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Original research

Incidence and survival of primary major salivary gland carcinoma in Germany over the last decade: A nationwide population-based study

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ABSTRACT

Background: Primary salivary gland carcinomas (SGC) are rare tumors comprising 5 % of head and neck cancers. While most published studies on SGC in Germany focus on state-level data, nationwide population-based data on incidence, demographics, and outcomes have not been reported.
Objectives: This study aimed to provide a nationwide overview of the incidence, clinicopathologic characteristics, and survival of patients with primary SGC of the major salivary glands in Germany.
Design and methods: Data were extracted from the German Centre for Cancer Registry Data (ZfKD), covering all 16 federal states, for the period 2009–2022. Patients with primary malignant neoplasms of the major salivary glands were included. Crude and age standardized incidence rates were calculated. Relative survival was estimated using the period approach, stratified by demographic and tumor characteristics.
Results: We identified 10,808 SGC cases. The most frequent subtypes were adenocarcinoma not otherwise specified (ANOS) (18.4 %), mucoepidermoid (MEC, 13.5 %), adenoid cystic (ACC, 13.3 %), acinic cell (Acin, 10.4 %), and salivary duct carcinoma (SDC, 5.7 %). The mean age-standardized incidence rate was 5.2/1000,000 person-years, 5.8 for men and 4.8 for women, and increased slightly over observation period. A decline in ANOS and increase in SDC incidence were observed, primarily among men. The five-year relative survival was 70 %, with a pronounced disparity observed between male (62 %) and female (80 %) patients. Survival declined with advanced tumor status, nodal involvement, and distant metastasis.
Conclusion: To date, this represents the largest epidemiological investigation of major SGC worldwide. Over the observation period, the incidence of major SGC has slightly increased in Germany. Men showed a distinctly more unfavorable prognosis than women and were more likely to be diagnosed with aggressive entities like ANOS and SDC.

1. Introduction

Primary salivary gland carcinomas (SGC) are rare tumors, accounting for approximately 3–6 % of all head and neck malignancies [1]. SGC are classified into 21 distinct histological subtypes due to their considerable heterogeneity in terms of morphology, clinical behavior, and recurrence risk [2–4]. While several potential risk factors, including previous radiation therapy and a history of cancer have been proposed, the etiology of SGC remains largely unclear [5].

Epidemiological data on SGC are limited, with most studies focusing

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on specific anatomical sites, such as the parotid gland, or on certain entities due to the rarity of this disease [6–8]. Epidemiologic studies reporting on clinical series and population-based studies have been published for European countries and for the USA [8–10]. Globally, the annual incidence of SGC ranges from 5.7 to 9.2 per 1000,000 person-years [7,9,11,12]. Studies from Europe and Asia have reported stable incidence rates over time [6], while research from the United States indicated a gradual increase [13,14].

Single-center studies have reported that due to the reclassification of cases initially classified as salivary carcinoma not otherwise specified (NOS; formerly adenocarcinoma NOS (ANOS)), the incidence of other entities, especially salivary duct carcinoma (SDC), increased. Conversely, the incidence of ANOS decreased. However, these findings have not yet been investigated in larger epidemiological studies [15,16].

The aim of this study was to provide an overview of the incidence, demographic characteristics, and survival of patients diagnosed with primary SGC of the major salivary glands in Germany. To date, this constitutes the largest epidemiological study of SGC worldwide.

2. Material & methods

2.1. Sample

This study utilized data from the German Centre for Cancer Registry Data (ZfKD), collected over more than a decade from January 1, 2009, to December 31, 2022. The nationwide cancer registry collects data from the 16 state cancer registries covering the whole population of Germany. Malignant neoplasms diagnosed in Germany are mandatory to be reported to the registries via pathology or clinical reports. Inclusion criteria for this study were patient age over 14 years with tumor localization codes from the International Classification of Diseases for Oncology (ICD-O-3, Supp. Table 3) for malignant neoplasms of the major salivary glands (C07, C08.0, C08.1, C08.9) and overlapping lesions (C08.8, tumors overlapping more than one major salivary gland). Squamous cell carcinomas (ICD-O-3 morphology codes 8050/3–8086/3) were excluded because there was insufficient data to distinguish between primary and secondary cases (n = 3184) [6,17,18]. Tumor characteristics such as tumor status (T), nodal status (N), distant metastases (M), and stage were analyzed based on the TNM Cancer Staging Classification (8th edition) at diagnosis [19], because the TNM 9th edition was published after the completion of the registration period, the analyses were carried out using the TNM 8th edition. The World Health Organization (WHO) Classification of Head and Neck Tumors: Salivary Glands (4th edition) was used in this study as cases were predominantly classified under this edition [20]. Grading was analyzed only for MEC and ACC, given that these entities can be assessed through the utilization of a standardized grading system that exhibits consistent reproducibility [21]. This study used fully anonymized cancer registry data containing no identifiable personal information that precluded the identification of persons and reporting centers. As no individual participants could be identified or contacted, and the data were analyzed solely for research purposes with strict confidentiality measures, ethical approval was not required in accordance with applicable guidelines and regulations. Despite this, the study adhered to the ethical regulations set forth by the Ethics Committee of the University of Cologne.

