Trends in Lung Cancer Survival in Switzerland

Andrea Bordoni, Matthias Lorez, Christine Bouchardy, Bertrand Camey, Daniel Betticher, Silvia Dehler, Oliver Gautschi, Isabelle Konzelmann, Kerri Clough-Gorr and the NICER Working Group§

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Introduction

Lung cancer is one of the most common cancers in the world, making up 17.1% of all cancers in men and 6.7% in women.[1] In Switzerland, approximately 2,500 and 1,200 new cases are diagnosed each year representing the second and the third most frequent tumour in men and women, respectively.[2] Worldwide over the past century a rapid increase in lung cancer incidence related to tobacco use has been observed. Smokers are estimated to be at a ten-fold increased risk of developing lung cancer relative to non-smokers. In fact, lung cancer trends reflect closely the patterns of tobacco use in a population. The increase in lung cancer incidence started earlier in men than in women because men started smoking in large numbers much earlier in the 1900's than women. In most developed countries, incidence and mortality rates in recent years have decreased in men but not in women.[3, 4] For example in the United States, lung cancer mortality rates in women are now higher than breast cancer mortality rates.[5] Furthermore, according to the literature non-smokers account for about 15% of lung cancer patients. Non-smoker cases are often attributed to a combination of genetic factors, occupational and environmental exposures (e.g. radon gas, asbestos, air pollution, second hand smoke).[6]

There are differences in type of lung cancer by gender. Adenocarcinoma (AC) has remained the most prevalent tumour among women over the past three decades, with incidence rates increasing slowly over time in many countries including Switzerland.[7] In contrast, squamous cell carcinoma (SqCC) has historically been the predominant tumour type in men. Incidence of SqCC in men has declined over time and is now similar to that in women, which had remained fairly stable overtime. This gender-specific pattern in type of lung cancer hypothesised to be related to changes in the composition of tobacco products and smoking behaviours (e.g. filters engendering deeper longer inhalation to maintain high levels of nicotine), as well as diagnostic procedures.

Similar to other cancer types, lung cancer prognosis depends on the extent of disease at the time of diagnosis. Lung cancer is one of the most difficult cancers to cure and is often diagnosed at a late stage. Because of these factors, lung cancer has one of the lowest survival and highest mortality rates worldwide. Lung cancer relative survival in Switzerland has been previously reported to be among the highest in Europe according to EUROCARE, a population-based study of cancer survival in European countries.[8]

One of the main objectives of Swiss cancer registries is to provide careful surveillance of trends in cancer survival in order to have comprehensive data for cancer control.

Figure 1: Relative survival curves (crude estimates) with 95% confidence intervals by gender in two calendar periods 1995-1999 and 2005-2009. Male and female lung cancer cases were pooled from eight Swiss cancer registries.

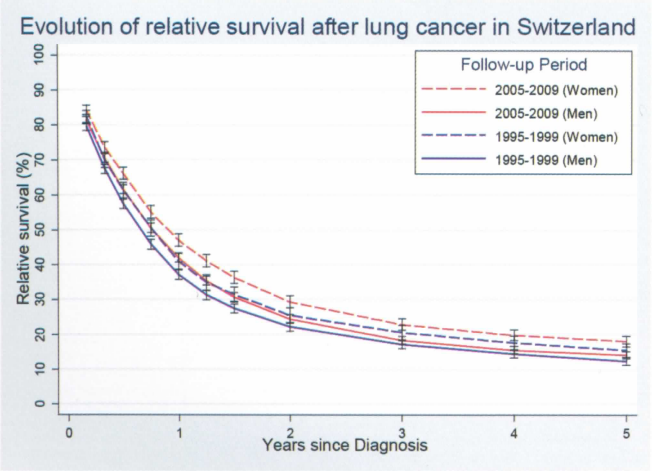
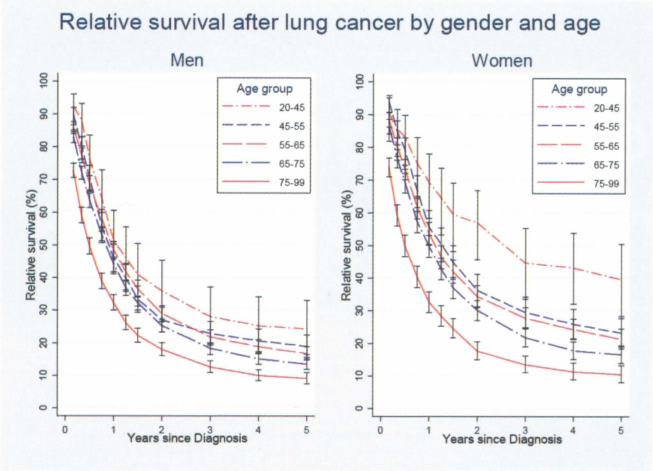


