Lung Cancer Trends by Histologic Subtype in Switzerland

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Introduction

Lung cancer has developed from a rare disease into a common cause of death in many countries, including Switzerland. Lung cancer is the most common cancer related death among men in Switzerland, and the second most common among women, causing 2,000 deaths every year among men, and 1,080 deaths among women, respectively [1]. The lifetime risk of developing lung cancer in Switzerland among men is close to seven out of hundred, six of which will die from it [1]. The corresponding values among women are four out of hundred, three of which will die from it [1]. Because tobacco smoking is the predominant risk factor for lung cancer, we expect lung cancer trends to mirror smoking patterns in the population, albeit with several decades delay for the effect of tobacco to manifest into a detectable cancer [2]. Most smokers begin the habit before age 18, mainly as a consequence of societal and peer-related factors [3]. Persons born around the same time and forming a so-called birth cohort, share general views about socially acceptable or desirable behavior, such as smoking. These views may slowly change in successive birth cohorts, e.g., because the health hazard of smoking became public knowledge since the 1950s [4], giving rise to decreased lung cancer incidence rates for all members of successive birth cohorts.

There is little information available on smoking prevalence in Switzerland before the inception of the Swiss Health Survey SHS [5, 6]. An early estimate of smoking prevalence in Swiss doctors (at least 1 cigarette daily) for 1955 yielded 52% among men and 24% among women [7]. In 1975, the smoking prevalence, representative for the Swiss population, was 52% among men, which declined to 46% (1981), 39% (1997), and 32% (2012) [5, 8]. The corresponding values for women were 29% (1975), 28% (1981), 28% (1997), and 24% (2012), respectively, thus, with only recent indication of a decline, mainly seen in women < 45 years of age [5, 8]. The data also showed that the smoking prevalence is lower in the German- than in the French/Italian-speaking parts of Switzerland, among both men and women [5, 8].

There are three main histologic subtypes of lung cancer: squamous cell carcinoma, adenocarcinoma, and small cell carcinoma [9]. Smoking can induce them all, but the association is stronger with squamous cell and small cell carcinoma than with adenocarcinoma, which is the leading subtype in never smokers [10]. The type of tobacco product consumed has been shown to exert different risks for different subtypes of lung cancer. Filter-tip cigarettes began replacing unfiltered cigarettes in the 1950s, accompanied by the introduction of low tar, low nicotine brands of tobacco in the markets [11]. Although filter tips and decrease in tar yield have contributed to downward trends of squamous cell and small cell carcinomas, the decrease in nicotine yield may have caused a more complex outcome. Smokers compensated for lower nicotine content with deeper inhalation, which increased the risk for lung cancer at the bronchioloalveolar regions and the smaller bronchi, where adenocarcinoma generally arises [12].

Despite widespread public awareness of the risks associated with smoking, supporting smoking cessation and preventive actions against smoking initiation are still needed, and careful monitoring of lung cancer is one of the key requirements in planning and evaluation of the progress against tobacco-related diseases. This report provides a comprehensive description of lung cancer incidence trends in Switzerland, with a focus on birth cohort-specific changes, stratified by histologic subtype, sex, age at diagnosis, and language region.

Materials and methods

Data sources

Cases of primary malignant lung cancer, defined as codes C33-C34 based on the International Classification of

Diseases, 10th revision (ICD-10) were extracted from the national Swiss cancer dataset, which combines pseudonymized data collected by the cantonal Cancer Registries (CR), and is managed by the National Institute for Cancer Epidemiology and Registration (NICER) [14]. CRs with at least 23 years of consecutive data since 1989 were selected: CR Zürich and Zug (ZH/ZG), CR Sankt Gallen and Appenzell (SG/AR/AI), CR Basel-Stadt and Basel-Land (BS/BL), CR Graubünden and Glarus (GR/GL), CR Geneva (GE), CR Neuchâtel and Jura (NE/JU), CR Vaud (VD), and CR Valais (VS). These data covered 53% of the total Swiss population in 1989 to 2011, 48% in 2012, and 39% in 2013, due to delayed submission of data to the national dataset by a few registries. In each calendar year, the proportion of cases registered from death certificates only, i.e., with true date of diagnosis unknown, was < 4%, and the proportion of cases with microscopically confirmed diagnosis was > 90%.