2.1.1. Statistical analysis

Incidence rates were reported as both crude and age-standardized rates expressed per 1000,000 person-years. Age standardization was performed using the old European Standard Population (ESP) and Global Burden of Disease World Standard Population (WSP, Supp. Table 1) to enable comparisons with international cohorts that have different age distributions [22,23]. According to International Agency for Research on Cancer multiple primary rules, patients with more than one SGC were counted separately. For incidence estimates, death certificate only (DCO) cases were included. In this analysis, age-standardized incidence rates (ASIR) and crude rates were reported. Relative survival estimates were calculated based on sex, age groups, morphology, primary site, T, N, and M status, and tumor grading using the period approach [24]. Due to known underreporting of deaths, data from Bavaria, Mecklenburg-Western Pomerania, Hessen, Brandenburg, Berlin, Thuringia, and Saxony-Anhalt (n = 4029) as well as DCO cases (n = 803) had to be omitted from the survival analysis. Relative survival was defined as the ratio of observed survival among cancer patients to the expected survival in the general population, matched by sex, age group, and calendar period 2018–2022 (n = 6567). Survival in the general population was estimated using sex- and calendar-year-specific life tables with the Ederer II method [25]. With the exception of the age-specific strata, all survival estimates were age-standardized according to the International Cancer Survival Standard (ICSS) 1. A complete-case analysis was performed, including 2827 cases, among which 1139 events were observed. The proportional hazards assumption was evaluated by visual inspection of weighted residuals. Tumor grading was excluded from the analysis due to a high proportion of missing values and violation of the proportional hazards assumption. All relative survival analyses were conducted using the periodR add-on package for R [24,26,27]. We calculated and report confidence intervals (95 % CI) to assess the precision of our estimates because our goal is estimation and not significance testing. We wish to avoid publication bias from preferential reporting of significant results. Instead, we judge the value of our estimates by their precision and validity.

3. Results

3.1. Demographics

The study population was comprised of 11,088 cases. The median age was 68, ranging between 15 and 105 years at diagnosis. Among all patients, 54 % were male and 46 % were female (Table 1). The registration completeness rate of the cancer registries exceeded 90 %. The overall proportion of cases diagnosed through death certificate only (DCO) was 7.2 %, and 84.3 % of all cases had been morphologically verified by the diagnosing institutions prior to reporting to the registry.

3.1.1. Tumor characteristics

SGC most frequently occurred in the parotid gland (77.2 %), followed by the submandibular gland (15.5 %). ANOS was the most common diagnosis (18.4 %). Mucoepidermoid carcinoma (MEC; 13.5 %), adenoid cystic carcinoma (ACC; 13.3 %), acinic cell carcinoma (Acin; 10.4 %), and SDC (5.7 %) completed the five most frequent entities (Table 1). The most common SGC of the parotid gland was ANOS, while the most frequent entity found in the submandibular and sublingual glands was ACC (Table 2). ACC was most frequent in women (16.8 %), while men were most frequently diagnosed with ANOS (22.7 %). Men also presented with a higher proportion of locally advanced tumors. T3/4 tumors were observed in 48.3 % of men compared to 35.7 % among women. Overall, T1–3 tumors were observed at similar frequencies (27.9–29.6 %), while T4 tumors made up 14.4 %. Of the five most frequently observed entities, ANOS and SDC showed the highest proportion of locally advanced tumors (T3–4) with 54.8 % and 60.3 %, respectively. MEC and Acin were predominantly diagnosed as T1–2 tumors with 70.0 % and 79.7 %, respectively.

The majority of all patients did not have cervical lymph node metastases (64.8 %). N1–3 was most frequently observed in ANOS and SDC with 59.2 % and 65.7 %, respectively. Nodal spread was more often observed in men than women (m:w, 42.7 %: 26.2 %). Advanced N-status (N2–3) was predominantly observed in men (m:f, 30.8 %: 16.4 %). The highest rates of lymph node metastases were found in primaries originating from the submandibular gland (39.1 %), followed by the parotid (34.4 %), and the sublingual gland (23.4 %).

Moreover, metastasized tumors were more frequent in men (m:f, 12.1 %: 7.6 %; Table 1). Distant metastases were found in over 10 % of

Table 1
Clinicopathologic characteristics of salivary gland cancers in Germany, 2009–2022.

