

Incidence and Mortality trends of Gastric Cancer in Switzerland 1988–2014

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Introduction

Gastric carcinoma is a prime example of a malignancy caused mainly by environmental factors. While cardia carcinoma can be caused by gastro-oesophageal reflux, obesity and tobacco consumption, non-cardia carcinoma (especially the intestinal type according to Laurén) is attributed to risk factors like dietary habits with e.g. heavily salted foods as well as infection with *Helicobacter pylori* [1]. This offers the chance of reducing the likelihood of gastric carcinoma by changing one's lifestyle and by the surveillance of exogenous biological agents.

This investigation utilises the data of cantonal and regional population-based cancer registries (PBCRs) to give an overview of gastric cancer incidence according to topography and histology and to present recent incidence and mortality trends of gastric cancer in Switzerland (CH). Furthermore, we intend to investigate whether the gastric carcinoma incidence pattern differs by histologic type in the past 27 years (1988–2014).

The Laurén classification from 1965 [2] is standard in clinical practice to assign histology groups of gastric carcinoma. It distinguishes between two main types, i.e., intestinal and diffuse adenocarcinoma. The intestinal type forms recognizable glands. The lesions develop typically via a metaplastic precursor into invasive neoplasia. The diffuse type consists of poorly cohesive cells diffusely infiltrating the gastric wall with little or no gland formation [2]. The precursor lesions for this tumour type are less well described.

Although the Laurén classification is widely used to guide therapeutic decision-making in Switzerland no national data are available. This is the first population-based analysis of gastric carcinoma incidence trends in Switzerland which considers Laurén histologic types.

Methods

The Foundation National Institute of Cancer Epidemiology and Registration (NICER) manages the popula-

tion-based national cancer dataset, with the purpose of providing comprehensive cancer surveillance data for Switzerland, as well as supporting epidemiological cancer research [3]. Population-based cantonal and regional cancer registries collect data directly from the patients' medical records and transmit a defined and pseudonymised subset of the information to NICER. Diagnoses from 1988 to 2014 of thirteen cantons where cancer registration covered at least nineteen consecutive years (ZH, GR, GL, SG, AR, AI, BS, BL, VD, NE, VS, GE, and TI) were included in this report. The first eight cantons represent the German-speaking part of Switzerland, and the remaining five cantons the French/Italian-speaking part. The respective cancer registries cover about 60% of the Swiss population. Estimated case counts for the whole of Switzerland are extrapolations by sex, age, tumour group, and Swiss language region.

Selection criteria for incidence analyses were all primary malignant tumours with topography code C16 from the International Classification of Diseases for Oncology, third edition (ICD-O-3) [4], and diagnosed between 1988 and 2014. This resulted in a total of 15,071 cases.

The topographical groups were defined as cardia (ICD-O-3 C16.0), non-cardia (C16.1–C16.6), and overlapping/not otherwise specified (NOS) (C16.8, C16.9). The cancer types were assigned according to the ICD-O-3 classification groups of malignant neoplasms considered to be histologically 'different' [4]: adenocarcinoma, other specific carcinoma (including squamous cell carcinoma, basal cell carcinoma, and other specific carcinoma), unspecified carcinoma NOS, sarcomas/soft tissue tumours (including mesothelioma and Kaposi sarcoma), B-cell neoplasm, other tumours of the haematopoietic and lymphoid tissue (including manifestations of myeloid leukaemia, T- and NK-cell neoplasm, Hodgkin lymphoma, mast-cell tumours, neoplasms of histiocytes and accessory lymphoid cells, as well as unspecified types) other specified types of cancer, and unspecified types of cancer.

For the incidence trend analysis, we restricted the analysis to the microscopically verified (MV) carcinoma cases of the main group of epithelial malignant neoplasms (only 59 diagnoses were not MV). This resulted in a total of

13,548 observed diagnoses, and about 24,000 expected for whole Switzerland. The sixty-two ICD-O-3 morphology codes used by the PBCRs were assigned according to the Laurén classification as follows: 1. intestinal type (M8140, M8144, M8210, M8211, M8221, M8261–M8263, M8480, M8481), 2. diffuse type (M8142, M8145, M8490), 3. other specific types of carcinoma (M8010–M8013, M8020–M8022, M8030–M8033, M8041, M8045, M8050, M8070–M8072, M8082, M8141, M8143, M8153, M8190, M8201, M8230, M8231, M8240–M8242, M8244, M8246, M8249, M8255, M8260, M8310, M8323, M8430, M8510, M8512, M8560, M8570, M8574, M8576, M8720, M8940, M8980), and 4. Unspecified cancer types (M8000–M8004).

