Incidence of Kaposi Sarcoma in Sweden is Decreasing

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Kaposi sarcoma is a rare skin cancer, and epidemiological research into Kaposi sarcoma is therefore scarce. The current epidemiological situation for Kaposi sarcoma in Sweden is unknown. The authors hypothesized that the incidence of Kaposi sarcoma should have decreased after the introduction of antiretroviral therapy in 1996. Using data from the Swedish Cancer Registry, this study aimed to determine the incidence rates and survival for Kaposi sarcoma in Sweden from 1993 to 2016. The results showed that a total of 657 patients (74.0% men, 26.0% women) were diagnosed with Kaposi sarcoma in Sweden during 1993 to 2016. The overall incidence per 100,000, age-standardized to the world population, decreased from 0.40 to 0.10 ($p = 0.003$) for both sexes combined, from 0.76 to 0.14 ($p = 0.003$) for men, and from 0.07 to 0.06 ($p = 0.86$) for women. The 10-year overall survival rate was significantly lower for the study population (30%) compared with the age- and sex-matched Swedish population (56%) ($p < 0.00001$). Over the study period, incidence rates of Kaposi sarcoma decreased significantly in men, especially during the late 1990s.

Key words: Kaposi sarcoma; incidence; Sweden.

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SIGNIFICANCE

This study shows that Kaposi sarcoma is an uncommon cancer in Sweden and that incidence rates decreased significantly in men, especially, during the late 1990s coinciding with the introduction of antiretroviral therapy. In general, Kaposi sarcoma is more common among men, and primarily affects the lower extremities and people above the age of 70 years in Sweden. Our results support the theory that the most common subtypes of Kaposi sarcoma in Sweden today are classic and/or immunosuppression-related Kaposi sarcoma. There is also a significantly lower survival rate among Swedish patients with Kaposi sarcoma compared with the age-matched Swedish population.

Kaposi sarcoma (KS) is a rare form of non-melanoma skin cancer (NMSC). Because of the rarity of KS, epidemiological research has been scarce. In Sweden, the latest epidemiological reports are from 1988 (1). KS is a malignant vascular tumour associated with human herpesvirus 8 (2). Although KS most commonly affects the skin, it can also be present in other organs. Four clinical subtypes of KS have been identified: classic, endemic, iatrogenic and epidemic or AIDS-related. Classic KS is a slow-progressing cutaneous disease, mainly affecting the lower extremities of elderly men of Mediterranean or Jewish origin. Endemic or African KS is usually a more aggressive form, affecting both children and adults. It is found in all parts of equatorial Africa. Iatrogenic KS can occur due to the immunosuppressive drugs given to organ transplant recipients. Epidemic or AIDS-related KS develops in HIV-infected persons and is an AIDS-defining illness (3). Classic and endemic forms are usually found in immunocompetent individuals, while iatrogenic and epidemic KS are associated with immunosuppression and usually regress with decreased immunosuppression (4).

In 1988, Dictor & Attewell (1) showed a significant increase in incidence of KS in Sweden prior to the HIV/AIDS epidemic. There is, however, no study showing the incidence trend after the introduction of antiretroviral therapy (ART) in 1996. Since Sweden has a mandatory registration of HIV-positive patients and general access to ART, in addition to strict laws regarding communicable disease notification in which HIV is included, the authors believe that this increased incidence of KS should have decreased, mainly due to better treatment for patients with HIV.

The aim of this study was to obtain a current epidemiological overview of KS in Sweden by analysing and describing the incidence and survival for KS, based on data collected from the Swedish Cancer Registry (SCR) between 1993 and 2016.

MATERIALS AND METHODS

This was a retrospective observational cohort study conducted by analysing patient data collected from the SCR, which was founded in 1958 and covers the whole Swedish population (5). It is compulsory for all Swedish healthcare providers working in public and private sectors to report every case of cancer to the registry. Hence, the SCR captures almost all cases of cancer in Sweden. Barlow et al. (6) showed the under-reporting of people with malignant disease to the SCR is less than 4%. However, it was not until 1993 that the registration of data became more specific. For example, it only became possible to separate different types of NMSCs more precisely when the second edition of the International Classification of Diseases for Oncology (ICD-O-2)

was introduced in 1993. The third version (ICD-O-3) including morphological tumour classification has been used since 2005. Thus, the actual number of patients with histopathologically verified KS can be calculated from 1993 onwards.