	Men N = 6024 (%[a])	WomenN = 5064 (%)	TotalN = 11,088 (%)
Age			
Median [10th-90th percentile]	69 [44–84]	67 [39–86]	68 [42–85]
Range	15–101	15–105	15–105
Primary site (ICD-O-3), n (%)			
Parotid (C07)	4697 (78.0)	3862 (76.3)	8559 (77.2)
Submandibular (C08.0)	929 (15.4)	790 (15.6)	1719 (15.5)
Sublingual (C08.1)	72 (1.2)	105 (2.1)	177 (1.6)
Major salivary, overlapping (C08.8)	49 (0.8)	39 (0.8)	88 (0.8)
Major salivary NOS (C08.9)	277 (4.6)	268 (5.3)	545 (4.9)
Histological group, n (%)			
Adenocarcinoma NOS	1368 (22.7)	668 (13.2)	2036 (18.4)
Mucoepidermoid carcinoma	680 (11.3)	814 (16.1)	1494 (13.5)
Adenoid cystic carcinoma	618 (10.3)	853 (16.8)	1471 (13.3)
Acinic cell carcinoma	463 (7.7)	687 (13.6)	1150 (10.4)
Salivary duct carcinoma	458 (7.6)	178 (3.5)	636 (5.7)
Carcinoma ex pleomorphicAdenoma	270 (4.5)	211 (4.2)	481 (4.3)
Epithelial-myoepithelialCarcinoma	171 (2.8)	204 (4.0)	375 (3.4)
Myoepithelial carcinoma	177 (2.9)	139 (2.7)	316 (2.8)
Basal cell adenocarcinoma	153 (2.5)	161 (3.2)	314 (2.8)
Poorly differentiated –Undifferentiated	127 (2.1)	52 (1.0)	179 (1.6)
Secretory carcinoma	45 (0.7)	52 (1.0)	97 (0.9)
Poorly differentiated – smallcell carcinoma	62 (1.0)	34 (0.7)	96 (0.9)
Polymorphousadenocarcinoma	50 (0.8)	40 (0.8)	90 (0.8)
Carcinosarcoma	45 (0.7)	34 (0.7)	79 (0.7)
Oncocytic carcinoma	43 (0.7)	25 (0.5)	68 (0.6)
Poorly differentiated – largecell neuroendocrinecarcinoma	29 (0.5)	15 (0.3)	44 (0.4)
Hyalinizing clear celladenocarcinoma NOS	21 (0.3)	22 (0.4)	43 (0.4)
Sebaceous adenocarcinoma	3 (0.0)	5 (0.1)	8 (0.1)
Unspecified	1115 (18.5)	821 (16.2)	1936 (17.5)
Other rare morphologies	126 (2.1)	49 (1.0)	175 (1.6)
T-status, n (valid %)			
1	1035 (24.0)	1330 (36.1)	2365 (29.6)
2	1191 (27.7)	1042 (28.2)	2233 (27.9)
3	1353 (31.4)	891 (24.2)	2244 (28.1)
4	726 (16.9)	426 (11.5)	1152 (14.4)
missing	1719	1375	3094
N-status, n (valid %)			
0	2338 (57.3)	2529 (73.8)	4867 (64.8)
1	487 (11.9)	335 (9.8)	822 (10.9)
2	970 (23.8)	464 (13.5)	1434 (19.1)
3	286 (7.0)	98 (2.9)	384 (5.1)
missing	1943	1638	3581
M-status, n (valid %)			
0	3504 (87.9)	3001 (92.4)	6505 (89.9)
1	484 (12.1)	247 (7.6)	731 (10.1)
missing	2036	1816	3852
UICC-stage, n (valid %)			
I	633 (16.6)	882 (28.9)	1515 (22.0)
II	620 (16.2)	631 (20.7)	1251 (18.2)
III	740 (19.4)	606 (19.9)	1346 (19.6)
IVA-C	1827 (47.8)	932 (30.5)	2759 (40.2)
Unknown	2204	2013	4217

[a] *Column percentage, NOS = not otherwise specified, UICC = Union internationale contre le cancer*

all ANOS, SDC, and ACC cases (Table 2). The highest rates of distant metastases were found in primaries originating from the submandibular gland (12.2 %), followed by the sublingual (10.8 %), and the parotid gland (8.9 %).

Lastly, advanced tumor stages 3 and 4 were predominantly observed in male patients (67.2 %), while early and advanced stage cancers were distributed evenly, 49.6 % and 50.4 % respectively, in female patients. All percentages mentioned refer exclusively to cases for which data was available. Further detailed distributions of tumor characteristics can be found in Tables 1 and 2.

3.1.2. Incidence

The age-standardized incidence rate (ASIR) for all SGC was 5.2/1000,000 person-years for the period 2009–2022. Men showed a higher ASIR than women, 5.8 and 4.8 (rate difference: 1.0, 95 %CI: 0.8–1.4) respectively. The incidence of ANOS and SDC was higher in men, while the incidence of MEC, ACC, and Acin was slightly higher in women (Table 3, Supp. Table 1).

The overall SGC ASIR slightly increased over time in both sexes. This increase was more pronounced among women than men (Fig. 1). Over the observation period, a decreasing ASIR for ANOS was seen in men in favor of an increase in SDC. For women, a similar trend, yet not as pronounced, as well as a slight increase in MEC incidence was seen (Fig. 2). The ASIR for the remaining observed entities stayed constant over the observation period.

3.1.3. Survival

The 5-year relative survival (RS) was 70 %. Men had a lower RS than women (m:w; 62 %: 80 %, survival difference: −17 % (95 %CI: 11–24)) even after adjusting for covariates (Supp. Table 4). A subsequent analysis of the most frequently observed entities showed that ANOS and SDC had the lowest RS ranging from 50 % to 53 %, while Acin demonstrated the most favorable RS with 88 %. Tumors of the parotid and submandibular gland showed comparable RS, with 70 % and 73 %, respectively. In contrast, sublingual tumors exhibited a higher RS of 83 %. RS declined with increasing tumor size, from 92 % for T1 tumors to 42 % for T4 tumors. Furthermore, advanced nodal spread, N2 and N3, showed low RS, with 41 % and 33 %, respectively. Distant metastases showed the least favorable prognosis with a RS of 21 %. Higher stage and tumor grading, employed for MEC and Acin only, was associated with poorer RS (Fig. 3, Supplemental Table 2).