Stomach cancer mortality was based on the vital statistics of the Swiss Federal Statistical Office for causes of death coded as C16 in the International Classification of Diseases, Revision 10 (ICD-10).

Incidence and mortality rates were expressed as N cases per 100,000 person-years (PY). Age-adjustment of rates for all ages combined, as well as within age groups, was based on the EU standard population [5]. The study is observational, thus, confidence intervals should only be interpreted as rough descriptors of uncertainty [6].

Annual percentage changes (APC) were estimated using a heteroscedastic simple linear model for logarithmic transformed age-standardised rates implemented in the Joinpoint Regression Program version 4.4.0.0 [7, 8]. Analyses

are based on yearly rates. To determine the year when a linear trend significantly alters direction, the grid search method was applied which creates a «grid» of all possible locations for such points in time, and tests the sum square of errors at each one to find the best possible fit [7]. We allowed for a single trend change in our analysis, restricted to minimally 3 data points away to either end of the time series.

Results

Distribution of cancer types in different topographic regions of the stomach (Fig. 1)

Looking at the different types of original tissues, epithelial neoplasms (72–98%) formed the main group of stomach malignancies. The second largest group with 10 to 15% were the tumours of the haematopoietic and lymphoid tissues. Other specific and unspecified types made up a small percentage of the defined anatomic sites cardia and non-cardia (less than 3%).

Distribution of population-based gastric cancer by topography, histology, basis of diagnosis (microscopically verified or death certificate only), and period of diagnosis in Switzerland (Tab. 1)

In the investigated time periods (1988–1996, 1997–2005, and 2006–2014), the proportion of malignancies in the cardia location increased by 6.7% from 22.1% to 28.8%; for non-cardia, it decreased by 15.6% from 55.3% to

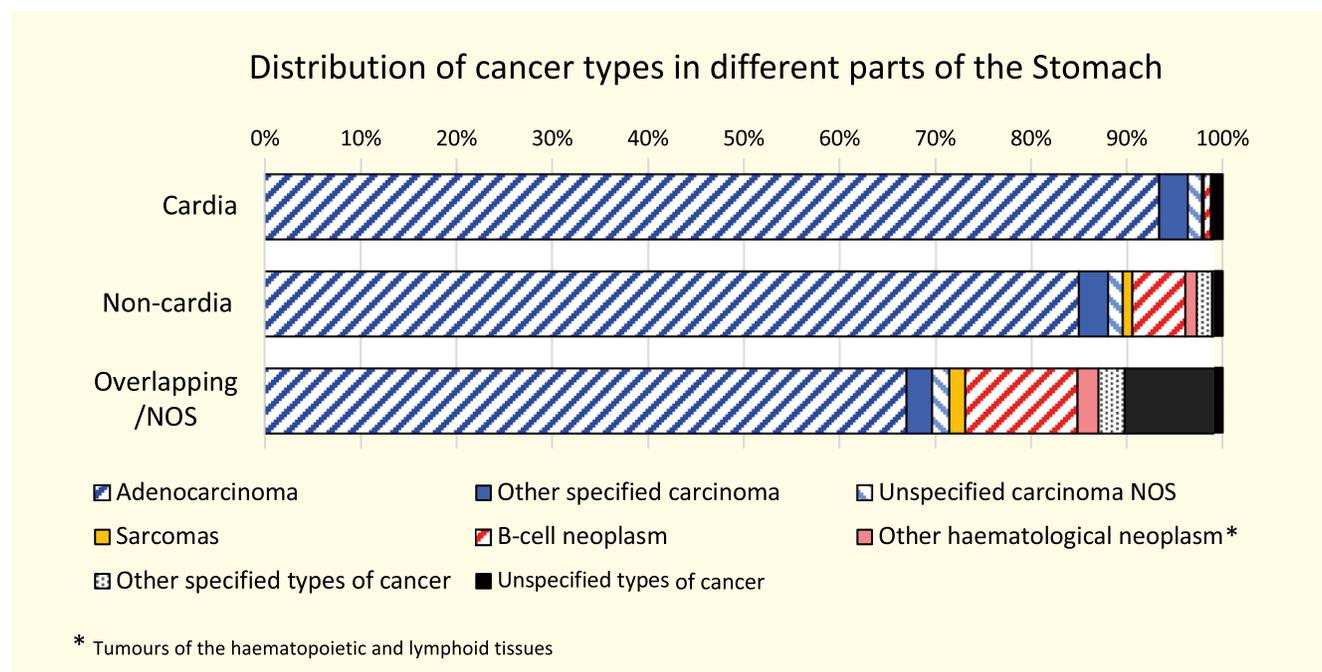


Fig. 1. Distribution of cancer types in different topographic regions of the stomach diagnosed in 1988–2014.

