burden of breast and other female gender-related cancers in Switzerland, its spatial disparities and future trends and to investigate the geographical patterns of case management procedures in the country. The results are particularly important for public health policy in Switzerland and in advancing epidemiology for prevention and care. This thesis is structured by addressing broader to increasingly more specific research questions.

Chapter 2 gives an overview of the burden of cancer for the society and for the health system in Switzerland, by estimating the prevalence of cancer, resp. the number cancer survivors by gender, time since diagnosis, cancer type and age group. Cancer survivors are a heterogeneous group with complex health problems. Data concerning its total number and growing dynamics for Switzerland were scarce and outdated. In this chapter back calculation methods (PIAMOD) were applied on nationwide mortality data and relative survival data from Swiss cancer registries, and trends estimated by Joinpoint analysis.

The analysis shows that there is a rapidly growing population of cancer survivors in Switzerland whose needs and concerns are largely unknown. The number of breast cancer survivors more than doubled from 1990 to 2010 and is projected to increase by another 28% from 2010 to 2020. Overall, the number of cancer survivors increased from 2.08% of the population in 1990 to 3.7% in 2010, with the current annual growth rate being 3.3% per year.

In *Chapter 3*, spatio-temporal disparities in female gender cancer mortality are investigated. Differences in the decrease and in spatial patterns within Switzerland have been reported according to urbanisation and language region and remained controversial.

Using modern Bayesian small area modelling and mapping techniques it was possible to show that all investigated groups of women in Switzerland have benefited from progress in cancer control regardless of place of residence in the past 40 years. Only small differences in the geographical variation of mortality are observed, present on a regional or canton-overspanning level, and different for each cancer site and age group. No general significant association with cantonal or language region borders could be observed.

Chapter 4 provides a more detailed analysis of breast cancer mortality disparities in Switzerland, with a focus on mammography screening programmes and socio-economic differences. In Switzerland, programmes have existed in some regions for over 20 years, while they do not yet exist in others, thus offering the possibility to analyse its effects with modern spatio-temporal methodology. The methodology of Chapter 3 was adapted to measure additional effects of screening and socio-economic disparities. Breast cancer mortality has strongly declined since the 1990s. No important spatial disparities are observed. The analysis shows that moderate geographical differences found are within credible intervals using modern Bayesian techniques. The duration of population-based screening programme and socioeconomic characteristics have no significant influence on breast cancer mortality and have been outweighed by important advances in treatment approaches.

In *Chapter 5* breast cancer mortality is projected by canton for 2015-2024. Projections of cancer mortality provide an estimate of the future burden of cancer and are important to assess the impact of novel approaches and future developments in breast cancer care, as well

as public health interventions. Projected mortality numbers can support healthcare planning. However, this has not been done for Switzerland so far.

Breast cancer mortality in Switzerland is projected to further decrease within the next ten years. However, the pace is regionally quite different. In more than half of the cantons, the number of breast cancer deaths is projected to increase with the demographic forecast playing a major role.

In *Chapter 6* geographical variation of hospital-based case management is assessed by measuring spatio-temporal differences of mastectomy rates by age group and hospital region. The FSO has collected hospital discharge records routinely since 1998, with information on diagnoses, co-morbidities, and treatments. This data with national coverage has not been used to describe disparities in breast cancer care patterns. Data on mammography screening programme duration and surgeon and gynaecologist density were also included.

The analysis shows an important decline of mastectomy rates in Switzerland in 2000-2012 for patients aged 50-69 and 70+, but no change for those under 50. Important geographical differences in rate estimates are present and rates are significantly influenced by age and co-morbidities of patients. Regions with higher surgeon and gynaecologist density have higher rates of mastectomies and regions with mammography screening programmes lower rates. A better insight into the differences in cancer management procedures will be useful for planning future demand and resource allocation for early detection, diagnosis, and treatment.

The main contributions of this thesis are (1) building awareness towards cancer survivors in Switzerland directly prompting several measures from policy to care, (2) identifying areas with high cancer rates and discrepancies of disease burden among areas in order to help health authorities in planning and evaluating cancer control activities (3) statistical methods for studying spatio-temporal patterns and projections of cancer mortality driven by data availability and characteristics in Switzerland that were applied and validated on real datasets, (4) smoothed maps of age-specific patterns of breast cancer mortality over time giving a better insight into the differences in cancer mortality rates between linguistic regions, urbanisation, affluence and cancer management procedures, (5) understanding the effect of differences in the uptake of screening programmes and socio-economic status on

breast cancer mortality in the population, (6) estimates of the geographical patterns of breast cancer mortality for the next 10 years, (7) identifying regions in which special attention is required to reduce healthcare inequalities and their impact on the community health, (8) determining the influencing factors for high mastectomy rates and (9) providing information for public health authorities for planning future demands and resource allocation for diagnosis and treatment.

Zusammenfassung

Geschlechtsspezifische Krebsarten haben einen grossen Einfluss auf die öffentliche Gesundheit und die Patienten, der durch den Zusammenhang mit Sexualität, Fortpflanzung und dem Geschlechterbild noch weiter erhöht wird. Diese Dissertation konzentriert sich auf die Tumoren der Frauen. Geschlechtsspezifische Krebsarten der Frauen machen etwa 42% aller neu diagnostizierten Krebsfälle und 29% aller krebsbedingten Todesfälle bei Frauen in der Schweiz aus. Dabei ist Brustkrebs mit einem Anteil von über 75% die in dieser Gruppe vorherrschende Krebsart.

Diese Dissertation hat das Ziel, strenge analytische Methoden auf Daten von Krebsregistern und des Bundesamtes für Statistik (BfS) anzuwenden und weiterzuentwickeln, um die Belastung durch geschlechtsspezifische Krebsarten in der Schweiz, geografische Unterschiede und ihre zukünftige Entwicklung zu quantifizieren, und um geografische Disparitäten des Fallmanagements zu untersuchen. Die Resultate sind von besonderer Bedeutung für die Gesundheitspolitik und das Voranbringen der Epidemiologie von Prävention und Krankenpflege. Die Dissertation ist so strukturiert, dass sie sich zunächst mit umfassenderen hin zu immer spezifischeren Forschungsfragen beschäftigt.

Kapitel 2 gibt einen Überblick über die Belastung durch Krebs für die Gesellschaft und das Gesundheitssystem in der Schweiz durch die Berechnung der Krebsprävalenz bzw. die Anzahl der „cancer survivors" nach Geschlecht, Zeit seit Diagnose, Krebsart und Altersgruppe. „Cancer survivors" sind eine heterogene Gruppe mit komplexen Gesundheitsproblemen. In der Schweiz sind aktuelle Daten zu ihrer Gesamtzahl und Wachstum nicht vorhanden. Es wurden dabei sogenannte Backcalculation Berechnungsmodelle (PIAMOD) auf die nationalen

Mortalitätsdaten und Daten zum Überleben nach Krebs der Schweizer Krebsregister angewendet und Trends per Joinpoint-Analyse bestimmt. Die Analyse hat gezeigt, dass es in der Schweiz eine rasch wachsende Population von „cancer survivors" gibt, deren Bedürfnisse und Sorgen weitgehend unbekannt sind. Die Zahl der Brustkrebs-„survivors" hat sich von 1990 bis 2010 mehr als verdoppelt und wird voraussichtlich im Zeitraum von 2010 bis 2020 um weitere 28% ansteigen. Insgesamt stieg die Zahl der Krebsüberlebenden von 2,08% der Bevölkerung im Jahr 1990 auf 3,7% im Jahr 2010 an. Die jährliche Wachstumsrate liegt bei 3,3%.

In *Kapitel 3* werden die zeitlichen und räumlichen Disparitäten bei der Mortalität geschlechtsspezifischer Krebsarten der Frauen untersucht. In der Vergangenheit wurde über geografische Unterschiede und Unterschiede in der zeitlichen Entwicklung je nach Urbanisation und Sprachregion berichtet. Die Ergebnisse blieben aber umstritten.

Unter Anwendung moderner Bayesischer Methoden zum Modellieren und Kartographieren kleiner geografischer Gebiete konnte nun gezeigt werden, dass alle Frauen in der Schweiz in den letzten 40 Jahren unabhängig von ihrem Wohnort vom Fortschritt in der Krebsbekämpfung profitiert haben. Es gab nur geringe geografische Unterschiede in der Mortalität auf regionaler oder kantonsübergreifender Ebene, die für jede Krebsart und Altersgruppe unterschiedlich waren. Es gab keinen signifikanten Zusammenhang mit Kantons- oder Sprachregionsgrenzen.

Kapitel 4 vertieft die Analyse der Disparitäten bei Brustkrebsmortalität in der Schweiz unter Einbezug des potentiellen Einflusses organisierter Screening Programme und sozio-ökonomischer Unterschiede. Diese Analyse ist möglich, da in manchen Regionen der Schweiz seit über 20 Jahren Screening Programme existieren, während es in anderen noch keine solchen Programme gibt. Die Methode aus Kapitel 3 wurde entsprechend angepasst. Die Brustkrebsmortalität hat seit den 1990ern stark abgenommen. Die beobachteten moderaten geografischen Unterschiede blieben innerhalb des Bayesischen Glaubwürdigkeitsintervalls. Die untersuchten Einflussfaktoren (Urbanisation, Sprachregion, Sozioökonomische Charakteristika und Dauer von Populationsbasierten Screening Programmen) hatten keinen signifikanten Einfluss auf die zeitliche und räumliche Entwicklung der Mortalität. Sie wurden von den grossen Fortschritten in der Krebsbehandlung überwogen.

In *Kapitel 5* wird die Brustkrebs-Sterblichkeit pro Kanton für 2015-2024 projiziert. Projektionen der Krebsmortalität ermöglichen eine Schätzung der zukünftigen Belastung durch Krebs und sind wichtig, um die Auswirkungen von neuartigen Ansätzen und zukünftige Entwicklungen in der Brustkrebsbehandlung und -nachsorge sowie staatlicher Gesundheitsinterventionen zu bewerten. Die projizierten Sterblichkeitszahlen können die Planung des Gesundheitswesens unterstützen. Für die Schweiz wurde eine solche Projektion bisher nicht durchgeführt.

Die Brustkrebsmortalität wird in der Schweiz voraussichtlich weiter sinken innerhalb der nächsten zehn Jahre. Die jeweils erwartete Geschwindigkeit ist pro Kanton aber deutlich unterschiedlich. In mehr als der Hälfte der Kantone wird die Gesamtzahl der Todesfälle durch Brustkrebs zunehmen, hauptsächlich durch die erwartete demografische Entwicklung.

In *Kapitel 6* werden geografische Unterschiede beim Case Management im Spital untersucht, insbesondere die zeitlich-geografische Entwicklung von Mastektomieraten nach Altersgruppe und Spitalregion. Das BfS erhebt seit 1998 jährlich die medizinische Krankenhausstatistik mit Informationen über Hospitalisationen, Diagnosen, Komorbiditäten und Behandlungen. Diese in der gesamten Schweiz erhobenen Daten sind bisher noch nicht benutzt worden, um Unterschiede in der Brustkrebsbehandlung zu untersuchen. Zusätzlich wurden auch Daten zur Länge von Mammographie-Screening-Programmen und Chirurgen- und Gynäkologen-dichte einbezogen.

Die Analyse zeigt eine starke Verringerung der Mastektomieraten in der Schweiz im Zeitraum 2000-2012 bei Patienten von 50-69 Jahren und 70 Jahre und älter, jedoch keine Veränderung bei Patienten unter 50 Jahren. Es bestehen deutliche geografische Unterschiede in den Raten, die signifikant vom Alter und den Komorbiditäten der Patienten beeinflusst werden. Regionen mit höherer Chirurgen- und Gynäkologendichte haben höhere Mastektomieraten und Regionen mit Mammographie-Screening-Programmen haben niedrigere Raten. Ein besseres Verständnis der Unterschiede ist hilfreich für die Planung zukünftiger Kapazitäten und des Resourcenbedarfs in den Bereichen Früherkennung, Diagnose und Behandlung.

Der Hauptbeitrag dieser Arbeit ist (1) die Sensibilisierung für die Situation der „cancer survivors“ in der Schweiz, indem sie unmittelbar mehrere Maßnahmen in der Politik und

Schaffung von Beratungsangeboten veranlasst hat, (2) die Ermittlung von Gebieten mit hohen Krebsraten und Diskrepanzen der Krankheitslast untereinander, um Gesundheitsbehörden bei Planungen zu helfen, (3) statistische Methoden für die Analyse von räumlich-zeitlichen Mustern und Projektionen der Krebsmortalität mit in der Schweiz verfügbaren Daten, die auf reale Datensätze angewendet und validiert wurden, (4) Karten mit geglätteten Interpolationen von altersspezifischen Verteilungsstrukturen von Brustkrebsmortalität zum besseren Verständnis der Unterschiede nach Sprachregion, Urbanisation, Affluenz und Krebsmanagement, (5) Verständnis für die Auswirkungen von populationsbasierten Mammographie-Screening-Programmen und Unterschieden in sozio-ökonomischen Stati auf Brustkrebsmortalität, (6) Abschätzung der geografischen Strukturen der Brustkrebs-Mortalität für die nächsten 10 Jahre, (7) die Identifizierung von Regionen, die besondere Aufmerksamkeit erfordern, um Ungleichheiten im Gesundheitswesen und deren Auswirkungen auf die öffentliche Gesundheit zu verringern, (8) Bestimmung der Einflussfaktoren für erhöhte Mastektomieraten und (9) die Bereitstellung von Informationen für die Gesundheitsbehörden zur Planung zukünftiger Anforderungen und Ressourcenverteilung in den Bereichen Diagnose und Behandlung.

Chapter 1

Introduction

1.1 Gender-related cancer

Among the many diseases called cancer, some are called gender-related. They either affect women or men and are localised on the genital organs, or linked with secondary sexual characteristics. In the case of women, these include cancers of the breast, corpus uteri, ovaries and cervix, and for men prostate and testicular cancers. This thesis focusses on the female cancers. Female gender-related cancers account for about 42 % of all newly diagnosed cancer cases and 29 % of all cancer-related deaths in women in Switzerland (NICER, 2017).

Gender-related cancers have a deep impact on patients and on public health. The psychological and social consequences are further pronounced through their direct link with sexuality, reproduction and gender identity. For these reasons, gender-related cancers receive particular attention in the EU research action on cancer, which is itself a priority in the EU research programme on major diseases. With strong support from the European Parliament, more than €400 million have been allocated to cancer research in the EU's Sixth Framework Programme for Research during the period 2002-2004 (European Commission and Directorate General for Research, 2006).

1.1.1 Breast cancer

Among female gender cancers, breast cancer is the predominant one, accounting for more than three quarters within this group of cancers in Switzerland. Female breast cancer is the most frequently diagnosed cancer in the female Swiss population and worldwide (Ferlay et al., 2013b). Figure 1.1 shows estimated breast cancer incidence in 2012. On a global scale, breast cancer incidence is highest in western European countries, North America, Australia, New Zealand and Argentina. Lowest incidence is observed in Asia and parts of Africa.

Within Switzerland, age-standardised incidence rates for breast cancer vary between 68/100'000 persons per year (PY) in St. Gallen-Appenzell and 103/100'000 PY in Geneva, which is one of the highest incidence rates globally (Curado et al., 2007).

Within the period from 2009 to 2013, almost 30'000 new cases of breast cancer were diagnosed in total in Switzerland, corresponding to more than 30% of the total female cancer incidence (NICER, 2017). The median age at diagnosis was 64 years (BfS, 2016).

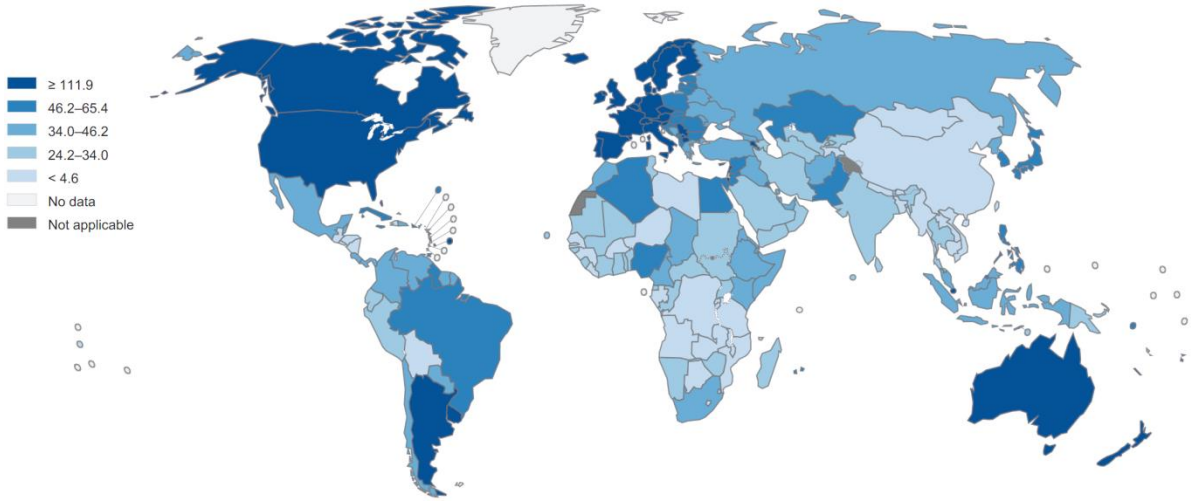

Figure 1.1: Estimated age-standardised (World) rates per 100'000 population of female breast cancer incidence in 2012. Source: Globocan 2012

Differences in the uptake of screening activities (mammography screening in women) contribute as much to differences in risk as other known risk factors such as age and genetic predisposition, overweight and obesity, reproductive factors and presumably hormone replacement therapy (McPherson et al., 2000, Kumle, 2008). Bouchardy et al. (Bouchardy et al., 2007) reported a statistical increase in the breast cancer incidence rates in younger women (<40) over the last years in Geneva which has not been observed in the data from the Vaud and Neuchâtel Cancer registries (Levi and La Vecchia, 2007). Breast cancer incidence rates have also increased in older women in Geneva where the prevalence of hormonal replacement therapy (HRT) is high (Verkooijen et al., 2009).

Overall, the rate of newly diagnosed breast cancers in Switzerland increased significantly from the period 1985-1989 to 2000-2004 and it has since remained stable (Figure 1.3) (BfS, 2016).

Globally, breast cancer is the fifth most common cause of death from cancer (Ferlay et al., 2013b) with a much higher degree of intracontinental variability compared to breast cancer incidence (Figure 1.2). Although the breast cancer mortality in Switzerland is very well below the European average (Ferlay et al., 2013c), breast cancer is the leading cause of cancer-related death among Swiss women.

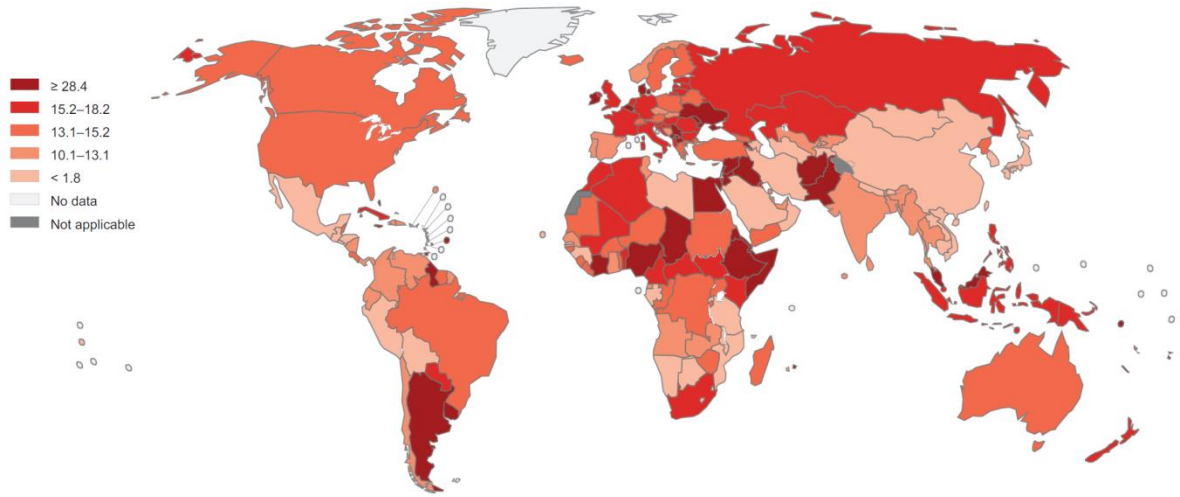

Figure 1.2: Estimated age-standardised (World) rates per 100'000 population of female breast cancer incidence in 2012. Source: Globocan 2012

Between 2009 and 2012, breast cancer accounted for about 20% of all cancer-related deaths in Switzerland, making up around 1'400 deaths per year (NICER, 2017). The median age at death was 73 years. Within Switzerland age-standardised mortality rates vary from 14.7 per 100'000 PY in Jura to 27.9 per 100'000 PY in Uri. While the French-Italian-speaking region had higher rates in terms of incidence, mortality rates are higher in the German-speaking region of Switzerland (BfS, 2016).

Age-standardised breast cancer mortality (European standard) has decreased from 35.2 per 100'000 PY in 1989-1993 to 21.8 per 100'000 PY in 2009-2013 (NICER, 2017). The decrease did not take place homogenously in all regions, i.e. no decline has been observed in the German-speaking cantons of Basel and Zurich (Bulliard et al., 2006). Also, the total number of breast cancer deaths decreased significantly over the same time period (Figure 1.3).

Survival rates after breast cancer have continuously increased over the last decades in Switzerland as well as in the rest of Europe, with differences largely resulting from differences in stage at diagnosis (Sant et al., 2015). A shift to more favourable stages at diagnosis was described for Switzerland for the period of 2003-2012 (Bouchardy et al., 2015). From the period 1983-1985 to 2000-2007 the 5-year cumulative relative survival rate improved from 75.7% to 84.6% (Figure 1.6) (Sant et al., 2003, Sant et al., 2009, De Angelis et

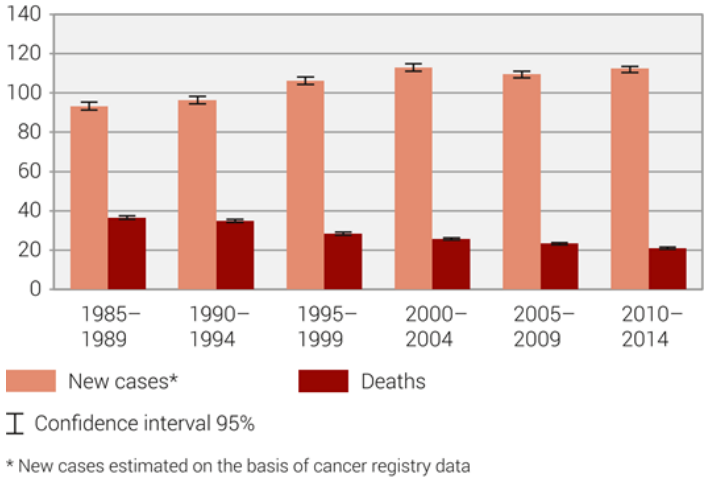

Figure 1.3: Female breast cancer trends in Switzerland, age-standardised rates per 100'000 (European Standard). Sources: NICER – New cases; FSO – Deaths, FSO2017

al., 2014). Currently, the 5-year relative survival rate after diagnosis in Switzerland is 85.1% and 10-year relative survival 72.9% (NICER, 2017). The lowest survival rate was described for the rural parts of German-speaking eastern Switzerland and the highest for urbanised regions of the north-western parts of the country (Fisch et al., 2005). Differences in early detection and case management of the disease may explain regional disparities.

1.1.2 Cancers of the corpus uteri, ovaries and cervix

Cancers of the corpus uteri, ovaries and cervix together account for about 10% of all newly diagnosed cancers in Switzerland. From 2009 to 2013, about 4'500 new cancers of the corpus uteri, about 3'000 new cases of ovarian cancer, and about 1'200 new cases of cervical cancer were diagnosed (NICER, 2017). Within Switzerland, age-standardised incidence rates for cancer of the corpus uteri vary between 11.1 per 100'000 PY in Ticino and 13.5 per 100'000 PY in St. Gallen-Appenzell; for cancers of the ovary between 7.4 per 100'000 PY in Zürich and 10.7 per 100'000 PY in Valais; and for cervical cancer between 2.7 per 100'000 PY in Geneva to 6.1 per 100'000 PY in Grisons-Glarus (Forman et al., 2013).

The incidence of cancers of both corpus uteri and cervix uteri has considerably decreased in the past decades (Figure 1.4) (BfS, 2016). The cervical cancer incidence in Switzerland is the lowest in Europe while cancer of the corpus uteri is about average (Ferlay et al., 2013c).

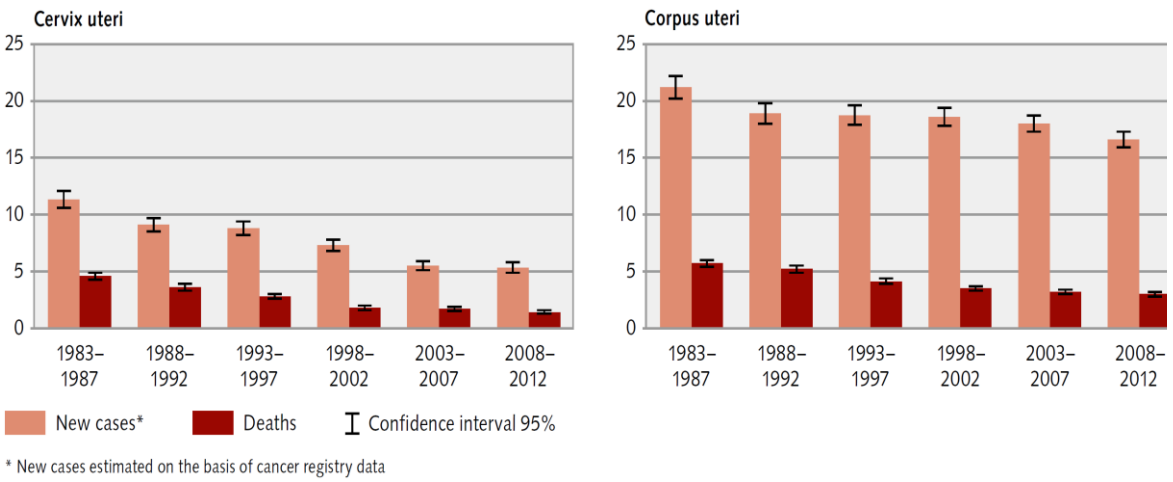

Figure 1.4: Time trends of cancers of the uterus in Switzerland, age-standardised rates per 100'000 (European Standard). Sources: NICER – New cases; FSO – Deaths, FSO2017

Within Switzerland, incidence and mortality rates of cervical cancers are considerably higher in German-speaking regions of Switzerland, than in other regions, although no significant differences were observed for cancer of the corpus uteri in those regions (BfS, 2016).

An important risk factor for cervical cancer is infection with the human papillomavirus (HPV), where the HPV types 16 and 18 are responsible for roughly three-quarters of the cases. Early detection can be done by pap smears. In all cantons of Switzerland, HPV vaccination is available free of charge for 11-14-year-old girls and is covered by health insurance for women aged 15-26 and men aged 11-26 (Krebsliga Schweiz, 2017a). Further risk factors include smoking and use of hormonal contraception (International Agency for Research on Cancer, 2012). An important improvement of survival in cervical cancer has been reported for Europe (Sant et al., 2015) while the relative survival rate has remained stable over the past decades in Switzerland (Figure 1.6). Currently, the 5-year relative survival after diagnosis is 65.5% and the 10-year relative survival 54.9% (NICER, 2017).

Surviva rates in cancers of the corpus uteri range between breast and cervical cancer with 5-year relative survival rates of 75.4% and 10-year relative survival rates of 68.6%. Over the past decades, survival has improved greatly from 68.8% in 1983-1985 to 78.5% in 2000-2007 (Figure 1.6). Important risk factors include high levels of sex hormones and hence early

menarche, late menopause, nulliparity, hormone replacement therapy, as well as obesity and the use of Tamoxifen as a part of treatment or prevention of breast cancer (International Agency for Research on Cancer, 2012).

The ovarian cancer incidence has decreased by about a quarter in the past 30 years in Switzerland (Figure 1.5)(BfS, 2016). In comparison with other European countries, the incidence in Switzerland is slightly below average (Ferlay et al., 2013c). Ovarian cancers share some common risk factors with breast cancer, such as age, number of ovulations (early menarche, infertility, low parity etc.), use of hormone replacement therapy (HRT) (Bouchardy et al., 2010, Verkooijen et al., 2009, Fournier et al., 2005), obesity and physical inactivity (Lahmann et al., 2004a, Lahmann et al., 2004c, Lahmann et al., 2004b), as well as a familial history of breast and ovary cancer including BRCA1 and BRCA2 gene mutations (Meindl et al., 2011). In contrast to breast cancer, little early detection efforts are done in ovarian cancer, which means that ovarian cancer is mainly diagnosed in advanced stages with poor survival rates (Levi et al., 1993, Coleman et al., 2003). Relative survival has slightly improved from 32.8% in 1983-1985 to 38.9% in 2000-2007 (Figure 1.6) (Sant et al., 2003, Sant et al., 2009, De Angelis et al., 2014). Nevertheless, the relative survival 5 years after the diagnosis is currently still 38.9% and only 27.1% after 10 years.(NICER, 2017).

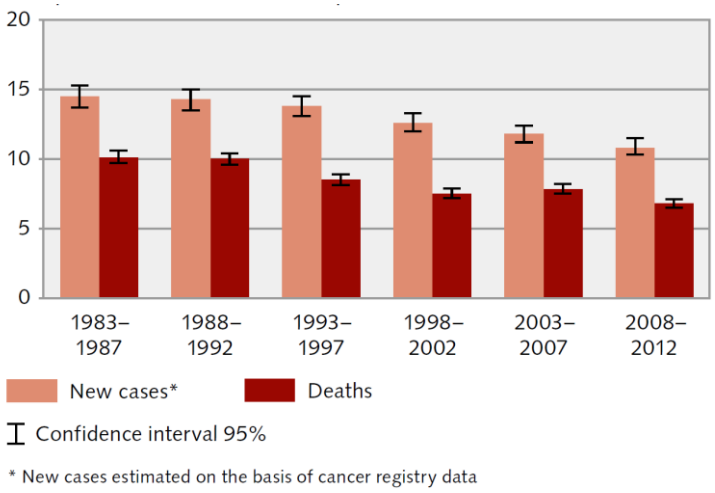

Figure 1.5: Ovarian cancer trends in Switzerland, age-standardised rates per 100'000 (European Standard). Sources: NICER – New cases; FSO – Deaths, FSO2017

Cancers of the corpus uteri, ovaries, and cervix uteri together account for about 10% of cancer-related deaths in Swiss women (around 700 deaths per year) (NICER, 2017). Similar to incidence, cervical cancer mortality is one of the lowest when compared to other European countries, while mortality of cancers of the corpus uteri and ovaries are about average.

Within Switzerland, age-standardised mortality rates for cancers of the corpus uteri vary from 0.9 per 100'000 PY in Obwalden to 6.7 per 100'000 PY in Jura. Over the past decades, there has been a pronounced decrease in mortality (Figure 1.4). Age-standardised rates fell from 5.2 per 100'000 PY in 1989-1993 to 3.0 per 100'000 PY in 2009-2013 for cancers of the corpus uteri (NICER, 2017, BfS, 2016).

For ovarian cancer, age-standardised mortality rates vary from 3.3 per 100'000 PY in Appenzell Innerrhoden to 9.4 per 100'000 PY in Uri. Comparable to the decrease in incidence, ovarian cancer mortality has decreased by about a third over the past decades (Figure 1.4). Rates have decreased from 9.8 per 100'000 PY in 1989-1993 to 6.6 per 100'000 PY in 2009-2013 (NICER, 2017, BfS, 2016).

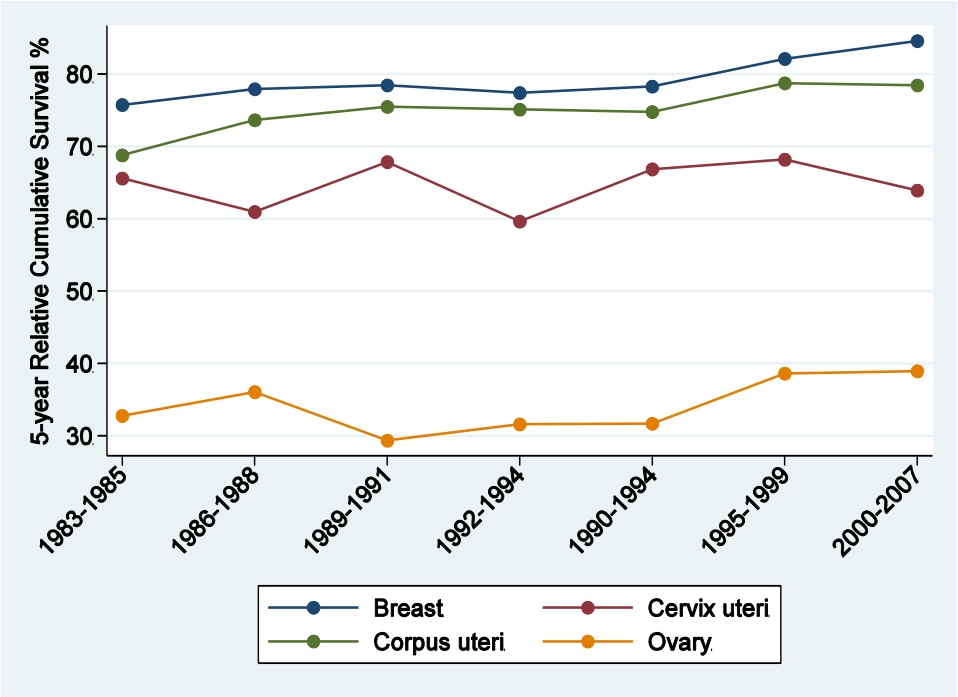

Figure 1.6: Development of cumulative relative survival after 5 years of diagnosis by cancer type in Switzerland. Sources: Eurocare 3-5.