4. Discussion

This population-based study provides the first nationwide overview of the incidence, demographic characteristics, and survival of patients with primary SGC in Germany. It represents the largest registry-based epidemiological analysis of SGC to date, based on currently available national cancer registry data.

The incidence of SGC in the present study is slightly lower than the previously reported range of 5.7–9.2 cases per 1000,000 person-years [28,29]. Regional differences in SGC incidence have been reported. Incidence rates of up to 12/1000,000 have been found in American studies, while recent European studies reported rates between 5.7 and 9.2 [6,13,14,30]. Differences in cancer registry coding, particularly regarding inclusion or exclusion of minor salivary gland tumors and squamous cell carcinomas, are a reason for differing rates and complicates direct comparisons between regions [7,18]. Furthermore, the use of different standard populations complicates comparability of found results. These points are apparently evident when comparing this study's results to de Ridder et al. [11]. In that study, they reported slightly higher incidences compared to our study (6.3–7.4/1000,000 person-years; ESP), however, they included squamous cell carcinoma, which have been reported to be as high as 16 % of all major salivary gland malignancies [31]. This may explain the found slight difference in SGC incidence in a comparable cohort. Lastly, unknown risk factors for SGC as well as under-reporting could be also potential reasons for regional differences in SGC incidence [32].

In our study men were more often diagnosed with SGC than women. While the sex difference in SGC incidence has been described before, no compelling causal evidence has yet been established [23], and higher SGC incidences in women have been also reported [12]. However, most retrospective studies show a slight dominance of male sex in SGC incidence [6,9,28]. One possible explanation could be that men have

Table 2
TNM and site distribution within the most frequent morphology groups in Germany, 2009–2022.

	ANOS, n (%[a])	MEC, n (%)	ACC, n (%)	Acin, n (%)	SDC, n (%)	Total, n (%)
T-status						
1	311 (19.5)	601 (46.1)	337 (26.7)	400 (40.4)	107 (18.5)	1756 (30.7)
2	409 (25.7)	311 (23.9)	350 (27.8)	389 (39.3)	122 (21.1)	1581 (27.6)
3	512 (32.2)	269 (20.6)	394 (31.3)	158 (16.0)	227 (39.3)	1560 (27.3)
4	359 (22.6)	122 (9.4)	179 (14.2)	43 (4.3)	121 (21.0)	824 (14.4)
missing	445	191	211	160	59	1066
N-status						
0	632 (40.8)	889 (74.6)	909 (77.6)	782 (86.9)	194 (34.3)	3406 (63.3)
1	225 (14.5)	130 (10.9)	107 (9.1)	56 (6.2)	78 (13.8)	596 (11.1)
2	565 (36.5)	144 (12.1)	130 (11.1)	55 (6.1)	201 (35.5)	1095 (20.4)
3	126 (8.1)	28 (2.4)	26 (2.2)	7 (0.8)	93 (16.4)	280 (5.2)
missing	488	303	299	250	70	1410
M-status						
0	1255 (83.1)	1038 (96.4)	1006 (89.7)	825 (96.4)	427 (85.6)	4551 (89.9)
1	255 (16.9)	39 (3.6)	115 (10.3)	31 (3.6)	72 (14.4)	512 (10.1)
missing	526	417	350	294	137	1724
Primary site						
Parotid	1586 (77.9)	1236 (82.7)	682 (46.4)	1095 (95.2)	505 (79.4)	5104 (75.2)
Submandibular	323 (15.9)	160 (10.7)	632 (43.0)	34 (3.0)	100 (15.7)	1249 (18.4)
Sublingual	18 (0.9)	30 (2.0)	82 (5.6)	1 (0.1)	3 (0.5)	134 (2.0)
Major salivary,overlapping	12 (0.6)	12 (0.8)	16 (1.1)	4 (0.3)	6 (0.9)	50 (0.7)
Major salivaryNOS	97 (4.8)	56 (3.7)	59 (4.0)	16 (1.4)	22 (3.5)	250 (3.7)
UICC-stage						
I	168 (11.3)	372 (36.7)	241 (22.2)	282 (35.4)	53 (10.0)	1116 (22.7)
II	154 (10.4)	175 (17.2)	219 (20.1)	270 (33.9)	42 (7.9)	860 (17.5)
III	227 (15.3)	203 (20.0)	272 (25.0)	134 (16.8)	91 (17.2)	927 (18.9)
IVA-C	936 (63.0)	265 (26.1)	355 (32.7)	111 (13.9)	344 (64.9)	2011 (40.9)
Unknown	551	479	384	353	106	1873

ANOS = Adenocarcinoma not otherwise specified; MEC = Mucoepidermoid carcinoma; ACC = Adenoid cystic carcinoma; Acin = Acinic cell carcinoma; SDC = Salivary duct carcinoma; UICC = Union internationale contre le cancer; [a]Column percentages.