Histologic subtypes

Lung cancers were grouped based on the International Classification of Diseases for Oncology, 3rd ed. (ICD-O-3) morphology into adenocarcinoma (AD): M8050, M8140-41, M8143-44, M8190, M8200, M8211, M8230, M8250-55, M8260, M8290, M8310, M8323, M8333, M8430, M8470, M8480-81, M8490, M8550, M8560; squamous cell carcinoma (SQ): M8052, M8070-76, M8078, M8082-84; small cell carcinoma (SM): M8002, M8041-45; large cell carcinoma (LA): M8012-14, M8082, M8123; other specified cancer: M8003-04, M8021-22, M8030-33, M8200, M8210, M8240-41, M8243-44, M8246, M8249, M8263, M8380, M8507, M8570, M8572, M8574, M8576; and un- or poorly specified cancer: M8010, M8020, M8046, M8000-1 [9]. The lists include only cancer types that were encountered in the dataset.

Statistical methods

CRs were divided into two groups: predominantly German-speaking (ZH/ZG, SG/AR/AI, BS/BL, GR/GL), and predominantly French-speaking (GE, NE/JU, VD, and VS). Observed cases in the German and French regions of Switzerland were multiplied by the inverse population coverage factor to estimate the number of cases expected for the ideal situation of full coverage of cancer registration in each language region, assuming equal cancer risk in the regions not covered as in the regions covered. Estimation of the expected number of cases was specific for language region, sex, year of diagnosis, and 5-year age group. Switzerland was estimated as the sum of both estimated language regions.

Incidence rates are expressed as events per 100,000 person-years (py) of mid-year risk population. All rates, including age group-specific rates, were age-standardized with the direct method using the European standard population [15]. For easier visual separation of incidence trends in