Cervical cancer mortality rates vary from 0.4 per 100'000 PY in Zug to 2.6 per 100'000 PY in Glarus. Mortality, similarly to incidence, is significantly higher in German-speaking parts compared to French and Italian-speaking parts of Switzerland. Over the past decades, cervical cancer mortality has decreased from 3.7 per 100'000 PY in 1989-1993 to 1.3 per 100'000 PY in 2009-2013 (Figure 1.4) (NICER, 2017, BfS, 2016).

1.1.3 Risk factors affecting mortality

The previously mentioned risk factors affect the incidence but are not necessarily linked to mortality (Barnett et al., 2008, Fasching et al., 2012). Elevated mortality is influenced by high incidence and/or low survival rates. Unfortunately, complete regional data on incidence, survival, stage distribution and treatment patterns are not available for Switzerland.

Cancer incidence, mortality, and survival are also related to socioeconomic factors (Faggiano et al., 1997), possibly due to differences in exposure to risk factors, access to healthcare facilities and receiving appropriate care. Cancer patients with a low socioeconomic status (SES) have an increased risk of dying as a result of their disease compared to the patients of higher SES. In the discussion of social inequalities in health, there has been much debate on the role of medical care. Access inequalities to early detection, appropriate care and state-of-the-art management as well as differences in tumour biology are possible explanations for survival differences between SES classes. Regional disparities have been described for Switzerland affecting the income, access to services, including access to healthcare services, education and other socioeconomic factors (Bundesamt für Statistik, 2009).

1.2 Spatial epidemiology of female gender cancer in Switzerland

In Switzerland, comprehensive data on cancer mortality are available from death certificates which have been collected and coded by the Federal Statistical Office (FSO) since the end of the 19th century but have been available in electronic form since 1969. They are geo-referenced and cover the whole country. In addition, geo-referenced data on hospitalisations including socioeconomic characteristics of the patient, diagnosis, and procedures have been collected annually by the FSO since 1998 and cover the whole country. Cancer incidence data are collected by the regional Cancer Registries which covered about 80% of the population by 2012. Some registries have existed for more than 25 years while others were established only

very recently. Population data are available every 10 years, issued by the census. The wealth of information provided in these databases have not been fully explored to assess space-time patterns and trends of breast cancer at different administrative levels and of the healthcare-related procedures for control and health-planning purposes.

Data from the Swiss cancer registries and the FSO have been used to obtain crude breast cancer incidence and mortality estimates by region and selected years (Luthi et al., 2005, Pury et al., 2007, Pury et al., 2007, Levi and La Vecchia, 2007, Levi et al., 2006). However, detailed analyses to assess spatio-temporal patterns of the diseases are scarce. The only maps of cancer mortality rates including female gender cancers are that of Schüler and Bopp (Schüler and Bopp, 1997), depicting geographical variation in mortality during 1970-1990 in a rather descriptive way. Covariate-adjusted and smooth, nationwide maps of female gender-related cancer mortality and incidence rates depicting the changes over time and space were not available.

Breast cancer can be detected at an early stage by the means of screening procedures. Important regional disparities in incidence, mortality early diagnosis and management have been described. In order to reduce regional and socioeconomic disparities quality-assured population-based mammography screening programmes have been introduced or are in planning in several cantons, and others are expected to follow soon (swiss cancer screening, 2015). Information on geographical patterns and temporal trends of the disease burden of cancer at different regional scales are important for the design, implementation, and evaluation of programmes for cancer control. Once available, the data can be used to target or intensify campaigns in high-priority areas in order to reduce disparities. Data on changes in disease incidence and mortality can also be helpful in the long run to assess the success of programme implementation.

Projections of breast cancer incidence, prevalence and mortality provide useful information for health-planning purposes. Estimates of the number of new cases, number of survivors and deaths are needed for proper resource allocation for screening, diagnosis, treatment and long-term care. Breast cancer incidence and mortality projections have been made in a number of European and other countries (Cleries et al., 2006, Wong et al., 2007, Erbas et al., 2010). Although national projections have been made up to 2019 for incidence (Rapiti et al.,

2014), mortality projections beyond 2000 were neither available at national nor at cantonal level in Switzerland. The most recent projections of cancer mortality were estimates up to the year 2000, using mortality data covering the period between 1950 and 1985 (Negri et al., 1990). Data and projections on prevalence beyond the 5-year prevalence after diagnosis were unavailable for Switzerland.

Switzerland has a nationwide common minimum reimbursement standard within its basic healthcare scheme, but apart from that, there is large geographical variation in health expenditures, control programmes, and treatment procedures. Healthcare policies are developed at cantonal level. For example, the first Swiss mammography pilot programme was established in 1993 in three districts of the French-speaking canton of Vaud. The programme in Vaud was expanded in 1999 to the whole canton as well as to the two French-speaking cantons of Geneva and Valais (60% French, 30% German). Other French-speaking cantons implemented population-based programmes in 2006. It was only in 2010 that the first organised programme in a German-speaking canton (St. Gallen) started, followed by the German-speaking cantons Thurgau and Grisons (76% German, 14% Romansh, 10% Italian). The Italian-speaking canton (Ticino) started in 2013. Disparities in breast cancer mortality are at least partially attributable to early detection efforts in these regions. Opportunistic screening is common especially in the urban areas of cantons with cancer registries but little is known about regions not covered by cancer registries. Geographical disparities in the self-reported use of mammography have been reported previously (Wanner et al., 2001).
Regional disparities in the state-of-the-art management of breast cancer were published in the beginning of this decade (Ess et al., 2010c, Ess et al., 2010a). Disparities included surgical, especially mastectomies, as well as non-surgical management issues. Since 1998, hospitals have reported diagnoses to the FSO, including several co-morbidities and procedures together with patient characteristics. These data, which are georeferenced, can give insight into some causes of disparities including age, language region and affluence, and have been explored very little up to now. With this data nationwide differences in breast cancer care, especially mastectomy rates, and relevant factors can be assessed.

1.3 Bayesian spatio-temporal modelling of cancer data

Spatial data can be broadly classified into three categories: viz-areal unit data, geostatistical data and point processes (Banerjee et al., 2003). The latter defines data observed at random locations, with the outcome of interest thus being the location itself. Area data arise when the outcome of interest is observed in an area, e.g. mortality rates within administrative regions. In this case, the entire study area is partitioned into a finite number of mutually exclusive and exhaustive regions, each of them having a positive area with a measurement attached to it. Geostatistical data arise when the outcome is observed at a finite number of geocoded locations, e.g. village-level surveys. Geographical dependency violates the independence assumption of standard statistical models, resulting in biased estimates of the parameters if it is not taken into account. Bayesian methods have been applied extensively in recent years for modelling spatial data because they allow flexible modelling and inference, and provide computational advantages via the implementation of Markov chain Monte Carlo (MCMC) methods (Gelfand and Smith, 1990). The spatial structure is commonly introduced in a hierarchical fashion via the prior distribution of area or location-specific random effects, although spatial dependence can be built directly on Gaussian response data. The choice of prior distributions or spatial models depends on the type of spatial data.

For area data, simultaneously autoregressive (SAR) models (Whittle, 1954), conditional autoregressive (CAR) and multivariate conditional autoregressive (MCAR) models (Clayton and Kaldor, 1987, Bernardinelli and Montomoli, 1992, Gelfand and Vounatsou, 2003, Best et al., 2005) and modifications (Besag et al., 1991, Marshall, 1991, Sun et al., 2000) as well as shared component models (Richardson et al., 2006) have been suggested as prior specifications. The models produce smooth maps of the observed rates, highlighting patterns of the disease. They are also useful in establishing associations between disease rates and potential individual and area-related risk factors. These models can include temporal trends and variation, allowing the estimation of spatio-temporal patterns. Model-based analyses of area-geographical data are called ecological analyses.

This thesis concentrates on ecological regression models on nationwide cancer data. Bayesian ecological regressions have previously been applied to assess site-specific tobacco-related

cancer morbidity and mortality in relation to age, gender, language, and urbanization level (Jurgens et al., 2013a).

Disease maps based on raw rates can be non-informative or misleading when the sizes of the population for some of the areas are small, resulting in a large variability in the estimated rates, and making it difficult to distinguish chance variability from real differences. Bayesian spatial models "smooth" or improve the estimate of an unstable rate by "borrowing" strength from its neighbours (Bernardinelli and Montomoli, 1992). Bayesian spatial models also assess the significance of risk factors, taking into account the geographical correlation. In addition, these models 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 of the last twenty years for assessing spatio-temporal patterns and trends. They have, however, not yet been applied to Swiss cancer data as far as we know.

Age-period-cohort models (Holford, 1983) are commonly employed in prediction of cancer rates. The models use period and birth cohort effects as proxies for risk factors and rate determinants that cannot be measured directly. Bayesian analogues have been employed in forecasting breast cancer mortality and incidence rates (Cleries et al., 2006, Wong et al., 2007). The models have been extended to generalised power-link models by Jürgens et al (Jurgens et al., 2014) and to take geographical variation into account (Lagazio et al., 2003, Schmid and Held, 2004, Jurgens et al., 2013b).

1.4 Objectives

The overall objective of this research was to assess the societal burden of female gender cancer and the potential spatio-temporal differences in Switzerland, as well as providing health planners with important baseline data which was either outdated or unavailable to date at the starting point of this research.

The specific objectives were to

- estimate national cancer prevalence, assess its temporal patterns including projection into the future to scale the burden and show its societal relevance by providing data which was unavailable to date;
- assess spatio-temporal patterns of female gender-related cancer mortality on municipality level to update spatial data on mortality and by applying rigorous methodology for analysis of spatio-temporal trends, overcoming restrictions of ecological studies to date;
- assess spatio-temporal patterns of breast cancer mortality, taking into account socioeconomic patterns and organised screening programmes to provide a more in-depth analysis for breast cancer mortality and evaluate the impact of mammography screening programmes on the population level;
- project breast cancer mortality by canton for 2015-2024 to provide outdated baseline data and enable the evaluation of treatments and prevention programmes;
- assess regional differences and trends in breast cancer surgical procedures (mastectomy in particular) and explore their relation to socioeconomic disparities, and screening patterns.

Chapter 2

Cancer survivors in Switzerland: a rapidly growing population to care for

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Abstract

Background: Cancer survivors are a heterogeneous group with complex health problems. Data concerning its total number and growing dynamics for Switzerland are scarce and outdated.

Methods: Population and mortality data were retrieved from the Swiss Federal Statistical Office (FSO). Incidence and relative survival for invasive cancers were computed using data from the cancer registries Geneva (1970-2009), St. Gallen - Appenzell (1980-2010), Grisons & Glarus (1989-2010), and Valais (1989-2010). We estimated prevalence for 1990-2010 using the Prevalence, Incidence Approach MODel (PIAMOD) method. We calculated trends in prevalence estimates by Joinpoint analysis. Projections were extrapolated using the above models and based on time trends of the period 2007-2010.

Results: The estimated number of cancer survivors increased from 139'717 in 1990 (2.08% of the population) to 289'797 persons in 2010 (3.70%). The growth rate shows an exponential shape and was 3.3% per year in the period 2008 to 2010. Almost half of the survivors have a history of breast, prostate or colorectal cancer. Among cancer survivors, 55% are women but the increases have been more marked in men ($p<0.01$, 3.9% annual increase in men vs. 2.7% in women since 2008). By the end of 2020 372'000 cancer survivors are expected to live in Switzerland.

Conclusions: There is a rapidly growing population of cancer survivors in Switzerland whose needs and concerns are largely unknown.

Keywords: cancer survivors; survivorship; survivorship care; complete prevalence; time trends; projections; Switzerland

2.1 Background

As a consequence of improved life expectancy, of the growth and the aging of the population, as well as cancer awareness and early detection strategies the number of new cancer cases has raised continuously in the last 30 years in Switzerland and worldwide (Curado et al., 2007). At the same time, due to earlier diagnosis and improved treatments, cancer mortality has declined and survival rates have improved (Bouchardy et al., 2011, Ess and Schwarz-Vucic, 2012). The conjunction of these factors has led to a large and rapidly growing number of cancer survivors.

There are several definitions of cancer survivor. Here, we use the term of cancer survivor to describe any person alive with a previous diagnosis of cancer, following the American Society of Clinical Oncology (ASCO) (American Society of Clinical Oncology, 2011) and others (NCCS, 2012, NCI, 2011, Richardson et al., 2011) who define survivorship as the "process of living with, through and beyond cancer", equalling the definition of complete prevalence.

It is not until recently that the special needs of this growing population of cancer survivors have been brought into the focus of researchers and stakeholders. In 2006 the Institute of Medicine (IOM) focused on the transition from primary treatment to follow up care and the necessity to provide patients with a comprehensive care summary and follow-up plan for guidance on follow-up care, prevention and health maintenance (Hewitt et al., 2006).

In 2010 a National Cancer Survivorship Initiative in the UK recognised that not enough attention has been given to the long-term consequences of a cancer diagnosis and treatment and that action is needed in order to support cancer survivors to live as healthy and active a life as possible (Department of Health and Macmillan Cancer Support and NHS Improvement, 2010, Department of Health, 2011). The ongoing needs of cancer survivors in Switzerland have received insufficient attention up to now.

Three distinct phases of cancer survival has been proposed: the first includes the time from diagnosis to the end of the initial treatment which may extend from some months to several years, the second includes the transition from treatment to extended survival and the third represents the long-term survival (Mullan, 1985).

Cancer survivors will have greater health needs than the general population because the disease and/or treatment may lead to long-term or permanent impairment. Moreover, people

with a history of cancer have an elevated risk for new primary cancers than the general population (Dong and Hemminki, 2001).

An increase in cancer survivors is expected to result in a need for additional specialised health personnel (Hewitt et al., 2006), and a substantial increase in training in survivorship care to support the delivery of multidimensional primary care for long-term survivors (Bober et al., 2009). In a review from 2011, Richardson et al. (Richardson et al., 2011) identified growing concern that the services required to meet the physical, social and emotional needs of survivors have not been adequately developed so far.

In order to adequately develop strategies and services required to meet the needs of this growing population updated epidemiological data is essential. In Switzerland, data on the number, growing dynamics and characteristics of cancer survivors are not available or outdated. Last published data for Switzerland correspond to prevalence estimates for 1992 and only for a limited number of malignancies (Lutz et al., 2003).

The aim of the present work is to provide estimates of the number and characteristics of cancer survivors by the end of 2010 and project trends until 2020 in order to better understand the challenges that this booming population poses to oncological and general health services in the near future.

2.2 Methods

2.2.1 Data sources

To estimate the Swiss complete prevalence for the period 1990-2010, we used data provided by the registries Geneva (1970-2009), St. Gallen - Appenzell (1980-2010), Grisons-Glarus (1989-2010) and Valais (1989-2010). These registries, that cover approximately 26% of the Swiss population, are the only Swiss registries to satisfy following conditions i) have published incidence data in Cancer in 5 Continents Volume IX, ii) have incidence data at least from 1990 onwards and iii) are able to provide survival data. These data is routinely collected by the registries as part of national and cantonal programmes. Following federal regulations, after anonymization excluding any identifiable information such as names and exact dates these data can be used in epidemiological studies without additional ethics committee approval.

Persons presenting with invasive cancers (International Classification of Disease, 10th edition, codes C0-C96, D45-D47) except non melanoma skin cancers [C44]) were included in the study. Individuals with multiple primaries were counted only once and considered to be prevalent since the first diagnosis of invasive cancer retrieved from the cantonal cancer registries. Aggregated population and mortality data for the corresponding cantons and for Switzerland by year, gender and age were retrieved from the Swiss Federal Statistical Office (FSO) (Swiss Federal Statistical Office, 2014).

Incident DCO ("death certificate only") cases were excluded, as the true incidence date is unknown. The DCO rate was similar for all regions and varied in 1990-2010 in the different regions from 0.1-2.3% with an overall average of 0.6%. Cancer patients lost to follow-up were included and account for 3.8% (95% Confidence Interval, CI: 3.6%-4.1%) of studied population. This proportion declined during the study period and was 0.2% in 2010.

2.2.2 Statistical methods

Complete cancer prevalence in Switzerland was estimated in a 3-step process by gender and cancer site, with all cancer sites being modelled as a single site. First, we estimated yearly incidence counts for Switzerland by single years of age using the pooled yearly incidence rates by age of the aforementioned registries and the population data of the FSO. Then, we estimated survival in Switzerland as the relative survival in the pooled cantons, where patients lost to follow-up were censored at time of last contact. And finally, with these data plus population and all-cause mortality data for Switzerland, we modelled cancer prevalence using the Prevalence, Incidence Approach MODel (PIAMOD) method (Verdecchia et al., 2002). The same software was used to project prevalence until 2020 basing the incidence estimation on the Age-Period-Cohort model with a linear period drift based on the period 2007 to 2010 and pertaining age and cohort effect. The survival, number of new-borns and mortality for all competing causes are assumed to remain constant at the level of 2010. The absolute number of prevalent cases in 2020 was estimated by multiplying the projected prevalence rates for 2020 by the population count forecast of the FSO using their reference scenario (scenario no. A-00-2010) (Kohli et al., 2010).

The tabulated relative survival in 6 month intervals for maximally 20 years of follow-up was calculated on the pooled dataset comparing observed survival with expected survival in

Switzerland using the Ederer II method (Dickman et al., 2009) with the so called mixed-approach (Brenner and Spix, 2003) by consecutive 3-year periods from 1981 to 2010 and 5 distinct age-groups (0-14, 15-49, 50-69, 70-79, 80+). In the age group of 80+-year-olds survival was restricted to a follow up duration of 15 years due to high variance in the survival estimates resulting from small number of cases.

The fit of the Age-Period-Cohort-model based incidence and hence prevalence was first evaluated on observed pooled incidence rates, and in a second step the final model parameters were selected by maximizing representativeness of the local data. Representativeness was measured by the sum of squared differences of the modelled expected mortality rates from observed national mortality rates. The observed national mortality rates were obtained from FSO data following the incidence selection criteria and

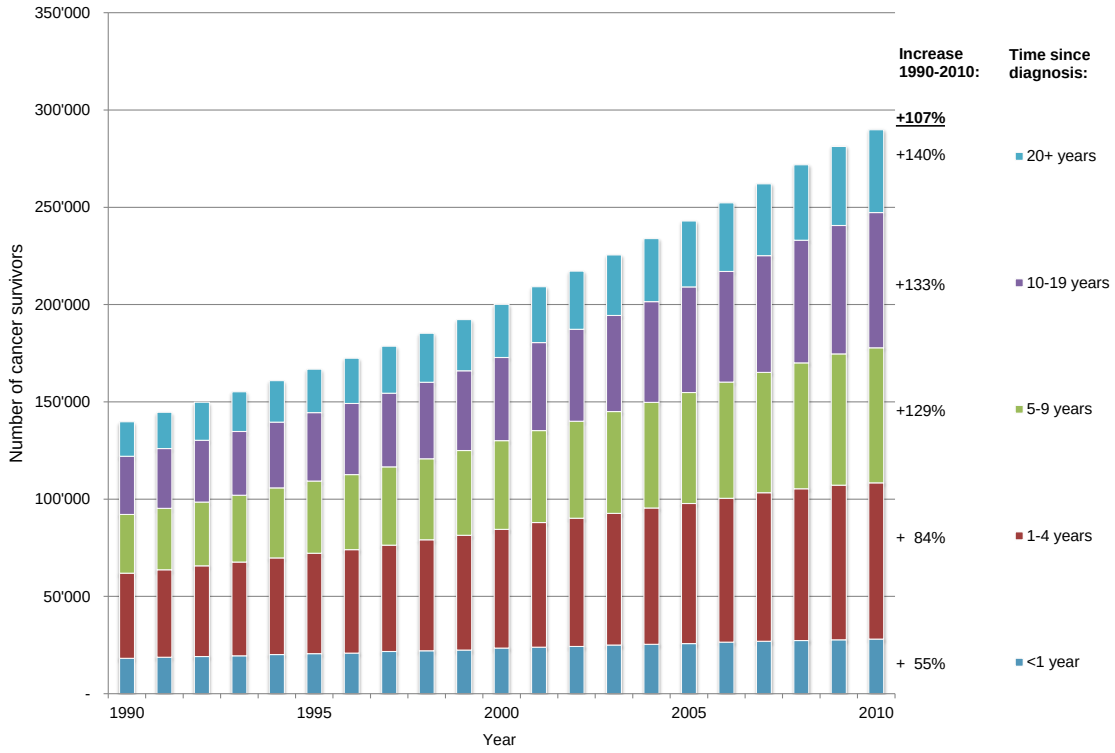

Figure 2.1: Estimated number of cancer survivors in Switzerland by time since diagnosis.
For any invasive malignancy excluding non-melanoma skin cancers. Percentages denote increases in the period 1990-2010.

using the applicable correction factors before the year 1995 because of the change of the directive of mortality codification occurred in our country (Berrut and Junker, 2008). For the final models the expected mortality differed per year averagely 4% for women and 5% for men in 1981-2010 from the national rates.

Temporal trends, their statistical significance and time points with significant changes in trend were assessed with Joinpoint models (Kim et al., 2000), using the JoinPoint Regression program of the National Cancer Institute. Joinpoint models were restricted to maximally 4 joinpoints and with a Poisson model of variation. A Monte Carlo Permutation method was used to test for a statistically significant change in trends. In addition, the goodness of fit of models with identity link (piecewise linear models) or log-link (for calculating annual percentage increases) was compared.

Aging trends in the population for 3 age groups (0-19, 20-64, 65-99) were analysed with Joinpoint models of the same kind.

2.3 Results

Figure 2.1 shows the exponential increase in the estimated number of those living with a history of cancer in Switzerland between the years 1990 and 2010 by time since diagnosis. Cancer survivors diagnosed less than 5 years ago constituted the largest group while the biggest rise is observed among very long term (20 years and more) survivors.

Table 2.1 and Figure 2.2 show time trends by type of cancer, gender, time since diagnosis and age group. The highest increase of cancer survivors prevalence was observed for prostate cancer with an almost 4 fold increase (+279% in 2010 vs. 1990), followed by skin melanoma (+184%) and breast cancer (+115%), all cancers with a high increase in incidence in the period studied. The estimate number of all cancer survivors was approximately 290'000 for the year 2010. For prevalence rates, the same pattern was seen.

Table 2.1: Trend in cancer prevalence in term of number of cases and crude rates per 100'000 in Switzerland between 1990 and 2010

	Prevalence							
	Number of persons				Rates per 100'000			
	1990	2010	Increase	[95%CI*]	1990	2010	Increase	[95%CI*]
Gender								
Men	56'201	132'330	+136%	[132%-141%]	1'714.5	3'436.2	+101%	[94%-108%]
Women	83'516	157'467	+89%	[85%- 92%]	2'431.8	3'962.6	+63%	[60%- 66%]
Total	139'717	289'797	+108%	[105%-111%]	2'081.5	3'703.5	+78%	[74%- 83%]
Time since diagnosis								
< 1 year	18'113	28'029	+55%	[51%- 60%]	269.8	417.6	+55%	[51%- 60%]
1-4 years	43'759	80'340	+84%	[76%- 93%]	651.9	1'196.9	+84%	[76%- 93%]
5-9 years	30'235	69'368	+129%	[118%-141%]	450.4	1'033.5	+129%	[118%-140%]
10-19 years	29'844	69'481	+133%	[123%-143%]	444.6	1'035.1	+133%	[123%-143%]
20+ years	17'765	42'578	+140%	[135%-145%]	264.7	634.3	+140%	[134%-145%]
Total	139'717	289'797	+108%	[105%-111%]	2'081.5	3'703.5	+78%	[74%- 83%]
Cancer type**								
Breast	30'892	66'513	+115%	[111%-119%]	460.2	850.0	+85%	[78%- 92%]
Prostate	12'012	45'421	+279%	[267%-291%]	179.0	580.5	+225%	[212%-239%]
Colorectal	16'186	28'567	+77%	[74%- 79%]	241.1	365.1	+52%	[49%- 55%]
Lung	4'689	7'833	+67%	[55%- 79%]	69.9	100.1	+44%	[36%- 53%]
Lymph./Leukaemia	13'470	26'086	+94%	[92%- 96%]	200.7	333.4	+67%	[57%- 78%]
Melanoma	8'367	23'743	+184%	[177%-191%]	124.6	303.4	+143%	[140%-147%]
Other	54'102	91'634	+70%	[66%- 73%]	806.0	1'171.1	+46%	[40%- 51%]
Total	139'717	289'797	+108%	[105%-111%]	2'081.5	3'703.5	+78%	[74%- 83%]
Age group								
0-14	740	1'061	+44%	[32%- 57%]	64.5	89.7	+40%	[31%- 49%]
15-49	21'192	36'285	+72%	[59%- 86%]	605.3	951.1	+57%	[56%- 59%]
50-69	53'236	112'657	+112%	[110%-114%]	3'848.7	5'949.8	+54%	[51%- 58%]
70-79	37'565	77'033	+106%	[95%-118%]	8'665.2	13'823.2	+60%	[54%- 67%]
80+	26'984	62'761	+132%	[112%-154%]	10'925.9	16'691.0	+53%	[47%- 60%]
Total	139'717	289'797	+108%	[105%-111%]	2'081.5	3'703.5	+78%	[74%- 83%]

*CI: Confidence Interval
**excluding non-invasive and non-melanoma skin cancers

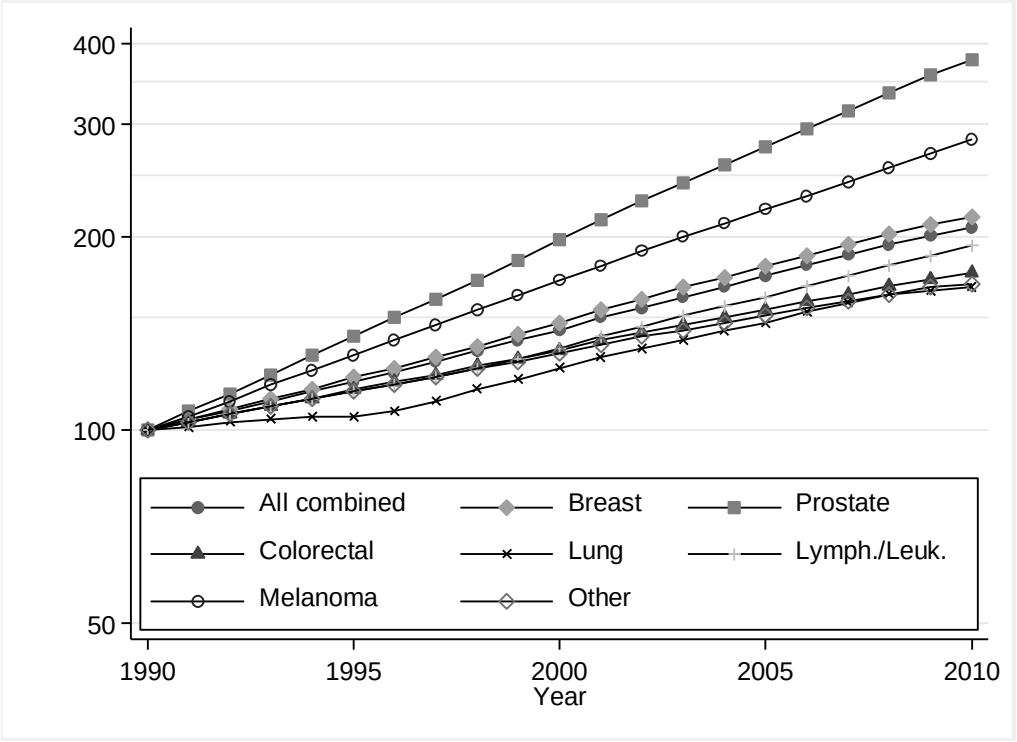

Figure 2.2: Trend of prevalence of cancer survivors by type of cancer in Switzerland
Expressed as the percent of 1990 value by type of cancer with highest incidence.
Excluding non-invasive and non-melanoma skin cancers.

In the same lapse of time the population grew by 12% (95% CI: 10%-15%) but the growth was unevenly among age groups: while the age group 65 years old and older grew by 36% (95% CI: 33%-38%) the number of those aged 0-19 increased only by 4% (95% CI: 1%-9%). Cancer incidence increased both in absolute numbers from estimated 24'335 in 1990 to 32'875 in 2010 ($p<0.01$) and in relative numbers from a rate of 362.5 /100'000 in 1990 to 432.5/100'000 in 2010 ($p<0.01$),while mortality decreased from 226.9/100'000 in 1990 to 209.9/ 100'000 in 2010 ($p<0.01$). At the same time 10-year observed survival increased by 24% (95% CI: 21%-28%) from 0.27 to 0.34.

The increase was assessed to be exponential in comparing models assuming either piecewise linear or piecewise exponential increase, with the latter having better fit. The exponential increase, measured as annual percent change (APC), was at all periods significantly different

from zero and higher in men than in women. In both genders the APC values increased from 1990 until a period around the year 2000 and declined since. For both genders combined the most recent (2008-2010) APC in the number of cancer survivors was 3.3% (95% CI: 3.1%-3.5%).

The results of our projection model showed a further continuation of this exponential increase for the next 10 years with an APC value close to the most recent one. We have estimated that until 2020 the total number of cancer survivors will increase by 28% to a total of 372'000 (i.e. 4.4% of the Swiss population). The projected number of cancer survivors and their increase since 2010 using the projection model by major cancer sites and gender can be found in 2.6 Annex 1. The biggest increases were predicted for melanoma and prostate cancer, while female breast cancer survivors were predicted to still be the biggest group.

2.4 Discussion

In Switzerland, the overall number of cancer survivors has increased exponentially in the last 20 years and is expected to rise by about 30% in the next 10 years. We estimated that in 2010, 3.7% of the Swiss population were living with a history of cancer. This trend is the result of several factors i) the continuing advances in the treatment of oncologic diseases, ii) the spread of early detection of common types of cancer such as prostate, breast cancer and melanoma and iii) demographic changes: a growing segment of the aged population and an increased life expectancy due to various reasons. In particular, advances in treatment of cardiovascular diseases lead to a significant reduction of premature deaths (Savidan et al., 2010).

Similar results both concerning trend and proportion of the population with a history of cancer have been reported in other European countries. In the Nordic countries (Sweden, Finland, Denmark, Norway, Iceland) 3.4 to 4.1% of the population is estimated to be a cancer survivor by the end of 2010 (Engholm et al., 2013). In the UK new estimations suggest that 2 million people representing 3.1% of the population live with a diagnosis of cancer in 2010 (Maddams et al., 2012). In Italy the projections for 2010 estimate that 4% of women and 3% of men are cancer survivors (De Angelis et al., 2007). Similar pattern has also been reported

in the USA (Siegel et al., 2012) with estimated 13.7 millions of Americans alive with a history of cancer on January 1, 2012.

In these publications a wide range of methods to estimate cancer prevalence was used based on the availability of data in time and space and the underlying question.

The method we used was also applied in De Angelis et al (De Angelis et al., 2007) and is specifically designed to estimate cancer prevalence in settings with incomplete registration, in contrast to e.g. discrete time models (Maddams et al., 2012) where a long time series of cancer registry data is necessary. Additionally, our approach allowed the investigation of time trends and -in using Joinpoint regression- the assessment of significant changes therein over time.

The exponential increase in the past 20 years is mainly attributable to cancer incidence growth driven by screening uptake especially of prostate cancer and breast cancer and to a lesser extent to the aging of the population. PSA screening has lead in Switzerland and worldwide (Welch and Albertsen, 2009) to 3-4- fold increases of incidence rates of prostate cancer. Moreover, median age at diagnosis decreased, further contributing to increases of survival and prevalence of prostate cancer survivors. The incidence rate of breast cancer has also doubled although the reasons for this increase remain controversial (Bleyer and Welch, 2012, Bouchardy et al., 2010). At the same time considerable advances in treatments and supportive care have been realised in breast cancer and other types of cancers. In particular, the number of survivors with haematological malignancies and lung cancer that has increased by 94% and 67% respectively testifies of these advances.

It is not possible to predict with accuracy the total number of survivors in the future. In order to reflect the present situation we used for the projections the most recent trends (e.g. those in period 2007-2010). Future numbers will depend on the evolution of incidence, survival and demographic changes, and therefore might differ from current predictions. E.g. incidence of breast cancer will probably increase as a consequence of the very recent introduction of mammography screening programmes in many of the German-speaking cantons.

Most cancer survivors living with a cancer diagnosis since more than one and less than 5 years are in the phase following initial treatment, some of them disease free, others are under long term maintenance therapy managing sequelae of their treatment. Most of the cancer

survivors in this phase will require additional treatment or special surveillance for relapse. Symptoms and problems may differ according to the type of cancer and the type of treatment applied. Breast cancer survivors may experience lymphedema of the arm, a common side effect of breast cancer surgery and radiation therapy that can develop soon after treatment or years later. Risk of lymphedema is reduced when sentinel node-biopsy rather than axillary dissection is performed to determine if the tumour has spread. In Switzerland less than 50% of women qualifying for sentinel node biopsy were operated with this technique in the years 2003 to 2005 (Ess et al., 2010c). Prostate cancer survivors treated with surgery or radiation therapy for early disease may experience symptoms and side effects of treatment including incontinence, erectile dysfunction and bowel complications (Sanda et al., 2008). Long term survivors of colorectal cancer may experience bowel problems and distress regarding cancer, specially fear of recurrence (Jansen et al., 2010).