Table 3
Mean age-standardized incidence rate per million person-years in Germany between 2009 and 2022 (European Standard Population).

	ASIR (95 % CI)		
Overall	**Total**	**Men**	**Women**
Overall	5.2 (5.1–5.3)	5.8 (5.7–6.0)	4.8 (4.6–4.9)
Histological group			
ANOS	1.1 (1.1–1.2)	1.6 (1.5–1.7)	0.7 (0.6–0.7)
MEC	1.0 (1.0–1.1)	0.9 (0.9–1.0)	1.1 (1.0–1.2)
ACC	1.0 (0.9–1.0)	0.9 (0.8–0.9)	1.1 (1.0–1.2)
Acin	0.8 (0.8–0.9)	0.7 (0.6–0.8)	1.0 (0.9–1.0)
SDC	0.3 (0.3–0.4)	0.5 (0.5–0.6)	0.2 (0.2–0.2)
Primary site			
Parotid	3.9 (3.8–4.0)	4.5 (4.3–4.6)	3.6 (3.4–3.7)
Submandibular	0.9 (0.8–0.9)	1.0 (0.9–1.0)	0.8 (0.7–0.9)
Sublingual	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)
Major salivary, overlapping	0.0 (0.0–0.1)	0.0 (0.0–0.1)	0.0 (0.0–0.1)
Major salivary NOS	0.2 (0.2–0.3)	0.3 (0.2–0.3)	0.2 (0.2–0.3)

ASIR = age-standardized incidence rate; CI = Confidence interval; ESP = European standard population; ANOS = Adenocarcinoma not otherwise specified; MEC = Mucoepidermoid carcinoma; ACC =Adenoid cystic carcinoma; Acin = Acinic cell carcinoma; SDC = Salivary duct carcinoma.

markedly larger salivary glands than women. This could arguably increase the risk for malignant cell degeneration, yet, as mentioned, no causal evidence has been established [33]. Also, there has been limited reporting of SGC incidence being associated with higher rates of smoking and alcohol consumption. Horn-Ross et al. specifically analyzed potential risk factors by sex and found that current smoking and heavy alcohol consumption were associated with increased incidence of SGC in men, but these factors were not strongly related to risk in women [32]. However, it has to be mentioned that these findings are confined to a limited number of case-control and population-based studies and have not been ultimately validated as risk factors. The incidence was slightly increasing for both sexes, especially in women. This trend has been observed in previous studies from the USA and Australia [9,34]. Since SGC are rare entities and the reported changes in incidence are subtle, it remains unclear if they are attributed to improved diagnosis of SGC or if they are merely random observations [14]. Several authors have discussed improvements in early detection through improved diagnostic possibilities as a possible explanation for increasing SGC incidence [14,35]. Mayer et al. have also lined out improved pathologic expertise as a possible reason for the increase of certain SGC entities [15].

Furthermore, the study revealed that men exhibited a lower RS compared to women. This finding, which aligns with the findings of previous studies, could be partially attributed to the higher incidence of aggressive entities including ANOS, undifferentiated carcinoma, and SDC in men [9]. In addition, a similar phenomenon is observed across various types of cancer including lung, colorectal and bladder cancer [36]. It has been demonstrated that men tend to have a lower rate of adherence to therapeutic regimen, follow-up care, and delayed initial consultations in comparison to female patients. This discrepancy in adherence has been shown to result in suboptimal therapeutic outcomes [37].

In this study, 78 % of all tumors were located in the parotid, 15 % in the submandibular, and 1 % in the sublingual gland. In other national and cross-national epidemiologic studies on SGC, lower percentages of parotid tumors (52 %) were reported [6]. However, this could be caused by the inclusion of minor salivary gland cancers, which were excluded in this study. Comparable studies excluding minor salivary glands demonstrate similar distributions between 70 % and 80 % of all tumors arising from the parotid gland [9,11].

The predominant tumor entity in the parotid gland was ANOS, while ACC was the most frequent tumor entity of the submandibular and sublingual glands, respectively. The sublingual gland was also the only tumor location that was more common in women. While numerous studies have reported that ACC is the most likely morphology in submandibular and sublingual glands, substantial variations have been observed in the frequency of entities identified in the parotid gland [28]. Larger population-based studies have reported either MEC (26 %) [28] or ACC [6,10] as the most frequent parotid malignancy. It is important to acknowledge that the aforementioned studies employed different