Study population

Patients with KS (ICD-O-2 or ICD-O-3 morphology code 91403) were identified from the SCR. As this morphology code is unique to KS, the collected data included all KS cases diagnosed in Sweden during the study period (1993–2016) with any International Classification of Diseases, 10th revision (ICD-10) code. Information received from the SCR included: patient's age and sex, KS diagnosis date, diagnosis according to ICD-10, TNM stage (collected by the SCR since 2004) and date of death, if applicable. Since KS is a rare malignancy, the SCR did not allow for the collection of data regarding patients' HIV status, use of immunosuppressive treatment and the cause of death to avoid the possibility of patient identification. Furthermore, all data provided by the SCR were anonymized prior to reception.

KS is not usually staged and there is no commonly used classification system for classic KS. Moreover, the American Joint Committee on Cancer (AJCC) TNM staging system for soft-tissue sarcomas specifically excludes KS (7, 8). In addition, there is no universally accepted classification available for AIDS-related KS (9). Despite the fact that there is no generally accepted TNM classification for KS, there were some patients with KS who had TNM stages recorded in the data provided by the SCR.

Statistical analyses

The crude incidence rate (the total number of new cases diagnosed in a specific year in the population category of interest, divided by the at-risk population for that category and multiplied by 100,000) (10) and the age-standardized incidence according to the distribution of the world average population between 2000 and 2025 (11), the new European standard population in 2013 (12), and the 2000 US standard population (10) were calculated. Logistic regression was used to test for trends of incidence rates over time, controlling for age group. The survival rate 0–10 years after diagnosing KS was estimated and compared with the survival rate for a Swedish age-matched population. Complete data were available for all study patients in a 10-year interval, so no data were censored. To compare proportions, Fisher's exact test was used. The statistical analyses were performed using R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) (13). A p-value of 0.05 was considered significant.

Ethics

Ethical approval was obtained from the Regional Ethical Review Board of Gothenburg (471-14) prior to the study.

RESULTS

Demographics

The demographics of the patients are presented in **Table I**. A total of 694 cases of KS in 657 patients were diagnosed in Sweden between 1 January 1993 and 31 December 2016. Twenty-seven patients had 2 diagnoses of KS, 2 patients had 3 diagnoses and 2 patients had 4 diagnoses. A significant majority (74.0%) of the patients diagnosed with KS were men ($p < 0.00001$). KS in Sweden proved to primarily affect elderly patients, with a median age of 74 years and a mean age of 67.8 years. The majority of patients (almost 60.0%) included in the study were over the age of 70 years. The distribution of KS in different age groups before and after the availability of ART (1993–1996 vs 1997–2016, respectively) is shown in **Fig. 1**. The distribution of KS in the age groups < 70 years and ≥70 years differed significantly ($p = 0.0003$) prior to and after the availability of ART.

Table I. Demographics of the patients diagnosed with Kaposi sarcoma during the period 1993 to 2016

Characteristics	All $n = 657$ (100%)	Men $n = 486$ (74%)	Women $n = 171$ (26%)
Age, years, mean (range)	67.8 (10–102)	64.0 (10–102)	78.6 (24–100)
Median	74.0	70.0	82.0
Age groups, n (%)			
0–19 years	1 (0.2)	1 (0.2)	–
20–29 years	15 (2.3)	13 (2.7)	2 (1.2)
30–39 years	63 (9.6)	60 (12.3)	3 (1.8)
40–49 years	76 (11.6)	74 (15.2)	2 (1.2)
50–59 years	61 (9.3)	51 (10.5)	10 (5.8)
60–69 years	50 (7.6)	42 (8.6)	8 (4.7)
70–79 years	152 (23.1)	109 (22.4)	43 (25.1)
80–89 years	198 (30.1)	117 (24.1)	81 (47.4)
≥ 90 years	41 (6.2)	19 (3.9)	22 (12.9)

