

Short Communication

High incidence of classic Kaposi's sarcoma in Mantua, Po Valley, Northern Italy (1989–1998)

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Summary The incidence of classic Kaposi's sarcoma was estimated in the province of Mantua, Po Valley, Northern Italy, yielding age-standardized rates of 2.5/100 000 men and 0.7/100 000 women (1989–98). Elevated rates in the rural zone of Viadana/Sabbioneta (5.0/100 000 men and 2.8/100 000 women) are among the highest so far reported for Italian communities. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

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The classic variant of Kaposi's sarcoma (KS) is not rare in Italy but it is unevenly distributed (Geddes et al, 1994). This pattern seems to be highly dependent on local rates of infection with the not ubiquitous human herpesvirus 8 (HHV-8), which is central in the pathogenesis of KS (Calabrò et al, 1998; Whitby et al, 1998). The reasons underlying geographical variations in HHV-8 seroprevalence and clustering of classic KS are unclear.

Following the report of an excess of soft tissue sarcomas in the city of Mantua (Costani et al, 2000), an ad hoc survey of all incident cases within the province disclosed a high number of KS cases. An epidemiological study of the disease in this area was therefore carried out. The Mantua province is of special interest because, though not served by a population-based Cancer Registry, it is located in the Po Valley, which has recently been shown to be among the 'hot spots' for HHV-8 infection in Italy (Calabrò et al, 1998; Whitby et al, 1998; Whitby et al, 2000).

MATERIALS AND METHODS

The province of Mantua (2339 km², one-eighth of the Po Valley, population: 365,000) in Lombardy (Figure 1) comprises 70 municipalities in 9 administrative 'zones'. It is a flat area of rivers, lakes, marshes and irrigation channels. Mantua's economy is chiefly concerned with the processing of cereal grains (wheat, corn and rice) and livestock farming.

Cases were individuals with a histological diagnosis of KS in the period 1989–1998 (M9140/3, ICD-O morphology code); HIV-related cases were excluded. Incidence rates were computed for each municipality and zone. Direct standardization of incidence rates was performed using the STATA package. Confidence intervals were computed using the Poisson distribution.

The following characteristics were estimated for each municipality: population by age and sex; altitude; urban–rural gradient (a 4-category socio-economic index calculated by applying factor

analysis to a subset of 13 variables, including population density and proportion of active population employed in agriculture (ISTAT, 1986); main rivers flowing through the territory; whether (or not) it was included among the endemic areas for malaria both in 1902–1903 (Biancorosso, 1935) and 1908 (Soliani, 1909). Cases were coded accordingly to residence at birth, during the first 15 years of life, and main residence. The 3 different incidence rates so computed for the 70 municipalities were treated as outcome variables in a multiple linear regression model, in which the previously mentioned characteristics were present as predictive variables.

RESULTS

There were classic KS cases in 44 men and 20 women (mean age: 72.2 (range: 26–92), male-to-female ratio: 2.6), as shown in Table 1. The overall standardized incidence rate was 2.5/100 000 in males and 0.7/100 000 in females. Incidence rates showed geographic differences. In the southwest (Viadana/Sabbioneta, zone 9) these were particularly high, both in women (2.8/100 000, 95% CI 2.04–7.84, based on 10 cases) and men (5.0/100 000, 95% CI 2.54–9.10, based on 11 cases). In Table 2, the estimated rates are compared with those of 5 other areas of the Po Valley (Figure 1).

As expected, rates increase with age and appear substantially higher among males though in the oldest age group (≥ 90), cases were observed only among females, perhaps reflecting the higher mean ages of women.

The multivariate analysis showed that the best-fit model included the independent variables listed in Table 3. Incidence according to residence during the first 15 years of life was the best outcome variable. Zones 4 and 9, which were selected by the model as being significantly associated with the incidence of KS, include 13 municipalities; of these, 9 were formerly endemic for malaria (69%). The corresponding proportion in the other zones is 39% ($P = 0.045$).

DISCUSSION

Elevated rates of classic KS were found far above those reported for Italy as a whole and for most European countries (Geddes et al, 1994; Zanetti et al, 1997). The estimated rates vary greatly among