We have observed the biggest increases in number of survivors among long-term survivors. Because of increased life expectancy and improvement in therapies it is anticipated that this group will grow substantially in the coming decade. Late toxicities of therapies such as cardiotoxicity after cytotoxic drugs, cognitive deficits, osteoporosis etc., will develop in long-term survivors. Moreover, this group is at enhanced risk to other primary cancers and may suffer of poorer health. Several studies (Hewitt et al., 2003, Elliott et al., 2011) have found that compared with individuals without a history of cancer or other chronic disease a substantial number of individuals who have a history of cancer were significantly more likely to report poor health and well-being, have a psychological disability, have limitations of activities of daily living and among those under the age of 65, being unable to work because of a health condition. These findings suggest the necessity of developing specific support for cancer survivors.

According to our estimates approximately one third of cancer survivors are younger than 65 and survivors in this age group have more than doubled in the 20 past years. In this age group resuming as normal a life as possible includes psychological and/or social support as well as professional reinsertion.

Cancer is increasingly an illness which might be cured or which might have the characteristics of a long term or chronic condition even in patients with advanced disease. It

seems therefore essential to inform patients and future providers of the long-term effects of cancer and its treatment and to identify psychosocial needs and resources to guide prevention and health maintenance in order to increase the quality of life.

A major limitation of this study is the fact that we based our estimation on the data from only 4 regional cancer registers covering about 26% of the population. As in the USA, where complete prevalence estimates are based only on SEER registries (Parry et al., 2011), it is only in 2012 that the coverage of cancer registration attained 80% in Switzerland. However, the data used are of high quality as ascertained by the controls performed at the International Agency for Research on Cancer (Curado et al., 2007), with high levels of microscopically verification (95%) and very low level of DCO cases (0.6%). Furthermore the data cover rural alpine and urban areas in the main language regions (French-speaking and German-speaking regions) and include administrative units (cantons) with and without breast cancer screening programmes. Additionally, the model parameters were chosen by minimizing squared differences of modelled with observed national mortality rates, and thus maximizing representativeness of the available data. The expected mortality rates of the final models showed very close fit to the national mortality rates. We are therefore confident that estimates reflect the true situation in Switzerland as close as possible.

This study is a first step into understanding the number and characteristics of people living with a cancer diagnosis in Switzerland. More research is needed to know the health status, the quality of life and the expectation of cancer survivors, their need in care and support. This will enable resource planners to better translate the available information into necessary formation of professionals, healthcare and social structures to adequately meet the specific needs of cancer survivors.

2.5 Conclusions

The success of cancer research, early diagnosis and treatment over the last 20 years as well as increases in life expectancy have led to exponential increases of individuals living many years with a cancer diagnosis. Further research is needed to better understand the special needs of survivors and to implement care according to these needs.

2.6 Annex 1 – Projected cancer prevalence

Table 2.2: Projected cancer prevalence in Switzerland for 2020.
This table presents the projected cancer prevalence in terms of number of cases by gender for major cancer sites in Switzerland for the year 2020.

	Projected Prevalence 2020			Percent increase since 2010		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
Cancer type*						
Breast	-	85'279	85'279	-	28%	28%
Prostate	71'697	-	71'697	58%	-	58%
Colorectal	18'588	15'812	34'400	22%	19%	21%
Lung	4'860	4'087	8'947	-1%	40%	14%
Lymph./Leukaemia	18'605	15'698	34'303	31%	32%	32%
Melanoma	16'357	21'488	37'845	69%	53%	59%
All sites combined*	173'575	198'742	372'317	31%	26%	28%

*excluding non-invasive and non-melanoma skin cancers

Chapter 3

40 years of progress in female cancer death risk: A Bayesian spatio-temporal mapping analysis in Switzerland

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Abstract

Background: In the past decades, mortality of female gender-related cancers declined in Switzerland and other developed countries. Differences in the decrease and in spatial patterns within Switzerland have been reported according to urbanisation and language region, and remain controversial. We aimed to investigate geographical and temporal trends of breast, ovarian, cervical and uterine cancer mortality, assess whether differential trends exist and to provide updated results until 2011.

Methods: Breast, ovarian, cervical and uterine cancer mortality and population data for Switzerland in the period 1969-2011 was retrieved from the Swiss Federal Statistical office (FSO). Cases were grouped into <55-year-olds, 55-74-year-olds and 75+-year-olds. The geographical unit of analysis was the municipality.

To explore age- specific spatio-temporal patterns we fitted Bayesian hierarchical spatio-temporal models on subgroup-specific death rates indirectly standardised by national references. We used linguistic region and degree of urbanisation as covariates.

Results: Female cancer mortality continuously decreased in terms of rates in all age groups and cancer sites except for ovarian cancer in 75+-year-olds, especially since 1990 onwards.

Contrary to other reports, we found no systematic difference between language regions. Urbanisation as a proxy for access to and quality of medical services, education and health consciousness seemed to have no influence on cancer mortality with the exception of uterine and ovarian cancer in specific age groups. We observed no obvious spatial pattern of mortality common for all cancer sites.

Rate reduction in cervical cancer was even stronger than for other cancer sites.

Conclusions: Female gender-related cancer mortality is continuously decreasing in Switzerland since 1990. Geographical differences are small, present on a regional or canton-overspanning level, and different for each cancer site and age group. No general significant association with cantonal or language region borders could be observed.

Keywords: neoplasm; breast cancer; ovarian cancer; cervical cancer; uterine cancer; Switzerland; Bayesian inference; disease mapping; time trends

3.1 Background

Female gender-related cancers, in particular cancer of the breast, corpus uteri, ovary and cervix uteri account for more than 40% of newly diagnosed cancers and for about 30% of cancer-related deaths in Swiss women (Ferlay et al., 2013b). In the past decades, female cancer mortality declined in Switzerland and the more developed countries (Ferlay et al., 2013b) mainly due to advances in the understanding of tumour biology and in early detection, as well as the introduction of targeted therapies. However, differences in the decrease within Switzerland have been reported, such as for breast cancer in four selected cantons (Bulliard et al., 2006).

Switzerland is a small, affluent and culturally diverse confederation of 26 relatively autonomous states called cantons. Healthcare policies are developed at the cantonal level resulting in a large geographical variation in health expenditures, control programmes and care planning. I.e. population-based mammography screening programmes were and are implemented at very different time points over a period of more than 20 years in the various cantons. Most studies, including the above, investigated differences on the same regional level –cantons–, but it remained unknown whether these are consistent geographical disparities related to cantonal decisions or artefacts due to the choice of geographical and time units; driven by sub regions or complete region. The only more detailed maps of female cancer mortality rates are those of Schüler and Bopp (Schüler and Bopp, 1997) depicting geographical variation in mortality during 1970-1990 on the basis of so called MS-regions, 106 'unofficial' regions smaller than cantons defined by mobility considerations. Since they have not applied temporal and geographical smoothing, the results may be distorted especially in areas where the population is small. This makes it difficult to distinguish chance variability from real differences. To our knowledge, covariate-adjusted and smooth, nationwide maps of female cancer mortality depicting the changes over time and space are not available.

Therefore, we studied geographical and temporal trends of breast, ovarian, cervical and uterine cancer mortality in Switzerland, adding 20 years of data to previous work, using state-of-the-art methodology for results with more detail and fewer artefacts, and without prejudice of geographical unit or shape of time trends. Hence, we used the most detailed

available data (municipality level) and accounted for non-linear time trends. We hypothesised similar patterns for the different cancer sites and/or age group. Bayesian spatial models are the state-of-the-art modelling approach for assessing spatio-temporal patterns and trends. They "smooth" or improve estimation of an unstable rate by "borrowing" strength from its neighbours (Bernardinelli and Montomoli, 1992). They can also assess the significance of risk factors taking into account the geographical correlation, and are able to show spatial patterns after adjustment for geographical differences in certain risk factors.

3.2 Methods

3.2.1 Data sources

Female cancer mortality data was obtained for the period 1969-2011 from death certificates coded centrally by the Swiss Federal Statistical office (FSO). The data include age at death, year of birth and death for each individual, nationality, municipality of residence, the cause of death and co-morbidities. Cause of death and co-morbidities are coded using the 8th revision of the International Classification of Diseases (ICD) until 1994/1995 and afterwards using 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 (Lutz et al., 2004a) 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), cervix (ICD-10 C53.0- C53.9), corpus uterine (ICD-10 C54.0-C55.9) and ovary (ICD-10 C56.9). According to federal regulations, mortality data excluding any identifiable information can be used in epidemiological studies without additional ethics committee approval.

Detailed population data on municipality level is only available from census that takes place in Switzerland every 10 years with the last one taking place in 2010. 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 2008-2011, in which population was assumed to be constant.

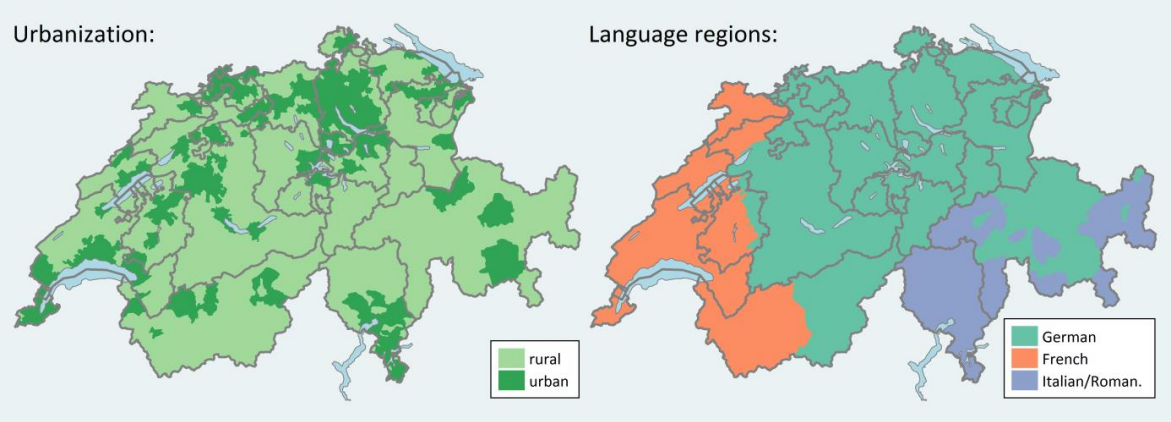

Figure 3.1: Urbanization classification and language regions in Switzerland

There are around 2,500 municipalities in the country. Over the study period, the number of municipalities has changed due to fusion, separation, deletion or new occurrences. We aligned all data on the 2011 municipality structure using spatial data for 2011 and municipality transition protocols for each year obtained from the FSO. From the same source, we retrieved data on language region (German, French and Italian/Romansh) and urbanisation. We grouped municipalities classified as central agglomeration city, greater agglomeration and isolated city into "urban" leaving the classification "rural" unchanged.

3.2.2 Statistical methods

Age was grouped into three groups (<55, 55-74, 75+-year-olds). The geographical unit of analysis was the municipality.

In a preliminary analysis, we investigated SMR ratio values in a non-spatial model. Spatio-temporal Poisson and negative binomial regression models were fitted separately for each age group on the number of deaths aggregated by municipality and year with the mean being equal to the product of the expected death count and age-standardised mortality rate. Indirect standardisation used 5 years age intervals. Expected mortality counts for each municipality, year and age group were obtained from the study population using nationwide age-specific mortality rates for all periods.

Space and temporal random effects as well as possible non-linear temporal trends were modelled on the log of the mean standardised mortality rate following model formulations of Jürgens et al (Jurgens et al., 2013a) (cf. 3.6). In particular, municipality-specific random effects were modelled via conditional autoregressive (CAR) models to filter out the noise and highlight the observed patterns. The models were formulated as hierarchical Bayesian

Table 3.1: Female cancer mortality in Switzerland by age group and time period corrected for coding changes.
PY=Person Years.

	Aged <55		Aged 55-74		Aged 75+	
Period	Total number of cases	Rate per 100,000 PY	Total number of cases	Rate per 100,000 PY	Total number of cases	Rate per 100,000 PY
Breast cancer						
1969-1972	995	10.3	2,185	89.5	997	161.6
1979-1982	1,062	11.1	2,336	92.6	1,556	169.5
1989-1992	1,110	11.0	2,345	89.0	2,512	210.6
1999-2002	908	8.6	2,184	74.9	2,169	159.4
2007-2010	813	7.4	2,303	68.1	2,501	160.9
Cervical cancer						
1969-1972	324	3.3	465	19.1	186	30.1
1979-1982	227	2.4	389	15.4	212	23.1
1989-1992	155	1.5	244	9.3	205	17.2
1999-2002	84	0.8	127	4.4	144	10.6
2007-2010	80	0.7	112	3.3	124	8.0
Uterine cancer						
1969-1972	114	1.2	693	28.4	340	55.1
1979-1982	66	0.7	498	19.7	458	49.9
1989-1992	46	0.5	416	15.8	607	50.9
1999-2002	53	0.5	326	11.2	457	33.6
2007-2010	43	0.4	316	9.3	467	30.1
Ovarian cancer						
1969-1972	321	3.3	823	33.7	304	49.3
1979-1982	281	2.9	892	35.3	496	54.1
1989-1992	224	2.2	816	31.0	718	60.2
1999-2002	165	1.6	713	24.4	717	52.7
2007-2010	165	1.5	790	23.3	775	49.9

models with parameter estimation via Markov chain Monte Carlo simulation (MCMC). We used the Deviance Information Criterion (DIC) to select the regression models from Poisson/ Negative binomial regression with or without an additional set of unstructured random effects for each municipality.

Data on language and urbanisation were included as covariates in the model. These analyses will indicate whether there are statistically significant differences in the cancer mortality for each one of the above covariates, assessed by 95% Bayesian Credible Intervals (CI).

From the estimates of the model, we produced smoothed maps displaying geographical patterns of female gender cancer mortality for each age group, cancer site and year since 1969 till recent almost to date.

3.3 Results

Table 3.1 shows the number of female cancer deaths and crude rates per 100,000 person years in Switzerland by age group within the 4-year periods under investigation. Among the cancer sites studied, breast cancer was the most common cause of death, followed by ovarian, uterine and cervical cancer.

Mortality rates continuously decreased for cervical and uterine cancer, and for ovarian cancer in the <55-year-olds. For breast cancer and the other age groups of ovarian cancer, mortality rates decreased only as from 1979-1982 and from 1989-1992 for 75+-year-olds respectively.

Table 3.2 shows the results of the spatio-temporal regression analysis by cancer site and age group. With the spatial analysis, we could confirm the time trends observed in the crude rates in table 3.1, while only in few cases the covariates had a significant effect on the standardised mortality ratio (SMR). Language region had in none of the models a significant effect on mortality, urbanisation only in 3 models: An urban environment was associated with a significantly lower mortality of 55-74-year-olds in uterine cancer and <55-year-olds in ovarian cancer, and associated with higher ovarian cancer mortality in 75+-year-olds.

Table 3.2: Spatio-temporal model estimates of age-specific female cancer mortality in Switzerland from 1969 to -2010.
Results from model 1 (cf. table 3). 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 Ratio (95% Bayesian Credible Interval)					
Age group	*<55*		*55-74*		*75+*	
Breast cancer						
Period						
1969-1972	1.00		1.00		1.00	
1979-1982	0.97	(0.89;1.06)	1.03	(0.97;1.09)	1.03	(0.95;1.12)
1989-1992	**0.90**	(0.83;0.98)	1.00	(0.94;1.06)	**1.22**	(1.14;1.32)
1999-2002	**0.64**	(0.59;0.70)	**0.84**	(0.80;0.89)	**0.91**	(0.84;0.98)
2007-2010	**0.50**	(0.46;0.55)	**0.77**	(0.73;0.81)	**0.91**	(0.84;0.98)
Language						
German	1.00		1.00		1.00	
French	1.09	(0.89;1.32)	0.95	(0.83;1.09)	1.07	(0.92;1.25)
Italian/Roman.	0.96	(0.71;1.34)	0.97	(0.77;1.22)	1.01	(0.80;1.29)
Urbanisation level						
Rural	1.00		1.00		1.00	
Urban	1.08	(1.00;1.18)	1.04	(0.99;1.10)	1.01	(0.96;1.07)
Cervical cancer						
Period						
1969-1972	1.00		1.00		1.00	
1979-1982	**0.65**	(0.55;0.77)	**0.80**	(0.70;0.91)	**0.76**	(0.62;0.92)
1989-1992	**0.39**	(0.32;0.46)	**0.49**	(0.41;0.58)	**0.55**	(0.45;0.68)
1999-2002	**0.18**	(0.14;0.23)	**0.23**	(0.19;0.28)	**0.34**	(0.27;0.41)
2007-2010	**0.15**	(0.12;0.20)	**0.18**	(0.14;0.22)	**0.25**	(0.20;0.31)
Language						
German	1.00		1.00		1.00	
French	0.98	(0.70;1.35)	0.97	(0.69;1.30)	0.95	(0.67;1.37)
Italian/Roman.	0.81	(0.41;1.45)	1.08	(0.64;1.75)	1.47	(0.81;2.78)
Urbanisation level						
Rural	1.00		1.00		1.00	
Urban	1.11	(0.94;1.33)	1.07	(0.92;1.24)	1.03	(0.87;1.23)

	SMR Ratio (95% Bayesian Credible Interval)					
Age group	*<55*		*55-74*		*75+*	
Uterine cancer						
Period						
1969-1972	1.00		1.00		1.00	
1979-1982	**0.52**	(0.38;0.71)	**0.68**	(0.61;0.76)	0.89	(0.77;1.03)
1989-1992	**0.33**	(0.23;0.45)	**0.55**	(0.49;0.63)	0.88	(0.77;1.02)
1999-2002	**0.32**	(0.23;0.45)	**0.39**	(0.35;0.45)	**0.57**	(0.49;0.66)
2007-2010	**0.23**	(0.16;0.33)	**0.33**	(0.29;0.38)	**0.51**	(0.44;0.59)
Language						
German	1.00		1.00		1.00	
French	1.16	(0.73;1.89)	1.25	(0.99;1.63)	1.00	(0.79;1.29)
Italian/Roman.	1.10	(0.44;2.43)	0.92	(0.57;1.40)	0.93	(0.59;1.44)
Urbanisation level						
Rural	1.00		1.00		1.00	
Urban	0.99	(0.76;1.33)	**0.89**	(0.81;0.99)	1.00	(0.89;1.11)
Ovarian cancer						
Period						
1969-1972	1.00		1.00		1.00	
1979-1982	**0.81**	(0.69;0.95)	1.04	(0.94;1.14)	1.09	(0.94;1.25)
1989-1992	**0.57**	(0.48;0.68)	0.91	(0.83;1.00)	**1.20**	(1.05;1.38)
1999-2002	**0.37**	(0.30;0.44)	**0.73**	(0.66;0.81)	1.06	(0.92;1.21)
2007-2010	**0.32**	(0.26;0.38)	**0.70**	(0.63;0.77)	1.00	(0.88;1.14)
Language						
German	1.00		1.00		1.00	
French	0.91	(0.68;1.25)	0.98	(0.81;1.18)	0.93	(0.74;1.16)
Italian/Roman.	1.17	(0.64;1.92)	1.00	(0.71;1.39)	0.72	(0.50;1.06)
Urbanisation level						
Rural	1.00		1.00		1.00	
Urban	**0.85**	(0.74;0.99)	1.04	(0.96;1.13)	**1.13**	(1.02;1.25)

	Spatial variation (95% Bayesian Credible Interval)					
Age group	*<55*		*55-74*		*75+*	
Breast cancer	0.27	(0.22;0.33)	0.23	(0.19;0.27)	0.25	(0.21;0.29)
Cervical cancer	0.41	(0.32;0.54)	0.36	(0.28;0.47)	0.41	(0.31;0.54)

	Spatial variation (95% Bayesian Credible Interval)					
Age group	*<55*		*55-74*		*75+*	
Uterine cancer	0.46	(0.32;0.67)	0.35	(0.28;0.44)	0.33	(0.26;0.43)
Ovarian cancer	0.36	(0.27;0.46)	0.29	(0.24;0.36)	0.32	(0.26;0.41)

In the elderly (75+-year-olds), a significant increase in breast and ovarian cancer mortality until 1989-1992 was observed and decreasing only since then (tables 3.1, 3.2).

The spatial patterns of mortality based on smoothed small area estimates (figures 3.2-3.5) are different for the female cancers and age groups and not homogenous among the country. No general, significant coincidence with cantonal or language region borders could be observed, with the latter additionally being confirmed by spatial regression for all cancer sites and age groups (table 3.2). The spatial patterns form either sub-cantonal areas or canton-overspanning areas.

For all cancer sites and age group combinations the model 1 with Poisson distributed data

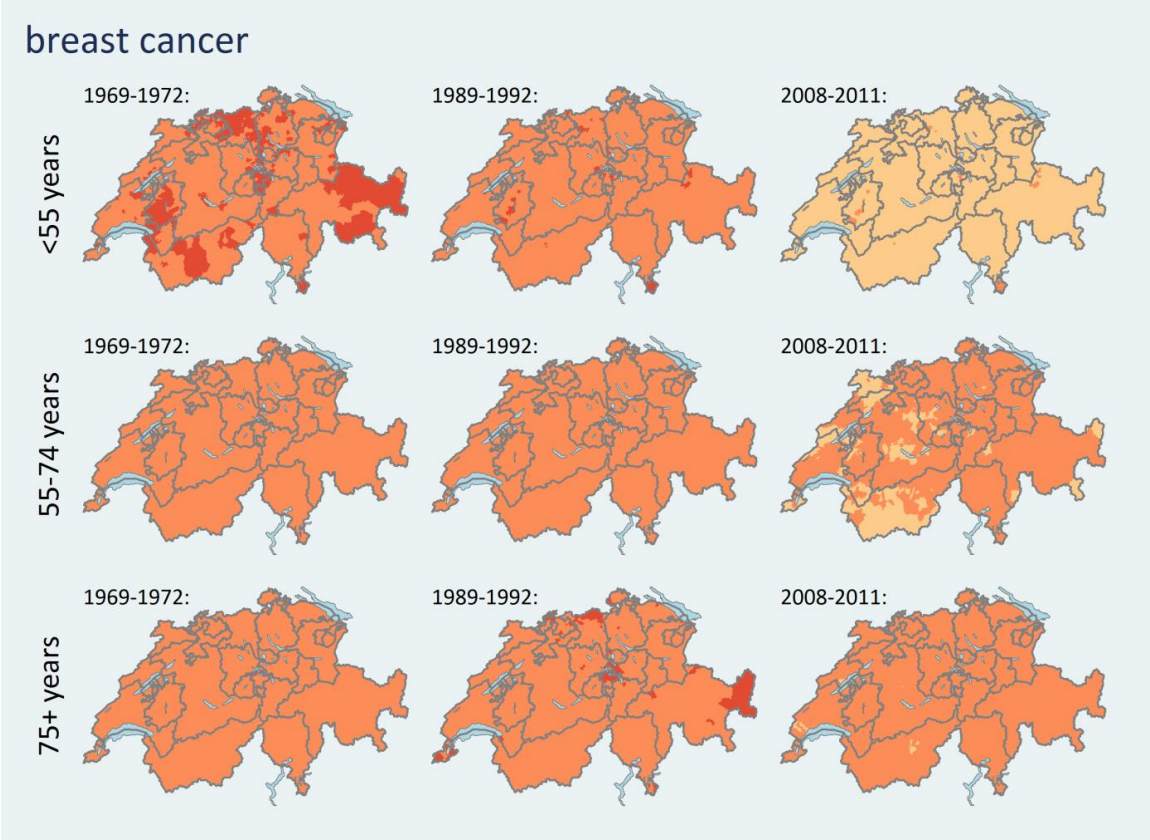

Figure 3.2: Trends and geographical distribution of age-standardised breast cancer mortality (SMR) by age group and among selected time periods.
Values are calculated and smoothed in relation to the cancer site and age-specific all period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period, a detailed colour key is provided in 3.7 Annex 2.

and only one, spatially structured, random effect was identified as the best model, with lowest DIC (see table 3.3). SMR ratios in the non-spatial models were close to the results presented in table 3.2, and significance was the same for all but 4 out of 84 coefficients, with their CIs being close to zero in both models.

3.4 Discussion

Using modern Bayesian small area modelling and mapping techniques we have been able to show that all investigated groups of women in Switzerland have benefited from progress in cancer control regardless of place of residence in the past 40 years. We observed only small

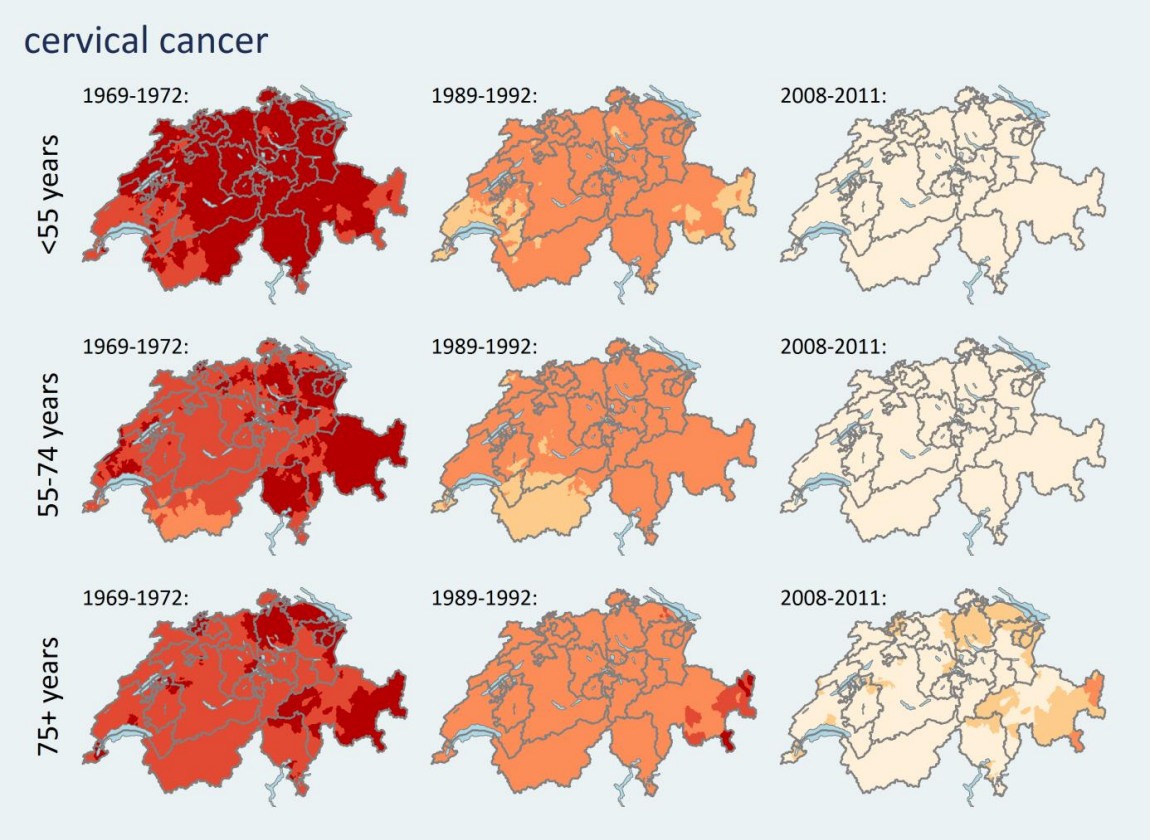

Figure 3.3: Trends and geographical distribution of age-standardised cervical cancer mortality (SMR) by age group and among selected time periods.
Values are calculated and smoothed in relation to the cancer site and age-specific all period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period, a detailed colour key is provided in 3.7 Annex 2.

differences in the geographical variation of mortality.

A factor, which may have contributed to breast and uterine cancer mortality reductions, is the change in the use of hormone replacement therapy (HRT)(Bouchardy et al., 2010). After an association of HRT use with breast cancer occurrence was reported (Beral and Million Women Study, 2003), its use declined sharply.

We were also not able to show similar spatial patterns in breast and ovarian cancer mortality although they share several life style related, environmental and genetic risk factors. It should be noted however, that hereditary cancer accounts only for about 5-10% of the cases in breast cancer (Campeau et al., 2008) and about 15% in ovarian cancer (Pal et al., 2005).

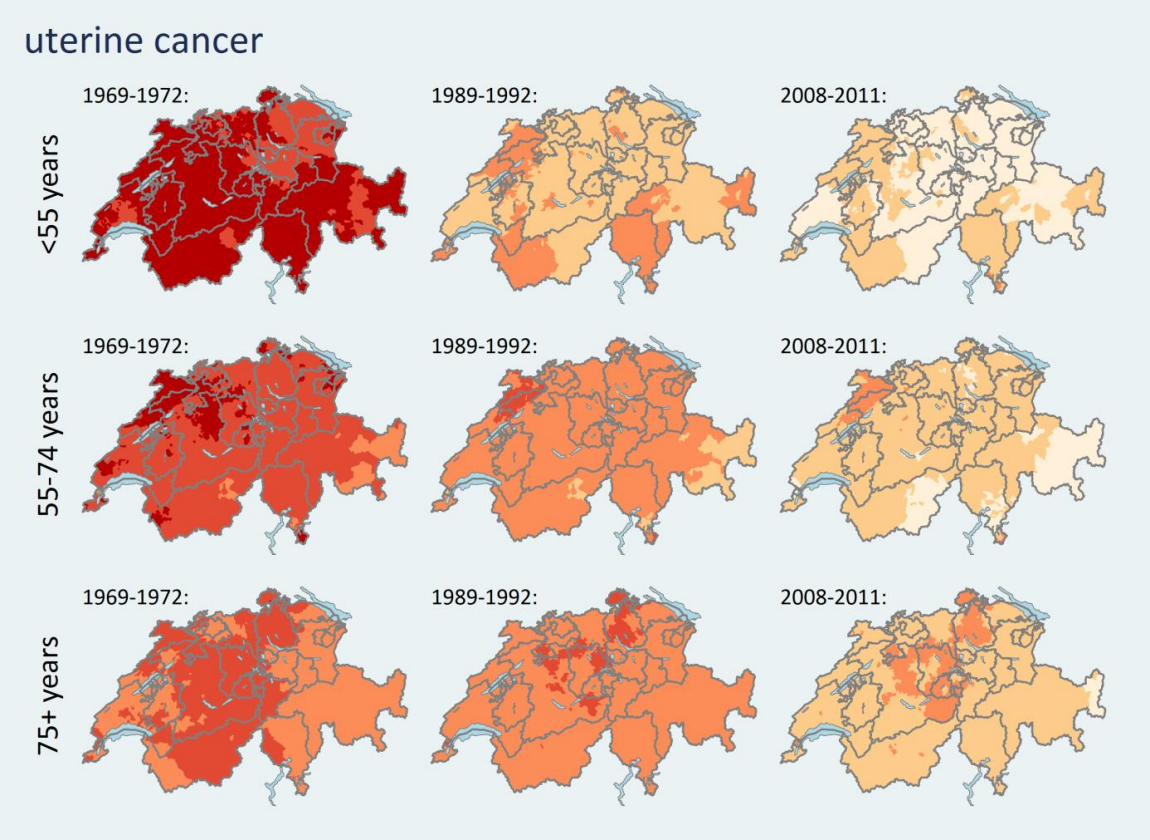

Figure 3.4: Trends and geographical distribution of age-standardised uterine cancer mortality (SMR) by age group and among selected time periods.
Values are calculated and smoothed in relation to the cancer site and age-specific all period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period, a detailed colour key is provided in 3.7 Annex 2.

They are shown to occur at younger age and more advanced stage; still, a visible effect on the mortality map may only be seen in areas with ethnic groups or very large families with a highly elevated risk for hereditary cancer. Such a risk has been described for Ashkenazi Jewish women. The BRCA Ashkenazi founder gene mutations are prevalent in approximately 2% of these women (Struewing et al., 1997) with communities of Ashkenazi mainly found in urban areas; largest communities are in the cities of Zürich, Geneva and Basel contributing to 1-2% of the population (Swiss Federal Statistical Office, 2014, SIG/FSCI, 2014). However, the breast and ovarian cancer risk in BRCA carriers is affected by genetic modifiers and non-genetic factors, for example, reproductive behaviour, hormonal exposure, lifestyle and risk

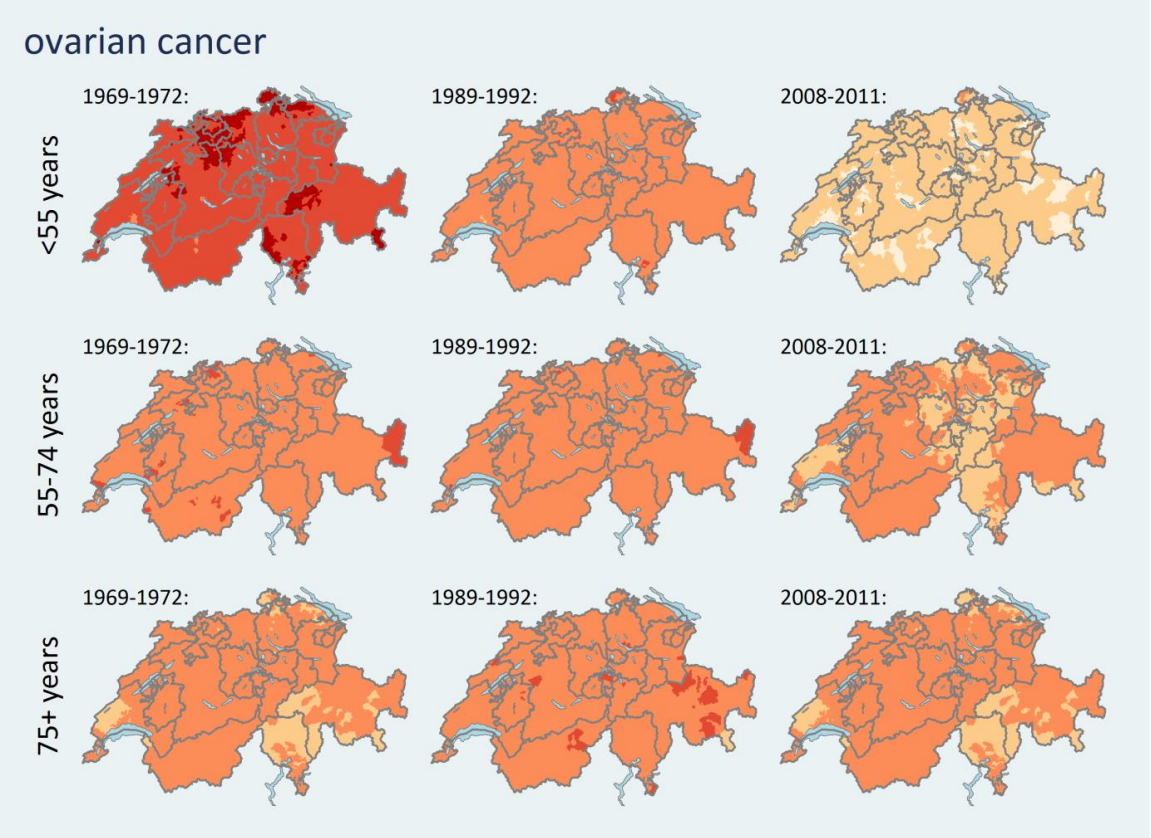

Figure 3.5: Trends and geographical distribution of age-standardised ovarian cancer mortality (SMR) by age group and among selected time periods.
Values are calculated and smoothed in relation to the cancer site and age-specific all period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period, a detailed colour key is provided in 3.7 Annex 2.

reduction surgeries (Levy-Lahad and Friedman, 2007). We could not observe an elevated mortality for the three cities in contrast to the surrounding area and it remains unclear to which extent the mortality rates are driven by these hereditary forms of cancer.