Tumour location

As most of the KS lesions (93.1%) were found in skin and subcutaneous tissue, we subdivided KS location into cutaneous (ICD-10 codes C44 and C49) and non-cutaneous (all other ICD-10 codes) (**Table II).** The most common site for the tumours was the lower extremity, which accounted for more than all other sites combined (55.8%). The mean age of patients with KS located on the lower extremities was 75 years, which was significantly higher than the mean age of 64 years in patients with KS on other locations ($p < 0.0001$).

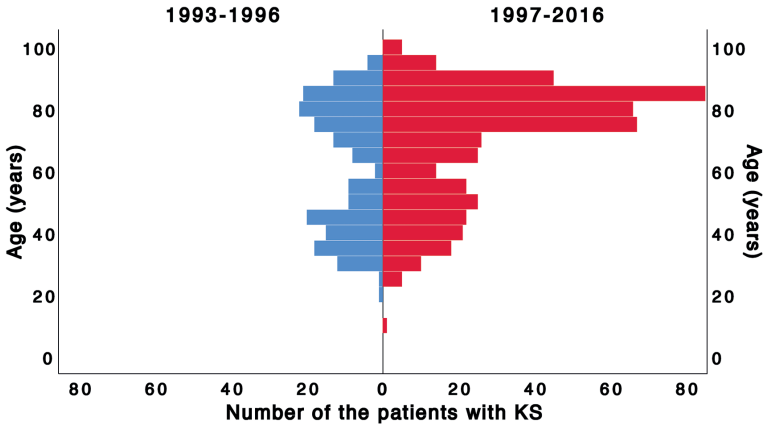

Fig. 1. Kaposi sarcoma (KS) in different age groups in Sweden before (*blue bars*) and after (*red bars*) the modern antiretroviral treatment era.

Table II. Tumour location for all registered cases of Kaposi sarcoma (KS) diagnosed during the period 1993 to 2016

Tumour location	*n* (%)
Cutaneous KS	
Head and neck	60 (8.6)
Trunk	44 (6.3)
Upper extremities	74 (10.7)
Lower extremities	387 (55.8)
Other	81 (11.7)
Non-cutaneous KS	
Oral cavity and pharynx	15 (2.2)
Gastrointestinal system	10 (1.4)
Respiratory system	5 (0.7)
Male genitalia	10 (1.4)
Other	8 (1.2)