Topography	Case distribution			Microscopically verified (MV)			Death certificate only (DCO)		
	1988-1996	1997-2005	2006-2014	1988-1996	1997-2005	2006-2014	1988-1996	1997-2005	2006-2014
Cardia [%]	22.1	24.1	28.8	98.8	98.5	99.0	0.1	0.4	0.2
Non-cardia [%]	55.3	48.7	39.7	97.7	99.3	99.0	0.1	0.0	0.1
Overlapping/NOS [%]	22.5	27.2	31.5	85.1	83.5	92.1	5.9	8.6	3.2
Total [%]	100.0	100.0	100.0	95.1	94.8	96.8	1.4	2.5	1.1
Histology									
Diffuse [%]	22.7	24.8	23.2	99.4	99.8	99.9	0.0	0.0	0.0
Intestinal [%]	65.6	64.6	65.9	99.3	99.9	99.7	0.1	0.1	0.1
Other specific [%]	7.4	5.5	7.8	99.2	96.7	98.5	0.0	2.8	1.2
Unspecific [%]	4.4	5.1	3.0	4.1	5.7	4.8	30.3	43.0	30.2
Total [%]	100.0	100.0	100.0	95.1	94.8	96.8	1.4	2.5	1.1
Total cases* [N]	9,109	7,550	7,351						

* Extrapolated from observed cases

Tab. 1. Proportions of population-based gastric cancer by topography, Laurén histologic type, basis of diagnosis (microscopically verified or death certificate only), and period of diagnosis in Switzerland.

39.7%. Substantial proportions of 22.5% (1988–1996) to 31.5% (2006–2014) of the stomach malignancies were assigned to overlapping and NOS parts of the stomach.

The overall percentage of microscopically verified (MV) cases was high, i.e., 97.9% to 99.3%, and the proportion of DCO of 1% to 3% overall was low (0.0% to 0.4% for the specified locations of cardia and non-cardia). As expected, the percentage of MV cases was much lower (85.1% to 92.1%) for overlapping parts of the stomach and NOS, and the percentage of DCO cases was higher (3.2% to 5.9%).

Looking at the distribution of the Laurén histologic groups, the intestinal type formed the largest group (64.6% to 65.9%), followed by the diffuse type (22.7% to 24.8%). The group of other specified morphologies (5.5% to 7.8%) and the unspecified group (3.0% to 5.1%) were small. MV gastric carcinoma diagnoses made up 96.7% to 99.9% and the DCO rate was 0.0% to 2.8%. As expected for the unspecified histology group, the percentage of MV diagnoses was low with 4.1% to 5.7%, and the DCO range was high, i.e., 30.2% to 43.0%. In contrast to the temporal changes in proportions at the topographical level, the proportion of Laurén histologic types remained stable.

Gastric Cancer Incidence Trends (Fig. 2, Tab. 2)

The age-standardised incidence rate (ASIR) was 18.9 (95% CI 17.7–20.1) per 100,000 PY for men and 8.2 (95% CI 7.5–8.9) per 100,000 PY for women in 1988–

1990. Men were 2.3 times more frequently affected by gastric cancer than women. The ASIR decreased significantly by 43.5% in men (ASIR 2012–14: 10.4 [95% CI 9.7–11.2] per 100,000 PY) and by 42.7% in women (ASIR 2012–14: 4.7 [95% CI 4.3–5.3] per 100,000 PY) in the investigated time period. In addition, the decrease has been stagnating since 2006–08 for men.

For both sexes, the incidence trends were not statistically different in the German and French/Italian-speaking region of Switzerland at the different time points.

The sex ratio of the ASRs male/female (M/F) did not change remarkably over the period observed (2.3 [1988–1990] vs. 2.2 [2012–2014]).