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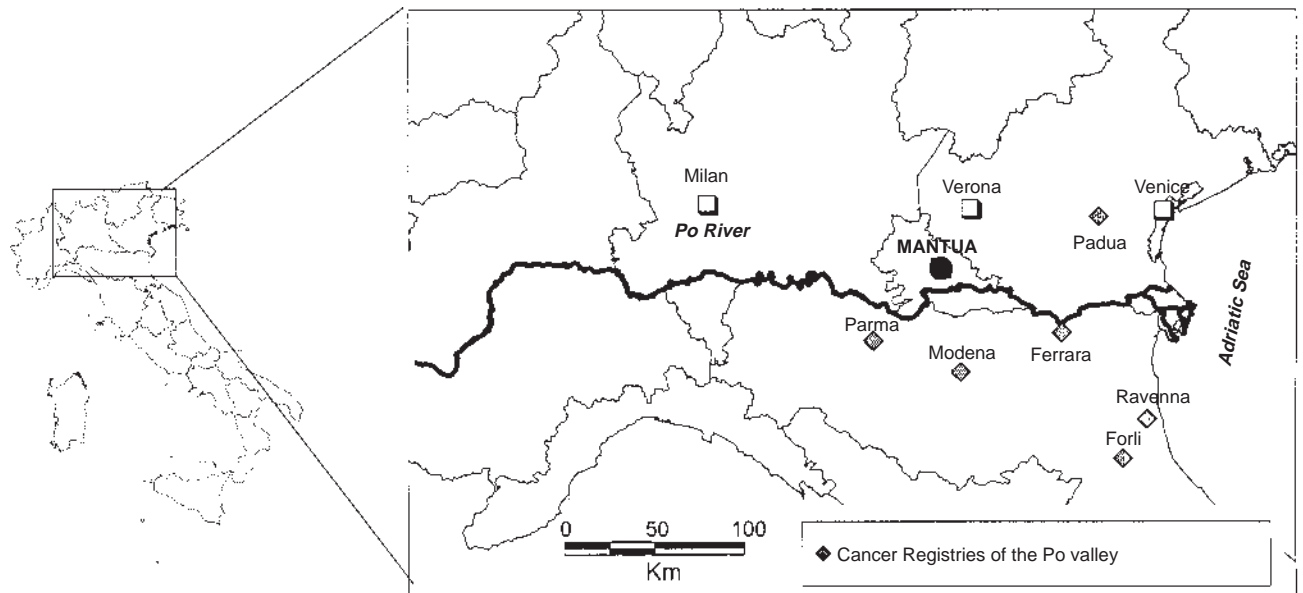


Figure 1 Location of the province of Mantua (Lombardy), upper Po Valley, Italy

Table 1 Number of cases^a and age/sex specific incidence rates of classic Kaposi's sarcoma (per 100 000 person/years) in the Mantua province, Po Valley, Northern Italy, between 1989 and 1998

Age (years)	Men			Women		
	No. of cases	Population (person/years)	Rate	No. of cases	Population (person/years)	Rate
0–29	1	644 270	0.16	–	614 500	0.00
30–39	1	258 910	0.39	–	253 790	0.00
40–49	–	249 220	0.00	1	247 420	0.40
50–59	4	239 770	1.67	1	250 120	0.40
60–69	12	213 300	5.63	2	255 340	0.78
70–79	16	120 200	13.31	6	181 120	3.31
80–89	10	41 890	23.87	8	86 710	9.23
>90	–	1 960	0.00	2	5 860	34.13
All	44	1 769 520	2.49	20	1 894 860	1.06

^aOnly 1 subject was born outside the Po Valley (Southern Italy).

Table 2 Annual incidence rates^a of Kaposi's sarcoma ($\times 100\ 000$ person/years) in the Mantua province and 5 areas of the Po Valley served by a Cancer Registry

Geographic area		Kaposi's sarcoma					
		Males			Females		
		Cases	Rate ^d	Histologic diagnosis (%)	Cases	Rate ^d	Histologic diagnosis (%)
Mantua ^b	1989–98	42	6.7	100	19	2.6	100
Ferrara ^c	1991–92	12	8.4	100	6	5.1	100
Forlì-Ravenna ^c	1988–92	13	3.0	95.7	8	1.5	91.7
Modena ^c	1988–92	17	3.3	84.6	6	0.9	100
Padova ^c	1988–92	18	2.6	97.1	11	1.0	100
Parma ^c	1988–92	8	2.1	90.2	0	–	–

^aAge-standardized to Italian population of 1991. ^bNot served by a Cancer Registry; HIV-KS excluded. ^cHIV-KS included. ^dRates are calculated according to the data derived from local Cancer Registries that include HIV-related KS cases (Zanetti et al, 1997). In order to make the figures comparable, age standardized rates are computed considering only cases and populations aged ≥ 50 , under the assumption that HIV-related KS cases should be below the age of 50.

Table 3 Multivariate linear regression analysis of incidence rates according to residence during the first 15 years of life. $F_{(6,63)} = 8.77$; $P_F < 10^{-4}$; Adjusted $R^2 = 0.40$

Variable*	β value	P_t^{\dagger}	95%Confidence interval
1 river ^a	0.113	0.771	-0.66-0.88
2 or more rivers ^a	0.936	0.007	0.27-1.61
Semi-urban feature ^b	0.485	0.256	-0.36-1.33
Semi-rural feature ^b	1.946	0.025	0.25-3.64
Rural feature ^b	1.079	0.007	0.31-1.85
Zone ^c	1.865	$<10^{-3}$	1.12-2.61
Constant	-0.343	0.377	-1.11-0.43

[†] P value associated with the t value obtained by testing β . ^aAbsence of river taken as reference. ^bUrban feature taken as reference. ^cZones 9 and 4 joined vs. all the others. *Based on municipality of residents.

nearby municipalities, and are particularly high both in men and women in a rural area lying within the confluence triangle of the Oglio and Po rivers (Figure 2). This may reflect geographical variations in the prevalence of HHV-8 infection, but may also be dependent on genetic homogeneity and/or as-yet-unknown environmental agents.