Figure 2: Age- and gender-specific lung cancer relative survival curves with 95% confidence intervals for the calendar period of follow-up 2005-2009. Cases were pooled from eight Swiss cancer registries.



The aim of the present study was to analyse relative and observed one-, three- and five-year survival of patients diagnosed with a lung cancer between 1980 and 2009 in Switzerland.

Methods

Data on lung cancer cases were extracted from the anonymised national cancer dataset managed by the Foundation National Institute for Cancer Epidemiology and Registration (NICER). Eight Swiss cancer registries contributed data to this study representing cantons Basel City and Basel Land (BS/BL), Fribourg (FR), Geneva (GE), Grison and Glarus (GR/GL), St. Gallen, Appenzell Ausserrhoden and Appenzell Innerrhoden (SG/AR/AI), Ticino (TI), Valais (VS) and Zurich (ZH). Registries recorded all incident cancer cases diagnosed in their resident population and assessed cases' survival through 31 December 2009. In four registries (BS/BL 2%, GR/GL 3%, VS 2%, ZH 6%) a small proportion of living cases had a last available follow-up date before 31 December 2009. The life-status of these cases was changed to lost to follow-up. The incidence date refers to the date of confirmation of diagnosis or the date of hospitalization if it preceded the diagnosis and was related to the lung cancer. Completeness of case ascertainment for lung cancer has been determined in GE, GR/GL, SG/AR/AI, TI and VS and found to be higher than the international standard of at least 90% within two years after the date of diagnosis.[9] We selected cases with primary malignant lung cancer (C33.9 to C34.9 in ICD-O, 3rd edition),[10] aged 20-99 years and diagnosed 1980-2009. For BS/BL the diagnosis period was 1980-2008. All morphologies were included. Lung cancer cases were retained even if preceded by a primary cancer with different topography.[11] We excluded all cases diagnosed at death (N=708, 2% of all cases).

Observed (OS) and relative survival (RS) probabilities were derived for consecutive time intervals after diagnosis during which the hazards were assumed to remain constant. Since the hazards are known to decrease more steeply in the first year after diagnosis, we assessed survival probabilities in intervals with increasing length (at 2, 4, 6, 9, 12, 15, 18, 24, 36, 48 and 60 month after diagnosis). RS was calculated as the ratio of the observed probability of survival of cancer cases and the expected survival of persons in the general population of corresponding age, sex, calendar year of death, and canton (i.e. estimation of mortality due to lung cancer by accounting for competing risk of death).[12, 13] Expected cancer survival proportions were estimated using Hakulinen's method applied to all-cause mortality tables supplied by the Swiss Federal Statistical Office.[14] Because it is well known that smoking is related to lung cancer and more prevalent among lung cancer cases, the expected survival is likely to be too high. However, this bias has negligible impact on RS estimates.[15] Probabilities, transformed from age-, sex-, calendar year- and canton-specific death rates, were interpolated and smoothed using the Elandt-Johnson formula.[16] RS ratios were estimated using the strs command (version 1.3.7)[17] written for the Stata Statistical Software.[18] Period analysis was used to derive more up-to-date relative survival estimates compared to those possible from traditional cohort analysis.[19] In brief, period analysis describes the survival experience of cases selected by a period of follow-up dates. This is achieved by left truncation of person-times at risk at the beginning of the specified follow-up period in addition to right censoring at its end. For OS and crude RS, 95% confidence intervals (95%CI) were estimated by applying the delta method to a transformation of the cumulative hazard and for age-standardized RS as described in Corazziari et al. (2004).[20, 21] In addition to crude (non-standardized) estimates, RS estimates were age-standardized using weigths specific for lung cancer from the International Cancer Survival Standards (ICCS).[21] Age groups with (standard weights) were: 20-45 (0.07), 45-55 (0.12), 55-65 (0.23), 65-75 (0.29) and 75-99 (0.29). Age-standardization affected the crude estimates (i.e. all ages combined) only slightly (less than 2%). To test for linear time trends of one- and five-year RS in gender-specific strata, piecewise Poisson regression models for the logarithm of excess number of deaths were fitted as linear functions of the logarithm of person-time, follow-up time (categorical variable), age (categorical variable) and calendar period of follow-up (numeric variable). The p-value for inclusion of calendar period as explanatory variable , based on the Wald test, indicated the significance of a linear trend. Average annual percentage change (AAPC) was estimated as $AAPC = 100((RS_{lastyear} - RS_{firstyear})/RS_{firstyear})\,\Delta t^{-1}$.