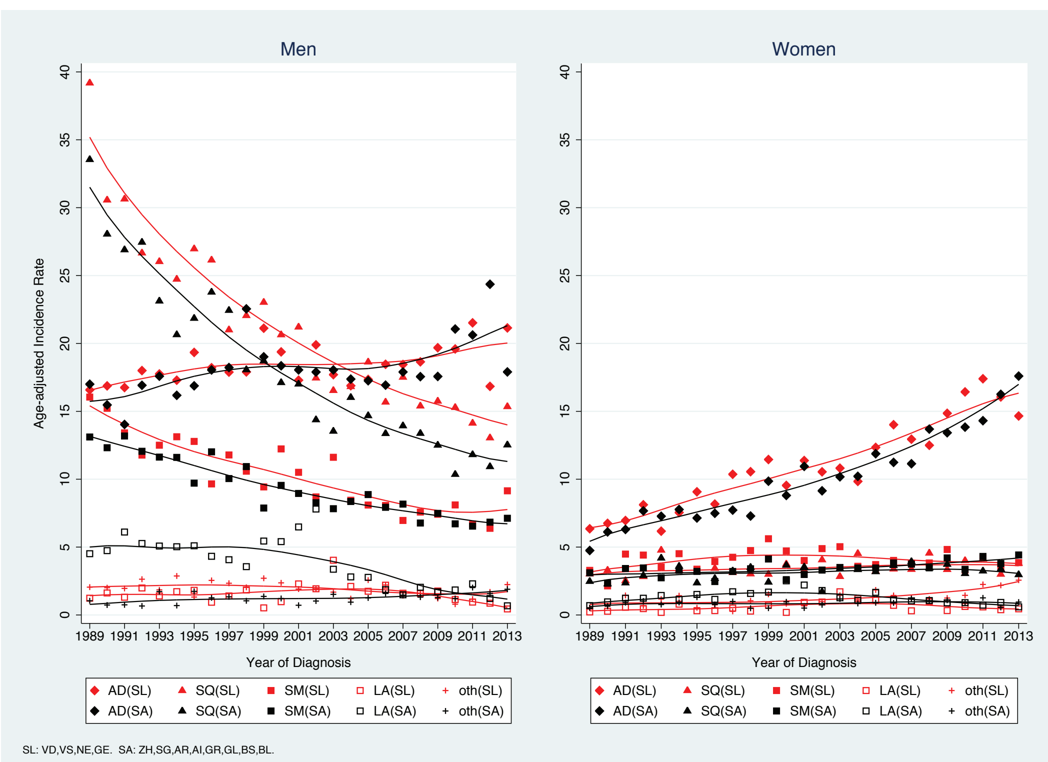

Fig. 1. Age-adjusted incidence rates for lung cancer by diagnosis year, gender, main histologic subtype (AD: adenocarcinoma; SQ: squamous cell; SM: small cell; LA: large cell; oth: other specified lung cancer), and Swiss language area (SL: predominantly French speaking; SA: predominantly German speaking). Age-adjustment based on the European standard population.

Figs. 1 and 2, locally weighted regression of data points was used [13]. Annual percentage change (APC), average annual percentage change (AAPC) in incidence rates, and points in time («joinpoints») when a linear trend significantly alters direction, were estimated with the Joinpoint Regression Program v4.4.0.0 [16]. In short, a heteroscedastic simple linear regression model for logarithmic transformed rates was used which assumed a linear trend between, and continuity at, the joinpoints. To determine the location of a joinpoint, the grid search method was applied which creates a «grid» of all possible locations for joinpoints specified by the settings, and tests the sum square of errors at each one to find the best possible fit [17]. We allowed for 3 joinpoints in our analysis (maximally 4 are recommended for time series of 25 points), restricted to minimally 3 data points away to either end of the time series, with a minimum of 4 points between joinpoints.
Year of birth was estimated by subtracting the age group mid-point from the diagnosis year.

Results

In the 25-year diagnosis period 1989 to 2013, we observed 32,733 cases of lung cancer among men and 15,050 among women. These lead to nation-wide estimates of 61,550 cases of lung cancer among men (about 2,460 annually), and 28,045 among women (about 1,120 annually) (**Table 1**). We observed different temporal trends for different subtypes of lung cancer, which also depended on sex (**Fig.** 1 and **Table** 1).