Gastric Cancer Mortality Trends (Fig. 2, Tab. 2)

The age-standardised mortality rate (ASMR) also decreased significantly by 60.1% in men (from 15.8 [95% CI 15.0–16.6] per 100,000 PY in 1988–1990 to 6.3 [95% CI 5.9–6.7] in 2012–2014) and by 57.1% for women (from 7.0 [95% CI 6.6–7.5] per 100,000 PY to 3.0 [95% CI 2.7–3.2] per 100,000 PY). The decrease of the ASMR has been stagnating for women since 2003–05 and for men since 2006–08.

For both sexes, no statistically significant differences in the mortality trend were observed between the two language regions during the different time periods.

The sex ratio of the ASRs (M/F) remained nearly unchanged with 2.3 in 1988–1990 and 2.1 in 2012–2014.

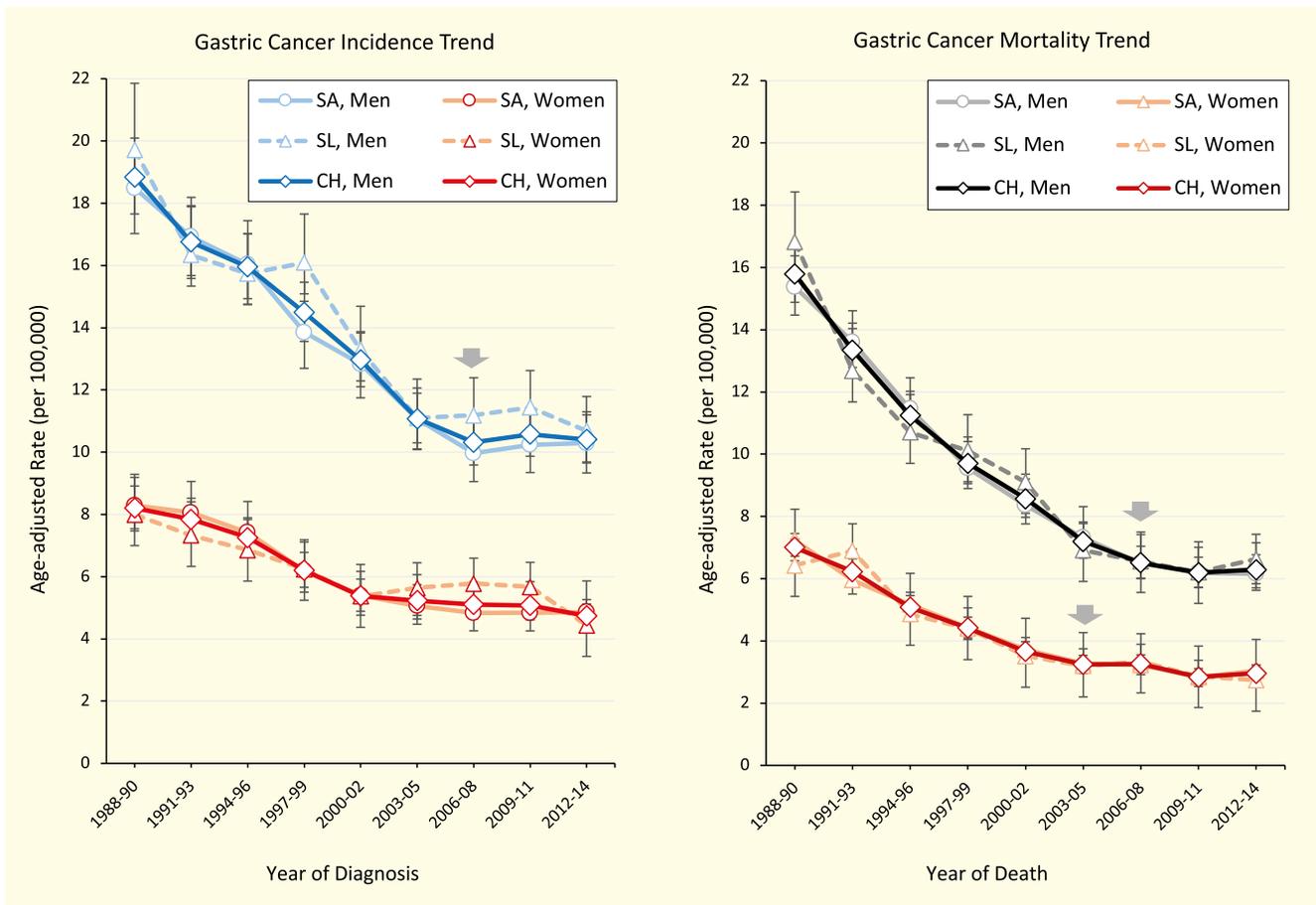


Fig. 2. Gastric cancer incidence and mortality trend by language group and gender. SA: German-speaking part of Switzerland, SL: French/Italian-speaking part of Switzerland, CH: whole Switzerland. The arrows indicate the time period with significant trend changes.