Table 1. Contribution of lung cancer cases to the pooled dataset by eight Swiss cancer registries (CR).

CR regional coverage*	Diagnosis period	Number of Patients		Person-years	% of pooled person-years
		Men	Women		
GE	1980-2009	4291	1852	11481.3	18.1
SG/AR/AI	1980-2009	4553	1334	8579.6	13.6
ZH	1980-2009	11495	4320	21417.0	33.8
BS/BL	1981-2008	4556	1721	10258.0	16.2
GR/GL	1989-2009	1625	518	2737.6	4.3
VS	1989-2009	2022	760	4412.3	7.0
TI	1996-2009	1765	776	3887.1	6.1
FR	2006-2009	352	172	515.9	0.8
Total		30659	11453	63288.8	100.0

*Representing approximately 50% of the total Swiss population.

Table 2: Observed (OS) and age-standardized relative survival (RS) estimates (in %) with 95% confidence intervals (95%CI) by gender and calendar period of follow-up for lung cancer cases pooled from eight Swiss cancer registries.

		Calendar period of death or censoring					
		1995-1999			2005-2009		
Gender	Years since diagnosis	OS	RS*	95%CI	OS	RS*	95%CI
Men	1	35.6	36.6	[35.2, 38.0]	41.4	42.4	[41.0, 43.8]
Women	1	39.7	40.4	[38.2, 42.7]	47.1	47.8	[46.0, 49.6]
Both	1	36.8	37.8	[36.6, 38.9]	43.6	44.5	[43.4, 45.6]
Men	3	15.0	16.3	[15.2, 17.5]	17.5	18.7	[17.5, 19.9]
Women	3	19.0	20.0	[18.1, 21.9]	22.4	23.3	[21.7, 25.0]
Both	3	16.2	17.5	[16.5, 18.5]	19.3	20.4	[19.5, 21.4]
Men	5	10.0	11.3	[10.3, 12.4]	12.8	14.4	[13.3, 15.5]
Women	5	13.4	14.6	[12.8, 16.5]	17.0	18.3	[16.7, 19.9]
Both	5	11.0	12.4	[11.5, 13.3]	14.4	15.9	[15.0, 16.8]

* Age standardized.

Results

Table 1 reports the available years of incidence, the number of lung cancer cases, and the person-years for each individual cancer registry. The pooled data included more than 42'000 lung cancer patients. Table 2 shows the OS and age-standardized RS by gender and 2 calendar periods of follow-up. The age-standardized RS for men and women combined increased for the 1st year after diagnosis from 37.8% (95%CI: 36.6, 38.9) to 44.5% (95%CI: 43.4, 45.6) and for the 5th year after diagnosis from 12.4% (95%CI: 11.5, 13.3) to 15.9% (95%CI: 15.0, 16.8). RS was consistently better in women than men at all time-points after diagnosis and in both calendar periods.