Considerable differences in health and health-related behaviour have been reported for the Swiss language regions including alcohol intake, smoking and a healthy diet (Calmonte et al., 2005, Lieberherr et al., 2010) but lacked significance as regression factors in our analysis.

Only for three cancer site-age group combinations was the urbanisation level identified as a significant factor. Urbanisation is serving as a proxy for access to and quality of medical services, education and health consciousness (Schüler and Bopp, 1997). By our regression with 20 years of new data, we could not formally confirm an urban-rural gradient for breast cancer as described by Schüler & Bopp (Schüler and Bopp, 1997) as significant.

Overall, no general pattern across age groups or cancer sites was present.

The reduction of mortality was stronger in the younger age groups, which is probably the result of better survival and therefore a shift in the age of death. This would also explain the temporary increase in breast and ovarian cancer death risk around the year 1990 in the 75+-year-olds. In addition, in this age group multi-morbid conditions and fewer treatments are common (Joerger et al., 2013). Sant et al (Sant et al., 2003) noted that poor survival for gynaecological cancers in the elderly could be due to advanced stage at diagnosis, or failure to give adequate treatment, perhaps because of comorbidity. In general, the interpretability of results in this age group is limited due to its small size, more multi-morbid conditions together with possible inconsistencies in death certification over time, because of only allowing one single cause of death.

Table 3.3: Model selection based on Deviance Information Criterion (DIC).
Lowest DIC values per cancer site and age group are highlighted in bold face. Models 1 and 3 are Poisson regression models (P), models 2 and 4 negative binomial (NB). Models 1 and 2 have one spatially structured random effect (re), models 3 and 4 an additional, unstructured random effect.

Deviance Information Criterion (DIC)												
Age group	*<55*	*55-74*	*75+*	*<55*	*55-74*	*75+*	*<55*	*55-74*	*75+*	*<55*	*55-74*	*75+*
Model	**Breast cancer**			**Uterine cancer**			**Cervical cancer**			**Ovarian cancer**		
1: P/1re	**13,430**	**20,328**	**18,161**	**2,140**	**8,521**	**8,327**	**4,300**	**5,459**	**4,167**	**5,417**	**11,887**	**9,404**
2: NB/1re	13,462	20,373	18,216	2,149	8,542	8,345	4,312	5,473	4,179	5,430	11,912	9,432
3: P/2re	13,457	20,371	18,212	2,142	8,539	8,345	4,309	5,469	4,180	5,431	11,920	9,424
4: NB/2re	13,494	20,428	18,275	2,149	8,562	8,371	4,325	5,488	4,196	5,449	11,951	9,457

3.4.1 Strengths and limitations

As cancer deaths are rare events and in order to increase the power, different geographical units have been used when analysing cancer mortality data in the past. Some authors have used selected cantons (Bulliard et al., 2006) and Schüler & Bopp (Schüler and Bopp, 1997) used for their cancer atlas somewhat smaller mobility regions based on the accessibility to goods and services but which do not take into account population size. As a result, this choice was too aggregated for some urban areas and not aggregated enough for some sparsely populated areas in order to reveal robust, underlying trends. In view that the choice of the geographical unit of analysis may greatly influence results (Woods et al., 2005), the combination of small geographical units with a state-of-the art smoothing technique enabled a more detailed analysis. With this analysis, we could additionally show the driving age groups or subareas of elevated or reduced mortality in certain regions, while reducing uncertainties due to small numbers and adding an investigation of non-linear time trends.

In general, smoothing allows an estimation of the underlying risk, in a sort of a long-year average, rather than the actual situation. However, for single municipalities, without fully eliminating it, the use of Bayesian smoothing reduces the probability to detect narrow areas with specifically high or low risk. Municipalities at the country border may not benefit from smoothing to the same extent as municipalities in the interior of the country due to unknown

data on the other side of the border. Therefore, in the interpretation of the results emphasis should be given to the broader spatial patterns rather than to single municipalities.

Comparing with the previous work of Schüler & Bopp (Schüler and Bopp, 1997) our study not only extended their work by 20 more years and corrected for non-linear time effects, more importantly, we were able to correct the foreseen overestimation in mortality numbers until 1994, which could not be adequately addressed earlier. Priority rules in the coding of causes of death led to an overestimation in cancer deaths due to their prioritization over other comorbidities. The applied methodology of age standardisation takes advantage of the actual age structure rather than a standard population.

There are important limitations to our study. Risk factors affect incidence but are not necessarily linked to mortality (Barnett et al., 2008). The progression stage of the tumours and their histological type could not be taken into account, as the ICD-classification does not include histological type for the sites studied. The regional case mix and its changes over time therefore may have distorted the results.

Further distortions may arise from the uncertainty as to what level the reported main cause of death and comorbidities are comparable in time and between regions, although the central coding speaks in favour of a certain homogeneity in the coding procedure. In the elderly with frequent multi-morbid conditions, the probability of misclassification is higher.

Furthermore, after prior analysis the covariates language region and urbanisation level were fixed in time for the municipalities, so that varying developments therein may have resulted in inaccuracies.

3.5 Conclusions

Female gender-related cancer mortality continuously decreased in Switzerland. In most age groups, this decline was significant and quite strong in the past decades, resulting in values more than 6 times lower within 40 years. The strongest reduction of mortality was observed for cervical cancer, followed by uterine, ovarian and breast cancer.

Geographical differences are small and do not follow cantonal borders. Spatial patterns were different for each cancer site and age group. The reasons for these differences are manifold,

rising awareness, major advances in cancer therapy and ongoing developments in the field had a major impact on the cancer mortality.

Information on the geographical patterns and temporal trends of the disease burden at different regional scales are important for the design, implementation and evaluation of programmes for cancer control. Access to specialised medical facilities should be increased especially in high priority areas in order to further reduce disparities. However, existing disparities are small.

3.6 Annex 1 – Model formulations

Observed age and cancer site-specific counts of deaths Y_{it} in municipality $i(i = 1, \dots, N)$ in period t to follow a poisson distribution $Y_{it} \sim Pois(\mu_{it})$. Age and cancer specific random effects as well as possible non-linear trends were modelled on the log of the mean Age-standardised Mortality Ratio (SMR).

$$\log(\mu_{it}) = \log(E_{it}) + \alpha + X_{ij}^{T}\beta_s + \Phi_i$$

where E_{it} is the age and cancer specific expected number of deaths, X_{is} the vector of covariates s related to municipality i and β_s the coefficients of associated covariates. Time periods are included as covariates. Spatial correlation by age and cancer specific random effects Φ_i on municipality level i, modelled via a Conditional Autoregressive (CAR) process. Spatial dependency among the municipalities was introduced by the conditional prior distribution of Φ_i with

$$\Phi_i \sim N\left(\frac{\gamma \sum_{\substack{q=1 \\ q \neq i}}^{N} c_{iq}\Phi_q}{w_i}, \frac{\sigma^2}{w_i}\right)$$

where c_{iq} characterises the degree of spatial influence of municipality i to the remaining municipalities, γ quantifying the overall spatial dependence and w_i being the number of neighbours of municipality i. We used the intrinsic version of this CAR model as proposed by Besag, York and Mollie (1991) where c_{iq} takes the value 1 if municipalities are adjacent and 0 otherwise, and γ being equal to one. As further prior distributions we used:

$$\frac{1}{\sigma^2} \sim \Gamma(2.01, 1.01)\,, \qquad \alpha \sim U(-\infty, +\infty)\,, \qquad \beta_s \sim N(0, 0.01)$$

3.7 Annex 2 - Detailed Figures of SMR development by cancer sites and age groups

The following figures show the development of age-standardised breast (figures 3.6-3.8), cervical (figures 3.9-3.11), uterine (figures 3.12-3.14) and ovarian (figures 3.15-3.17) cancer mortality (SMR) and spatial differences therein among all time periods by age group.