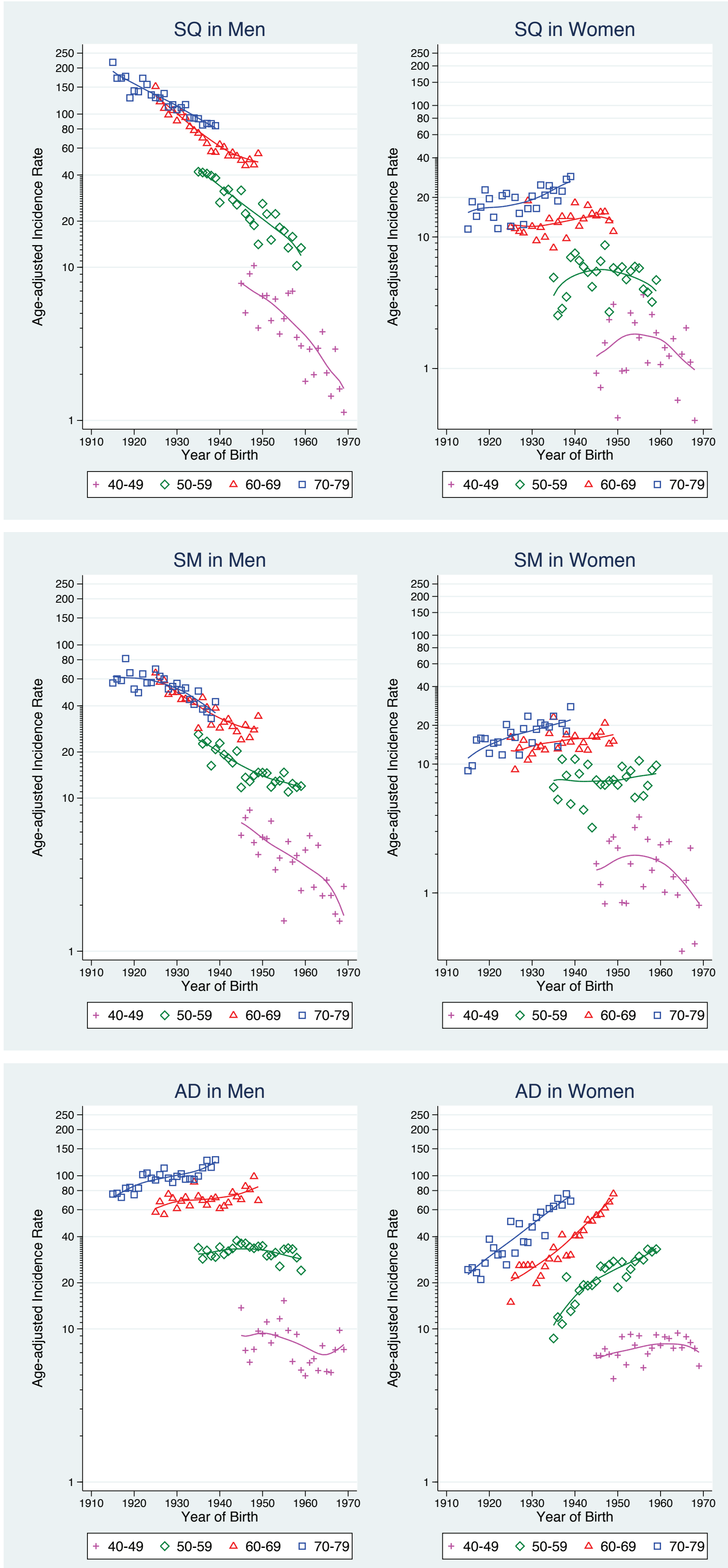

Fig. 2. Incidence trends in lung cancer by age at diagnosis, year of birth, main histologic subtype, and gender in Switzerland. SQ: squamous cell carcinoma; SM: Small cell carcinoma; AD: adenocarcinoma.