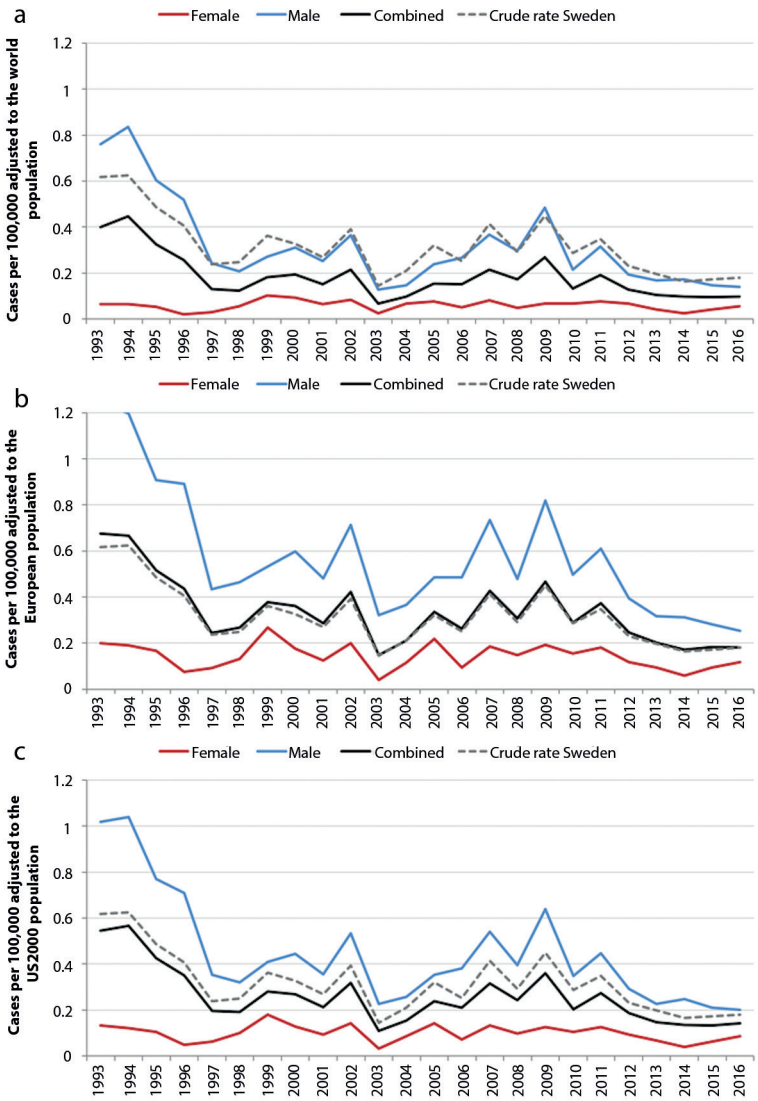

Fig. 2. Incidence rates of Kaposi sarcoma (KS) in Sweden during the period 1993 to 2016, age-standardized to (a) the world population, (b) the European standard population, and (c) the 2000 US standard population in women, men and both sexes combined.

Incidence rates

Incidence rates are shown in **Fig. 2**. The incidence decreased significantly over time from 1993 to 2016 for both sexes combined, regardless of the type of age standardization ($p \leq 0.003$). The crude incidence for both sexes decreased from 0.62 to 0.18 ($p=0.003$); for men alone, it decreased from 1.02 to 0.22 ($p=0.001$) and, for women, it decreased from 0.23 to 0.14 ($p=0.13$). During the study period, the overall incidence for men and women, age-standardized to the world population, decreased from 0.40 to 0.10 ($p=0.003$). For men alone, the decrease was from 0.76 to 0.14 ($p=0.003$) and for women, the decrease was from 0.07 to 0.06 ($p=0.86$). Changes in incidence rates, age-standardized to the European population, were from 0.68 to 0.18 for both sexes ($p=0.002$), from 1.25 to 0.25 for men ($p=0.001$) and from 0.20 to 0.12 for women ($p=0.18$) during the study period. Incidence rates adjusted to the 2000 US standard population decreased from 0.54 to 0.14 overall ($p=0.002$), from 1.02 to 0.20 for men ($p=0.001$) and from 0.13 to 0.09 for women ($p=0.18$). During the whole study period, the incidence was significantly higher among men ($p<0.00001$).

Survival analysis

Survival analysis included the patients whose KS was diagnosed between January 1993 and December 2006 ($n=413$). Survival calculations were based on the number of patients with KS and not KS cases. Only the first diagnosis of KS was included in calculations if a patient had multiple KS lesions. Data regarding disease-specific survival were not available. **Table III** and **Fig. 3** show overall survival of the patients diagnosed with KS compared with the expected survival in an age- and sex-matched population in Sweden. The overall survival rate 10 years after the KS diagnosis was significantly lower ($p<0.00001$) for the study population (30%; 95% confidence interval (95% CI) 26–34%) compared with the age- and sex-matched Swedish population (56%). For women, the 10-year survival was 25% (95% CI 17–34%) ($p=0.003$) and for men it was 31% (95% CI 27–37%) ($p<0.00001$) lower compared with the expected survival of the age- and sex-matched general population.