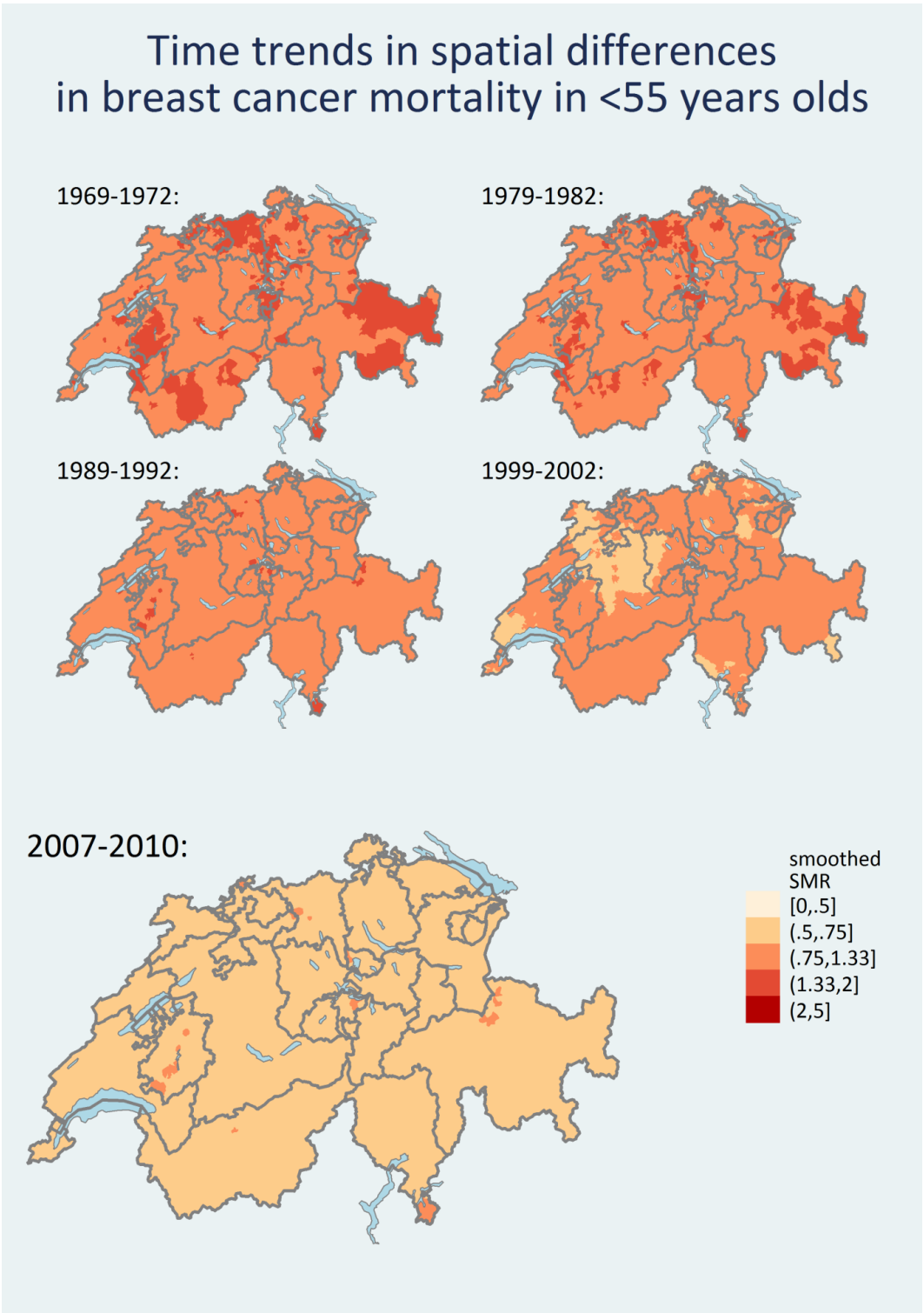

Figure 3.6: Development of breast cancer SMR, <55-year-olds

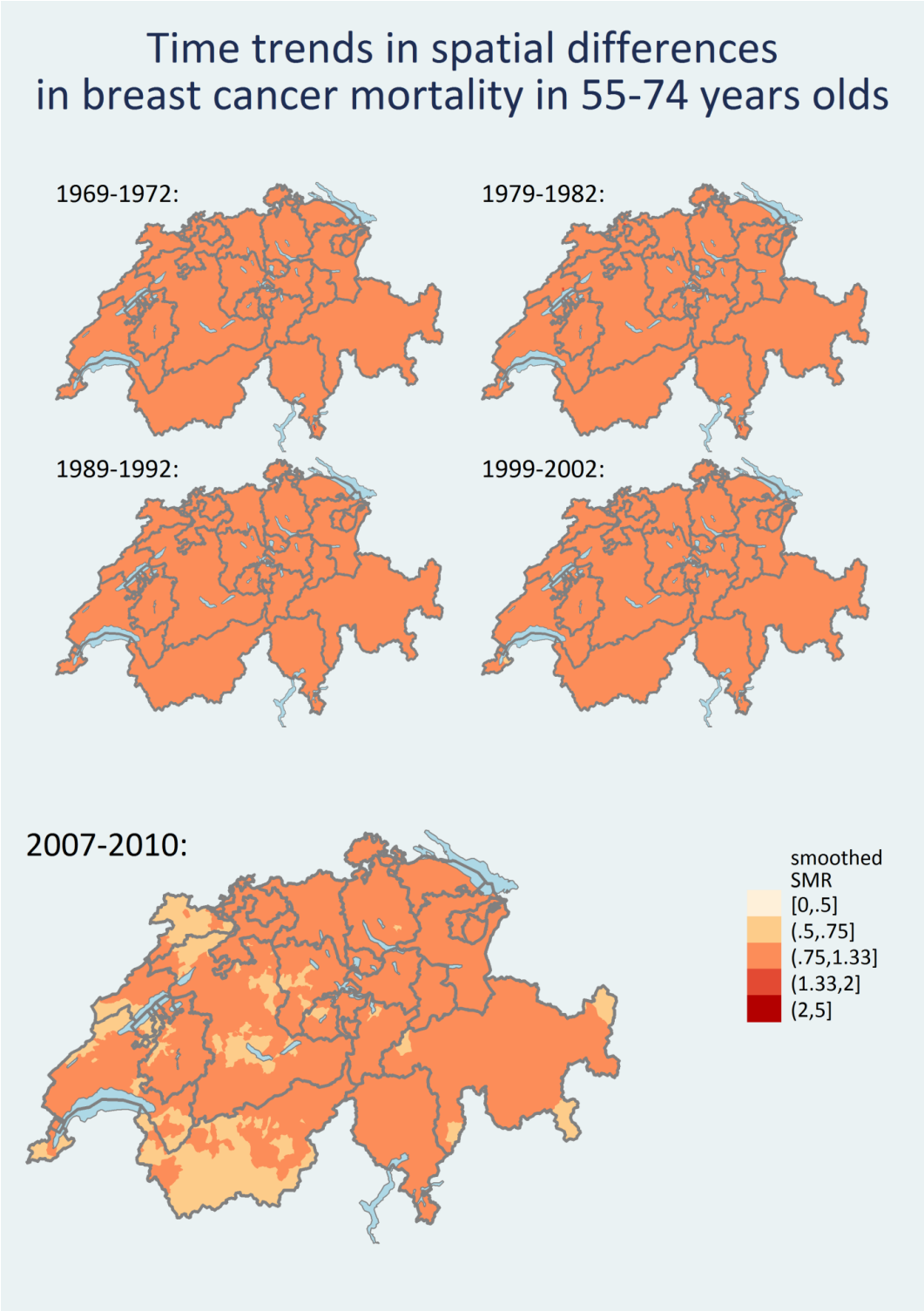

Figure 3.7: Development of breast cancer SMR, 55-74-year-olds

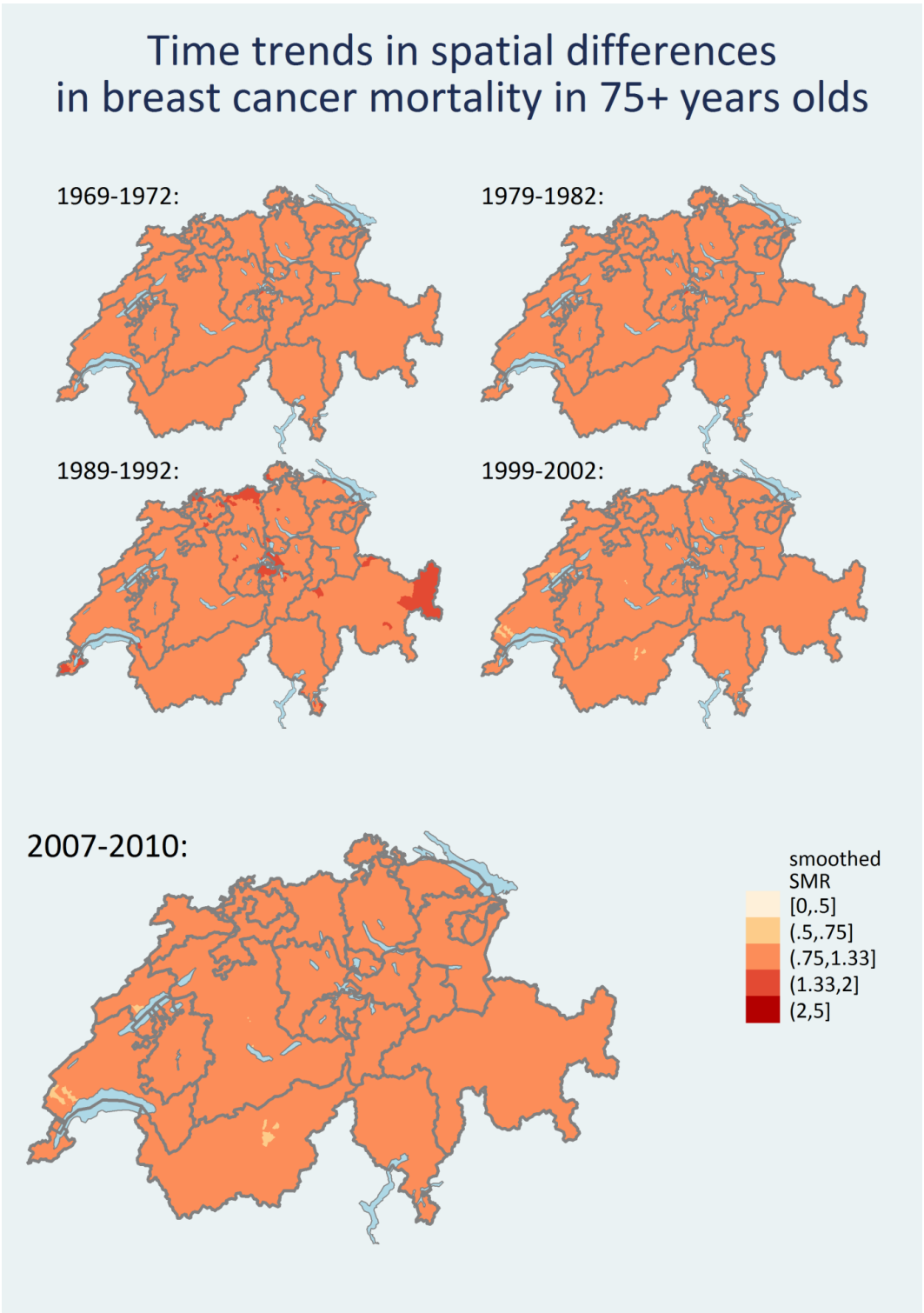

Figure 3.8: Development of breast cancer SMR, 75+-year-olds

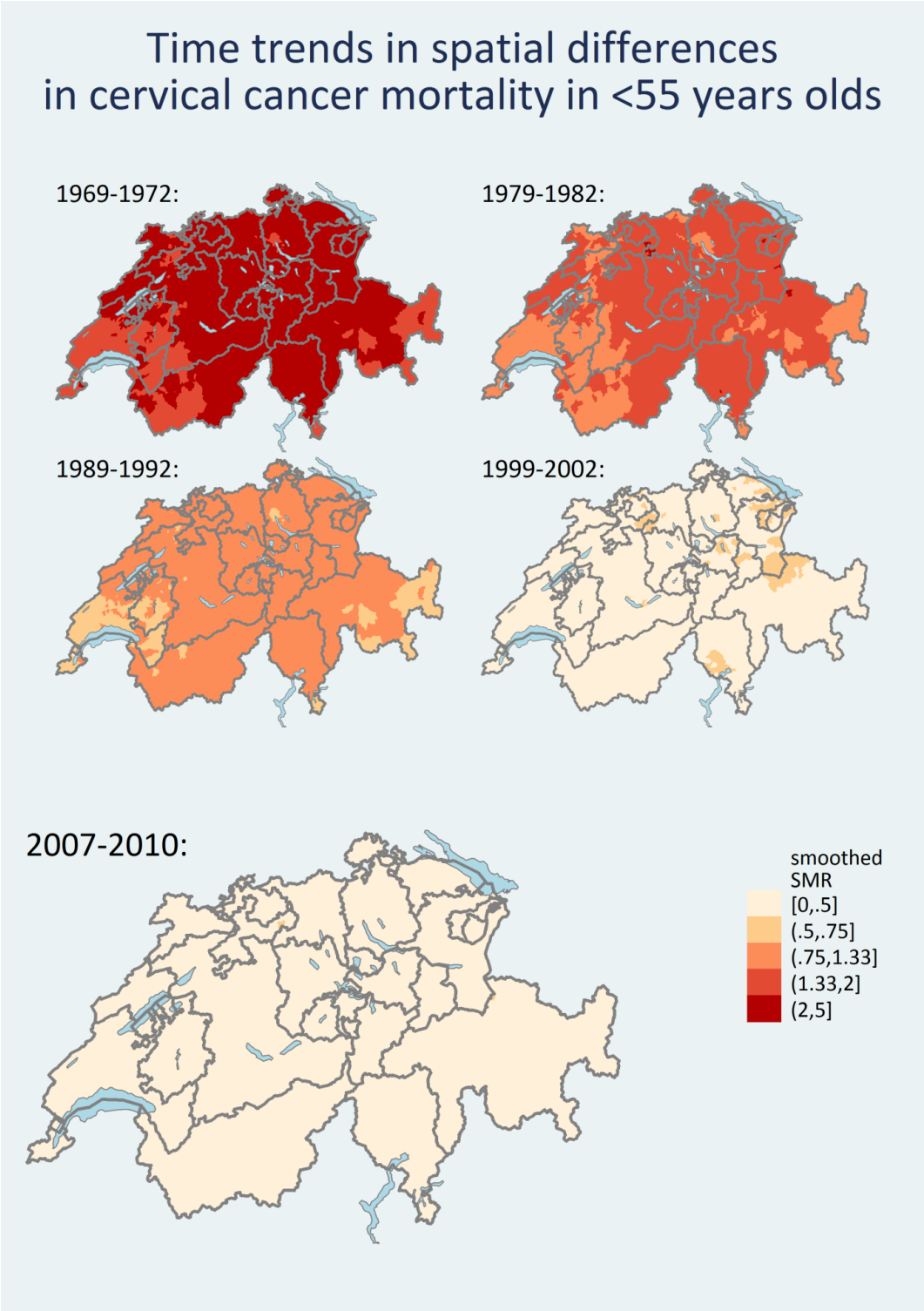

Figure 3.9: Development of cervical cancer SMR, <55-year-olds

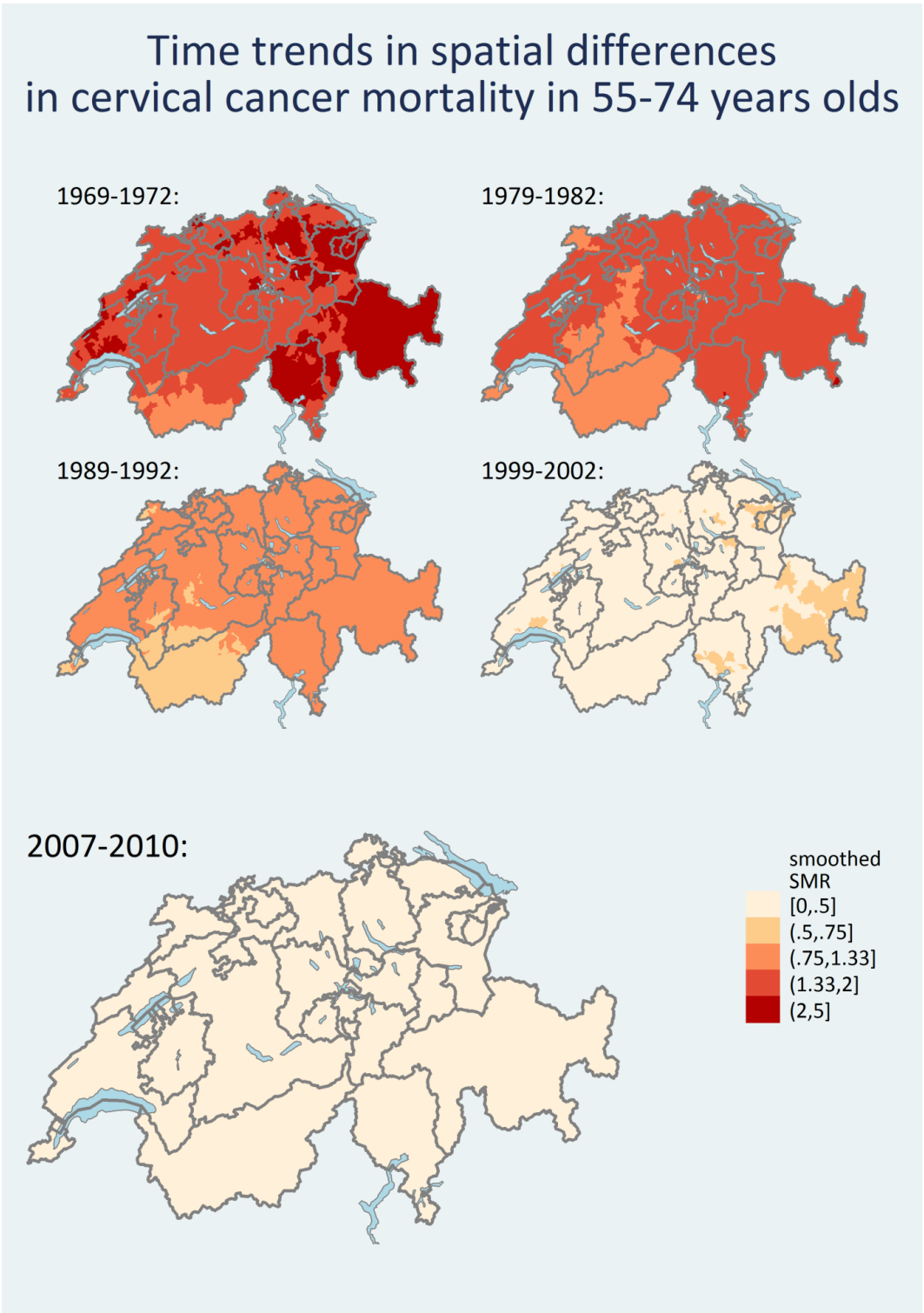

Figure 3.10: Development of cervical cancer SMR, 55-74-year-olds

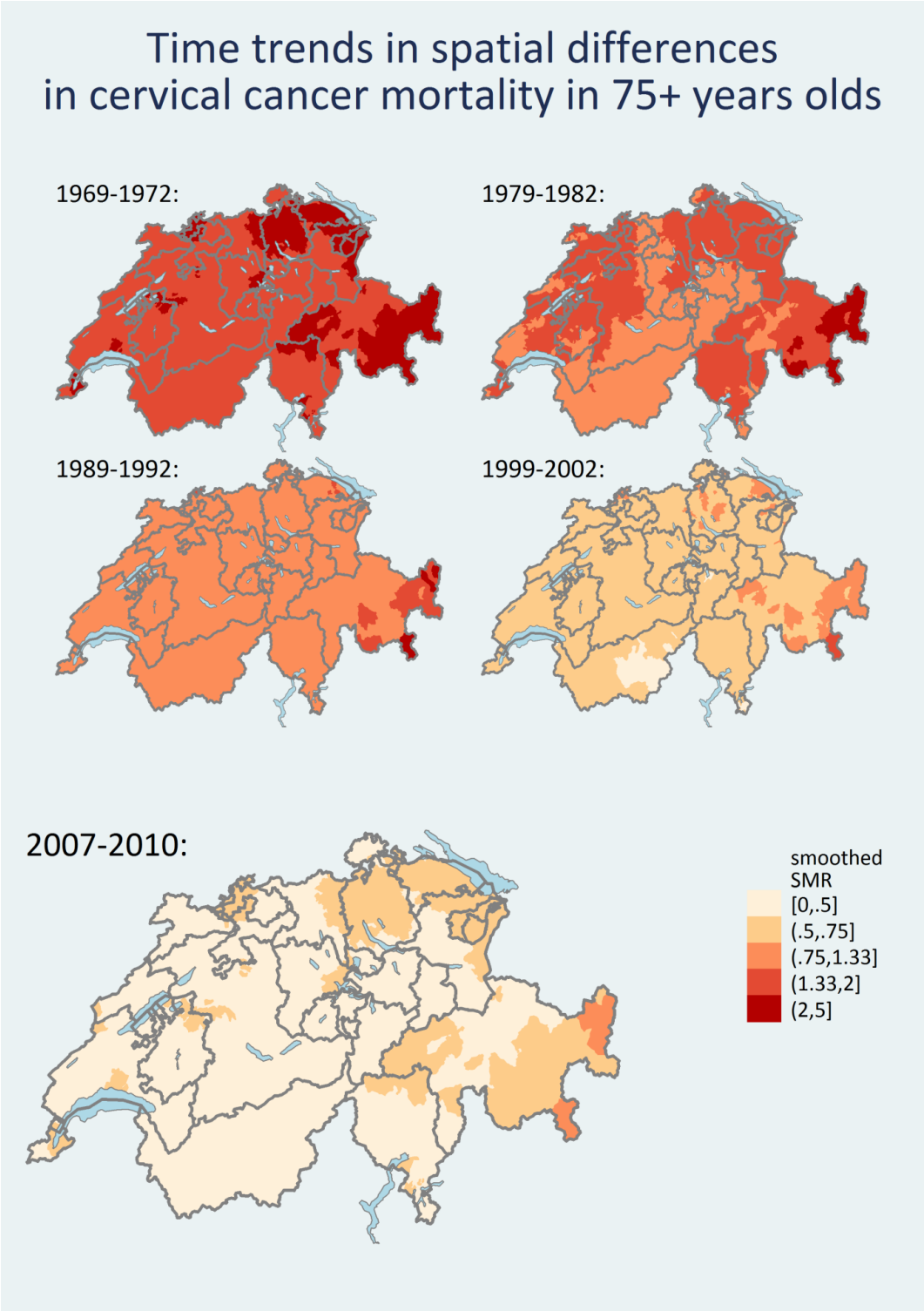

Figure 3.11: Development of cervical cancer SMR, 75+-year-olds

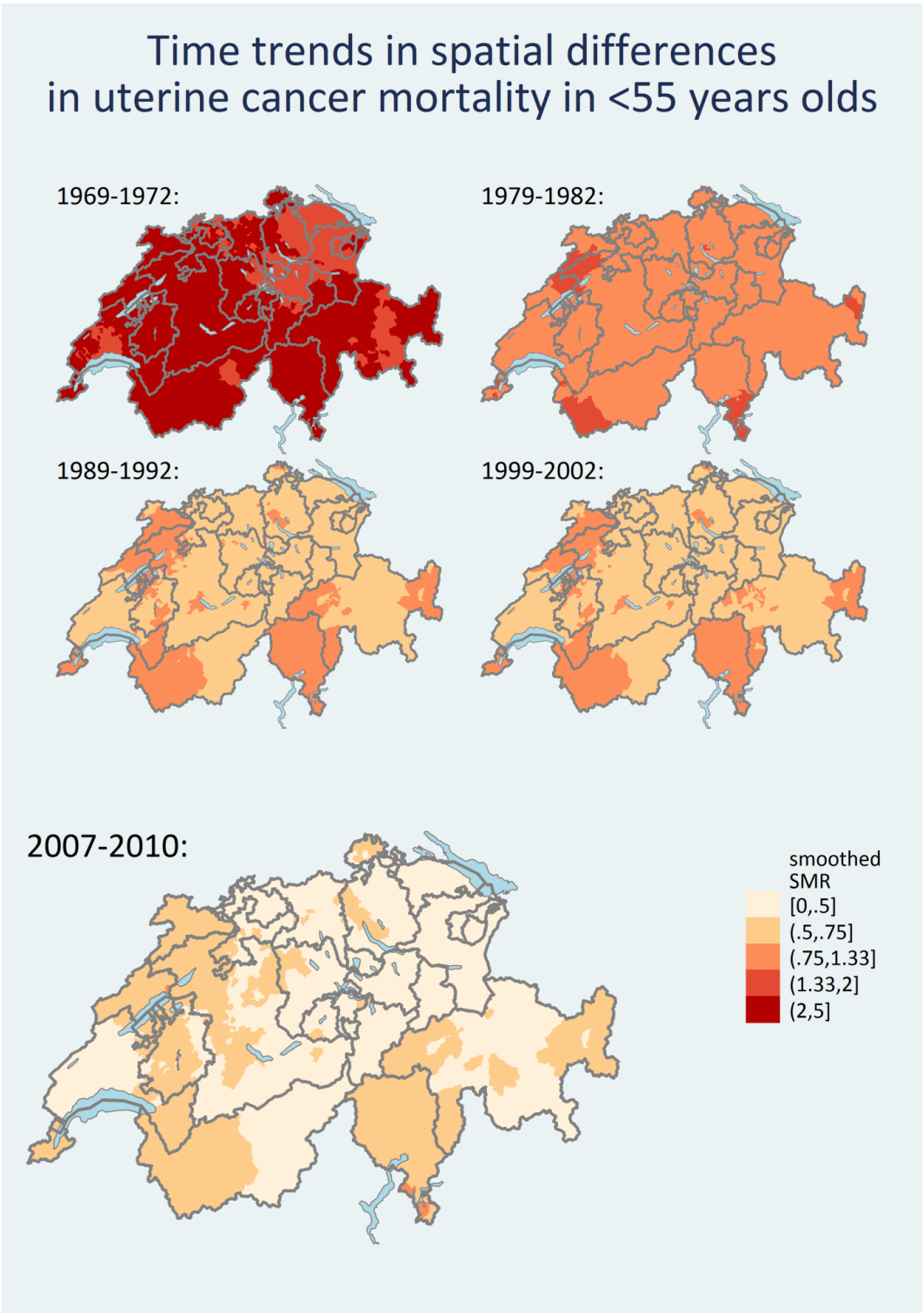

Figure 3.12: Development of uterine cancer SMR, <55-year-olds

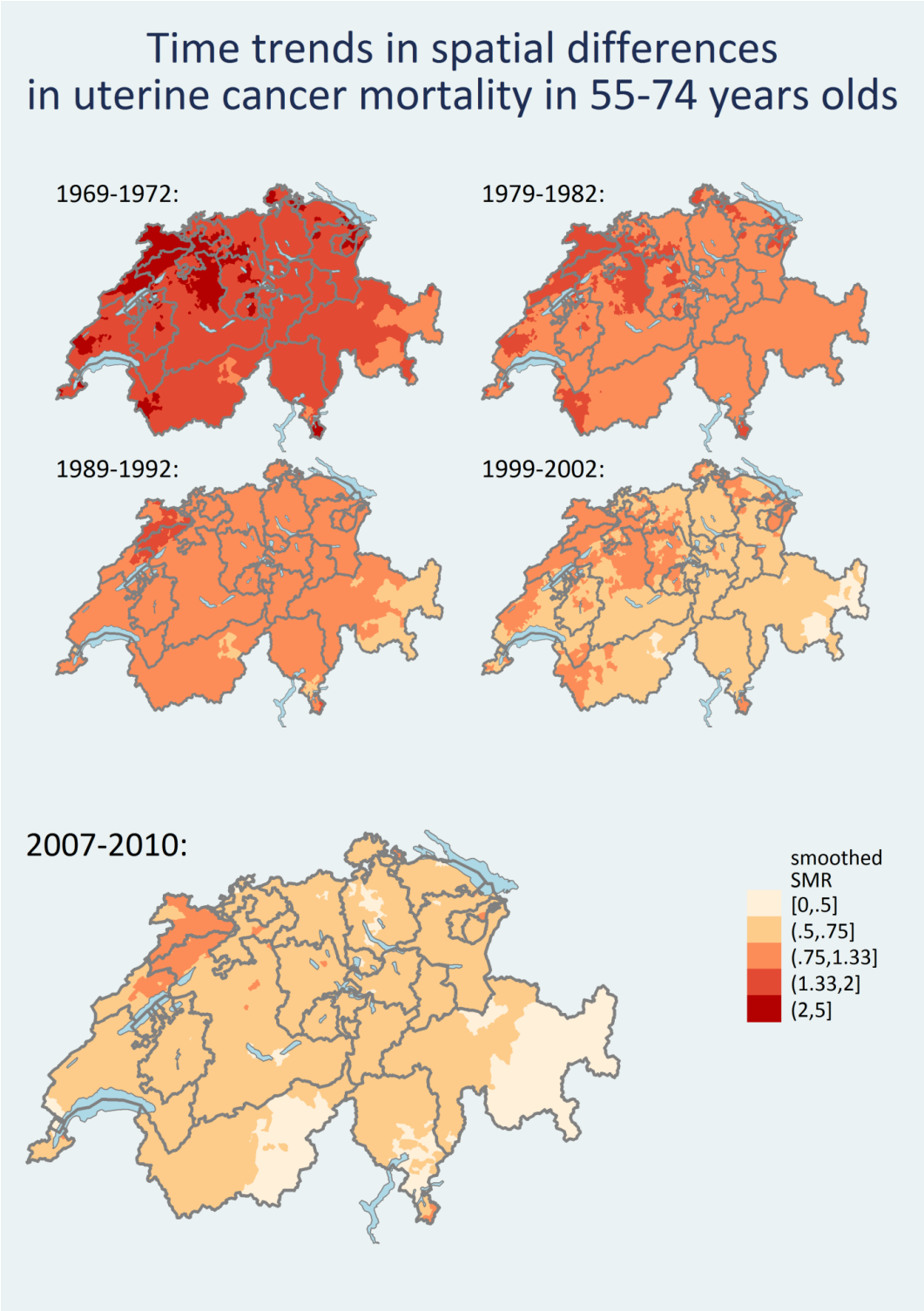

Figure 3.13: Development of uterine cancer SMR, 55-74-year-olds

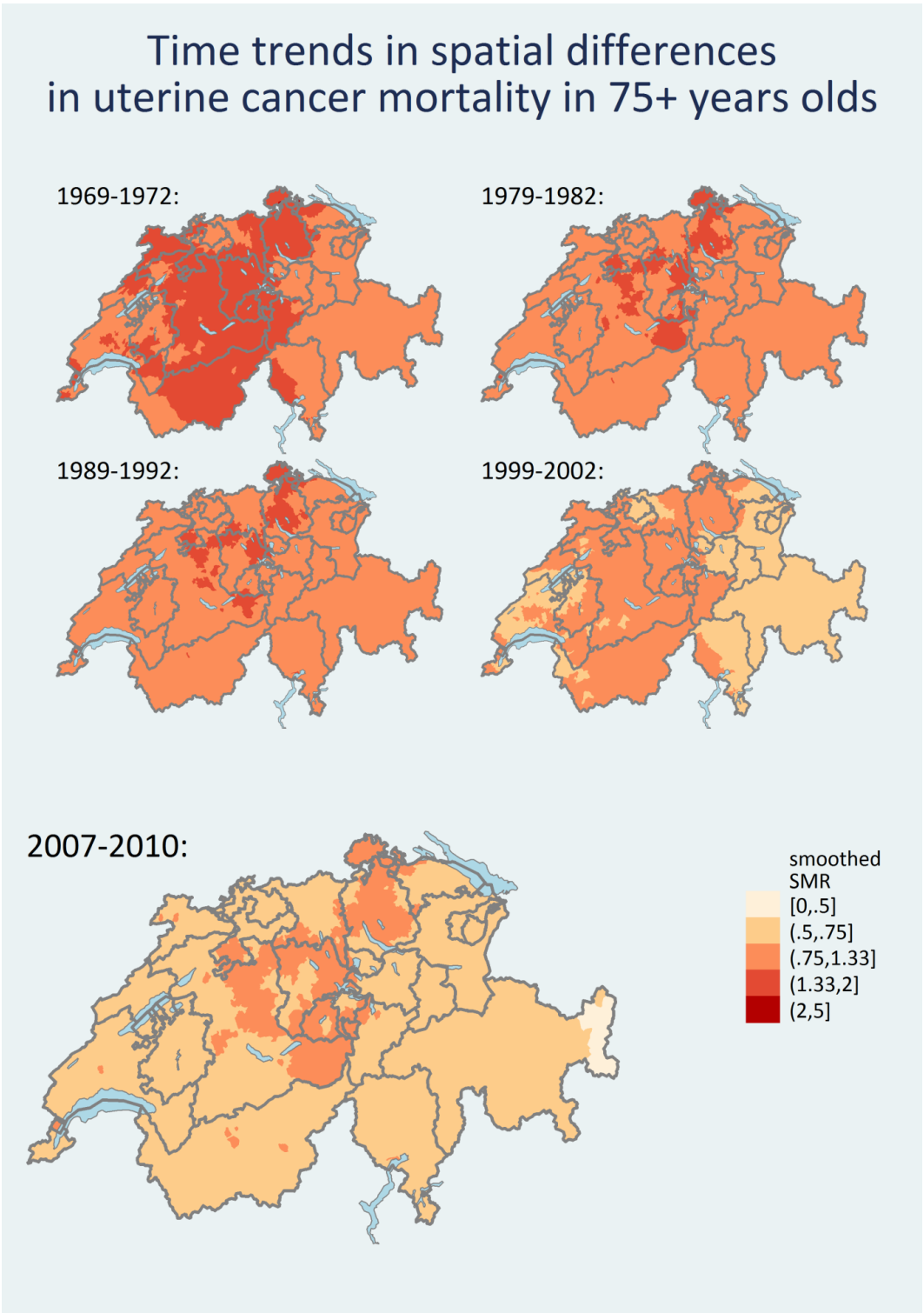

Figure 3.14: Development of uterine cancer SMR, 75+-year-olds

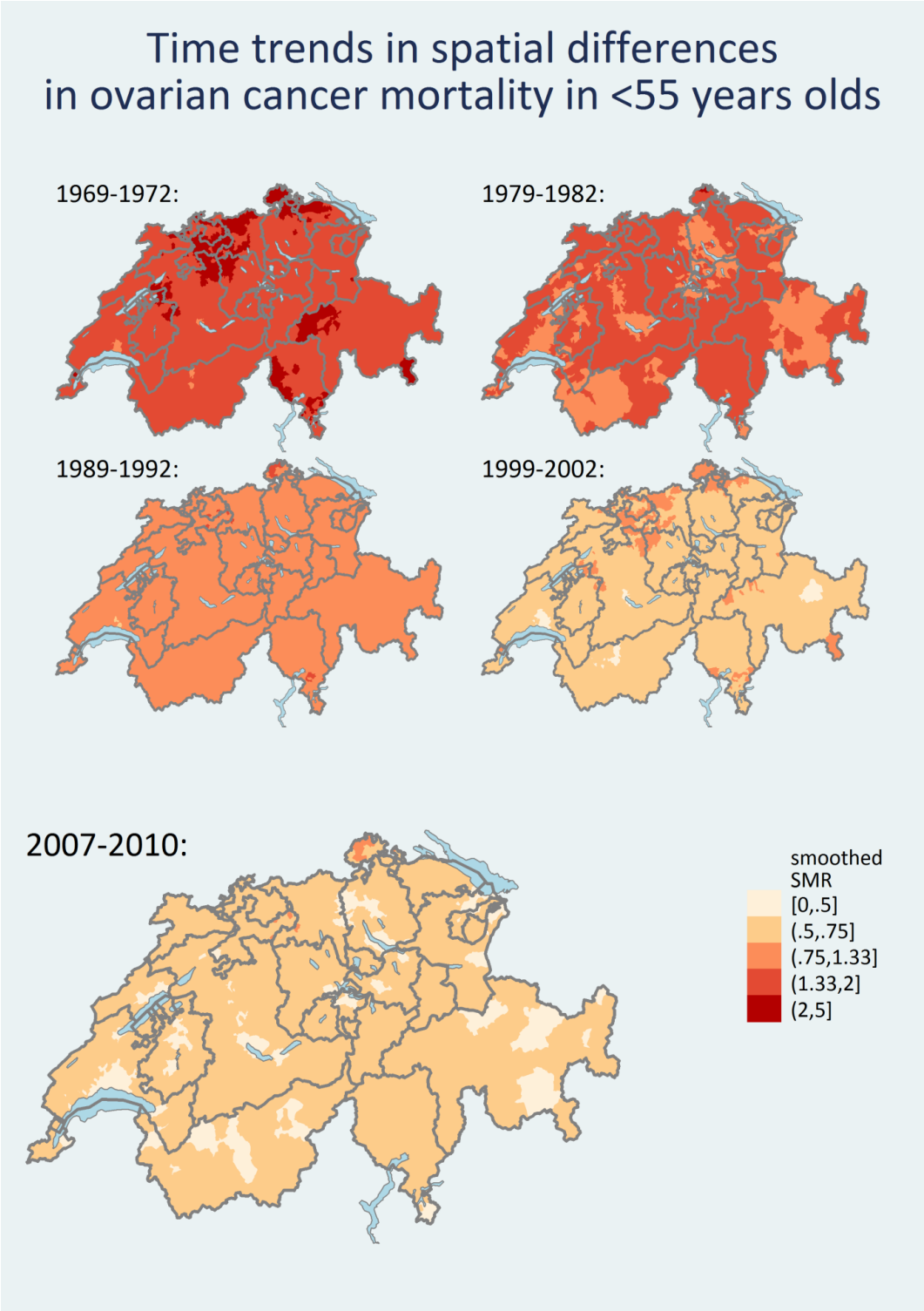

Figure 3.15: Development of ovarian cancer SMR, <55-year-olds

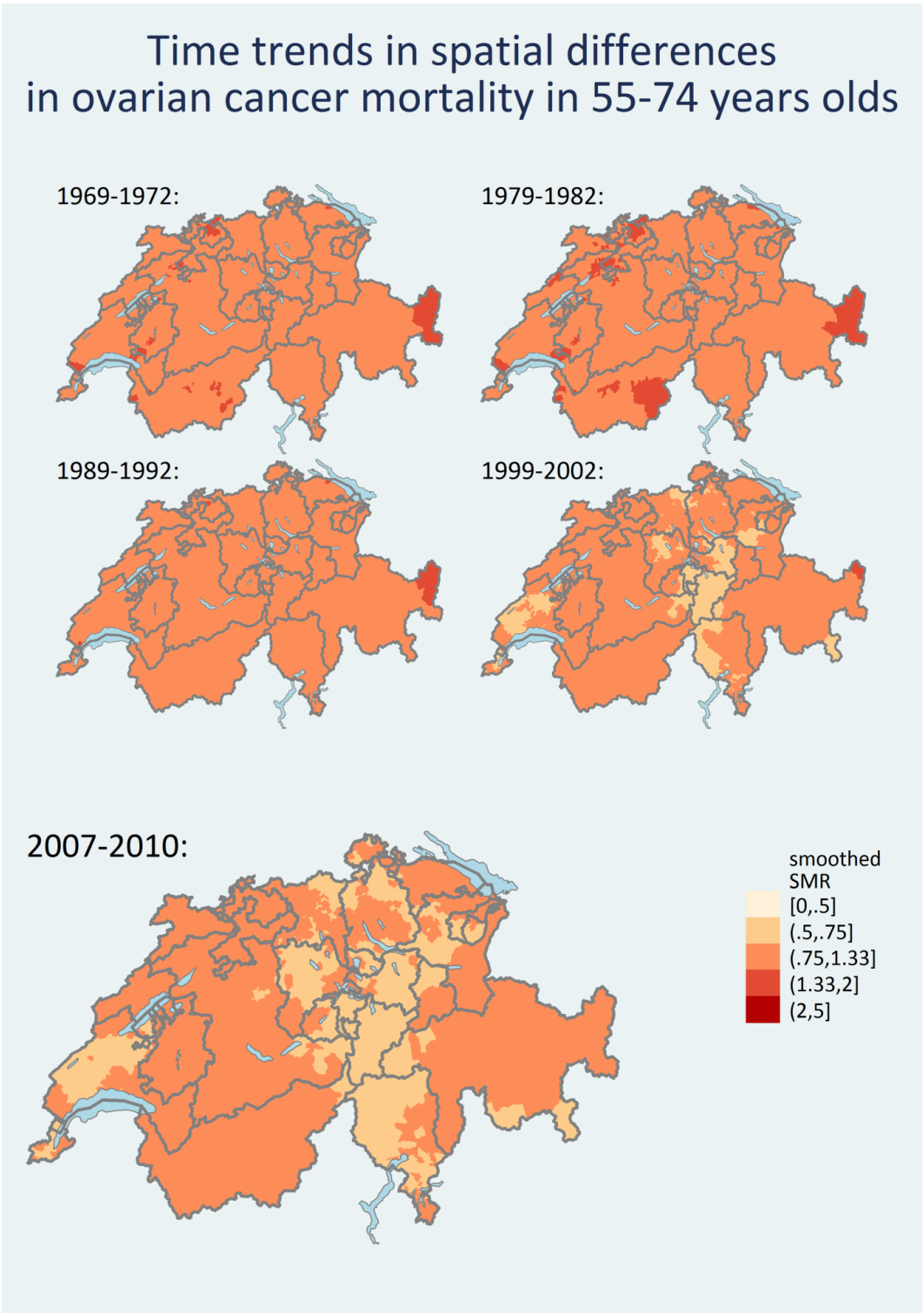

Figure 3.16: Development of ovarian cancer SMR, 55-74-year-olds

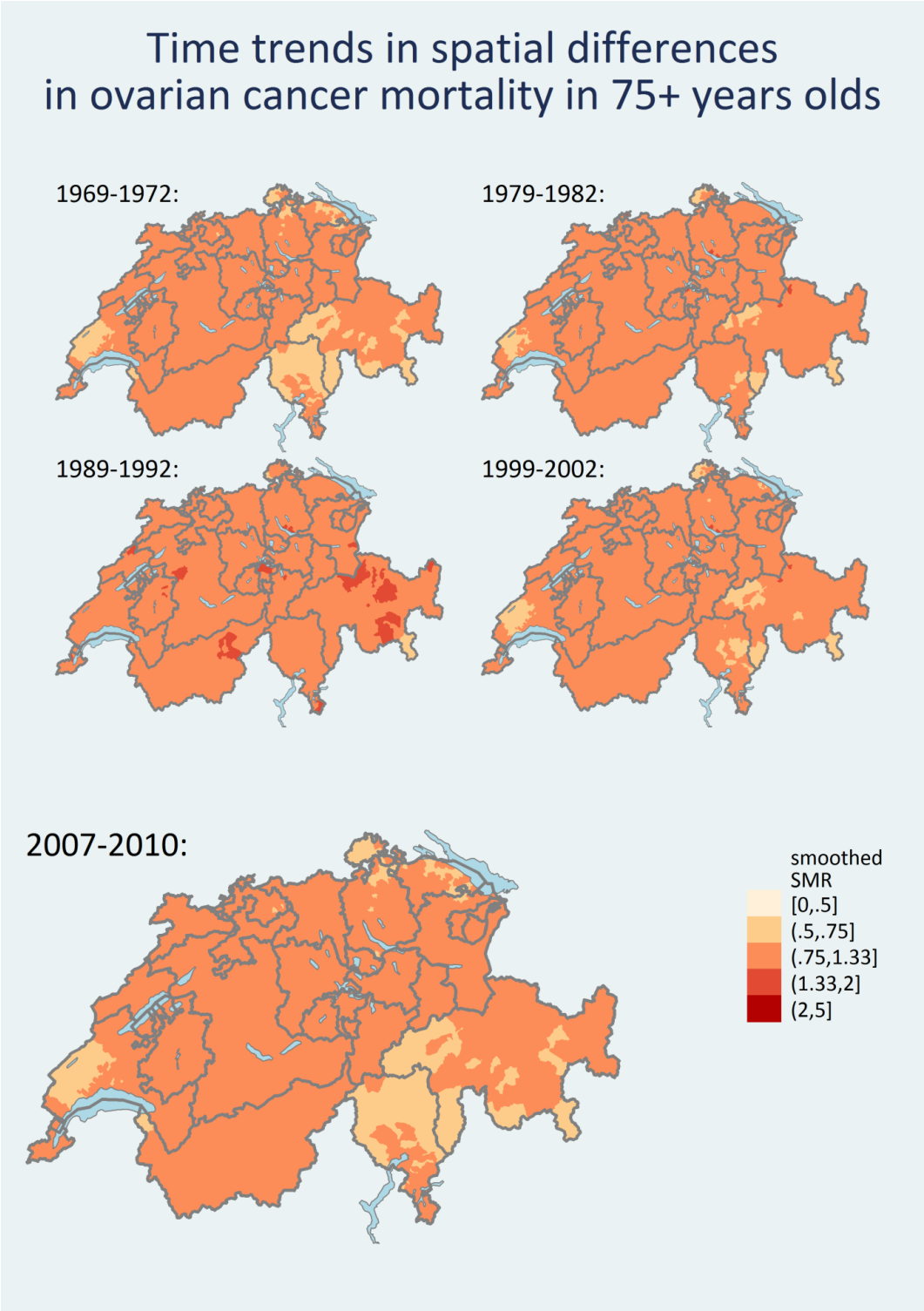

Figure 3.17: Development of ovarian cancer SMR, 75+-year-olds

Chapter 4

Spatio-temporal modelling of breast cancer mortality in 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.

4.1 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.

4.2 Introduction

In Switzerland breast cancer is the most frequently diagnosed cancer in women(Ferlay et al., 2013a), it is the leading cause of cancer-related deaths(NICER, 2017) and of premature mortality for Swiss women(Savidan et al., 2010). Mortality due to breast cancer has declined considerably in the past decades in Switzerland and other developed countries(World Health Organization (WHO), 2015). 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(Marmot et al., 2013) 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(Ess et al., 2010b) 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 (Autier et al., 2011) compared countries in Europe but a criticism was that different countries may have different health

systems. Kalager et al.(Kalager et al., 2010) 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.(Olsen et al., 2013) 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(Organisation for Economic Co-operation and Development (OECD), 2006) and many health- and cancer-related resources.(Department of Health Systems Financing, 2013, Jonsson and Wilking, 2007, Jonsson and Wilking, 2005) 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(Wanner et al., 2001). 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 (Calmonte et al., 2005, Lieberherr et al., 2010), as well as differences in the age at first child birth and number of children born to a mother(Swiss Federal Statistical Office, 2017). 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(Bulliard et al., 2006) 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(Herrmann et al., 2015) 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(World Health Organization (WHO), 2015) and attributed to early detection by mammography and to improved treatment (Jemal et al., 2011, Berry et al., 2005, Levi et al., 2005). 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(Schüler and Bopp, 1997) and additionally for area-based socio-economic factors, which may have influenced results in the previous study.

4.3 Methods

4.3.1 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(Lutz et al., 2004b) 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.

Table 4.1: 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

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(swiss cancer screening, 2015), 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(SNC, 2015) based on the census data of 2000.
Table 4.1 shows the observed number of deaths and mortality rates for each of the co-variates.

4.3.2 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(Herrmann et al., 2015), 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).

4.3.3 Patient involvement

No patients were involved in this study.

4.4 Results

In Switzerland, more than 61,000 women died from breast cancer between 1969 and 2012. Table 4.2 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 4.1.

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 4.3)

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 4.2) 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.

Table 4.2: 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)

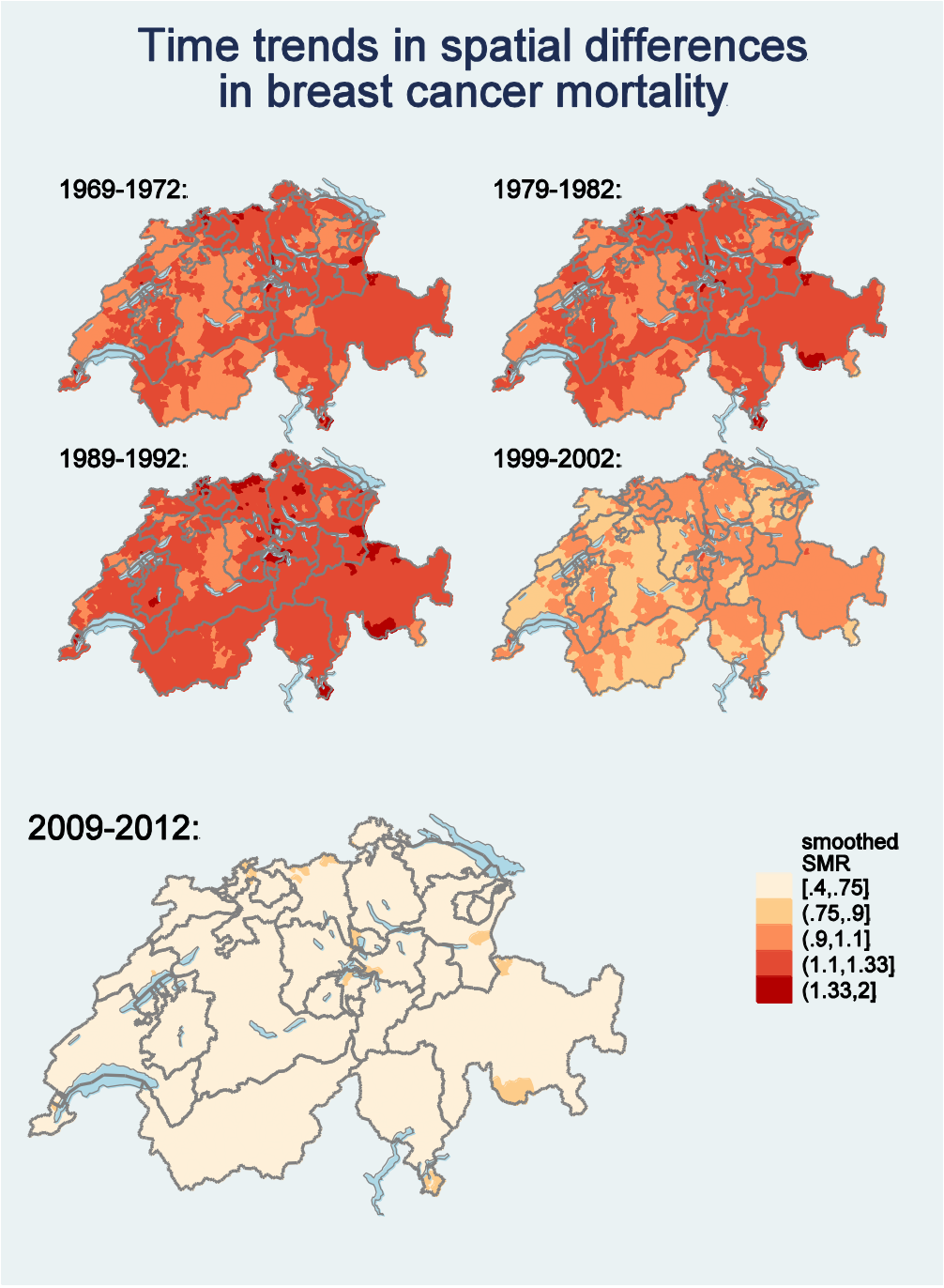

Figure 4.1: Development of age-standardised breast cancer mortality (SMR) and spatial differences therein among time.
Values are calculated and smoothed in relation to the all-period combined mortality. Darker colours represent a higher mortality for the specific age structure and population in that area and time period.

Table 4.3: Spatio-temporal model estimates of age-specific breast cancer mortality in Switzerland within 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)

4.5 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(World Health Organization (WHO), 2015). 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(Lieberherr et al., 2010) affect incidence but are not necessarily linked to mortality(Barnett et al., 2008). 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(Verkooijen et al., 2009). 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.

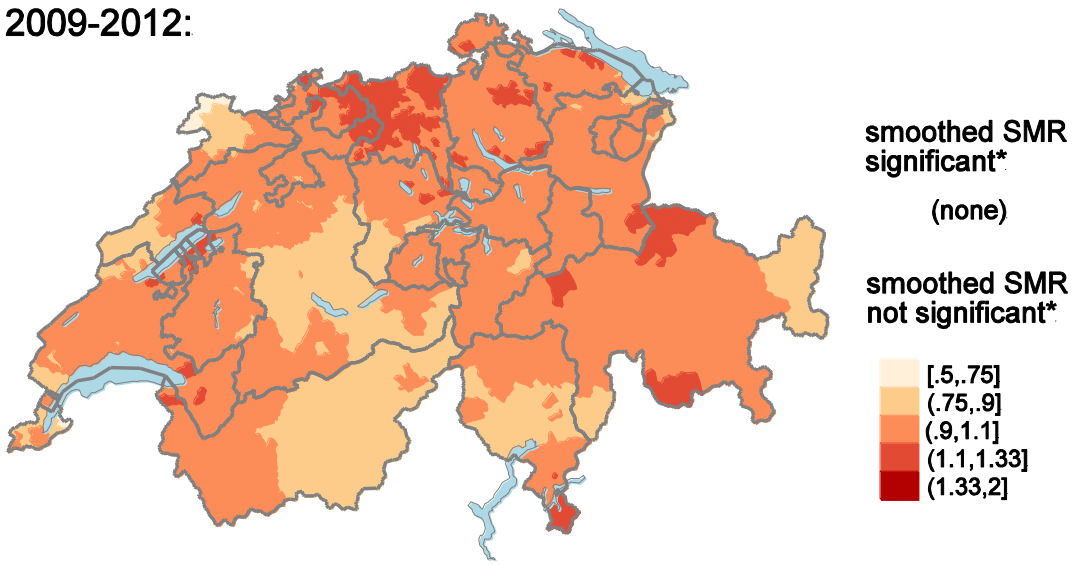

Figure 4.2: Geographical differences in age-standardised breast cancer mortality (SMR) in 2009-2012.
*Significance is denoted as values significantly different at 95%CI from 1, the national mean

Because screening has been identified as a potential source of mortality reduction(Berry et al., 2005), 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.(Autier et al., 2010). Moreover, the level of opportunistic screening in Switzerland has been described to be quite high(Chamot et al., 2007), 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% (Bulliard et al., 2016).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 (Figure 4.3).

The present study is an in-depth analysis of our previous study(Herrmann et al., 2015), 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(Panczak et al., 2012). The additional correction served the disentanglement of affluence from the urbanisation parameter –which is connected with access to medical services– and further possible distortions.(Clough-Gorr et al., 2015)

A strength of Bayesian spatial models is their "smoothing" or improvement of estimation of an unstable rate by "borrowing" strength from its neighbours(Bernardinelli and Montomoli, 1992). 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(Hodges and Reich, 2010). 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.

4.6 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.

4.7 Annex – Classification of Swiss regions

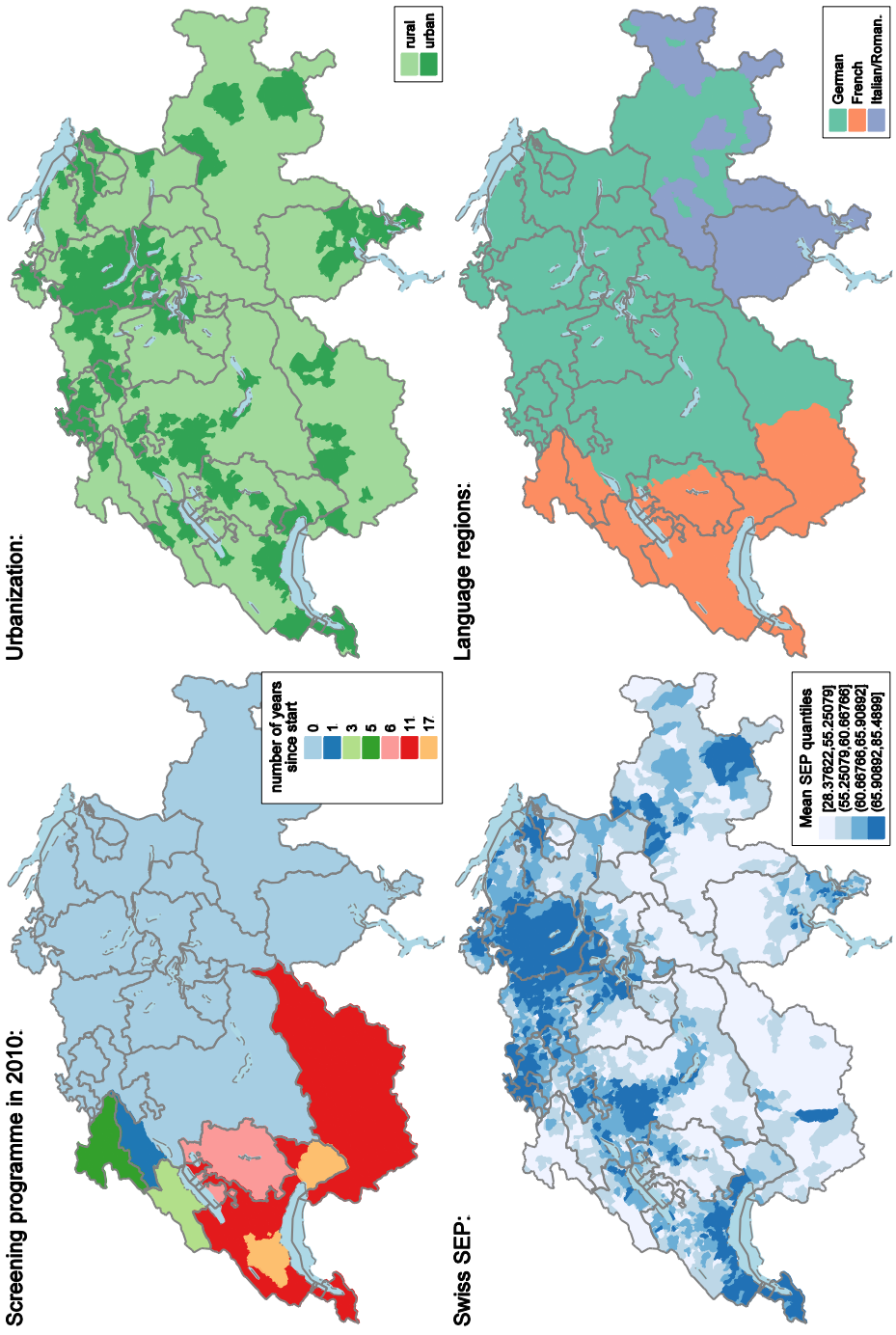

Figure 4.3: Figures depicting urbanization classification, language regions Screening duration and Swiss Socio-Economic Position (SEP) in Switzerland.