		MEN							WOMEN						
		Adeno-carcinoma	Squamous cell carcinoma	Small cell carcinoma	Large cell carcinoma	Other specified histologies	Un-specified histologies	All	Adeno-carcinoma	Squamous cell carcinoma	Small cell carcinoma	Large cell carcinoma	Other specified histologies	Un-specified histologies	All
1989-1991	ASR#	15.8 (14.8, 17.0)	30.6 (29.1, 32.2)	13.5 (12.5, 14.5)	4.1 (3.5, 4.7)	1.2 (0.9, 1.5)	9.6 (8.8, 10.4)	74.7 (72.4, 77.1)	6.0 (5.4, 6.7)	2.5 (2.2, 3.0)	3.1 (2.6, 3.5)	0.8 (0.6, 1.1)	0.8 (0.6, 1.0)	1.9 (1.6, 2.2)	15.0 (14.1, 16.0)
2011-2013	ASR#	20.5 (19.5, 21.7)	12.4 (11.6, 13.3)	6.9 (6.2, 7.6)	1.3 (1.0, 1.6)	1.8 (1.5, 2.2)	6.6 (6.0, 7.2)	49.5 (47.8, 51.2)	16.0 (15.1, 17.0)	3.3 (2.9, 3.8)	4.1 (3.6, 4.6)	0.7 (0.5, 0.9)	1.3 (1.1, 1.6)	3.4 (3.0, 3.8)	28.9 (27.6, 30.1)
1989-2013	N	18392	18824	9380	3039	1453	10463	61550	12487	3984	4186	1252	1161	4976	28045
	%	29.9	30.6	15.2	4.9	2.4	17.0	100.0	44.5	14.2	14.9	4.5	4.1	17.7	100.0
	AAPC##	+0.8 *	-4.4 *	-3.0 *	-5.6 *	+0.7	-1.8 *	-1.8 *	+4.3 *	+0.8	+1.0 *	-0.9	+2.2 *	+2.0 *	+3.4 *
German language region (SA)	N	13129	12869	6541	2592	913	6053	42096	8669	2704	2810	1047	743	2797	18769
	%	31.2	30.6	15.5	6.2	2.2	14.4	68.4	46.2	14.4	15.0	5.6	4.0	14.9	66.9
	AAPC##	+0.8 *	-4.3 *	-2.9 *	-6.4 *	+2.0 *	-0.7	-1.8 *	+4.4 *	+0.8	+1.4 *	-1.3	+1.0	+3.4 *	+2.9 *
French language region (SL)	N	5263	5955	2838	448	540	4410	19454	3818	1281	1377	204	418	2179	9276
	%	27.1	30.6	14.6	2.3	2.8	22.7	31.6	41.2	13.8	14.8	2.2	4.5	23.5	33.1
	AAPC##	+0.5 *	-4.2 *	-3.2 *	-1.5	-1.8 *	-3.0 *	-1.8 *	+4.0 *	+0.7	+0.4	+1.6	+3.9 *	+0.4	+1.8 *

Age-standardized incidence rate (ASR) per 100,000 person years. 95% confidence interval in brackets.
Average annual percentage change. Significant AAPC marked with asterix.
Blue color % refers to column totals. Green color % refers to row totals.

Tab. 1. Temporal trend, estimated numbers (N) and proportions (%) of lung cancer diagnoses in Switzerland between 1989 and 2013, by lung cancer histologic subtype, gender, and Swiss language region. The overall trend of age-adjusted incidence rates is presented as average annual percentage change (AAPC), and by comparing age-standardized rates (ASR) in the beginning (1989-1991) and the end of the observation period (2011-2013).

Men were predominantly diagnosed with SQ in the beginning of the observation period, the associated age-adjusted risk being twice as high as for AD or SM (**Fig. 1** and **Table 1**). At the end of the observation period, AD has become predominant among men, while the risks for SQ and SM dropped to about half of the initial values. The corresponding rates during 1989-1991 were: 30.6 per 100,000 py for SQ, 13.5 for SM, and 15.8 for AD, respectively (**Table 1**). Later, during 2011-2013, the rates have changed to only 12.4 per 100,000 py for SQ and 6.9 for SM, but have increased to 20.5 for AD (**Table 1**). The associated average annual percentage changes (AAPCs) were -4.4% (SQ), -3.0% (SM), and +0.8% (AD) (**Table 1**). Rates and rate changes for LA, other remaining specified types of lung cancer, and un-specified types were smaller, except for a reduction in LA, restricted to the German-speaking part of Switzerland (SA) (**Fig. 1** and **Table 1**). Overall, lung cancer incidence rates among men declined from 74.7 per 100,000 py to 49.5 per 100,000 py, an average reduction of 1.8% annually (**Table 1**).