Gastric Carcinoma Incidence Trend by Histology (Fig.3, Tab. 2)

The ASIR of the intestinal and diffuse type (MV) decreased significantly by 44–49% in women over the entirely investigated time period. A statistically significant decrease was also observed in men until 2003–2005 for the intestinal type with stagnation afterwards and as of 1997–1999 for the diffuse type (previously the ASIR was stable).

The sex ratio of the ASRs (M/F) were more pronounced in the intestinal type with a ratio of 2.6 (1988–1990) and 2.8 (2012–2014) than the diffuse type with a ratio of 1.6 (1988–1990) and 1.4 (2012–2014).

No statistically significant difference in the incidence trend was observed for the group of other specified carcinoma (MV). The sex ratio of the ASRs (M/F) with 1.5 almost balanced out in 2012–2014 compared to a sex ratio of the ASRs of 4.7 in 1988–1990.

The negative trends of diagnoses with no specified histology (not restricted to MV) were statistically significant, but at low incidence rates.

Discussion

Gastric carcinoma forms the main group (approx. 86%) of the stomach malignancies, followed by tumours of the haematopoietic and lymphoid tissue (approx. 6%) and sarcoma/soft tissue tumours (1.5%). The group of other specific types (2.5%) includes rare tumours such as melanoma und malignant gastrointestinal stroma tumours. It also includes, to a small percentage, morphologies unusual for the stomach. 4.6 % of the tumours are not further classified. These are cases for which the PBCRs do not receive more specific details. One reason can be that the malignancy is only suspected clinically or that the PBCR has no more information than the one on the death certificate.

	Time	Men						Women						ASR-R ⁴
		ASR ¹	LB ¹	UB ¹	Trendanalysis			ASR ¹	LB ¹	UB ¹	Trendanalysis			
					APCpre ³	CP ²	APCpost ³				APCpre ³	CP ²	APCpost ³	
Gastric cancer mortality														
All histologic types	1988-1990	15.8	15.0	16.6	- 5.4*	2006-2008	- 0.6	7.0	6.6	7.5	- 5.4*	2003-2005	- 1.3	2.3
	2012-2014	6.3	5.9	6.7				3.0	2.7	3.2				2.1
Gastric cancer incidence														
All histologic types	1988-1990	18.9	17.7	20.1	- 3.3*	2006-2008	0.3	8.2	7.5	8.9	- 2.5*	/	/	2.3
	2012-2014	10.4	9.7	11.2				4.7	4.3	5.3				2.2
Intestinal type#	1988-1990	13.2	12.3	14.3	- 3.3*	2003-2005	- 0.2	5.0	4.5	5.6	- 2.9*	/	/	2.6
	2012-2014	7.4	6.8	8.1				2.6	2.3	3.0				2.8
Diffuse type#	1988-1990	3.9	3.1	4.2	+ 0.8	1997-1999	- 4.5*	2.5	2.1	2.9	- 1.9*	/	/	1.6
	2012-2014	2.0	1.6	2.3				1.4	1.2	1.8				1.4
Other specific type#	1988-1990	1.4	1.1	1.8	- 2.1	/	/	0.3	0.2	0.5	0.6	/	/	4.7
	2012-2014	0.9	0.7	1.1				0.6	0.4	0.8				1.5
Unspecified cancer type	1988-1990	0.6	0.4	0.9	- 4.1*	/	/	0.4	0.3	0.5	- 4.9*	/	/	1.6
	2012-2014	0.2	0.1	0.3				0.1	0.1	0.2				2.1

¹ Age-standardised rate; LB/UB: lower/upper 95% confidence limits

² Change point in time with significant trend change. /: no significant change point found

³ Annual percentage change in ASR; pre/post: before/after change point

⁴ Sex ratio of ASRs

* APC significantly different from zero (P<0.05)

Restricted to microscopically verified diagnoses

Tab. 2. Estimated age-standardised gastric cancer incidence and mortality rates (ASR per 100,000 PY) by gender. Trends are estimated as annual percentage change in ASR, including testing whether an apparent change in trend is statistically significant. Age-standardised rates are shown for the 1st and the last analysis time period.