DISCUSSION

As expected, the incidence rate of KS in Sweden decreased significantly during the study period 1993 to 2016. The largest

Table III. Survival after diagnosis of Kaposi sarcoma (KS) compared with an age- and sex-matched population in Sweden for the whole study period (1993 to 2006) as well as the years before (1993 to 1996), during (1997 to 2001) and after (2002 to 2006) the introduction of antiviral therapy

	1993–2006		1993–1996		1997–2001		2002–2006		
Years after diagnosis	Number at risk	Survival % (95% CI)	Number at risk	Survival %	Number at risk	Survival %	Number at risk	Survival %	Age- and sex-matched population in Sweden Survival %
0	413	97.6 (96.2–99.1)	179	96.2	121	99.2	113	98.3	100.0
1	321	75.9 (71.9–80.1)	136	73.1	96	78.7	89	77.4	94.4
2	267	63.1 (58.7–67.9)	106	57.0	84	68.9	77	67.0	89.0
3	229	54.1 (49.6–59.1)	87	46.8	75	61.5	67	58.3	83.8
4	202	47.8 (43.2–52.8)	76	40.9	65	53.3	61	53.0	79.0
5	186	44.0 (39.5–49.0)	72	38.7	58	47.5	56	48.7	74.4
6	172	40.7 (36.2–45.6)	68	36.6	55	45.1	49	42.6	70.1
7	157	37.1 (32.8–42.0)	61	32.8	50	41.0	46	40.0	66.1
8	147	34.8 (30.5–39.6)	56	30.1	48	39.3	43	37.4	62.4
9	134	31.7 (27.5–36.4)	49	26.3	45	36.9	40	34.8	59.0
10	126	29.8 (25.7–34.5)	46	24.7	41	33.6	39	33.9	55.8

decrease was seen between the years 1993 and 1997, especially for men. The decrease was most likely caused by the introduction of ART in 1996, which led to fewer HIV-infected patients developing KS, which is an AIDS-defining illness (14, 15). This decrease in AIDS-related incidence of KS since the mid-1990s was also observed in other countries: the USA (14, 16), Italy (17), Switzerland (18), Uganda and Zimbabwe (19).

The age-standardized incidence was calculated based on the world, European and US standard populations. Regardless of the population used, the incidence of KS in men was higher than in women. This is in line with the study by Stiller et al. (20), who showed that the incidence of KS in men in Europe during 1995 to 2002 was more than 3 times that in women. In the current study, almost 3 out of 4 patients with KS were men when analysing the whole study period of 1993 to 2016. Predominance of men among the patients with KS was also observed in other studies performed before and after the introduction of ART (1, 19–21).

KS predominantly affected older patients in Sweden during the study period, with most patients being 70 years or older (median age 74 years). This predominance was also observed in Sweden and other Nordic countries prior to the ART era (1, 22). As classic KS mostly affects elderly men, one may hypothesize that classic KS is probably the most common subtype in Sweden today. An Italian study found that classic KS accounted for 97% of all cases over the age of 65 years (23). This hypothesis is further supported by the findings of studies performed in China (21) and the USA (24), where classic KS was more common than AIDS-related KS in older patients. In contrast, patients with AIDS-related KS are usually in their 30s or 40s (25, 26). In addition, the lower extremities were the most common body site for KS in Sweden, with 55.8% of patients presenting with tumours in this area. There was also a significant association between lower extremity KS and older age. This further supports the hypothesis that classic KS predominantly affecting the lower extremities is more common in Sweden than