None of the variables considered in the multivariate analysis appears to have a major role in predicting the incidence within the province, except 'belonging to certain geographic areas' where the proportion of municipalities formerly endemic for malaria is significantly higher than in others. The presence of 2 or more rivers and the rural/semi-rural environment may also be relevant.

No data are available regarding HHV-8 seroprevalence in Mantua though several of the co-factors claimed to be associated with an increase in the risk of KS are present such as (i) areas formerly endemic for malaria; (ii) rural lifestyle and cereal

farming (Cottoni et al, 1997); (iii) presence of iron oxide-rich clay in soils (Ziegler, 1993); (iv) plenty of blood-sucking insects (McHardy et al, 1984).

There is some evidence that certain zones in the Po Valley are 'endemic' for HHV-8 infection and KS. Incidence rates in Ferrara (delta of the Po River) are among the highest in the world (Zanetti et al, 1997). Classic KS has been documented among Po Valley people from Lombardy (Rabbiosi, 1959; Zanca et al, 1973; Brambilla et al, 1988), Emilia-Romagna (Martinotti, 1938) and Piedmont (Vineis et al, 1987). More recently, serological (Calabrò et al, 1998; Whitby et al, 1998; Whitby et al, 2000) and molecular-based studies (Luppi et al, 1996; Monini et al, 1996) have shown that HHV-8 infection is present in healthy subjects of the Po Valley. Our findings contribute to the mapping of classic KS in Italy and, besides the south of Italy, Sardinia and Sicily, indirectly confirm the Po Valley as a high-risk area. A sero-epidemiological survey of the prevalence of HHV-8 infection in the KS-free population is in progress.

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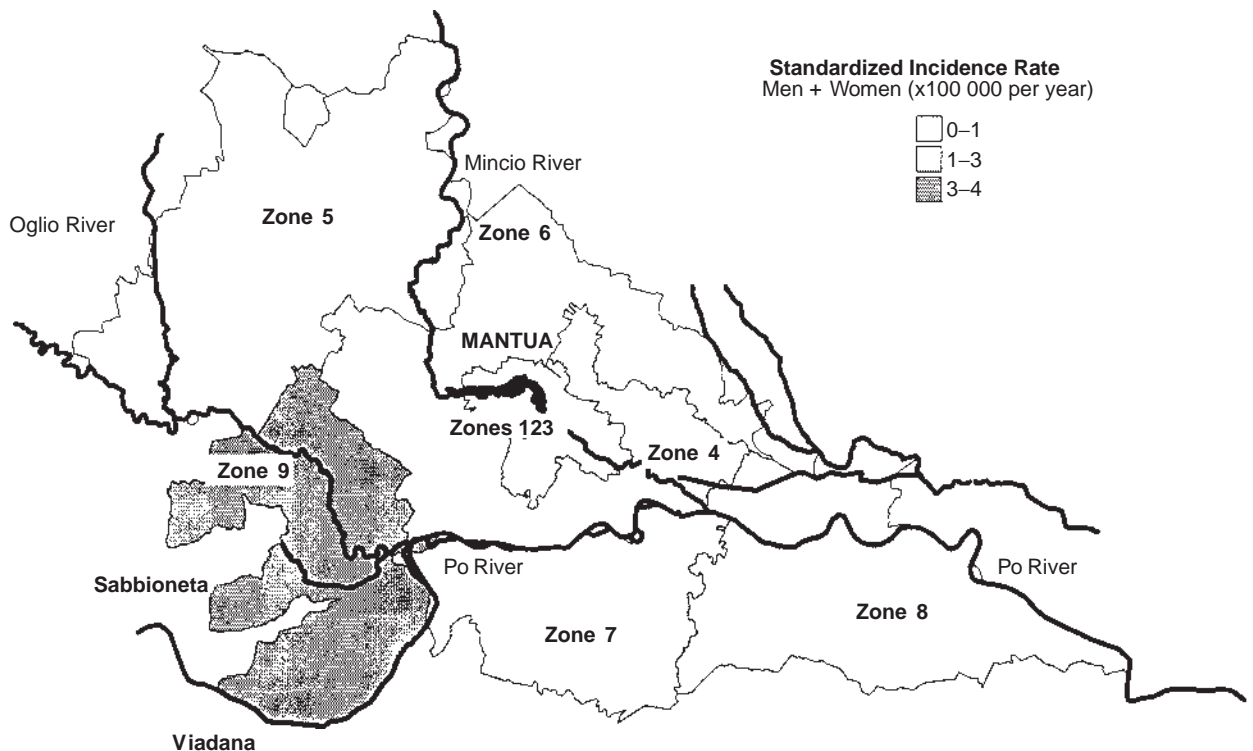


Figure 2 Geographical distribution of standardized incidence rates by zone, for men and women together

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