In the present observation period (1988 to 2014), 25% of the stomach malignancies occurred in the cardia, 48% in the non-cardia site and 27% in the overlapping or not further specified parts. Comparable results were reported by Wu et al. (cardia 24%, non-cardia 46%, overlapping or non-specified 30%) [9], and by Feller et al. [10]. This high proportion of unspecified coding complicates the interpretation of changes at the specific topographies.

The gastric cancer ASIR has been continuously decreasing in both sexes in Switzerland, and it is stagnating in Swiss men since 2006–08. A decrease in the ASIR was also seen in Germany (G) and Austria (AU) (CH/G/AU (EU standard 2013): 1988: 8/18/32 (women), 19/32/61 (men), 2013: 5/8/12 (women), 10/16/22 (men)) [11, 12]. The differing H. pylori prevalence rates of 18.9% in Switzerland and of 35.3% in Germany reported by Hooi et al. may be one possible explanation for the differences in the incidence rates [13]. Additionally, dietary habits such as the intake of fresh fruit/vegetable and the intake of heav-

ily salted meat are well known factors to affect the development of gastric carcinoma [14, 15].

In Switzerland, the gastric cancer ASMR is twice as high in men as in women and has been stagnating in the past six years. A decrease in the ASMR and a comparable sex ratio is also observed in Germany (CH/G/AU (EU standard 2013) 1988: 7/12/24 (women), 16/23/49 (men), 2014: 3/5/7 (women), 6/9/15 (men)) [11, 12].

Neither the gastric cancer ASMR nor the ASIR at each time point were statistically significantly different by the Swiss language regions.

The percent distribution of the histology group intestinal, diffuse and other specified gastric carcinoma did not change significantly in the observed period. The most common group was the intestinal type (65.4%), followed by the diffuse type (23.6%), and other specified morphologies (6.9%). The results are comparable to other major studies by Wu et al. [9] and Henson et al. [16]. They reported proportions of 74% and 76% for the intestinal