Chapter 5

Breast cancer mortality in Switzerland – projections for 2015-2024

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Abstract

Background: Projections of breast cancer (BC) mortality provide an estimate of the future burden of cancer and are important to assess the impact of public health interventions, of novel approaches and of future developments in BC care. Projected mortality numbers can support healthcare planning. We hypothesised that there are regional differences in Switzerland in terms of current and future trends in BC mortality.

Methods: Mortality and population data for the period of 1981-2014 as well as geographical data and population forecasts for 2015-2024 by canton and age group were provided by the Swiss Federal Statistical Office (FSO). We used hierarchical Bayesian Poisson and negative binomial age–period–cohort (APC) models with conditional autoregressive spatial random effects at canton level to estimate BC mortality rates. The spatial APC model was extended to predict future breast cancer mortality rates up to the year 2024.

Results: In Switzerland, the age-standardised breast cancer mortality ratio (ASR, European standard) is projected to decrease considerably from recently 36.8 per 100'000 person years (PY) in 2010-2014 to 33.4 in 2015-2019 and 30.3 in 2020-2024. The ASR is projected to decrease in nearly all regions, with the exception of Valais (VS), Uri/Obwalden/Nidwalden (UR/OW/NW) and Appenzell Ausserrhoden/Appenzell Innerrhoden (AR/AI) that have a marginal increase. Furthermore, future changes of ASR differ between the regions.

In 2010-2014, an overall number of 6'808 breast cancer deaths were observed. Taking demographic changes into account, the number of BC deaths is projected to increase to 7'002 in 2015-2019 and to 7'190 in 2020-2024, corresponding to an increase of 3% and 6% respectively compared to 2010-2014.

Conclusion: We estimate that age-adjusted BC mortality rates in Switzerland will be further reduced within the next ten years. However, the pace of decline differs by region. In more than half of the cantons the number of breast cancer deaths will increase with the demographic forecast playing a major role.

5.1 Introduction

Breast cancer (BC) is the most common cancer in females in Switzerland and Europe in terms of incidence and mortality (Ferlay et al., 2013b). It is the leading cause of cancer-related deaths (around 1500 deaths per year) (NICER, 2017) and of premature mortality for Swiss women (Savidan et al., 2010). Since the 1990's a decrease in BC mortality was observed in Switzerland and in most European countries (Ferlay et al., 2013b), as a result of improved knowledge in cancer biology, early detection efforts, and targeted therapies.

Projections of cancer morbidity and mortality quantify the future burden of the disease. They help scientists and health planners to evaluate long-term consequences of current interventions for reducing the impact of cancer and consequently allocate resources (Bray and Moller, 2006). For Switzerland, only short term projections for breast cancer incidence up to the year 2019 are available (Rapiti et al., 2014), while up-to date mortality projections are not available to our knowledge. Mortality reduction is a main objective of screening and early treatment and it is an indicator of the effectiveness of cancer control strategies (Cleries et al., 2013).

In Switzerland, the implementation of policies related to cancer prevention and care is mainly decided and governed at the cantonal level and contributes to geographical variation in disease incidence and mortality. For example, the decision to initiate or abandon an organised mammography screening programme is taken by the parliament of the respective canton. We therefore hypothesised that the current and future trends in BC mortality differ among the cantons and projected BC mortality at the cantonal level for the periods 2015-2019 and 2020-2024. The short term prediction (2015-2019) offers a good estimate for current rates, while the longer-term projection (2020-2024) provides an insight into what could happen if current trends would continue (Bashir and Esteve, 2001). A complementary factor especially for health policy planning and estimation of capacity needs are total numbers, based on the projected rates combined with foreseeable demographic development in the future.

5.2 Methods

Mortality data at individual level and population data by age-group at canton level for the period of 1981-2014 were provided by the Swiss Federal Statistical Office (FSO). From the same source we retrieved population data until 2015 and population forecasts for 2016-2024 by canton and age group as well as geographical information on cantonal borders.

Causes of death were coded using the 8th and 10th Revision of the International Classification of Diseases (ICD). During the period under consideration there was a transition from ICD-8 to ICD-10 in the year 1994/1995 together with changes in death certificate coding practices (priority rules) that we took into account using cancer site and age-dependent correction factors (Lutz et al., 2004a).

Data were arranged by canton in eight 5-year periods (1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2014 and 2015-2019, 2020-2024) and fourteen 5-year-age groups (30-34,…,90-94,95+), resulting in twenty-one overlapping cohorts (1886-1894, 1891-1899, … , 1986-1994). Cantons with 40 cases or less were merged with their neighbours to allow for a reliable estimation: Appenzell Ausserrhoden (AR) was merged with Appenzell Innerrhoden (AI), Glarus (GL) with Graubünden (GR), Uri (UR) with Obwalden (OW) and Nidwalden (NW).

Hierarchical Bayesian Poisson and negative binomial Bayesian age–period–cohort (APC) models were applied to the mortality counts μ_{ijk} as follows:

$$\log(\mu_{ijk}) = \log(n_{ijk}) + \alpha_{ik} + \beta_{jk} + \gamma_{j-i,k} + \phi_k$$

where n_{ijk} is the population for age group i, period j and region k. Following previous formulations (Bray, 2002, Lagazio et al., 2003, Schmid and Held, 2004, Jurgens et al., 2013b), the smoothed period β and cohort effects γ were extrapolated by an autoregressive prior structure and undirected smoothing of the age parameter α (Bashir and Esteve, 2001).

The models include main effects for age, period, cohort and spatial effects at canton level, using Markov random field specifications (Besag et al., 1991). Two Poisson and two negative Binomial Bayesian models with assumed global and region-specific variances of APC effects were employed and their model fit was assessed by the deviance information criterion (DIC). Markov chain Monte Carlo (MCMC) simulation methods were employed for model fit. The

spatial APC model was extended to predict future breast cancer mortality rates up to the year 2024. Results are presented as rates and as total numbers.

5.3 Results

In Switzerland, the age-standardised breast cancer mortality ratio (ASR, European standard) is projected to decrease considerably from recently 36.8 per 100’000 person years (PY) in 2010-2014 to 33.4 in 2015-2019 and 30.3 in 2020-2024, corresponding to a 9% and 17% decrease compared to the most recent ASR. The projected change of ASR is quite different for the regions and ranges in the period of 2015-2019 from a 26% decrease in Jura (JU) to a 1% increase in Valais (VS) (Table 5.1). In nearly all regions the ASR is projected to decrease for both periods, with the exception of VS, UR/OW/NW and AR/AI that suggest a marginal increase which is, however, not statistically significant (Table 5.1). Only the estimated decreases in Basel-Stadt (BS) and JU for 2015-2019 were statistically significant (Figure 5.1 and Table 5.2). The observed and projected rates including 95% Bayesian Credible Interval (CI) by region are shown in Figure 5.1.

In the period of 2010-2014, 6’808 breast cancer deaths were observed. The total numbers take demographic changes into account, so in contrast to the rates, the number of BC deaths is projected to increase to 7'002 in 2015-2019 and to 7'190 in 2020-2024, corresponding to an increase of 3% and 6% respectively compared to 2010-2014. Table 5.1 shows that the projected total number of breast cancer deaths have an increasing trend in 12 of the 22 regions, which is however not significant.

The DIC was lowest for the Poisson model with only global precision parameters for the APC effects. Hence, the results shown are derived from that model. An assessment of mortality rates indicates an age-period effect in Switzerland (see 5.6).

Table 5.1: Observed number of deaths in 2007-2011 and posterior predicted median of number of deaths in 2012-2016 and 2017-2021 by region (cantons) in Switzerland, and percent change of projected number of deaths compared to 2007-2011.

Change is shown as total percent change in number of deaths ("total"), percent change in age-standardised rates ("est. risk") and their difference ("other"), mainly due to population change. Cf. 5.6 for canton abbreviations.

	2010-2014	2015-2019		% change to 2007-2011			2020-2024		% change to 2007-2011		
Canton	deaths	deaths	95% CI	total	est. risk	other	deaths	95% CI	total	est. risk	other
ZH	1'171	1'161	(810-1'656)	-1%	-13%	12%	1'111	(516-2'244)	-5%	-27%	21%
BE	894	919	(644-1'324)	3%	-8%	10%	954	(454-1'974)	7%	-14%	21%
LU	315	312	(204-488)	-1%	-13%	13%	304	(135-678)	-4%	-25%	22%
SZ	102	98	(57-172)	-4%	-19%	15%	90	(35-242)	-11%	-35%	23%
ZG	89	87	(49-153)	-3%	-18%	15%	84	(32-229)	-6%	-33%	27%
FR	212	235	(146-383)	11%	-1%	12%	265	(112-639)	25%	-2%	27%
SO	255	274	(177-437)	8%	-3%	10%	300	(136-719)	18%	-4%	22%
BS	192	160	(98-259)	-17%	-25%	8%	128	(51-314)	-33%	-44%	10%
BL	267	271	(175-426)	2%	-10%	12%	274	(122-603)	3%	-20%	23%
SH	77	73	(41-129)	-5%	-13%	7%	71	(27-180)	-8%	-24%	16%
SG	368	367	(243-555)	0%	-12%	12%	368	(159-776)	0%	-23%	23%
AG	530	563	(381-843)	6%	-8%	15%	596	(270-1'283)	12%	-17%	30%
TG	197	204	(128-324)	3%	-11%	14%	206	(89-494)	5%	-21%	26%
TI	358	401	(263-598)	12%	-3%	15%	448	(196-988)	25%	-7%	32%
VD	575	612	(411-896)	7%	-6%	13%	646	(291-1'389)	12%	-13%	26%
VS	252	284	(181-456)	13%	1%	12%	326	(143-760)	29%	1%	28%
NE	150	144	(86-241)	-4%	-11%	7%	135	(57-354)	-10%	-22%	12%
GE	384	425	(281-650)	11%	-1%	11%	472	(210-1'067)	23%	-1%	24%
JU	48	41	(21-79)	-14%	-26%	12%	34	(12-98)	-29%	-48%	18%
UR/OW/NW	112	126	(74-211)	12%	1%	11%	147	(60-355)	31%	0%	31%
GL/GR	192	175	(113-283)	-9%	-22%	13%	156	(69-376)	-19%	-39%	21%
AR/AI	68	70	(37-129)	3%	0%	2%	76	(28-210)	12%	2%	10%
Sum	**6'808**	**7'002**		**3%**	**-9%**	**12%**	**7'190**		**6%**	**-17%**	**23%**

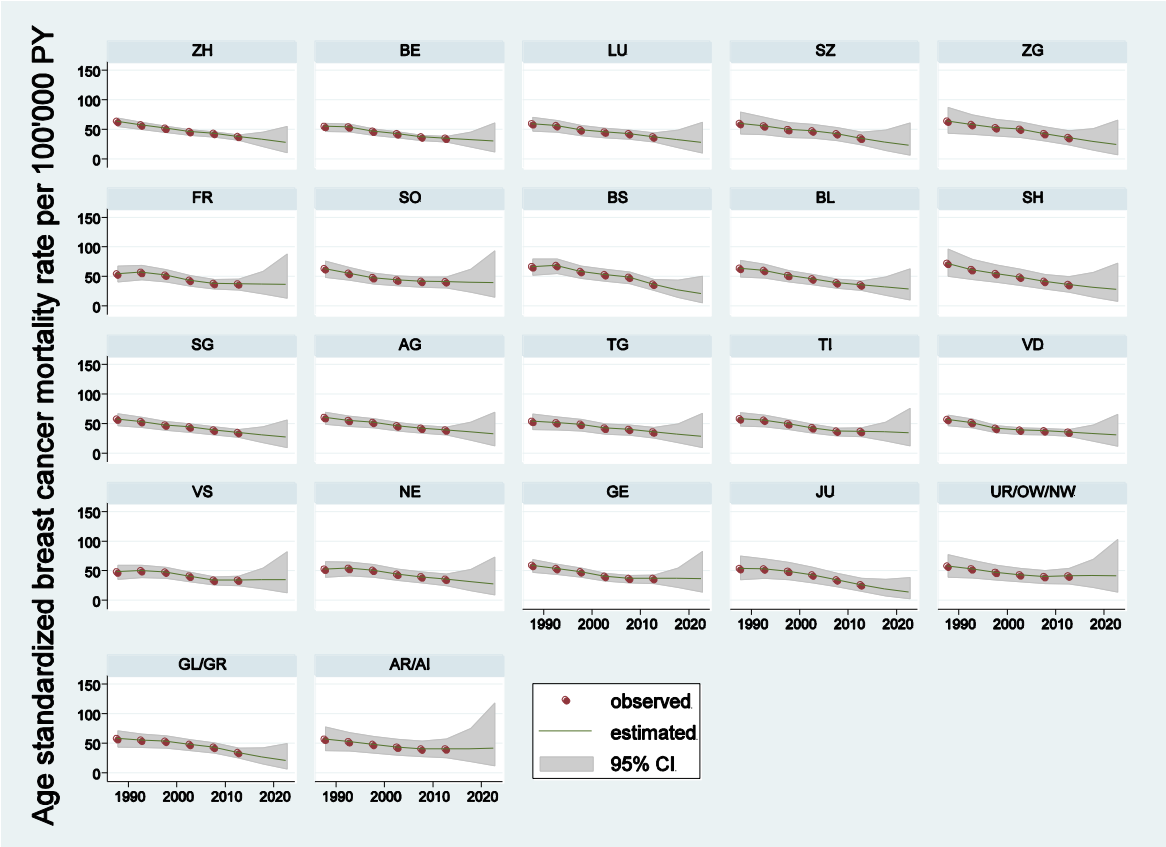

Figure 5.1: Time trends in observed cantonal age-standardised breast cancer mortality (ASR) and model estimated/predicted median ASR in Switzerland.

5.4 Discussion

To our knowledge this is the first study projecting breast cancer mortality in the mid-and longer term in Switzerland.

Many favourable improvements in breast cancer care and early detection have led to an improvement of breast cancer mortality in the recent decades. Despite favourable trends in mortality rates the total numbers of breast cancer deaths are estimated to increase, especially due to population changes. The contribution of improved prevention and care reflected in the predicted decrease in age-adjusted breast cancer mortality in some regions is often unable to outweigh the contribution of demographic aging on the absolute number of breast cancer

deaths. The absolute numbers by cantons are important for policy planning and estimation of capacity needs, i.e. in end-of-life care.

Projecting future cancer mortality is fraught with uncertainty and trends in the past do not necessarily hold in the future. It is therefore necessary to be aware of any underlying assumptions and limitations. It should be noted that the trend in our model already indicates a further decrease in mortality rates, as observed previously after introduction of mammography and therapies (i.e. tamoxifen, trastuzumab)(Herrmann et al., 2015). Comparing current projections with future then current rates will show whether the reduction in mortality has in fact continued. Research in tumour biology and implementation of targeted therapies and public health interventions may pronounce the estimated mortality trends even more, especially in the three regions that show no clear downward trends now. It should be furthermore noted that the introduction of new interventions doesn't have an immediate effect on breast cancer mortality since many are implemented gradually and also take effect on mortality with a time lag.

The uncertainty of projection is also illustrated by the wide 95% confidence bands in the rates. Only in two regions (BS and JU) a significant decrease in the rates for 2015-2019 was found. While the small numbers in some regions are a limitation to this analysis, a trade-off was sought between providing numbers for cantonal health planning as specific as possible and having regions with a sufficient number of cases for analysis. A strength of this study is that, by combining small regions preferably with each other, the projections for the other cantons represent only that particular canton. The difference between the region with most cases in 2010-2014 (Zürich (ZH), 1'171 BC deaths) and the region with the smallest number of cases (JU, 48 BC deaths) is quite large. However, although the small numbers in JU may have contributed to a more extreme projection of nearly halving the risk until 2020-2024 compared to other regions, JU is also one of the only two cantons with a statistically significant projected decrease in BC mortality rates for 2015-2019.

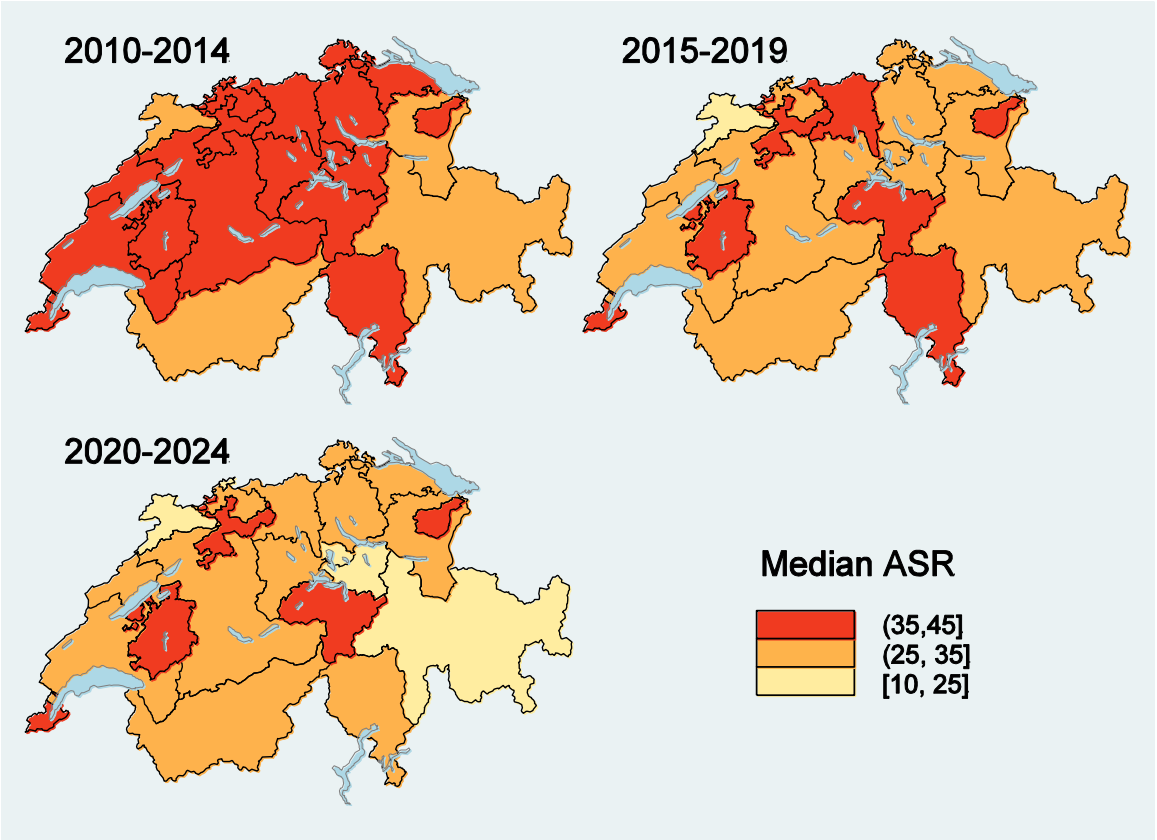

Figure 5.2: Cantonal posterior median of age-standardised breast cancer mortality (ASR) in Switzerland in 2010-2014 and predicted median ASR for 2015-2019 and 2020-2024.

Potential misclassification of the cause of death can lead to further uncertainty. We used correction factors (Lutz et al., 2004a) to account for changes in priority rules. And we performed a robustness analysis to assess a potential bias of BC deaths being misclassified as unknown cause of death. While mortality data showed canton-specific time trends in unknown causes of death, the impact on BC deaths was too small to result in different trends.

Besides APC models, several other methods have been used for cancer projections (log-linear, power models, cubic splines) (Clements et al., 2005, Moller et al., 2003). A strength of the chosen APC model is the use of the spatial structure, allowing for projections for sub regions and even for lesser populated areas, by "borrowing" strength from their neighbours. In three regions (VS, AR/AI and UR/OW/NW) the observed ASR seemed to show a recent trend-

change to increasing mortality rates (Figure 5.1) contrary to the overall trend in Switzerland. However, when taking the spatial structure into account, estimated rates remain at least stable for these regions. Comparison with future rates will show if mortality will further decrease also in these regions, as in the rest of the country.

Since projections always hold assumptions, these assumptions may even be wrong when validated on past data in a dynamic area such as cancer detection and treatment. We believe that –in view of ongoing developments in the field as well as due to implementation of population-based screening programmes and other public health interventions– our assumption will be at least as good or better as assuming the mortality rate will stay equal to 2010-2014 with a changing population. This has been demonstrated for incidence by Moller et al. (Moller et al., 2003).

We present the results under the assumptions of having or not having a trend in mortality in Table 5.1. Including the trend in mortality rates, the change in mortality numbers is displayed in the columns "total %change". Excluding rate trends, hence assuming equal rates in the future, the change in mortality numbers is displayed in the columns "other %change". Of course, it is very important to at least maintain current interventions in order for the mortality to not increase again.

In a recent publication we showed that organised screening programmes in Switzerland are (currently) not significantly related to breast cancer mortality and regional differences therein on a population level (Herrmann et al., 2018). Also, we could not find a significant difference between regions classified by urbanisation, language and socio-economic position (Herrmann et al., 2015, Herrmann et al., 2018). Hence, these factors were not specifically included in the projection of breast cancer mortality.

As for the reason of the wide differences in estimated mortality numbers, this cannot be pinpointed to one single factor. Although differences in the patterns of care were observed, they are expected to rather have an effect on the quality of life than on mortality (Ess et al., 2009). Also, survival trends are not congruent to mortality trends. I.e. St. Gallen (SG) has always had a significant lower survival than Geneva (GE) (Allemani et al., 2015), but a steeper decrease in mortality rates. Incidence rates are influenced by differences in risk factors and early detection and are also not matching the mortality differences. An important factor in

the projection of mortality numbers is the accuracy of the population forecast. The forecast used in this study was done by the Federal Statistical Office and depends on their assumptions and trend calculations. For the population structure the trend towards an ageing population is the same for all regions, but the current age structure is quite different (see 5.6). I.e. the proportion of 80+-year-olds in the female population in 2010-2014 ranges from 4.7% in Fribourg (FR) to 9.3% in Basel Stadt (BS).

An important next step would be the projection of breast cancer incidence and the estimation of stage distribution also in areas without registration coverage. While short term projections for all stages combined up to 2019 was recently performed (Rapiti et al., 2014), long-term projections and stage information are highly valuable data to complement this research for effective health planning. Furthermore, individual data on stage, risk factors, screening and treatment would be important to improve predictions and particularly to estimate how projections depend on changes in these factors.

5.5 Conclusion

Projections of breast cancer mortality in Switzerland indicate a further reduction of mortality rates in the upcoming ten years. However, the pace is regionally quite different. Furthermore, in more than half of the cantons the total number of breast cancer deaths is projected to increase, with the population change playing a major role. The numbers show the importance of projecting breast cancer mortality to aid healthcare planning. Our estimates will help assessing the impact of novel approaches and future developments in breast cancer care, as well as public health interventions.

5.6 Annex – Additional tables and figures

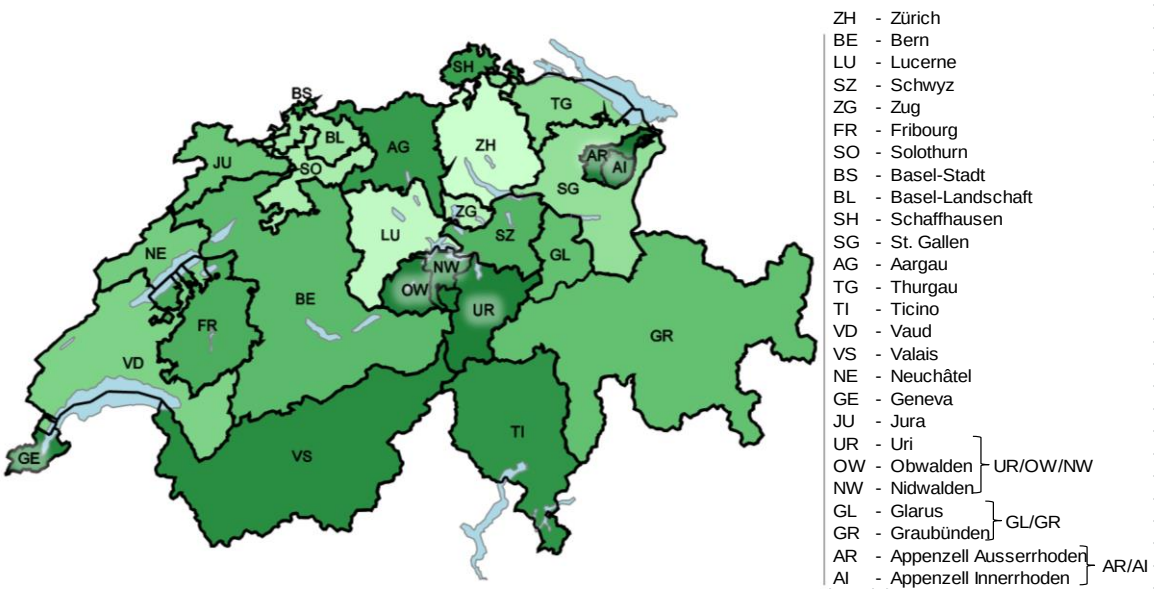

Figure 5.3: Canton abbreviations.

Table 5.2: Observed number of deaths in 2007-2011 and posterior predicted median and 95% Credible Interval (CI) of number of deaths in 2012-2016 and 2017-2021 by region (cantons) in Switzerland, and percent change of projected number of deaths compared to 2007-2011.

Change is shown as total percent change in number of deaths ("total"), percent change in age-standardised rates ("est. risk") and their difference ("other"), mainly attributable to population change. Significant changes in est. risk are highlighted in bold typeface.

	2010-2014	2015-2019	% change to 2007-2011			2020-2024	% change to 2007-2011			
Canton	deaths	deaths 95% CI	total	est. risk 95% CI		other	deaths 95% CI	total	est. risk 95% CI	other
ZH	1'171	1'161 (810-1'656)	-1%	-13% (-32% - 11%)		12%	1'111 (516-2'244)	-5%	-27% (-62% - 33%)	21%
BE	894	919 (644-1'324)	3%	-8% (-26% - 17%)		10%	954 (454-1'974)	7%	-14% (-54% - 57%)	21%
LU	315	312 (204-488)	-1%	-13% (-31% - 11%)		13%	304 (135-678)	-4%	-25% (-60% - 38%)	22%
SZ	102	98 (57-172)	-4%	-19% (-36% - 7%)		15%	90 (35-242)	-11%	-35% (-66% - 33%)	23%
ZG	89	87 (49-153)	-3%	-18% (-36% - 7%)		15%	84 (32-229)	-6%	-33% (-65% - 35%)	27%
FR	212	235 (146-383)	11%	-1% (-22% - 28%)		12%	265 (112-639)	25%	-2% (-48% - 89%)	27%
SO	255	274 (177-437)	8%	-3% (-23% - 25%)		10%	300 (136-719)	18%	-4% (-47% - 86%)	22%
BS	192	160 (98-259)	-17%	**-25% (-43% - -2%)**		8%	128 (51-314)	-33%	-44% (-72% - 11%)	10%
BL	267	271 (175-426)	2%	-10% (-29% - 16%)		12%	274 (122-603)	3%	-20% (-57% - 45%)	23%
SH	77	73 (41-129)	-5%	-13% (-31% - 13%)		7%	71 (27-180)	-8%	-24% (-61% - 43%)	16%
SG	368	367 (243-555)	0%	-12% (-30% - 11%)		12%	368 (159-776)	0%	-23% (-60% - 37%)	23%
AG	530	563 (381-843)	6%	-8% (-28% - 17%)		15%	596 (270-1'283)	12%	-17% (-56% - 54%)	30%
TG	197	204 (128-324)	3%	-11% (-29% - 12%)		14%	206 (89-494)	5%	-21% (-57% - 51%)	26%
TI	358	401 (263-598)	12%	-3% (-23% - 21%)		15%	448 (196-988)	25%	-7% (-51% - 73%)	32%
VD	575	612 (411-896)	7%	-6% (-27% - 17%)		13%	646 (291-1'389)	12%	-13% (-55% - 60%)	26%
VS	252	284 (181-456)	13%	1% (-20% - 31%)		12%	326 (143-760)	29%	1% (-45% - 95%)	28%
NE	150	144 (86-241)	-4%	-11% (-31% - 16%)		7%	135 (57-354)	-10%	-22% (-58% - 61%)	12%
GE	384	425 (281-650)	11%	-1% (-21% - 27%)		11%	472 (210-1'067)	23%	-1% (-47% - 89%)	24%
JU	48	41 (21-79)	-14%	**-26% (-44% - -3%)**		12%	34 (12-98)	-29%	-48% (-73% - 4%)	18%
UR/OW/NW	112	126 (74-211)	12%	1% (-21% - 28%)		11%	147 (60-355)	31%	0% (-46% - 87%)	31%
GL/GR	192	175 (113-283)	-9%	-22% (-37% - 1%)		13%	156 (69-376)	-19%	-39% (-67% - 18%)	21%
AR/AI	68	70 (37-129)	3%	0% (-24% - 30%)		2%	76 (28-210)	12%	2% (-48% - 102%)	10%
Sum	**6'808**	**7'002**	**3%**	**-9%**		**12%**	**7'190**	**6%**	**-17%**	**23%**

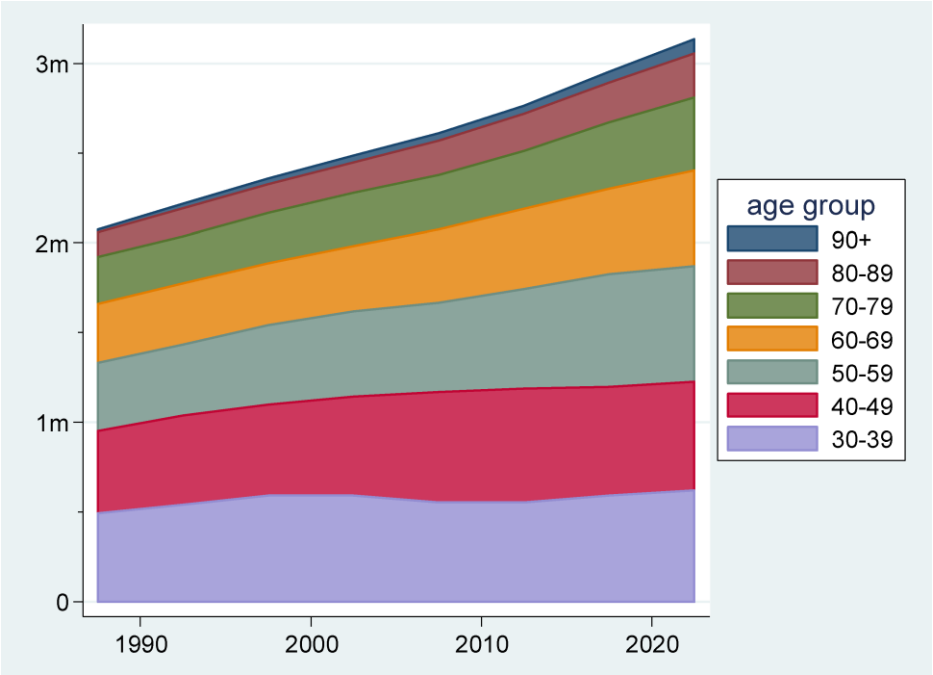

Figure 5.4: Population development in Switzerland.
Historical and expected female population count by age group above 30 years of age.