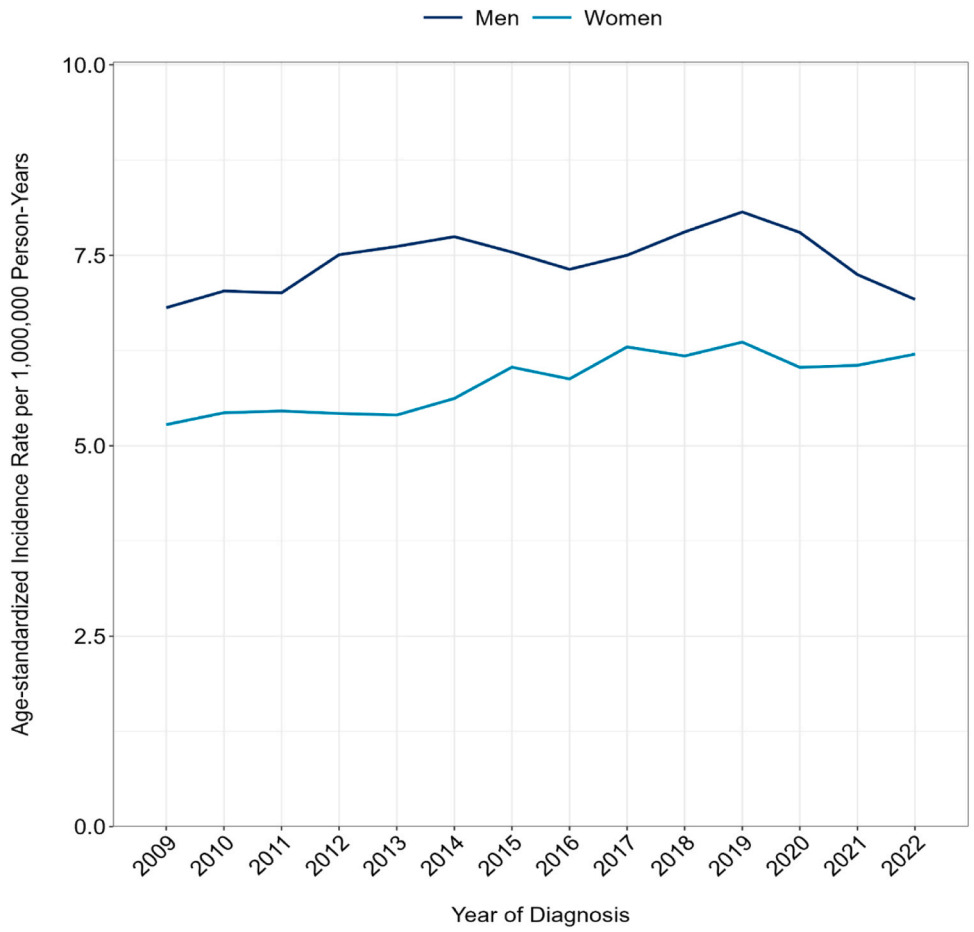

Fig. 1. Change of age-standardized incidence rates for all salivary gland cancers per million in Germany between 2009 and 2022. [a] values smoothed by 3-year moving average.

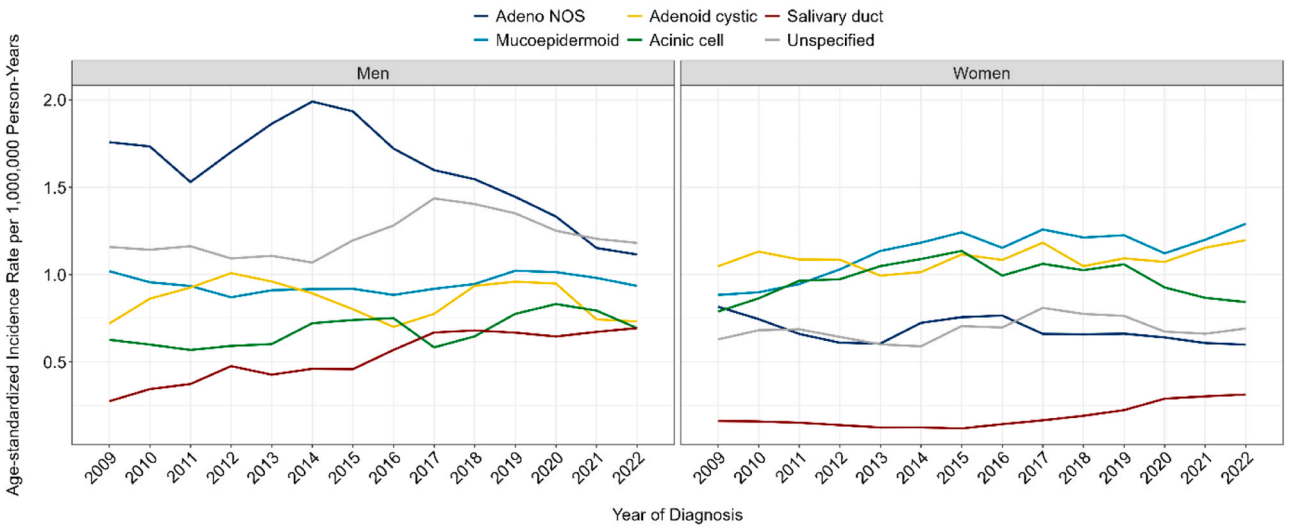

Fig. 2. Change of age-standardized incidence rates for selected entities per million in Germany between 2009 and 2022. [a] values smoothed by 3-year moving average.

methodologies regarding the in- or exclusion of specific tumor sites. Furthermore, regional disparities in the incidence of specific entities have been documented [28]. These circumstances may have altered the proportion of parotid malignancies, thereby explaining the observed differences between studies [30].