The histologic pattern of lung cancer among women is different with AD always being the predominant type (**Fig. 1**), contributing 44.5% of all cases during 1989-2013 (**Table 1**). The overall proportion of SQ was only 14.2%, as compared with 30.6% among men (**Table 1**). The proportions of SM (14.9%), LA (4.5%), other specified (4.1%), and un-specified (17.7%) were almost identical to those among men (15.2%, 4.9%, 2.4%, and 17.0%, respectively, **Table 1**). Rates and rate changes among women for all non-AD groups were smaller as compared with AD (**Fig. 1** and **Table 1**). Overall, lung cancer incidence rates among women almost doubled from 15.0 per 100‘000 py in 1989-1991 to 28.9 per 100‘000 py in 2011-2013, an increase of 3.4% annually on average (**Table 1**). The lung cancer rate ratio for women as compared with men was 0.20 (95% confidence interval: 0.19, 0.22) in 1989-1991, and increased to 0.58 (0.55, 0.62) in 2011-2013. Sex-specific distribution of lung cancer subtypes became more similar over time (**Fig. 1**).

Incidence rates in the predominantly French-speaking region of Switzerland (SL) were slightly higher than rates in the SA region, but trend pattern by histologic subtype or sex were very similar (**Fig. 1**). The SL region differed from the SA region by a larger proportion of cases falling into the group of un-specified histology (22.7% versus 14.4% among men, 23.5% versus 14.9% among women, **Table 1**).

We observed that most patients were diagnosed between age 60 and 79 (63% of all lung cancer cases among men and 57% among women), that AD seemed to be diagnosed

		MEN							WOMEN						
Age at diagnosis		Adeno-carcinoma	Squamous cell carcinoma	Small cell carcinoma	Large cell carcinoma	Other specified histologies	Un-specified histologies	All	Adeno-carcinoma	Squamous cell carcinoma	Small cell carcinoma	Large cell carcinoma	Other specified histologies	Un-specified histologies	All
40-49	N	1119	591	568	240	126	358	3001	1032	200	224	133	105	203	1898
	%	37.3	19.7	18.9	8.0	4.2	11.9	4.9	54.4	10.6	11.8	7.0	5.5	10.7	6.8
	APC#	-1.9 *	-6.0 *	-4.2 *	-	-	-	-3.2 *	+0.7	-2.1	-1.4	-	-	-	+1.5/-5.5* 1961
50-59	N	3707	2776	1809	598	294	1226	10410	2663	597	888	258	219	595	5219
	%	35.6	26.7	17.4	5.7	2.8	11.8	16.9	51.0	11.4	17.0	4.9	4.2	11.4	18.6
	APC#	+1.7/-1.5* 1945	-4.8 *	-3.1 *	-	-	-	-2.7 *	+3.8 *	-0.6	+0.3	-	-	-	+3.9 *
60-69	N	6109	6169	3193	1006	390	2531	19398	3692	1244	1420	357	259	1141	8113
	%	31.5	31.8	16.5	5.2	2.0	13.0	31.5	45.5	15.3	17.5	4.4	3.2	14.1	28.9
	APC#	0.9 *	-4.2 *	-3.4 *	-	-	-	-2.1 *	+5.5 *	+1.0	+1.0	-	-	-	+3.6 *
70-79	N	5262	6637	2828	849	424	3405	19405	3219	1389	1231	330	290	1411	7870
	%	27.1	34.2	14.6	4.4	2.2	17.5	31.5	40.9	17.6	15.6	4.2	3.7	17.9	28.1
	APC#	+2.5 *	-3.5 *	0.0/-3.9* 1926	-	-	-	-0.5/-2.8* 1929	+5.0 *	+2.0 *	+2.5 *	-	-	-	+3.6 *
80+	N	2021	2586	935	321	126	2912	8900	1709	528	391	152	175	1599	4554
	%	22.7	29.1	10.5	3.6	1.4	32.7	14.5	37.5	11.6	8.6	3.3	3.8	35.1	16.2

Annual percentage change (APC). Significant APC marked with asterix. Year of birth for cohort associated with change in APC is indicated. Blue color % refers to total N (all ages). Green color % refers to row totals.