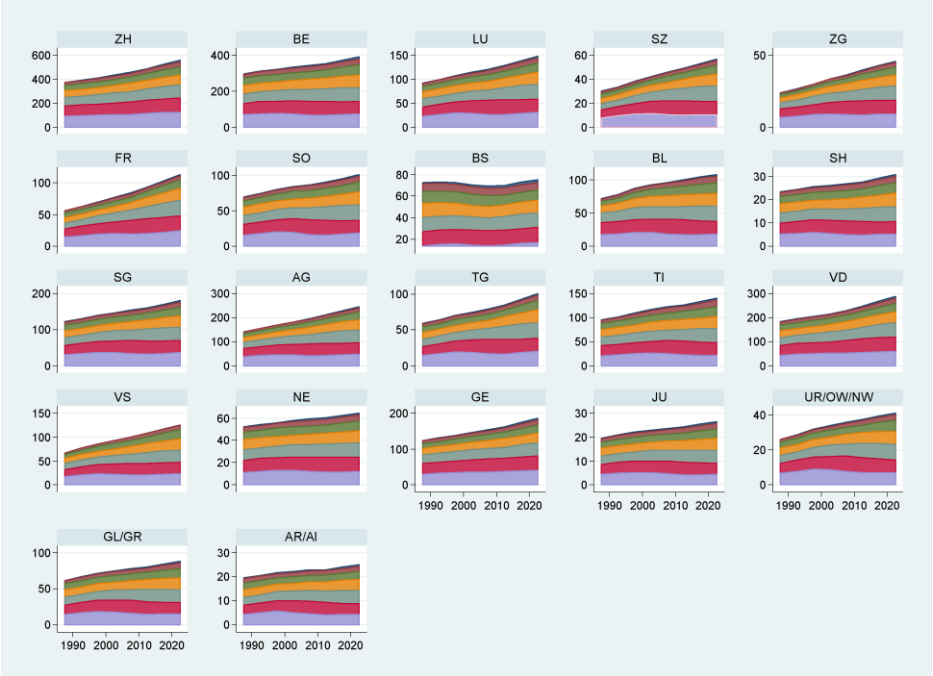

Figure 5.5: Historical and expected female population count in 1000's by age group and canton.
For Legend see Figure 5.4

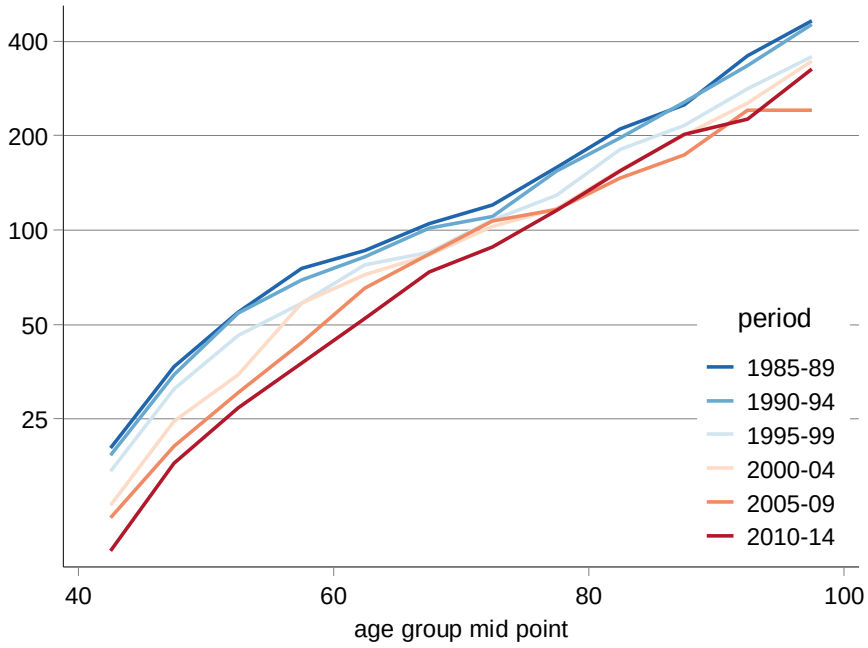

Figure 5.6: Age-standardised mortality rates (ASR) in Switzerland by 5-year age classes (A) and 5-year periods (P), each represented by their mid-point.

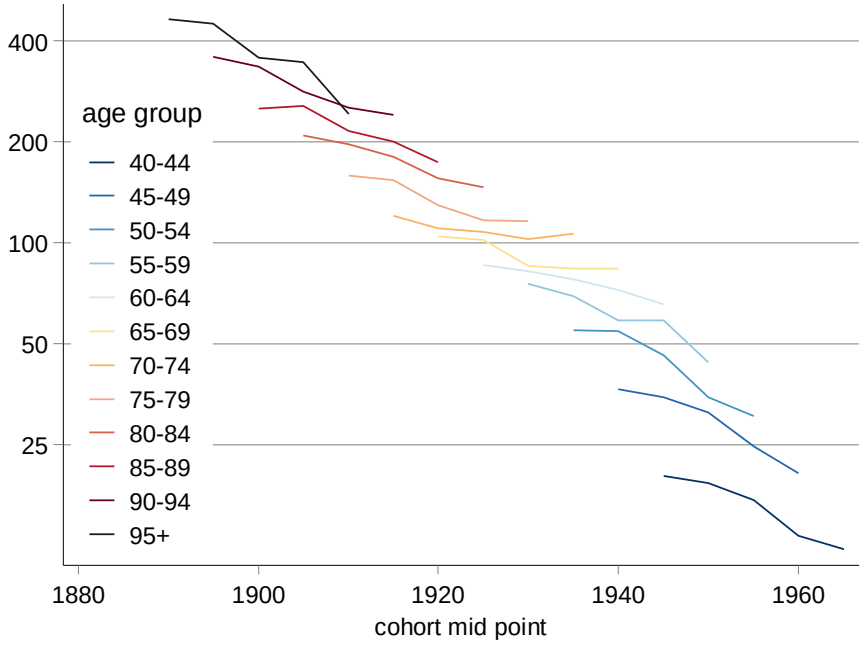

Figure 5.7: Age-standardised mortality rates (ASR) in Switzerland by 5-year age classes (A) and 10-year cohorts (C), each represented by their mid-point.

Chapter 6

Regional differences and trends in breast cancer surgical procedures and their relation to socioeconomic disparities and screening patterns

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Abstract

Background: In Switzerland, breast cancer is the most frequently diagnosed cancer in women. Important regional disparities in patterns of care in breast cancer have been recently described. In Switzerland, nationwide data on hospitalisations have been collected since 1998. They have not been used up to now to explore space-time patterns and trends of breast cancer healthcare related procedures for control and health planning purposes.

Objectives and Goals: The objective is to assess geographical and temporal variation of mastectomy rates.

Methods of investigation: Bayesian Poisson spatio-temporal models have been applied on hospital-based data with national coverage to describe disparities in breast cancer surgery patterns. Covariates included patient characteristics as provided in the hospital data, as well as data on mammography screening programme duration and surgeon and gynaecologist density.

Results: We analyzed more than 70'000 patients. Mastectomy rates declined from 43% to 30% in Switzerland between 2000 and 2012 for patients aged 50-69 and from 61% to 43M for those 70+ and remained stable for those under 50. Important geographical differences in rates were present. Rates were significantly influenced by age (Relative Rate Ratio (RR) 50-69: 0.92, RR 70+: 1.25), differences in co-morbidity (RR one comorbidity: 1.17, RR more than one: 1.35). Regions with higher surgeon or gynaecologist density had significantly higher rates of mastectomies (RR surgeons: 1.01, RR gynaecologists: 1.06), whereas regions in the French-speaking part or with mammography screening programmes showed significantly lower rates (RR French language region: 0.72, RR screening: 0.87). No difference was found for patients in different socio-economic groups or with different insurance types.

Conclusion: This research unveiled important information which was not available for the whole country before. The results play an essential role in the identification of regions where special attention is required.

6.1 Introduction

Female breast cancer is the most frequently diagnosed cancer in the female Swiss population (Ferlay et al., 2013b). In the period of 2010-2014, almost 6000 new cases of breast cancer were diagnosed per year, corresponding roughly to 30% of the female cancer incidence. Within Switzerland, age-standardised incidence rates for breast cancer vary between 83.1 /100'000 PY in Appenzell Innerrhoden and 136.8/100'000 in Jura (NICER, 2017). Differences in uptake of screening activities (mammography screening in women) contribute as much to differences in incidence, as do other known risk factors such as age and genetic predisposition, overweight and obesity, reproductive factors and presumably hormone replacement therapy (McPherson et al., 2000, Kumle, 2008).

Breast surgery is the cornerstone in the treatment of localized breast cancer, representing 95% of all newly diagnosed BC patients. The aim of the surgical resection is to remove all cancer tissue. Adjuvant therapies (radiotherapy, endocrine therapy and chemotherapy) are aimed to reduce the risk of relapse and dissemination of cancer cells to other tissues. While adjuvant therapies are generally performed in the ambulatory setting, breast surgery is always performed in Switzerland in a hospital setting, therefore, being the basis for this study. Mastectomy (resection of the whole breast) has been the traditional type of breast surgery until results from well-designed randomized trials in the 1980s showed, that less mutilating surgical procedures preserving the most part of the breast (breast-conserving surgery) like lumpectomy or quadrantectomy had similar rates of overall survival and disease-free survival as mastectomy but preserving quality of life (Veronesi et al., 1981). The study-update with a 20-year follow-up confirmed the preliminary findings, establishing the concept of breast conservation as a standard of care (Veronesi et al., 2002). In fact, mastectomy patients compared to conserving surgery patients usually reported a lower body image and sexual functioning (Montazeri, 2008). There are, however, several reasons to perform a mastectomy in contrast to a breast-conserving surgery (BCS). Reasons might be of personal, medical or preventive nature, such as an increased risk of getting a second cancer due to BRCA mutations. Medical reasons include larger tumours, affection of multiple areas of the breast by cancer, and inflammatory breast cancer. BCS should be combined with radiotherapy to result in the same survival as mastectomies (McLaughlin, 2013, Fisher et al.,

2002). Mastectomies might therefore also be chosen when radiation therapy is medically contraindicated, when previous BCS with radiation therapy did not remove the cancer, or –on an individual level– if the patient lives far from facilities offering radiation therapy (Mac Bride et al., 2013). In comparison with BCS, mastectomy is a more serious procedure that sometimes results in complications such as infection, poor healing, and lymphedema and requires longer hospital stays (Andersen and Kehlet, 2011). Discomfort and pain are less after BCS, but (time-consuming) radiation and surveillance by mammography are necessary and might result in higher anxiety about recurrence.

In Switzerland, geo-referenced data on hospitalisations including socioeconomic characteristics of the patient, diagnosis, and procedures have been collected annually by the Federal Statistical Office (FSO) since 1998 and cover the whole country. To our knowledge, the wealth of information provided in this database has not been fully explored to assess space-time patterns and trends of breast cancer healthcare related procedures for control and health planning purposes.

There has been much debate on the role of medical care in the discussion of social inequalities in health. Access inequalities to early detection, appropriate care and state-of-the-art management as well as differences in tumour biology are possible explanations for survival differences between socio-economic classes. Regional disparities have been described for Switzerland affecting the income, access to services including access to healthcare services, education and other socioeconomic factors (Bundesamt für Statistik, 2009).

Availability of public or private resources to be allocated to health is high. Switzerland is one of the richest countries in the world and has one of the highest expenditure per person in terms of health (Department of Health Systems Financing, 2013) and direct purchasing power-adjusted costs for cancer (Jonsson and Wilking, 2007). In Switzerland, the standard of care is high, uptake of new drugs is above average within Europe (Jonsson and Wilking, 2005), life expectancy is one of the highest in the world. However, since healthcare policies are developed at cantonal level, there is a considerable amount of geographical variation in health expenditures, control programmes and treatment procedures. Opportunistic screening

is common especially in the urban areas of cantons with cancer registries, but little is known about regions not covered by cancer registries (Wanner et al., 2001).

Important regional disparities in the state-of-the-art management of breast cancer among regions covered by cancer registration have been recently published (Ess et al., 2010c, Ess et al., 2010a). Disparities included surgical as well as non-surgical management issues. Predictors of guideline compliance on the patient level were treatment by a surgeon with high caseload, residence, and age of the patient, but not socio-economic factors. They described pronounced differences in mastectomy rates from 24% in Geneva to 38% in St. Gallen in 2003-2005. The differences persisted after adjustment by age and tumour size. Using the hospital discharge dataset, we can assess if these differences have persisted over time and how their results relate to the situation in the whole country.

The aim of this research is to assess spatio-temporal patterns of mastectomy rates in Switzerland and explore their relation to socioeconomic disparities and screening patterns. The assessment of the geographical variations in the country will help to identify regions in which special attention is required to reduce healthcare inequalities and their impact on community health.

6.2 Methods

Data from the Swiss Discharge Hospital database until 2012 was retrieved from the Federal Statistical Office (FSO). The database was initiated in 1998 and includes each inpatient hospitalisation discharge providing information on the age, the gender of the patient, year of hospitalisation, diagnosis and co-morbidities, treatment procedures, class of stay, and administrative characteristics. Its data is available for research in anonymised form in two variants. We used the geographic variant, including information on the region of the patients' residence and canton of hospitalisation, and chose them over the type of hospital. In both cases, the exact hospital cannot be identified. We excluded data before 2000 due to insufficient data quality. I.e. unique person identifiers were missing in a significant proportion. The FSO described data completeness and quality issues for the first years after the start of data collection. Although participation is mandatory, only 85% of hospitals,

representing 73% of cases, sent data for the year 1999 (Bundesamt für Statistik, 2003). Since 2000, data has continuously improved, reaching 99% of hospitals and representing 91% of cases in 2002 and reaching 100% in 2011 (BFS, 2017). In our study we included females with breast cancer (BC, ICD-10 codes C50.0-C50.9) as the main reason for hospitalisation, who had at least one BC-related surgery as defined below in any hospital stay, in order to exclude patients solely treated with palliative intentions or BC-unrelated conditions. Patients who presented with distant metastases at first visit (ICD-10 codes C78-C79) were also excluded. Table 6.1 summarizes the characteristics of included patients. Patients were only counted once per year even with multiple admissions, but counted again, when they undergo surgical treatment for breast cancer in another year.

Table 6.1: Characteristics of patients included in the study

	Patients	%
Age		
0-39	3'601	5%
40-49	12'325	17%
50-59	16'447	23%
60-69	18'603	26%
70-79	13'332	19%
80+	7'347	10%
Language region (place of treatment)		
German	47'200	66%
French	19'291	27%
Italian	5'164	7%
Mammography screening duration in 2012 (place of residence)		
0 (no programme)	54'111	76%
1-4 years	5'369	7%
5-9 years	6'887	10%
10+ years	5'288	7%
Insurance class		
1 basic	43'505	61%
2 half-private	18'159	25%
3 private	9'991	14%
Comorbidity score (excl. breast cancer)		
0 (only BC)	64'857	91%
1	4'923	7%
2+	1'875	3%
No. of Admissions		
1	45'546	64%
2-4	24'334	34%
5+	1'775	2%
No. of Surgeries		
1	55'400	77%
2	13'717	19%
3+	2'538	4%

The outcome of interest was the ratio of patients with mastectomies per all included patients and its trend per hospital region (canton). Data on treatments were coded according to the Swiss operation classification of 2012 (CHOP classification). CHOP codes begin with the letter 'Z' followed by 2 to 6 numbers in groups of two, separated by a period. Operations involving the breast have codes beginning with "Z85". To identify women with mastectomies we used the codes "Z85.23" and "Z85.33" to "Z85.48". For (therapeutic) surgeries we used the codes "Z85.2", "Z85.20"– "Z85.22", and "Z85.25" additionally. Other codes in the "Z85"-group included diagnostic procedures, reconstructions, transplantations etc.

We assessed the comorbidity score for each patient based on the hospital record. We used the Charlson score with ICD-10 modification and performed the calculation with the Stata program „charlson" (Quan et al., 2005). For the score we excluded the breast cancer and any breast cancer-related lymph node invasions in order to reflect the impact of additional health disorders and not to mask any further cancer disease.

On the basis of the hospital database, we determined breast cancer patient characteristics for each region and year. After prior analysis, patients were categorised into 3 age groups: <50 years old, 50-69 years old and more than 70 years old. This coincides with the age of invitation (50-69-year-olds) in Swiss mammography screening programmes. We categorized patients also by the number of admissions (one versus multiple BC related admissions), by the number of BC surgeries (one versus multiple BC surgeries), the comorbidity score (score of 0 = only BC vs. score of 1 vs. scores of 2 or more) and insurance class (basic vs. half-private or private insurance). This insurance class is a proxy for affluence but may in part also reflect differences in treatment. While in principle the same medical services are provided in all classes, patients within the private class are normally treated by more senior staff.

We evaluated also a different covariate in relation to socio-economic status. Data on socio-economic position (SEP) by municipality was provided by the Swiss National Cohort (SNC, 2015) and is based on census data of 2000, including measures of affluence, education etc. We linked the municipality of residence of the patient to the SEP-score of the municipality and grouped all BC patients by SEP quartile. The score ranged from 55 to 71 with the median being 64 and the interquartile range being 60-67.

We furthermore included covariates in relation to the analysis region, the canton. Data on language region were retrieved from the FSO (Swiss Federal Statistical Office, 2017). Regions were classified according to their predominant language into German, French or Italian/Romansh. Patterns of mammography screening were obtained as years of population-based mammography screening programmes by year and canton from (swiss cancer screening, 2015). The regions were classified according to the existence of a population-based mammography screening programme for a given year.

The number of surgeons and gynaecologists per 1'000 population by year and canton was retrieved from the Swiss Medical Association (FMH, 2017). The FMH provides numbers only by main medical discipline.

In the analysis the cantons of Uri, Obwalden and Nidwalden, and of Appenzell Innerrhoden and Appenzell Ausserrhoden were combined in two regions in order to increase power.

We assessed space-time patterns of mastectomy rates by fitting areal models with temporal trends. Patient characteristics, socio-economic status, screening patterns, language region and surgeon and gynaecologist density were explored by including these factors in the model as covariates. The geographical unit of analysis was the canton of the hospital.

For each patient characteristics-combination (insurance type, SEP quantile, comorbidity, admissions, surgeries) observed counts of mastectomies Y_{ijt} in canton i ($i = 1, \dots, N$), age group j and year t to follow a Negative binomial distribution $Y_{ijt} \sim NegBin(\mu_{ijt})$. Random effects, as well as possible trends, were modelled on the log of the mean mastectomy rate. Time dimension was included as an autoregressive term (AR(1)), conditioned on the mastectomy rates in the year 2000.

$$\log(\mu_{ijt}) = \log(P_{ijt}) + \alpha + \sum X_{its}^{T}\beta_s + \gamma_j + (\delta + \varepsilon_j)\ \log(\mu_{ij(t-1)})\ +\ \Phi_i$$

where P_{ijt} is the number of patients, X_{its} the vector of covariates s related to canton i and year t, β_s the coefficients of associated covariates, γ_j effects of age group j, δ time trend and ε_j interaction of time and age group j. Spatial correlation by random effects Φ_i on canton level i, modelled via a Conditional Autoregressive (CAR) process. Spatial dependency among the cantons was introduced by the conditional prior distribution of Φ_i with

$$\Phi_i \sim N\left(\frac{\gamma \sum_{\substack{q=1 \\ q \neq i}}^{N} c_{iq}\Phi_q}{w_i}, \frac{\sigma^2}{w_i}\right)$$

where c_{iq} indicates the degree of spatial influence of canton i to the remaining cantons – taking the value 1 if they are adjacent and 0 otherwise– and γ quantifying the overall spatial dependence and w_i being the number of neighbours of canton i. The final model was selected based on lowest DIC (Deviance information criterion) score.

6.3 Results

71'655 patients were included in our study. 22% were aged <50 at hospitalisation, about half 50-69 and 29% above 70. Two-thirds were treated in the German-speaking region, 27% in the French-speaking region and 7% in the Italian-speaking region. 61% of patients had

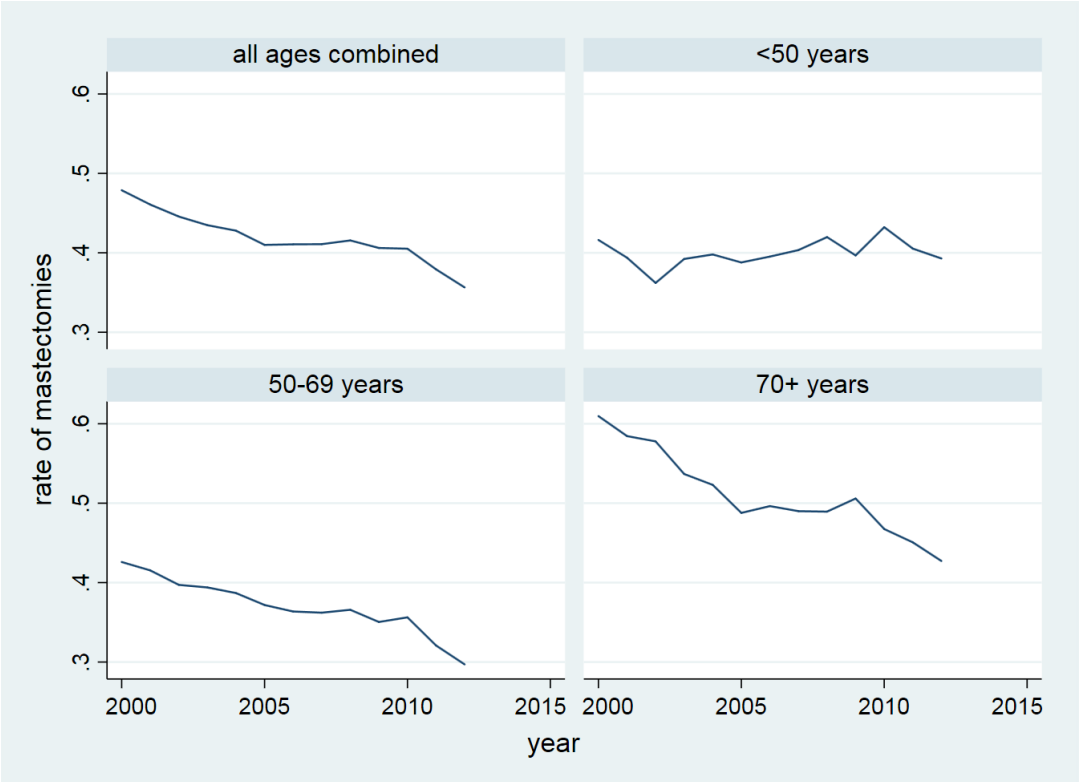

Figure 6.1: Observed mastectomy rates by time and age group in Switzerland.

mandatory basic insurance, 25% half-private and 14% private insurance. 9% of patients had further co-morbidities at hospitalisation, 64% were only hospitalised once and 77% had only one breast cancer-related surgery. Three-quarters of patients lived in a canton with no established mammography screening programme at their time of hospitalisation.

Overall mastectomy rates have decreased from 48% of all surgically treated women in 2000 to 36% in 2012 (Figure 6.1). The rate and trend for mastectomy rates are quite different for the three age groups studied. While rates for women below 50 years of age are more or less stable around 40% –with an apparent slight increase–, rates in the two other groups have decreased. The strongest decrease can be observed in the 70+-year-olds from 61% in 2000 to 43% in 2012. Mastectomy rates in 50-69-year-olds were much lower and decreased at a slower pace, from 43% in 2000 to 30% in 2012.

The rates vary considerably among the cantons. Figure 6.2 visualises the relative differences in the estimated mastectomy rates for all ages combined by 4-year periods compared to the national mean for the period of 2001-2012. In 50-69 and 70+-year-olds a very similar distribution and trend of relative rates is observed, with the exception of the canton Zurich, where a stronger reduction was observed in the 70+-year-olds. The spatial patterns and trends in the less than 50-year-olds are somewhat different from the other age groups (Figure 6.3, Figure 6.4, Figure 6.5).

For the Bayesian regression, the DIC was lowest when all available covariates were included in the model. The regression results are presented as rate ratios (RR) and 95% Bayesian Credible Intervals (CI) in Table 6.2. When taking spatial dependence of the analysis regions, as well as other confounding factors into account, the time trends included in the model did not show significance.

Other statistically important positive effects, increasing the rate of mastectomies, were age above 70 years, co-morbidities, surgeon and gynaecologist density. Significant decreasing effects were the presence of organised mammography screening programmes, treatment in the French language region and age 50-69. The number of surgeries per patient and SEP quartile and insurance type of patients were not significant, but important for model fit in terms of DIC.

Maps with relative differences by age group and periods are presented in section 0 (Figure 6.3, Figure 6.4 and Figure 6.5). I.e. while the overall mastectomy rates stayed high throughout in central Switzerland (UR/OW/NW), in the age group <50 years rates decrease considerably from high to average. Geographical differences in 50-69 and 70+-year-olds are with the exception of Zürich nearly identical.

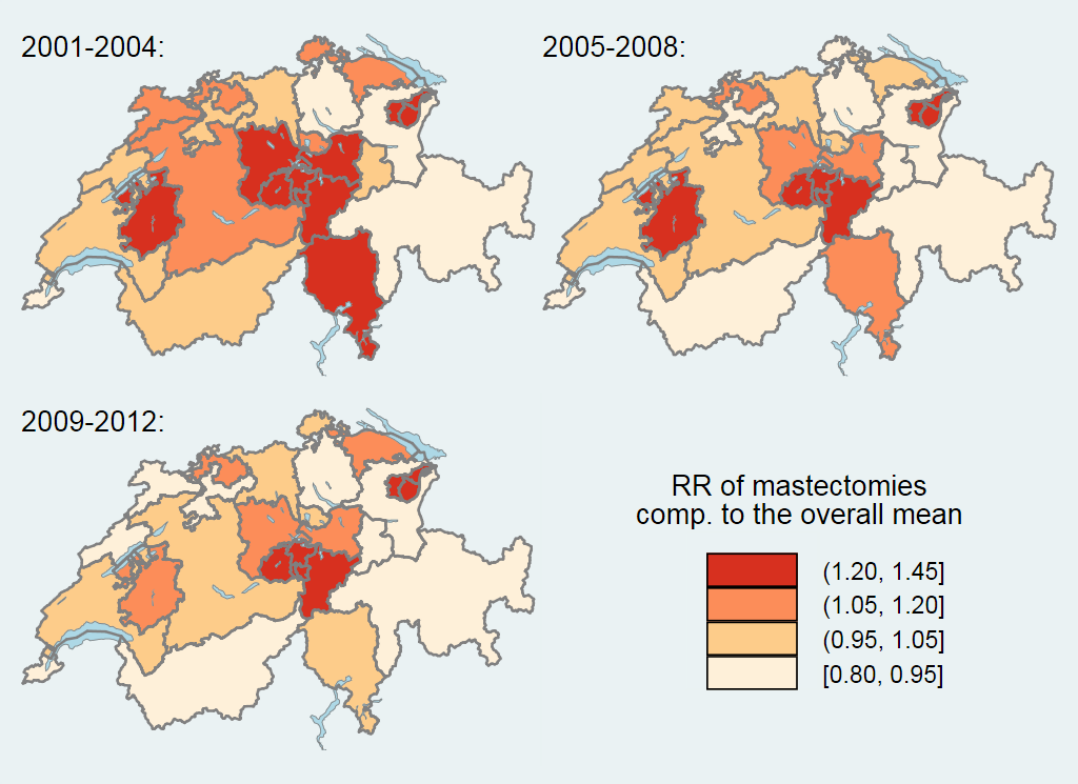

Figure 6.2: Estimates of mastectomy rate ratios in Switzerland by time period in relation to the overall mean.

Table 6.2: Mastectomy rate ratios, multivariate Bayesian regression results including 95% Credible Interval (CI).

Bold values denote significant difference from 1 for covariates. Spatial variation (standard deviation of spatial random effects): a value of 0 means that there is no spatial correlation.

	Median	95% CI interval	
Time (1 year change)	1.008	1.003	1.013
Time:age group interaction			
time:<50 years	1	(reference)	
time:50-69 years	0.995	0.987	1.001
time:70+ years	0.999	0.993	1.005
Age group			
<50 years	1	(reference)	
50-69 years	**0.915**	0.870	0.953
70+ years	**1.254**	1.205	1.290
Co-morbidity score			
0 (only BC)	1	(reference)	
1	**1.171**	1.105	1.250
2+	**1.349**	1.268	1.454
insurance class			
basic	1	(reference)	
half-private/private	0.982	0.951	1.015
multiple admissions	**1.431**	1.033	1.790
multiple BC surgeries	1.231	0.959	1.674
average SEP at patients' residence			
Q1 (lowest quartile)	1	(reference)	
Q2	0.965	0.926	1.011
Q3	0.970	0.930	1.019
Q4 (highest quartile)	0.987	0.950	1.041
Language region of treatment			
German	1	(reference)	
French	**0.719**	0.615	0.815
Italian/Romansh	0.878	0.792	1.013
Hospital region profiles			
Surgeon density per 1000 population	**1.010**	1.002	1.015
Gynaecologist density per 1000 population	**1.058**	1.045	1.063
mammography screening programme exists	**0.868**	0.820	0.949
Spatial variation	**0.3098**	0.3882	0.5353

6.4 Discussion

Our study shows that after taking into account differences in age and case mix (comorbidities), considerable geographical differences persist in the proportion of women that have a mastectomy as the surgical procedure for breast cancer. In most regions the rate of mastectomies declined over time or was already low.

We could also show the importance of taking spatial dependency and other influencing factors into account, rather than limiting the analysis to age groups. We could show that the observed differential trends in the age groups were likely a combined result of trends in all factors. Nevertheless, a significantly higher proportion of 70+ year-olds received mastectomies compared to <50-year-olds, who again had a significantly higher rate of mastectomies than the 50-69-year-olds.

Comparison of results with previous publications

Regional differences in mastectomy rates in 2003-2005 have been previously reported for Switzerland (Ess et al., 2010c). Ess et al. analysed data from 11 cantons covering about half of the Swiss population, with a main focus on patterns of breast cancer care. They described significantly different rates of mastectomies among some study regions. When compared with our results, all participating regions in the above study had lower mastectomy rates in the spectrum of all cantons, with the exception of Appenzell Innerrhoden and Ausserrhoden.

Trends and influence factors of mastectomy rates have been studied for various countries. The rates and observed trends vary greatly among the countries. Most studies also found significant geographical variation within one country. In the United States, mastectomy rates decreased significantly from 40.8% in 2000 to 37% in 2006, based on SEER data (Habermann et al., 2010). The rates are lower compared to the situation in Switzerland, but it should be noted that they excluded patients above 80 years of age. The trends among the age groups are comparable to our findings, as is the range of relative differences among the regions. The lowest mastectomy rates were found in Connecticut, being 27.5% or 0.71-times the total average, and the highest in Louisiana with 50.9% or 1.32-times the average.

In Germany, a significant reduction from 36.5% in 2006 to 30.6% in 2010, also excluding 80+-year-olds, was reported (Heil et al., 2013). Germany started a nationwide breast cancer screening programme in 2005.

In Norway, mastectomy rates halved from 1993 to 2008 for women aged 40-79. In 2000, the mastectomy rate was 62% and thus higher than in Switzerland, but decreased stronger, to 40% in 2008 (Suhrke et al., 2011).

The Netherlands reported an overall 40% mastectomy rate in 2003-2006. Within the subset of patients with T1T2 breast cancers, they found a significant decrease in women aged 40-69 and 70+ and no decrease in <40-year-olds, similar to our results but with slightly different age groups. The regional variation in The Netherlands was significant and had a similar magnitude to our findings, with adjusted odds ratios ranging from 0.7 to 1.49 in <40-year-olds, from 0.65 to 1.45 in 40-69-year-olds, and from 0.65 to 1.85 in 70+-year-olds (van Steenbergen et al., 2010).

Rosato et al. also used hospital discharge records to determine differences in breast cancer surgery in 2000-2004 in the Piedmont region in North-western Italy (Rosato et al., 2009). 33.5% of the patients received a mastectomy. Rosato et al. described a significant decrease in mastectomy rates (OR 0.70) for the observed period.

No time trend was observed in mastectomy rates in Alberta, Canada, in 2002-2010 (Fisher et al., 2015). The overall rate was 56% and ranged from 52% in Calgary to 72% in Central Alberta. Rates were significantly higher for patients aged 70-79 and 80+.

Also no change in BCS rates and hence mastectomy rates were found in a nationwide study in France, with rates being 27% in 2005 and 26% in 2012 (Rococo et al., 2016).

Influence of covariates

More mastectomies were performed if a canton had more surgeons or gynaecologists per 1'000 population. This could have several reasons. On the one hand, those variables may have acted as a proxy for hidden variables not available to this study, such as urbanisation or hospital type profiles. The density was also declining over the period capturing some of the time trends in mastectomy rates. Direct reasons for influence may include that women choose mastectomies more easily if immediate breast reconstruction is available

(McLaughlin, 2013), i.e. with a higher concentration of plastic surgeons. Also, lower case-volumes have been previously linked to higher mastectomy rates (Hawley et al., 2006, Katz et al., 2005). But if any of this played a role in the results in relation to surgeon or gynaecologist density could not be established by this study since this type of data was not available.

Mastectomy rates in the French language region were generally significantly lower. This is the language region where mammography screening programmes started the earliest. However, we included the existence of population-based mammography screening programmes in our model and showed an additional significantly reduced rate of mastectomies of about 13%. In 2001 three cantons had established screening programmes. Until 2012 10 cantons had screening programmes for more than 10 years and 3 for at least 5 years. Screening programmes lead to a downshift in stage distribution in the respective cantons (Bulliard et al., 2016, Bulliard et al., 2011). And Ess et al. showed a significantly lower rate of mastectomies in Switzerland for breast cancer patients with lower stages (Ess et al., 2010c).

Patients with a higher number of comorbidities had a significantly elevated mastectomy rate. This is in line with prior expectations. Patients with a higher number of co-morbidities and more severe health condition tend to receive mastectomies in order to avoid further deteriorating effects of otherwise necessary adjuvant therapies such as chemotherapy and radiation.

We could show that patients were treated similarly in terms of mastectomies regardless of socio-economic groups or insurance type. These variables remained in the final model since they increased model fit.

We corrected for multiple admissions and multiple breast surgeries per patient. Both factors are strongly overlapping. More admissions/ surgeries per patient would suggest that these patients underwent re-excisions and/or mastectomies after a BCS with an insufficient result. More than three-quarters of patients in our study received only one surgery and the variation in this rate was small. However, the inclusion of and correction for both characteristics lead to a significantly better model fit. Due to the data structure, we deemed this approach superior to excluding patients with mastectomies after BCS.

While the results were expected in terms of co-morbidities and screening, the other significant covariates indicate possible starting points for reducing geographical disparities. It should be kept in mind that further confounding variables possibly exist, which were or could not be included in the model.

However, after correction especially for co-morbidities, it is surprising that 70+-year-olds have more mastectomies than 50-69-year-olds. The significantly higher rates in elderly patients are not observed at a similar magnitude in other countries. Cultural and personal factors may have played a greater role in this age group, but the magnitude is a reason for concern and would need more detailed research. In general, it is important to note that rates above or below average rates are not the same as "too high" or "too low" since this study is of an ecological design. The decision to undergo mastectomy or BCS is ideally done on an individual level by a well-informed patient and is based on medical reasons and personal preferences. Both types of surgery have their advantages and disadvantages, but analysing the differences in rates and trends may help to gain a clearer insight into the decision-making process in the surgical treatment of breast cancer.