Table 3 shows trends in one- and five-year age-standardized RS after a lung cancer diagnosis in seven successive three-year periods of follow-up. Comparing the first and last calendar periods (1989/1991 versus 2007/2009) for both sexes, we found an increasing linear trend in one- and five-years age-standardized RS from 32.1%, (95% CI; 30.6, 33.7) to 43.9% (95%CI: 42.4, 45.2) and from 10.2%, (95% CI; 9.1, 11.4) to 15.0% (95%CI: 13.9, 16.1), respectively. The AAPC was 1.8% at 1 year and 2.2% at 5 years for both sexes combined. Women had a larger AAPC in one- and five-year lung cancer RS over follow-up than men. Figure 1 displays crude (all ages combined) RS curves for males and females according to two periods, 1995-1999 and 2005-2009.

Figure 2 shows RS by gender and age-group for the last calendar period 2005-2009. Differences in RS by age-group were more marked in females. For both genders RS decreased with advancing age at lung cancer diagnosis. The better RS among women than among men was particularly marked in the youngest age group (one-year RS at age 20-45 years among women was 69.3% (95%CI: 58.3, 78.0) versus 51.3% (95%CI: 41.1, 60.6) among men. The corresponding results for five-year RS were 39.6% (95%CI: 28.4, 50.5) versus 24.3% (95%CI: 16.4, 33.1), in females and males respectively. RS of men and women over 75 years of age at diagnosis was almost identical (1-year RS was 32.6% (95%CI: 29.5, 35.9) among women versus 32.3% (95%CI: 30.0, 34.7) among men. The corresponding values for 5-year RS was 10.4% (95%CI: 8.0, 13.2) versus 9.1% (95%CI: 7.5, 11.0), in females and males respectively.

Discussion

Lung cancer remains a tumour with low survival probability worldwide.[8] Regional and international survival differences have been mainly attributed to differences in treatment patterns.[22] The data presented herein showed an increasing trend of RS in Switzerland since 1995. Earlier diagnosis and improved treatments (surgery, chemotherapy and radiotherapy) over the study period are plausible explanations for the observed trend. However, since no secondary prevention for lung cancer is implemented Switzerland we expect little effect of systematic earlier diagnosis on RS. Unfortunately though we were not able to characterize changes in RS related to improved diagnostic procedures and/or patterns of treatments in this study.
Surgery is still considered the best choice for treating fit patients with early stage non-small-cell lung cancer (NSCLC). Emphasis on surgical procedures for treatment

Table 3. Trends in age-standardized relative survival (RS) of lung cancer cases in Switzerland for successive three-year calendar periods of follow-up between 1989 and 2009.

		Calendar period of death or censoring									
		1989/1991	1992/1994	1995/1997	1998/2000	2001/2003	2004/2006	2007/2009			
Gender	Years since diagnosis	RS (%) [95% CI]	RS (%) [95% CI]	RS (%) [95% CI]	RS (%) [95% CI]	RS (%) [95% CI]	RS (%) [95% CI]	RS (%) [95% CI]	Difference*	AAPC#	p-Value$
Men	1	32.4 [30.6, 34.1]	33.5 [31.7, 35.2]	34.3 [32.6, 36.0]	36.2 [34.5, 37.8]	39.9 [38.1, 41.6]	40.5 [38.8, 42.3]	41.6 [39.9, 43.4]	9.2	1.4	< 0.001
Women	1	31.6 [28.4, 34.9]	34.3 [31.4, 37.1]	38.5 [35.7, 41.4]	39.7 [37.1, 42.3]	45.1 [42.6, 47.7]	44.9 [42.5, 47.2]	47.5 [45.2, 49.7]	15.9	2.4	< 0.001
Both	1	32.1 [30.6, 33.7]	33.5 [32.1, 35.0]	35.6 [34.1, 37.0]	37.2 [35.8, 38.6]	41.5 [40.1, 42.9]	42.1 [40.7, 43.5]	43.9 [42.4, 45.2]	11.8	1.8	< 0.001
Men	5	9.7 [8.4, 11.1]	9.3 [8.2, 10.6]	10.4 [9.2, 11.7]	11.4 [10.1, 12.7]	12.2 [11.0, 13.6]	14.5 [13.1, 16.1]	13.1 [11.9, 14.4]	3.4	1.7	0.146
Women	5	11.0 [8.7, 13.6]	11.3 [9.1, 13.8]	14.2 [12.0, 16.6]	14.0 [12.0, 16.2]	16.5 [14.3, 18.8]	16.4 [14.5, 18.4]	18.2 [16.2, 20.2]	7.2	3.1	0.072
Both	5	10.2 [9.1, 11.4]	10.0 [8.9, 11.1]	11.6 [10.5, 12.8]	12.2 [11.2, 13.4]	13.6 [12.5, 14.8]	15.2 [14.1, 16.4]	15.0 [13.9, 16.1]	4.8	2.2	0.032

* Difference in RS between last and first calendar period.