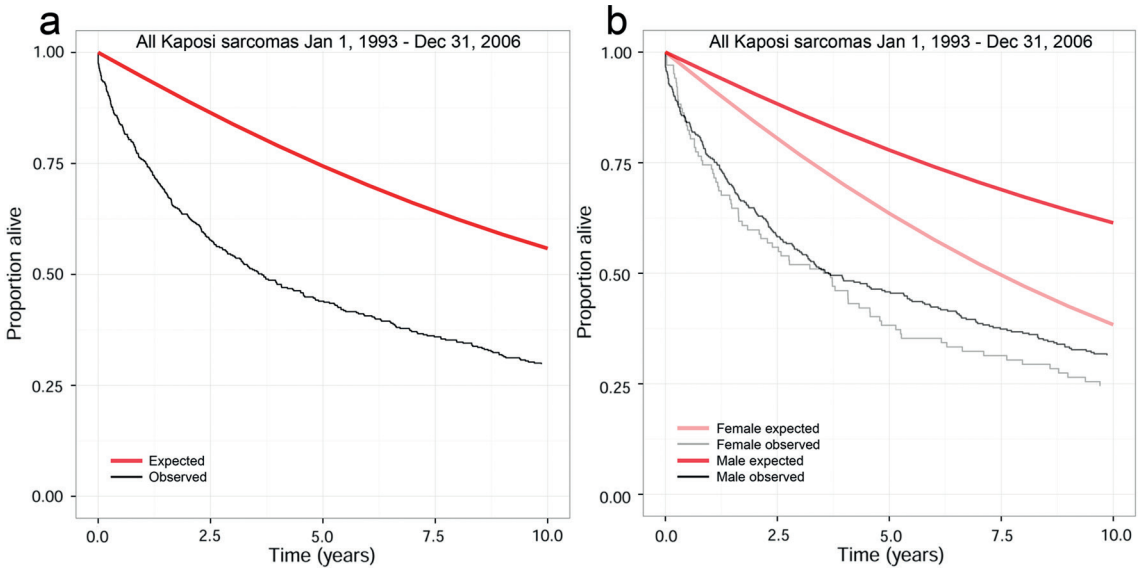

Fig. 3. Kaplan–Meier analysis of the overall survival of the patients diagnosed with Kaposi sarcoma (KS) between 1993 and 2006 compared with the expected survival: (a) all patients; (b) all patients divided by sex.

other types (24). It is well-known that classic KS has a higher incidence in specific ethnic groups (16, 21, 22, 27), but, unfortunately, the SCR contains no information regarding the patients' ethnic background or birthplace.

This study showed a significant decrease in cases of KS among the Swedish male population. Although the SCR does not collect data on whether patients were infected with HIV, the largest decrease in incidence rates for KS was observed between 1993 and 1997. This may suggest that AIDS-related KS was more common in Sweden before 1997, when the prevalence of AIDS was at its peak. The peak of reported AIDS cases in Sweden took place in 1995 and, since then, the number of AIDS cases decreased to approximately 50 diagnoses per year in 2010 to 2011 and only 35 cases in 2014, according to the Swedish Public Health Agency (28, 29).

The overall 5- and 10-year survivals for the current study population were 44% and 30%, respectively. In comparison, a European study showed that, depending on the period studied, the 5-year survival increased from 17% to 72% for people diagnosed with KS under the age of 65 years, while it was 66–74% for those aged 65 years and above (20). In a prospective study including patients with AIDS-related KS (age not specified), the 5- and 10-year overall survival rates were 83–92% and 81–88%, respectively (30). The reason for the low survival rate in the current study is not clear. One possible explanation could be unknown co-morbidities (24). However, as the data regarding the cause of death were not available during the study, no definite conclusion can be drawn.

Limitation

As this is a registry-based study, there are some potential limitations. The most significant limitation is the risk of misclassification caused by inadequate or incomplete registration. Under- and over-registration could arise from limited biopsies or registering of the same tumour more than once. To avoid this limitation, the SCR cross-referenced the clinical registry (ICD) with the registry used by pathologists (SNOMED), both of which are mandatory in Sweden. The SCR is regarded to have almost 100% coverage. Thus, it is very likely that almost all "true cases" of KS have been captured. Another limitation was the lack of data regarding which type of KS the patients had. Lastly, a relevant analysis of the TNM stage at diagnosis could not be performed, since >80% of the patients with KS did not have available data regarding TNM in the SCR.

Conclusion

This study shows that KS is an uncommon cancer in Sweden, and that incidence rates decreased significantly in men, especially during the late 1990s coinciding with the introduction of ART. In general, KS is more common among men, and primarily affects the lower extremities and people above the age of 70 years in Sweden. This study supports the theory that the most common subtypes of KS in Sweden today are classic KS and/or iatrogenic (immunosuppression-related) KS, and that AIDS-associated KS may have been more common in the mid-1990s. Interestingly, there is a significantly lower survival rate among Swedish patients with KS compared with the age-matched Swedish population, which cannot be explained by the findings of this study.

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The authors have no conflicts of interest to declare.

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