Tab. 2. Estimated numbers (N) and proportions (%) of lung cancer diagnoses in Switzerland between 1989 and 2013, by lung cancer histological subtype, gender, and age at diagnosis. Age-specific trend pattern is reported as the annual percentage change (APC) of the age-specific incidence rates. The year of birth for the cohort associated with a statistically significant change in APC is indicated.

more often in younger men or women, whereas SQ seemed to be associated with diagnosis at higher ages (**Table 2**). There was a clear increase in proportions of un-specified lung cancer with age, reaching values of 32.7% among men and 35.1% among women at age 80 and older (**Table 2**). For this reason, we excluded ages 80 and older from our lung cancer subtype-specific trend analyses by age group.

Age-specific lung cancer trends are preferentially presented as (logarithmic transformed) rates versus year of birth instead of year of diagnosis, as shown in **Fig. 2**, because the risk is strongly determined by societal and peer-related factors shared within birth cohorts. The data spans 55 calendar years but is not complete: it lacks lung cancer rates at an early age for early birth cohorts because CRs were not yet established at the time. Similarly, lung cancer rates at old age for recent birth cohorts are still unobserved because members have not yet reached old age. But there is sufficient data for birth cohorts 1930 to 1960 to generate the impression that their age-specific curves run in parallel, indicating the influence of generation on risk (**Fig. 2**). We sought to identify birth cohorts associated with changes in the slopes of age-specific curves, possibly indicating the outcome of alterations in smoking habits. SQ trends among men were uniformly falling but slopes appeared to become increasingly negative for younger birth cohorts, with APC -3.5% at age 70-79 and old birth cohorts to -6.0% at age 40-49 and young birth cohorts (**Table 2**). This was also observed for SQ among women, but trends were still positive for ages ≥ 60 and old birth cohorts (+2.0% and +1.0% for age 70-79 and 60-69, respectively), turning into non-significant negative trends for ages < 60 and young birth cohorts (APC -0.6% and -2.1% for age 50-59 and 40-49, respectively) (**Table 2**). Among women, the slope seemed to turn since around 1950 for SQ and SM (**Fig. 2**), but was statistically significant only for the case of all histologic types combined: APC changed from +1.5% to -5.5% for women aged 40-49 at diagnosis and the cohort born 1961 (**Table 2**). SM trends were similar to SQ trends for both genders, albeit generally less negative at each age group and birth cohort: among men, the trend was even flat for age 70-79 and the oldest birth cohorts until 1926 (APC 0.0%), after which the trend became negative (APC -3.9%) (**Table 2**). AD trends among men were positive in older age groups and birth cohorts, but switched to negative in birth cohort 1945 (APC went from +1.7% to -1.5%; age 50-59) (**Table 1**). Among women, AD trends observed were uniformly positive, albeit increasingly less steep in younger age groups and birth cohorts.