Other factors that may alter the incidence of certain SGCs are pathological reclassification and improved diagnosis. This study shows that the incidence of ANOS decreased slowly over the observation period that may have conversely contributed to the increasing incidence of SDC and partially also MEC [15]. In recent studies by Rooper et al. and Mayer

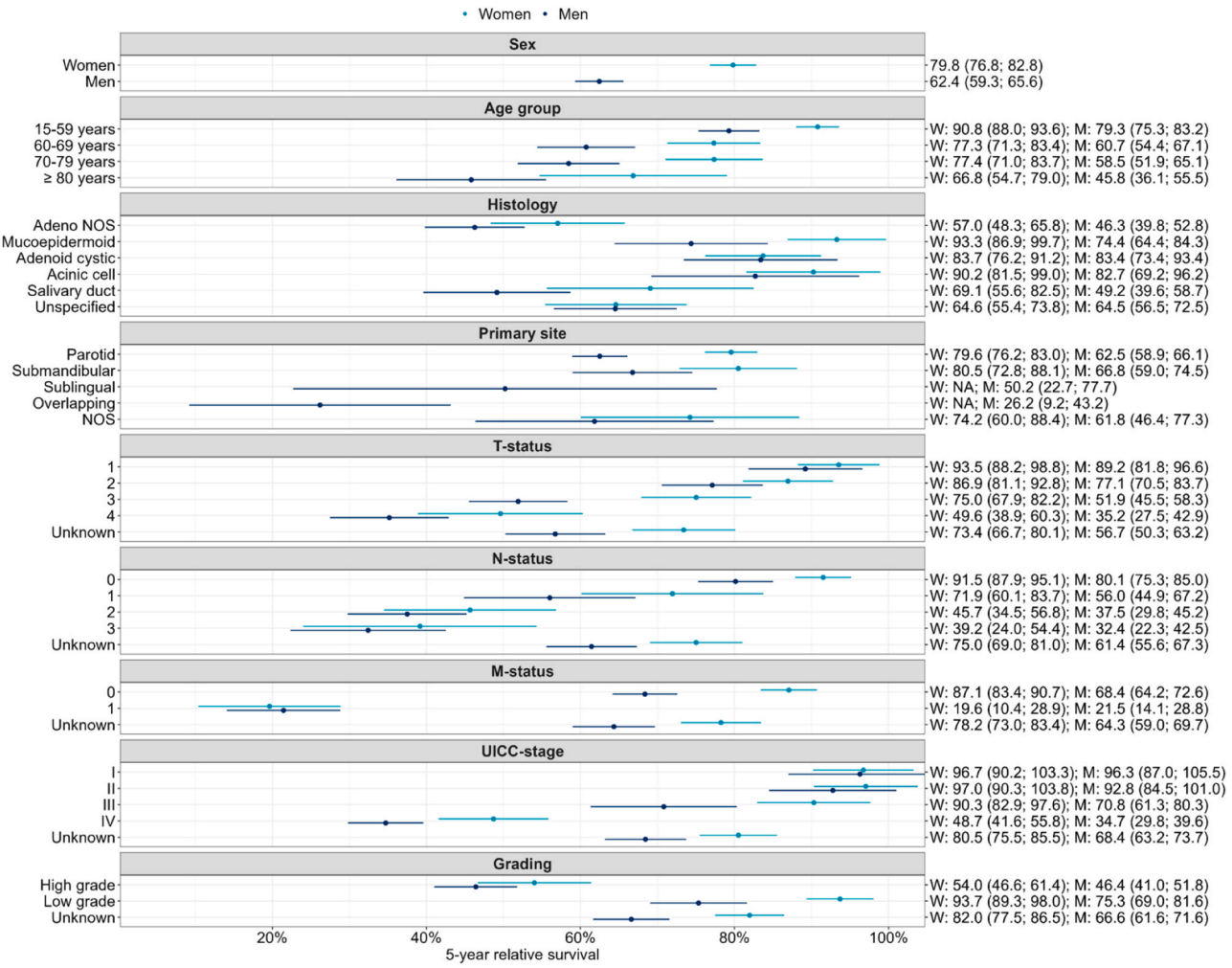

Fig. 3. Relative 5-year survival of salivary gland cancers by gender in Germany[a], calendar period 2018–2022 (n = 6567). [a] Bavaria, Mecklenburg-Western Pomerania, Hessen, Brandenburg, Berlin, Thuringia, and Saxony-Anhalt were excluded.

et al. it was shown that, after expert pathological reassessment of SGC, up to 39 % of SGCs initially diagnosed as ANOS were subsequently reclassified as SDC [15,16]. ANOS is a diagnosis of exclusion and comprises a heterogeneous subset of SGCs. An increase in SDC has been observed over the past 10 years, coinciding with the development of advanced immunohistochemical profiling and specialized pathological expertise. Concurrently, the diagnosis of ANOS has experienced a decline [16]. In the present study, a decline in ANOS and a concurrent increase in SDC incidence were particularly noticeable among men. As anticipated, the change was more pronounced in men given that the majority of SDC patients are men [38]. Another indication that many ANOS cases are in fact SDC cases, is the observed homogeneity among tumor characteristics and survival between the two entities. Full pathology reports were not available within this registry dataset. Consequently, it was not possible to perform a central pathology review or reevaluate histological slides to reduce the likeliness of misclassification of SDC and other entities as ANOS, which may have led to the comparably high incidence of ANOS.