Average annual percentage change.

$ p-Value of Wald test for calendar period as explanatory variable (linear trend test).

of lung cancer may represent an important factor influencing the age-specific survival trends observed in other countries.[23] Similar to other countries, our Swiss analyses also showed an age-specific survival difference with a lower survival probability in older age-groups. Older patients commonly have increased surgical risk due to age-related co-morbidities and functional decline prohibiting a surgical approach. If surgery leads to better outcomes than younger patients being more often judged fit for surgery may at least in part explain the better RS in young patients reported in this study. However, the introduction of less invasive surgical techniques, such as video-assisted thoracoscopic surgery, should increase the proportion of patients in all age-groups undergoing surgical treatments.[24] Improved radiotherapy and the recent advent of stereotactic ablative radiotherapy are also valid alternatives to surgery, particularly in patients deemed unfit for surgery. Changes in treatment options over time influence lung cancer survival accordingly future studies are needed too account for changes in treatment patterns.

Furthermore, developments in diagnostics are also directly influencing treatment decision-making. Over the past few years, the emergence of targeted or combination treatment strategies have created new demands on histopathological diagnostics. It is now recognised that the efficacy and toxicity of some new drugs are related to the specific histological type of the tumour. Consequently, the exact determination of histological type by a pathologist has become an essential part of adequate clinical decision-making. In this context, a recent study performed in Southern Switzerland showed an association between the integration of conventional histomorphological analysis with an immunohistochemical panel (including markers of squamous p63, cktokeratin CK5/6, and glandular TTF-1, CK7 cell differentiation), allowing more accurate identification of histotype.[25] Remarkably, this approach reduces the proportion of lung cancers diagnosed as NSCLCs thus improving the quality of treatment decision-making. The described change in the diagnostic procedure may have influenced the incidence and survival distribution by different histotypes of lung cancer.[25]

The higher survival probability observed in women compared to men in this study is consistent with reports from other countries (diagnosed before 2000)[26] and those previously reported in GE (diagnosed before 1990).[27] This gender-specific difference may at least in part be related to the different histological distribution of lung tumours between men and women. For instance, it is known that AC has better RS and represents a more frequent histotype in women. Whereas SqCC and SCLC, with lower RS, are more frequently diagnosed histotypes in men.[25] Additionally, a study of women with a previous breast cancer in GE (compared with expected outcomes in the general population) showed breast cancer patients receiving antiestrogen treatment for their breast cancer had lower lung cancer mortality. This study's finding suggest that oestrogens may modify carcinogenesis of lung cancer and potentially influence survival as well.[28]

In conclusion, we observed over the study period an overall increase in lung cancer RS. These population-based re-

sults reflect expected progress in treatment modalities and Improvements in diagnosis. Additional studies on lung cancer survival in Switzerland are needed that account for stage at diagnosis, method of diagnosis, histological type, and treatment patterns over time. Importantly, increased RS over the study period does not diminish the need for improvement, including public health strategies for decreasing exposure to known risk factors (particularly smoking), occupational and environmental exposure and/or implementation of scientifically proven effective screening strategies for high-risk populations.

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* For additional information on lung cancer in Switzerland please see the NICER website http://nicer.org/default.aspx?NavigationID=42

§Members of the NICER Working Group for these analyses included: Basel - G. Jundt, Fribourg - B. Camey, Geneva - C. Bouchardy, Grison/Glarus - H. Frick, St. Gallen/Appenzell - S. Ess, Ticino - A. Bordoni, Valais - I. Konzelmann, Zurich - S. Dehler.

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Correspondence:
Matthias Lorez, PhD, Biostatistician
National Institute for Cancer Epidemiology and Registration (NICER)
University of Zürich, Seilergraben 49
CH-8001 Zürich
ml@nicer.org