Discussion

This presentation of lung cancer trends by histologic subtype and sex is the first on the Swiss national level and our main findings are: (1) overall decreasing lung cancer rates among men, but increasing rates among women; (2) increasing proportions as well as rates of AD subtypes among both sexes; (3) peak risks for SQ in men have occurred among cohorts born before 1915 (the first cohort in our analysis), for SM among cohorts born in the mid-1920s (a significant change point in 1926 for age 70-79), and for AD among cohorts born in the mid-1940s (significant change point in 1945 for age 50-59); (4) indication of peak risks in women for SQ as well as SM among cohorts born in the late 1950s, and AD risks reaching a plateau among cohorts born in the early 1960s. These findings confirm regional studies in Switzerland [18, 19], and more comprehensive analyses for other countries with a longer history of public health databases [20, 21]. Trends in the US in particular have been scrutinized extensively, based on cancer incidence records since the 1970s from the Surveillance, Epidemiology, and End Results (SEER) Program [22] as well as smoking prevalence data going back to the 1880s [23]. Among U.S. whites, SQ incidence rates were the first to show a downward turn among men associated with birth cohorts around 1905, a little later for SM around 1915, and again later for AD around 1930. Subtype-specific incidence trends among women also expressed a temporal sequence, but with a 10-30 year delay as compared with men (SQ peaked around the 1930 cohort, SM peaked around the 1935 cohort, and AD peaked around the 1940 cohort) [20, 21]. When incidence trends for U.S. whites are analyzed based on the time of diagnosis, SQ trends among men peaked around 1970, SM in the 1980s, and AD in the 1990s, while the turning points for subtypes among women were the 1990s for SQ and SM, and around the year 2000 for AD rates [20]. These data become comprehensible using the simple but reasonable assumptions of an average age of 20 years at smoking initiation plus 45 years latency to cancer manifestation [2], which is close to the median age of lung cancer patients [1, 24]. Apart from temporal shifts, white women experienced a different subtype distribution of lung cancer compared to men, with AD always being predominant, whereas SQ was predominant among men until about 1995 when SQ rates were surpassed by AD rates [20]. This sex-specific distribution of subtypes has been reported in many other countries, including Switzerland [18, 19]. Not only did women start smoking cigarettes later, they also smoked lower-tar brands as compared with men and consequentially developed a different profile of histologic subtypes [25]. The International Agency for Research on Cancer (IARC) undertook a comprehensive age-period-cohort analysis of international lung cancer trends for SQ and AD histologic subtypes, including Australia, Canada, U.S. Blacks and Whites, and 4 European countries (Denmark, France, Spain, and the Netherlands) [21]. Apart from Spain, incidence trends in the studied European countries were rather similar: among men, SQ rates peaked around the 1910 birth cohort, and AD around 1950 in Denmark, while France and the Netherlands remained on a plateau until at least 1963. SQ rate peaks among women were associated with cohorts around 1940 in Denmark and the Netherlands, but in France trends were increasing until the 1963 cohort. AD trends among women in these three European countries were positive until the 1963 cohort. The European countries are apparently delayed in the phase of the lung cancer epidemic by 5 to 30 years as compared with U.S. whites. An early age-period-cohort analysis for two CRs in Switzerland (VD and NE) also revealed a peak in SQ rates among men born around 1910 and increasing AD rates among men and women until the last birth cohort studied (1952) [18]. SQ rates among women seemed to have plateaued since the mid-1930 cohorts [18]. The study reported unexpectedly stable age-specific SM trends among all birth cohorts, possibly caused by small numbers of cases available on the regional level [18]. Another regional study of lung cancer trends by subtype indicated that SQ and SM incidence trends among men in the canton ZH started falling around diagnosis year 1985, thus also suggesting an association with the late 1910s / early 1920s birth cohorts using a 65 year median age at diagnosis of lung cancer patients [19]. Our study adds the novel observation of peak lung cancer risk among Swiss women associated with the 1961 birth cohort. Thus, lung cancer incidence rates among women might be expected to start decreasing in the late 2020s.

There are a number of limitations to our study. The available data covered only half of the Swiss population, about 45% of the SA, and about 70% of the SL language regions, respectively, depending on diagnosis year. We assumed that these data were nationally representative. The extent to which changes in classification and coding impact on the interpretation of trends is an obvious concern. Following the introduction of the ICD-O-3 classification in 2001, a new code had been introduced for non-small cell carcinoma (M8046) [26]. This has likely contributed to the observed reduction in LA incidence rates, seemingly confined to the SA language region [19]. Incidence rates are also affected by developments in diagnostic techniques. Several new bronchoscopic technologies improved diagnostic tissue yield from peripheral lesions where most AD arise [27]. Although contributing to increasing incidence rates, it is unlikely to explain the magnitude of the observed change.

The continuing increase in lung cancer among women, and the relative and absolute increase of AD among both sexes, are of concern. Further dissemination of detailed trends by lung cancer subtypes are needed to help in the planning and evaluation of public health interventions to fight the lung cancer epidemic.

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