Furthermore, we observed that higher T status was associated with poorer survival. A markedly lower survival was observed among T4 tumors, which were most apparent in SDC, ANOS, and ACC, in contrast to T1 tumors, which were predominantly found in MEC and Acin. The RS showed a striking difference depending on the presence of regional lymph node metastases. The survival was favorable at 86 % for N0 tumors and dropped steeply to 63 %, 41 % and 32 % for N1, N2 and N3 tumors, respectively. Moreover, 35.1 % of all patients were diagnosed with lymph node metastases at initial diagnosis. This proportion is higher than the values hovering between 18 % and 24 % reported in previous comparable studies [6,39]. Nodal spread was predominantly diagnosed in SDC, with over 66 % of patients presenting with lymph node metastases. N2 and N3 status were found in 51.9 % of all SDC patients. These findings suggest that frequently practiced stratification of SGC into broad T status categories (T1–2 vs T3–4) and binary nodal status (N0 vs N +) may inadequately predict clinical outcomes, as these simplified dichotomizations lead to outcome categories with broader and more imprecise prediction ranges [40,41].

Similar to regional metastatic spread, patients with distant metastases had the poorest survival among all independent tumor characteristics. Distant metastases were most frequently observed in SDC, ANOS, and ACC. Unfortunately, no detailed data on the exact localization of these metastases are available, so the frequency distribution of the affected organs, such as the lungs, cannot be determined. Notably, ACC was the only entity of the aforementioned three that showed favorable 5-year survival. The growth pattern of ACC may explain the difference, as the metastatic process is generally slow after diagnosis with ACC, but it eventually affects more than half of all patients. ACCs are usually treated with resection, yet even after R0 resection and adjuvant radiotherapy they have a strong tendency to develop lung metastasis 5–10 years after diagnosis, possibly due to early perineural invasion [42,43].

Grading showed worse outcomes for patients with high-grade transformation from MEC and Acin compared to those with low grade carcinomas. Amidst the more aggressive behavior and higher recurrence

rates of high-grade malignancies, both entities lack systematic therapeutic approaches. This deficiency further contributes to the poor survival outcomes observed [2].

The findings of this study must be interpreted in the light of their limitations as the study was based on retrospective data over the period of 2009–2022. While the use of registry data lowers the risk of a selection bias, potential over- or under-estimation of incidence rates and tumor characteristics may still occur due to false reporting by practitioners [44]'. Furthermore, due to the nature of the data we were unable to reassess the pathologic diagnosis of SGC entities which leaves diagnosis prone to possible pathologic misclassification, which has been proven to occur frequently in SGC [15]. At present, the ICD-O-3 coding system does not provide separate morphology codes for the specific subtypes of carcinoma ex pleomorphic adenoma preventing a more granular classification within registry-based datasets. Future measures improving morphology assessment and reporting, such as revised and improved pathologic profiling and the introduction of ICD-O-4, will very likely increase the incidence of SDC, partially myoepithelial carcinoma, and other entities while lowering the incidence of ANOS and carcinoma ex pleomorphic adenoma. The ZfKD has recently begun collecting clinical data with information on progress and therapies, however, only from 2020 onwards, which limits the findings of our study solely to epidemiological data. In the future, studies related to the effect of therapies and studies on progression-free survival may therefore also be examined using nationwide data. Also, no data on minor salivary gland tumors were analyzed as registry data cannot sufficiently grasp these tumors as they do not have a distinguishable ICD-code. An additional limitation of the study is that the data does not provide center-level data to identify potential inter-center variation. Conversely, a notable strength is that this analysis represents the largest registry-based study on SGC published to date.

5. Conclusion

This study is the first to provide a nationwide, population-based analysis of SGC in Germany. To date, it is the largest published epidemiological SGC study. The study showed slightly increasing SGC incidences, while confirming the previously documented tendency of the decreasing diagnosis of ANOS in favor of SDC. Furthermore, men were more likely to be diagnosed with SGC and were prone to aggressive entities like SDC and ANOS that were associated with poor survival. High T status disease, especially T4 tumors, lymph node involvement, and distant metastases were associated with markedly lower survival and were more commonly observed in men.

CRediT authorship contribution statement

Hiltraud Kajueter: Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Andreas Stang:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Marcel Mayer:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Lisa Nachtsheim:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Louis Jansen:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Jens Peter Klussmann:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Florian Oesterling:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Sofia Kourou:** Writing – review & editing, Visualization, Investigation, Conceptualization. **Andras Szentkiralyi:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Alexander Quaas:** Writing – review & editing, Visualization, Supervision, Methodology. **Lena Hieggelke:** Writing – review & editing, Supervision, Methodology. **Julia van de Loo:** Writing – review & editing, Visualization, Investigation, Conceptualization. **Philipp Wolber:** Writing – review & editing, Supervision, Conceptualization.

Consent for publication

N/A.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116196.

Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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