No overall decline in mastectomy rates in the age group of <50-year-olds was observed. This might be due to a higher proportion of hereditary forms of breast cancer where radical mastectomies of both breasts are combined curative and preventive measures (Graeser et al., 2009, Rebbeck et al., 2004). However, mastectomy is not universally used for treating hereditary forms of breast cancer and might change over time with reviewed evidence (Paradiso and Formenti, 2011).

Strengths and limitations

One major limitation of the study is that the hospital data did neither include information on the stage of the breast cancer nor intent of treatment (palliative or curative). Also, we could not distinguish breast cancer by laterality since this information has benn included in the dataset only recently and is thus missing for most of the years. In order to reduce a possible bias due to preventive contralateral mastectomy, we only counted one mastectomy per woman.

A second major limitation is that no detailed information about the hospital was available. All hospitals in a canton were pooled in the available dataset, making it impossible to distinguish them from another. Therefore, we had no information about the type of hospital (university, central, rural, private etc.). While this information could be used with the other variant of the hospital database, excluding geographical information, information on total hospital volume and the number of breast cancer patients treated would only be available in the combined dataset. In other countries, both type and hospital volume were described as significant factors for mastectomy rates, i.e. in Italy (Rosato et al., 2009), Finland (Peltoniemi et al., 2011), the USA (Hiotis et al., 2005) and Germany (Heil et al., 2013).

The surgeon density was only available for the profession as a whole and not by area of expertise or case-load. Therefore, the results and possible implications need further research. Urbanisation could not be used since the hospital data was only available on a cantonal level.

The advantage of the current study is the population-based nature of the database, resulting in a large representative sample of more than 70‘000 patients included in our study. The results mirror the real-world situation in Switzerland. Bayesian regression models have not been employed to date to explore differences in cancer management. To our knowledge, this is the first study that utilises the Swiss Hospital database to explore space-time patterns of care in oncology research.

6.5 Conclusion

This is the first time that the wealth of information of the national hospital discharge database has been used to analyse geographical differences in breast cancer care, in particular mastectomies. Mastectomy rates have importantly declined in Switzerland in the period of 2000-2012 for patients aged 50-69 and 70+ and have remained stable for those under 50. Rates were highest for 70+-year olds and lowest for those aged 50-69. Regional differences in mastectomy rates are as pronounced in Switzerland as in other countries.

We showed the importance to take spatial dependence and other influencing factors into account when comparing mastectomy rates among age groups and geographical areas.

Patients from different socio-economic groups or with different insurance type did not receive a different treatment with regard to mastectomies. Rates were significantly influenced by differences in co-morbidity. Regions with a higher surgeon and gynaecologist density had higher rates of mastectomies and regions with mammography screening programmes had lower rates. This research has unveiled important information which had not been available for the whole country to date. Further research is needed to understand the combined role of region specific and hospital-specific factors, such as hospital type and hospital volume, in terms of breast cancer care differences.

6.6 Annex

6.6.1 Canton abbreviations

Zurich (ZH), Bern (BE), Lucerne (LU), Uri (UR), Schwyz (SZ), Obwalden (OW), Nidwalden (NW), Glarus (GL), Zug (ZG), Fribourg (FR), Solothurn (SO), Basel-Stadt (BS), Basel-Landschaft (BL), Schaffhausen (SH), Appenzell Ausserrhoden (AR), Appenzell Innerrhoden (AI), St. Gallen (SG), Graubünden (GR), Aargau (AG), Thurgau (TG), Ticino (TI), Vaud (VD), Valais (VS), Neuchâtel (NE), Geneva (GE), Jura (JU).

6.6.2 Maps by age group

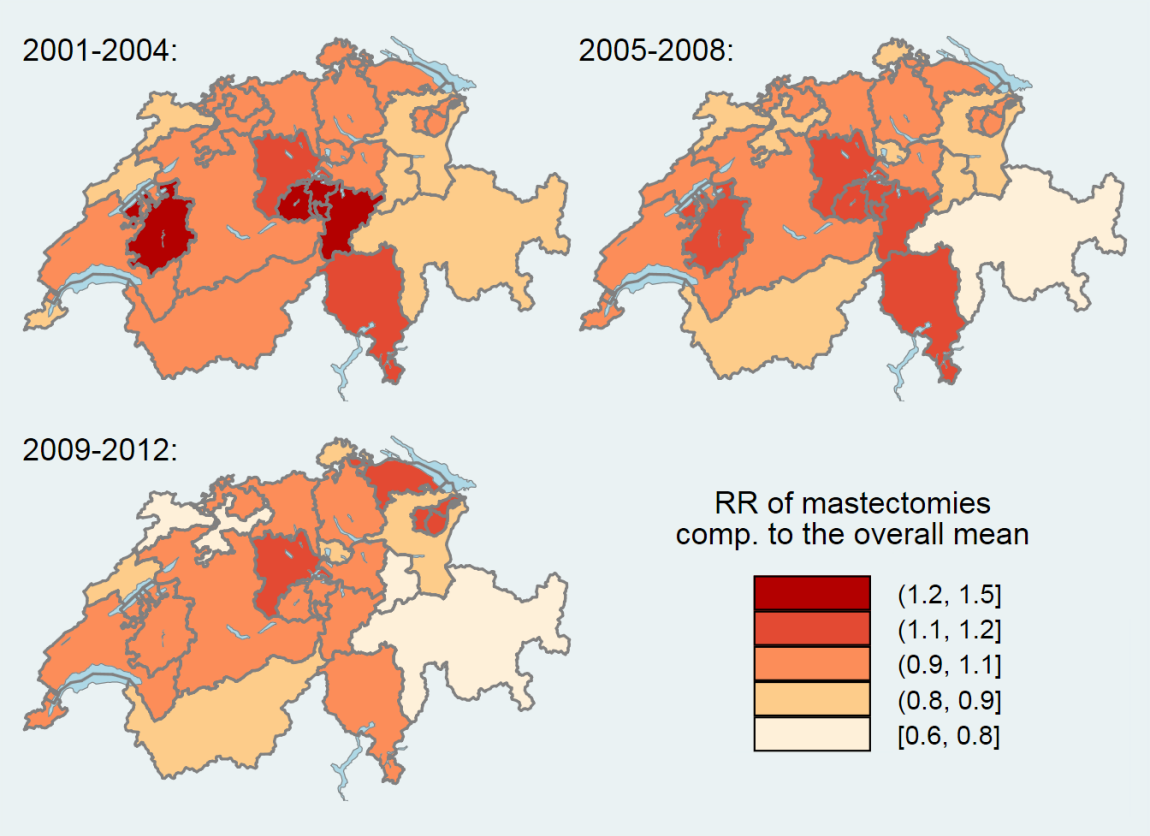

Figure 6.3: Estimates of mastectomy rate ratios for <50-year-olds in Switzerland by time period in relation to the overall mean.

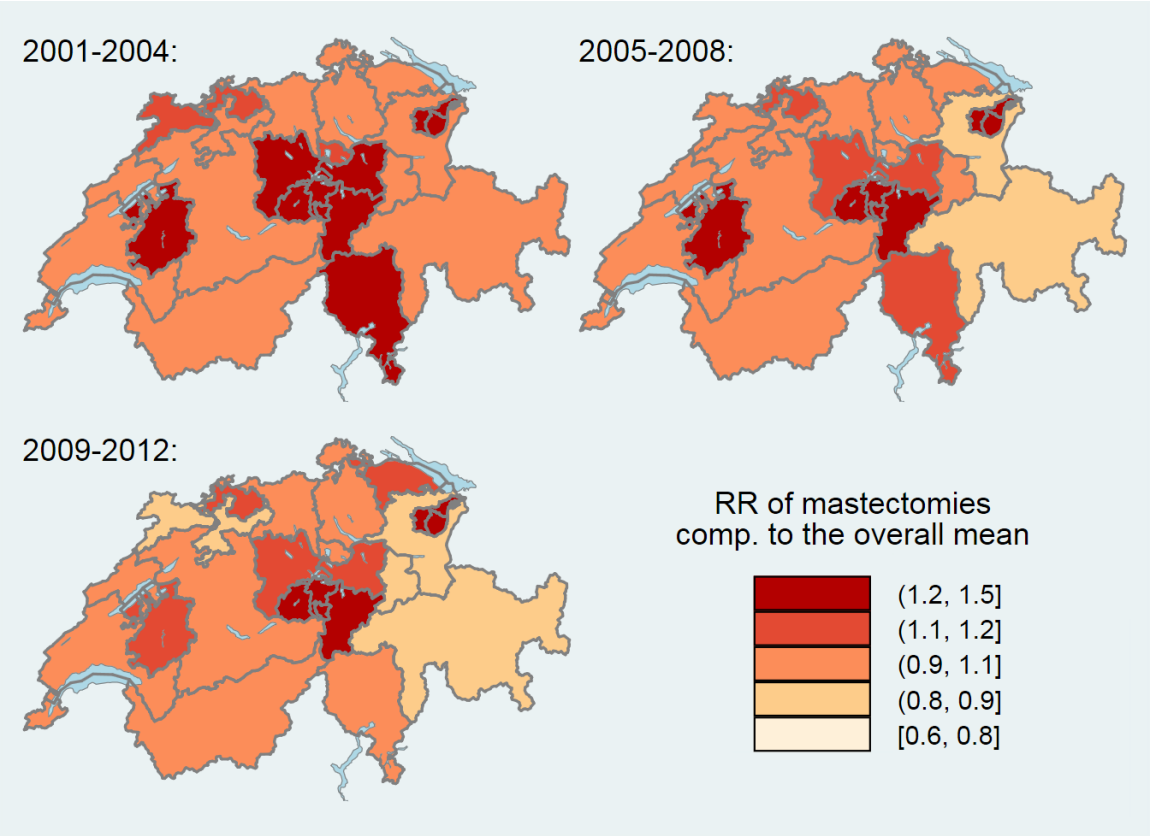

Figure 6.4: Estimates of mastectomy rate ratios for 50-69-year-olds in Switzerland by time period in relation to the overall mean.

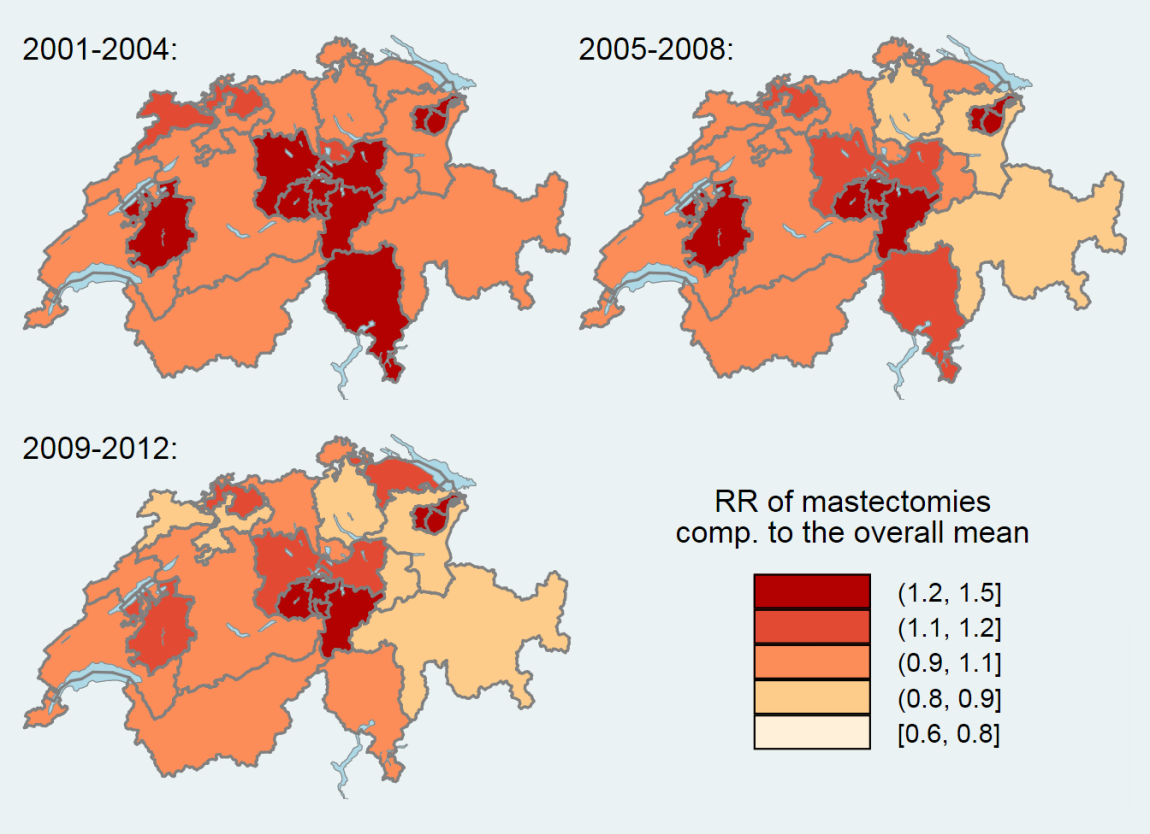

Figure 6.5: Estimates of mastectomy rate ratios for 70+-year-olds in Switzerland by time period in relation to the overall mean.

6.6.3 Hospital types in Switzerland by canton

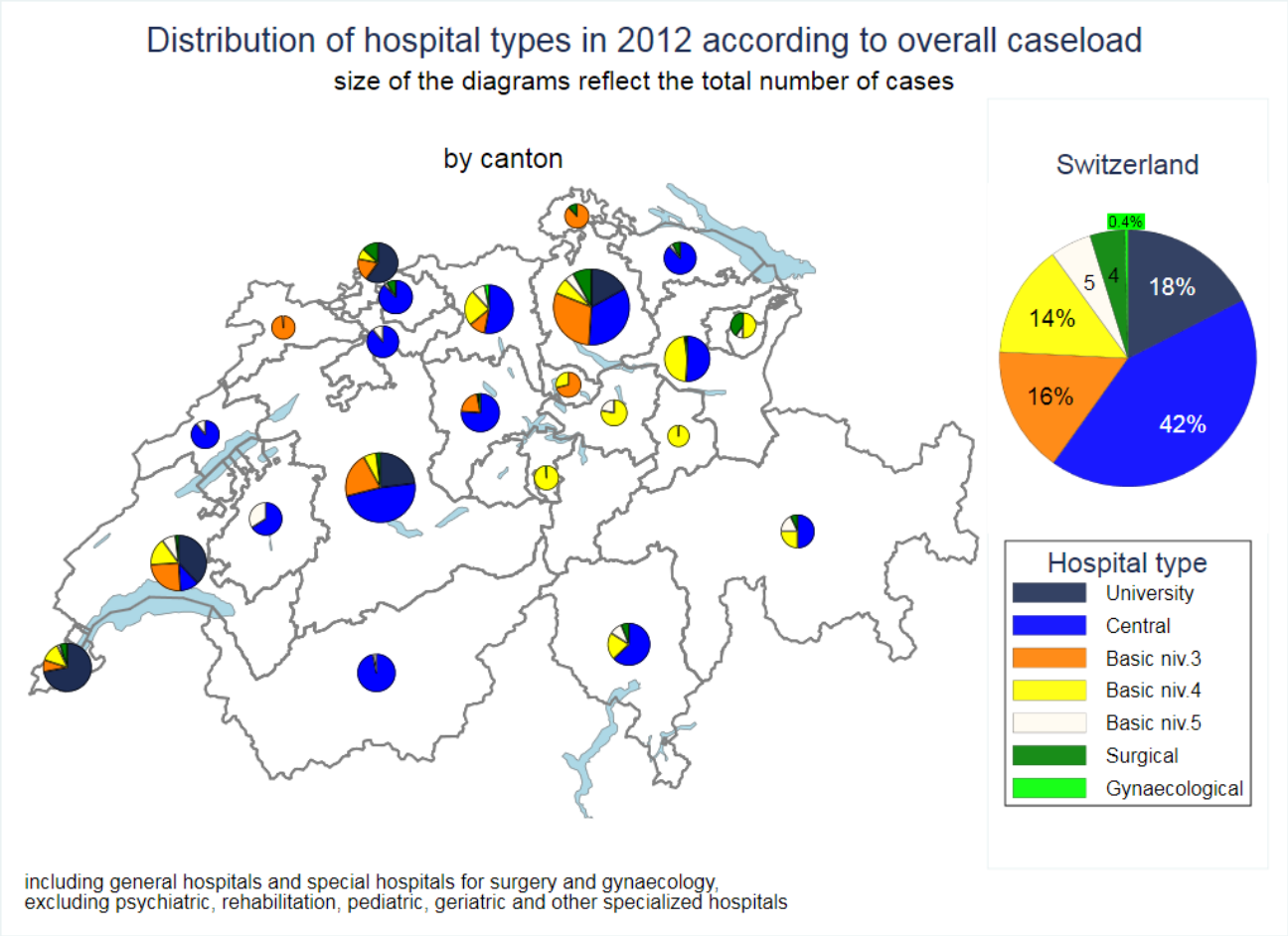

Figure 6.6: Hospital types in 2012 in Switzerland according to overall caseload.

Chapter 7

Discussion

This PhD thesis contributes to the field of female gender-related cancers with statistical methodology and epidemiological knowledge on spatio-temporal patterns and future developments of cancer mortality, treatment procedures, and cancer survivorship.
The applied methods and results are presented and discussed in the manuscripts included as chapters in this thesis. Each chapter provides a detailed discussion while this section gives an overview of the main findings, the limitations and impact of the studies, and potential future research needed.

7.1 Significance

The results of this thesis are particularly important for public health policy in Switzerland and in terms of advancing epidemiology for prevention and care. This research has an impact on modelling approaches of cancer data. The significance of this thesis is presented under respective subheadings below. Our research on survivorship proved of high importance and is addressed in a separate subheading.

7.1.1 Survivorship

Cancer prevalence or survivorship is an indicator of the overall cancer burden for the society and the health system in Switzerland. Using the definition of being a cancer survivor after a cancer diagnosis at any time, cancer survivors comprise of a heterogeneous group with complex health problems. Cancer also affects the life of colleagues, friends and family members, also called extended survivors, therefore the societal burden of cancer is even bigger than measured by the number of cancer survivors or complete prevalence.
For most countries, only 1-, 3- and 5-year prevalences are reported (Ferlay et al., 2013b). Also, data concerning the total number and growing dynamics of the group of cancer survivors were not available in Switzerland. This thesis contributed to filling this gap by estimating the number of cancer survivors by gender, time since diagnosis, cancer type and age group. This was done by applying back-calculation methods on nationwide mortality data and relative survival data from Swiss cancer registries and estimating trends (Chapter 2).
The analysis showed that there is a rapidly growing population of cancer survivors in Switzerland whose needs and concerns are largely unknown. The number of breast cancer survivors more than doubled from 1990 to 2010 and is projected to increase by another 28%

from 2010 to 2020. Overall, the number of cancer survivors increased from 2.08% of the population in 1990 to 3.7% in 2010, with the current annual growth rate being 3.3% per year.

Our study showed the paramount importance to care for this rapidly growing population, and provoked manifold actions. Cancer survivorship was put on the national agenda via the national strategy against cancer (Kramis et al., 2013) and several cancer leagues beginning with Eastern Switzerland (Krebsliga Ostschweiz, 2017) and the national league (Krebsliga Schweiz, 2017b) started a variety of measures shortly after publication of the results, such as counselling and rehabilitation of cancer survivors. Also, results were promoted in the research community by highlighting the publication in the national science report (Ess and Herrmann, 2014) and by bringing the issue to the general public on national television (Tobler, 2017).

Furthermore, the issue was taken up by the National Institute for Cancer Epidemiology and Registration (NICER), which is pooling data from the Swiss cancer registries, publishing a series of articles in a special issue of the "Schweizer Krebsbulletin"(Cavalli and Lerch, 2016). Based on our research it is advisable to continue this kind of monitoring of complete prevalence on a regular basis.

Experience from other countries shows how bringing awareness to cancer survivorship can lead to policy change. In Switzerland, a first step was done by putting survivorship on the national agenda. In Italy, patient advocacy groups (i.e. Italian Association for cancer patients, relatives and friends (AIMAC)) were driving policy changes due to increased knowledge and an awareness of their political power. In Italy, there are more than 3 million cancer survivors. After a survey by the Italian Federation of Volunteer-based Cancer Organizations (FAVO) in 2003, several legislative measures were taken into effect by an alliance of FAVO, AIMAC, scientific and oncological societies, cancer institutes and Ministries of Health, Welfare and others. New and changed laws included the reduction of the time to disability recognition (2006, 2009), innovative drugs being immediately made available all over the country, after previous delay for various regions (2012, 2013), giving employees with cancer the right to switch from full-time to part-time positions during treatment, and to reverse to full-time according to their needs and capabilities (2003, 2007) (Ianelli, 2016).

Switzerland might very well benefit from these experiences since the foundation of bringing awareness to public and health professionals has now been laid. Policy makers and healthcare professionals as well as laypersons may also profit from other European efforts such as the work package 8 (recommendations for high-quality survivorship care and rehabilitation) within the project "European Guide on Quality Improvement in Comprehensive Cancer Control" (CanCon) co-funded by the EU Health Programme (Albreht et al., 2017). The European society of medical oncology (ESMO) and the European cancer patient coalition (ECPC) have developed survivorship guidelines, including for family and friends, and an interactive guideline app (European Society for Medical Oncology et al., 2017).

7.1.2 Public Health

Several results of this thesis have an impact on public health and public health planning. The impact of our findings in relation to survivorship on public health is discussed in section 7.1.1.

The projections of breast cancer mortality numbers provide valuable and necessary information for public health authorities concerning the planning of future demands and resource allocation for diagnosis and treatment. Even more so, as our research shows that the pace is regionally quite different. In more than half of the cantons, the number of breast cancer deaths is projected to increase with the demographic forecast playing a major role. This information had not been available in Switzerland so far. Projections of cancer mortality provide an estimate of the future burden of cancer and are important to assess the impact of novel approaches and future developments in breast cancer care, as well as in terms of public health interventions.

The assessment of the geographical variation of hospital-based case management in the country and its relation with the disease mortality helps to identify regions in which special attention is required to reduce healthcare inequalities and their impact on community health. In previous research important data on patterns of care using a regional subset of cases (Ess et al., 2010c) have been described, but the entire situation in Switzerland has become clear only now. The differences in mastectomy rates are pronounced, significantly influenced by age, co-morbidities, surgeon density, mammography screening programmes, and insurance

class. The understanding of influencing factors on mastectomy rates gives an important starting point on how to tackle the differences in breast cancer care and guideline adherence.
Differences in the decrease and in spatial patterns of female gender-related cancer mortality within Switzerland have been reported according to urbanisation and language region and remained controversial. Using modern Bayesian small area modelling and mapping techniques, it was possible to show that all investigated groups of women in Switzerland have benefited from progress in cancer control, regardless of place of residence in the past 40 years. In particular, the used methodology is very well suited to deal with small numbers, which allowed for the usage of smaller geographical units as otherwise possible and previously done. We could show that only small differences in the geographical variation of mortality were present and that no general significant association with cantonal or language region borders could be observed.
In Switzerland, mammography programmes have existed in some regions for more than 20 years, while they do not yet exist in others. This offered the possibility to analyse effects of these programmes with a modern spatio-temporal methodology. We could show that duration of a population-based screening programme and socioeconomic characteristics have no significant influence on breast cancer mortality on the population level as well as the other factors studied (urbanisation, language) and have been outweighed by important advances in treatment approaches.

7.1.3 Spatio-temporal modelling of cancer data

This research contributed with statistical methods to studying spatio-temporal patterns and projections of cancer mortality driven by data availability and characteristics in Switzerland that were applied and validated on real datasets. The applications contributed with (i) smoothed maps of age-specific patterns of breast, cervical, corpus uteri and ovarian cancer mortality over time, (ii) a better insight into the differences in cancer mortality rates between linguistic regions, urbanisation, affluence and cancer management procedures, (iii) estimates of the geographical patterns of breast cancer mortality for the next 10 years.
This is the first time that rigorous analytical methods have been applied and further developed on female gender cancer data collected from cancer registries and the FSO in order

to quantify the burden of mortality in Switzerland, its future trends and to investigate the geographical patterns of case management procedures in the country.

The smoothed maps of cancer mortality rates in Switzerland will assist in identifying areas with high cancer rates and discrepancies of disease burden among areas. These maps increase awareness for routine screening and can help health authorities in planning and evaluating cancer control activities. In fact, the success of future control programmes (e.g. organised mammography screening for breast cancer) can be evaluated only when baseline estimates of the geographical patterns of the disease are available to be compared with those after the implementation of the control programme.

Finally, the experience gained and the models developed will be very useful and directly applicable to similar studies in Switzerland aiming to quantify the burden of overall and site-specific cancer morbidity and mortality by linking and fully exploring the data routinely collected from the cancer registries and the FSO.

7.2 Limitations

Strengths and limitations are discussed in detail in the manuscripts included as chapters of this thesis. This section deals with major and overall limitations to the research topic.

7.2.1 Screening

One particular problem in disentangling the effects of screening on mortality with the effects of improved therapies, early detection, and breast cancer awareness is the use of voluntary screening options outside of quality assured programmes. In Switzerland, a high use of voluntary screening was described (Chamot et al., 2007); however, detailed data on its use is not available to date. The Federal Statistical Office (FSO) collects data on the ever use of mammography screening by its health survey (Lieberherr et al., 2010), but not concerning the type or time frame. The survey cannot answer the question on the regular attendance or attendance rate by type of screening. Data on participation in screening within or outside a population-based programme was assessed for selected years and regions within a few studies (Chamot et al., 2007). However, comprehensive data on voluntary screening use

would only be available from the high number of Swiss health insurance companies. Hence no information on voluntary screening could be included in the models. If this data had been available additional research questions might have been answered.

Data on participation in population-based screening programmes, on the other hand, are published in a national monitoring report and rates are nearly identical across the programmes (Bulliard et al., 2016).

Another issue was that nearly exclusively cantons in the French-speaking language region started population based screening sufficiently long ago (de Koning and Heijnsdijk, 2015). The analyses with regard to screening should be reassessed in the next years when the screening programmes in Eastern Switzerland will have had sufficient running time.

7.2.2 Intercensal population

The analysis of cancer mortality at municipality level has been done for the four years around the censuses. We did not consider mortality for the intercensal years, as population data were only provided for the census years. By assuming no big changes in the size of the population occurred for the years close to the census, and in order to increase power, we pooled those years. As Switzerland is separated into nearly 2'700 municipalities, this resulted in many zero counts in municipalities characterised by the subgroups. Therefore, a simple linear interpolation between two censuses was inappropriate, as several factors should be taken into consideration to achieve realistic estimates. For example, migration plays an important role in the estimation of population development and differs depending on the location. Since 2010, the FSO has provided own intercensal population estimates. As soon as estimates on the previous intercensal years are available, an analysis with a continuous time variable will be possible.

7.2.3 Survival data and registration coverage

For the calculation of prevalence, we assumed that the pooled survival information from the participating cancer registries will reflect the national survival after cancer diagnosis. It should be noted that information on stage distribution and survival estimates were not

available for regions without registration coverage. Registration coverage in Switzerland is shown in Figure 7.1. Furthermore, only registries with high-quality data and registration since 1990 (for details see Chapter 2) were included for the estimation of the nationwide survival. These four registries (GE, VS, SG+AI+AI, GL+GL) cover about 26% of the population. The choice of registries and the used methodology minimises the deviation from the true situation. The four registries cover rural alpine and urban areas in the main language regions and include cantons with and without breast cancer screening programmes. The model parameters were chosen by minimizing squared differences of modelled rates with observed national mortality rates, thus maximizing the representativeness of the available data. In a few other countries, survival and complete prevalence estimates are also based on partial registration coverage (Parry et al., 2011).

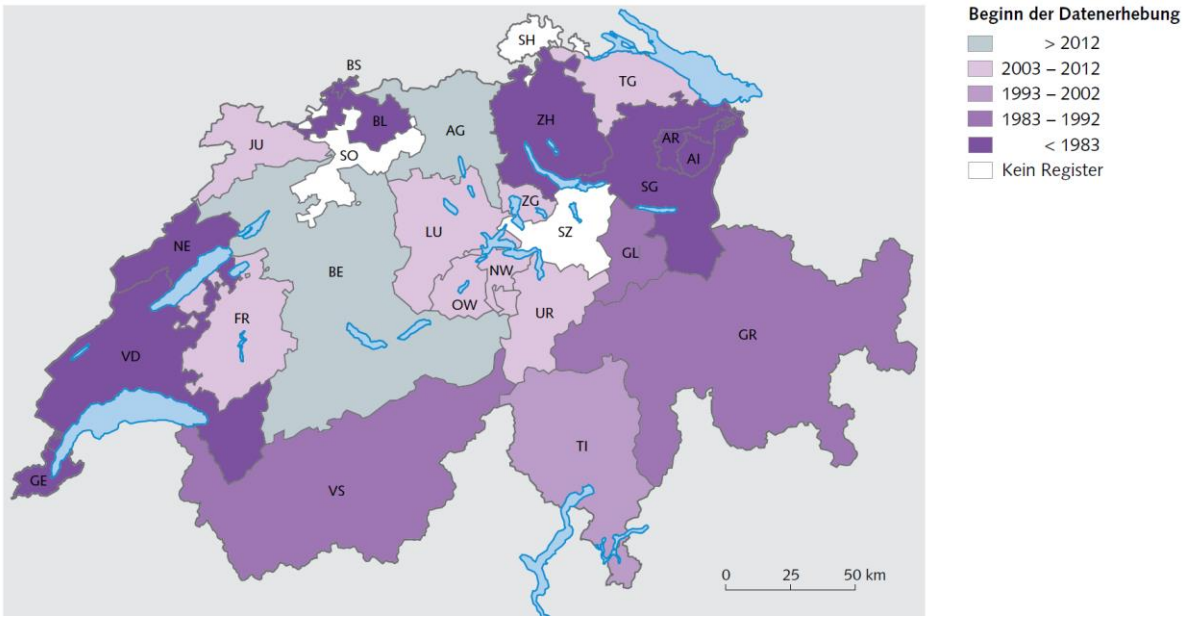

Figure 7.1: Cantons with cancer registration in 2015. Sources: NICER, BFS, ThemaKart, 2016
Colours are based on the different commencements of registration, white denotes “no registration”.

However, with the available data, some uncertainty remains about the results. Moreover, more detailed investigation of spatio-temporal patterns of prevalence and incidence were not possible. In a recent development, a new national law was adopted in Switzerland making cancer registration mandatory and aiming at harmonisation of registration according to international standards (Heusser et al., 2017). Future studies may benefit from more complete and homogeneous data.

7.3 Extension of the work

Apart from a few studies (Bouchardy et al., 2007, Levi and La Vecchia, 2007, Verkooijen et al., 2008), little is known about regional differences in incidence trends and associated risk factors in Switzerland. For a complete burden estimation in Switzerland, this data is needed. The cancer registries in Switzerland which compile incidence data have only covered about 80% of the population since 2012. Thus, estimating spatio-temporal patterns of incidence at high spatial resolution is not straightforward. Mortality/incidence ratios (Colonna et al., 1999) have been used to estimate incidence from mortality data for countries lacking nationwide coverage of cancer registries. However, this approach assumes that there is no regional variation in patients' survival. Back-calculation is an alternative method for estimating incidence from mortality data, taking into account the survival probability among those with cancer (Verdecchia et al., 1989, Capocaccia et al., 1990, Grande et al., 2006, Mezzetti and Robertson, 1999). These models are sensitive to the chosen survival distribution. To our knowledge, these models have not been validated and adapted for Switzerland. In addition, Bayesian hierarchical spatio-temporal models have neither been employed to analyse Swiss cancer registry and mortality data nor to explore differences in cancer management to this date.

Furthermore, models developed for other cancers with high lethality (Mezzetti and Robertson, 1999) are not appropriate for cancer types with a significant curable proportion, i.e. the cause of death being different from cancer, such as for breast cancer.

Therefore, further important extension of the work will be the development of appropriate models for the estimation of gender cancer survival in areas without registration coverage,

taking into account cure proportions. This will allow the extension of this work to analysing geo-spatial differences in female gender cancer incidence.

Additionally, this work can be applied to other cancer types and chronic diseases in Switzerland.

The lack of intercensal population can be overcome by the development of Bayesian migration models to allow for an estimation of the number of men and women in each age group and municipality. These models will take into account migration patterns and demographic developments.

Progress in cancer management has led to a strong increase in survival after breast cancer diagnosis, coinciding in time with the decrease in mortality. Several other time-dependent factors influence the occurrence of breast cancer deaths, and breast cancer incidence is still increasing. However, an in depth-analysis about the significance of these effects had been out of the scope of this thesis.

An important endpoint for screening is mortality reduction. While the impact of mammography screening programmes on mortality on a population level needs to be re-evaluated in the next decade, another important end point is quality of life and quality adjusted life years (QALYs) as impacted by screening. One particular question is how negative factors of screening on QALYs –such as increased distress after positive mammograms, living longer with a cancer diagnosis and overdiagnosis– balance out with positive factors, such as peace of mind, extended lifespan, diagnosis at lower stages and hence less aggressive treatments.

Important information would be detailed screening patterns of women, including opportunistic screening, either by a better-suited questionnaire than currently used or in collaboration with health insurance providers.

After bringing awareness to cancer survivors in Switzerland, it is now important to classify the needs of cancer survivors by survivorship research and also determine the measures with the highest positive impact for them.

Some important follow-up questions arose from the research on cancer care. For example, more research is needed to understand the underlying factors of surgeon density and insurance class on mastectomy rates. Also, concerning the regions with unchanged high

mastectomy rates, a more detailed analysis using registry data will help to identify possible areas of improvement. Given ethical approval, using the full hospital discharge dataset will help to understand the combined role of region-specific and hospital-specific factors on breast cancer care differences.

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Peer-reviewed scientific publications as a co-author:

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Book contributions

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Excluded: peer reviewed publications as part of a working group (37 publications), presentations at conferences (12), scientific reports (26).