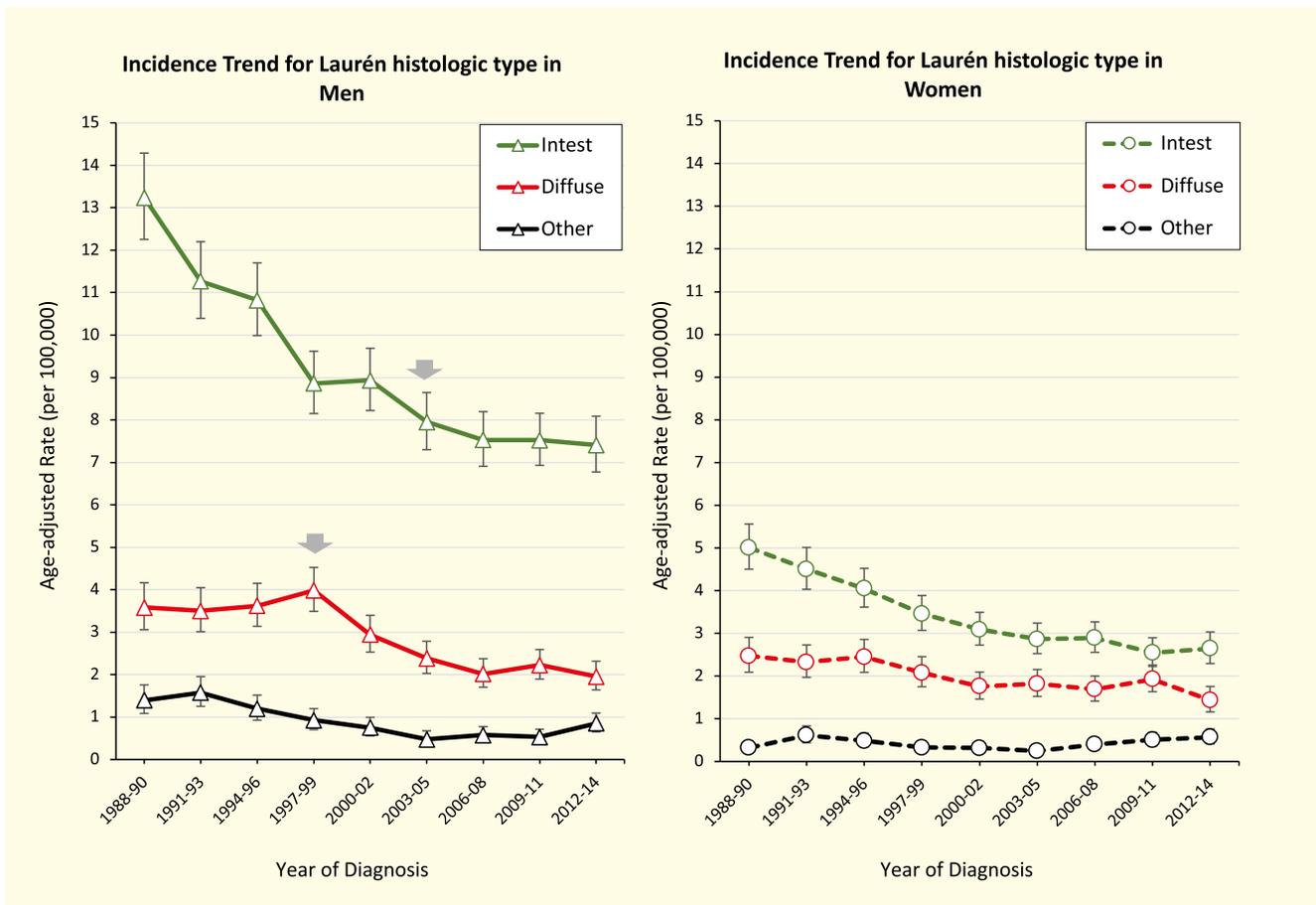


Fig. 3. Trends in Swiss gastric carcinoma incidence by Laurén histologic type and gender. The arrows indicate the time period with significant trend changes.

type, 16% and 13% for the diffuse type, and 10% and 11% for others.

The statistically significant decrease in the ASIR of the intestinal and diffuse type is comparable to the results of Olafsdottir et al. [17] and Wu et al. [9]. Henson et al. observed a decrease of the intestinal type but an increase of the diffuse type [16]. In addition, our study showed type-specific temporal trends with ASIR for diffuse type remaining stable until 1997–1999 while the ASIR of intestinal type carcinoma steeply decreased. Differing temporal trend patterns suggest heterogeneous etiology [9].

Men were generally more often affected than women and this was more pronounced for the intestinal type (2012–2014: sex ratio of the ASRs (M/F) 2.8 for intestinal, 1.4 for diffuse, 1.5 for other). The sex ratio of the ASRs for the diffuse type is becoming more and more similar. Comparable results are reported by Olafsdottir et al. [17] and Wu et al. [9]. Camargo et al. described in their meta-analysis that longer exposure to oestrogen ef-

fects may decrease stomach cancer risk. This supports the hypothesis that the differences in the sex ratio could be explained by the influence of sexual hormones [18].

The missing changes in the other specific morphologies compared to overall trends might indicate that this is an etiologically different group. However, this is the smallest group in terms of numbers, so this should be interpreted with caution.

There are a number of limitations to our study. The data covered only 60% of the Swiss population, reducing the generalisability of observations to the whole country. The high percentage (a quarter) of cases for which the anatomic site was not specified or overlapping and the use of a large number of morphology codes (partly without the necessary basis of diagnosis in the form of histology) suggest inadequate reporting and erroneous coding. There is no international consensus for the assignments of WHO codes in histology groups for the Laurén classification. The comparability of the results with other studies is therefore

limited. Possible effects of classification changes may have played a negligible role in this study, as only ICD-O-2 and ICD-O-3 were used in the selected study period and the two versions differ only slightly in the rare morphology codes.

Conclusion

The incidence and mortality trends observed in Switzerland are comparable to other developed countries and may reflect changes in the prevalence of known exogenous risk factors. Looking at the incidence trends by histology pattern, the Laurén classification proved to be useful in identifying three different histology groups that have a different change in incidence pattern over time and that probably differ in their genesis. The «intestinal» type is characterised by the highest ASIR, male dominance and sharply declining incidence trend, whereas the «diffuse» type was characterised by moderate ASIR and sex preference, and «other specified carcinoma» was characterised by stable incidence trend and low sex preference. Further examinations, e.g. an age cohort study, are indicated to get deeper insight into the genesis of gastric carcinoma.

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