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**POSSIBLE ASSOCIATION OF KAPOSI'S SARCOMA AND MULTIPLE TUMOURS: EPIDEMIOLOGICAL EVIDENCE FROM THE CANCER REGISTRY OF NORTH SARDINIA****MARIO BUDRONI\***, ROSARIA CESARACCIO, ANTONIO COSSU, GIUSEPPE PALMIERI, MASSIMILIANO OGGIANO, AMELIA SECHI, DANIELA PIRAS AND FRANCESCO TANDA

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**CASE REPORT**

**ABSTRACT. BACKGROUND:** The observation of multiple tumours is becoming more and more frequent. The immune deficiency caused by infectious diseases, cancer and/or pharmacological treatment may contribute to the onset of a second cancer. Some of the risks may be due to the increased site-specific medical surveillance. Conversely, some associations are difficult to be explained. **METHODS:** Incidence of Kaposi's sarcoma (KS) linked to or not linked to the epidemic of acquired immunodeficiency syndrome (AIDS) was assessed in North Sardinia. The presence of synchronous or asynchronous tumours was included into the models for the definition of the relative risk. **RESULTS:** The KS European adjusted rate was found higher in males (3.9%) than in females (1.4%). Incidence of KS in Sardinia is slowly decreasing despite both the spread of AIDS epidemic and the ageing of population (some social changes may be responsible for this phenomenon). The relative risk of multiple tumours in KS was higher compared to those observed in all the other tumours. Altogether, a second primary malignancy was observed in 15/106 (14%) KS males and 3/45 (7%) KS females. Among males, KS was increasing until 1997 before registering its trend inversion; among females, KS incidence is still increasing. **CONCLUSION:** Our findings strongly indicate that patients affected by Kaposi's sarcoma present a risk for the occurrence of multiple tumours.

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## 1. INTRODUCTION

Kaposi's sarcoma (KS) is a tumour of the vascular endothelium, occurring in four clinical-epidemiological forms: classic Kaposi's sarcoma (CKS), African sarcoma, acquired immunodeficiency syndrome (AIDS) or immunosuppressive therapy-associated KS. All forms are correlated with infection by the human herpesvirus-8 (HHV-8) [1]. At early stages, KS induces a state of immune deregulation that precedes lesion appearance. HHV-8 probably stimulates abnormal proliferation of lymphocytes through virally-encoded cytokine homologues (v-interleukin 6) or proteins that interfere with cell cycle control (v-cyclin or latent nuclear antigen) [2-3]. The spread of AIDS epidemic has stimulated interest in KS because of the incidence pattern variation. The KS is a rare tumour and shows heterogeneous distribution in different geographic areas. It presents a high incidence in Mediterranean area [4], and it is very uncommon in the United States [5] and England [6] before the AIDS epidemic. In Sardinia, KS is a comparatively common disease and some epidemiological studies have been carried out [7].

We here defined the incidence of such disease as well as any variation due to AIDS epidemic and the association with other tumours in Sardinian population. The rationale of this study was based on controversial data obtained from the literature. In some recent Italian studies, a very high incidence of KS has been described [8], whereas a decline of CKS in elder people along with a steady rise of AIDS-associated KS was found in some other areas of the country [9]. Furthermore, an association (adjusted relative risk = 1.58) between KS in AIDS and immunoblastic lymphoma was demonstrated [10]. While some authors have not observed an increased risk of additional cancers among individuals who initially developed KS [11], others found a risk of cancer after the KS onset or, alternatively, a risk of KS in patients with a diagnosed primary cancer [12-13].

Therefore, we performed an epidemiological analysis in North Sardinia, where a well-recognized cancer registry exists [14]. Data from such a geographical area presenting a high incidence of KS

allowed to better define how much the AIDS epidemic and the increased population ageing have changed the disease incidence trend as well as how much KS increased the risk of multiple tumours.

## 2. MATERIALS AND METHODS

Data from the cancer registry of the province of Sassari, accounting for the entire northern part of the Sardinia island and including all incident cases of KS as well as all other types of cancer during a period of ten years (1992-2001) [15] were used for this study. In 2001, this geographical area had an estimated population of 470,000 inhabitants. Identification of cases was made according to standardized criteria and procedures of population cancer registries [14-15], particularly based on accurate linkage of record files for all hospitals and clinics across the province. The inclusion criteria for KS cases were based on the histological examination. The diagnosis of KS was made

TABLE 1. KAPOSI'S SARCOMA IN NORTH SARDINIA.

AGE CLASS	NO. OF MALES	RATE IN MALES	NO. OF FEMALES	RATE IN FEMALES
20-24	0		2	1.09
25-29	2	1.01	0	0.00
30-34	1	0.51	4	2.07
35-39	3	1.65	0	0.00
40-44	3	1.79	1	0.59
45-49	5	3.19	1	0.65
50-54	4	2.77	1	0.69
55-59	3	2.30	4	3.07
60-64	12	10.22	2	1.60
65-69	14	13.77	1	0.89
70-74	14	17.20	6	6.20
75-79	15	27.74	8	11.64
80-84	21	59.78	4	8.20
85+	9	29.29	11	25.70
Totale	106	4.58	45	1.91
EAR		3.93		1.41

NOTE: Number of cases and rates per 100,000 inhabitants. EAR, European adjusted rate.

TABLE 2. DISTRIBUTION BY AGE OF KAPOSI'S SARCOMA IN MALES, AS A FIRST (UPPER TABLE) OR SECOND (LOWER TABLE) CANCER IN CASES WITH MULTIPLE TUMOURS.

SECOND TUMOUR	AGE CLASSES								TOTAL
	25-29	45-49	65-69	70-74	75-79	80-84	85-89	90-94	
OESOPHAGUS					1				1
COLON								1	1
RECTUM		1							1
CHOLEDOCUS							1		1
LUNG						1			1
MELANOMA							1		1
SKIN			1			1	2		4
PROSTATE					1				1
BLADDER						1			1
LNH	1	1		1	1				4
TOTAL	1	2	1	1	2	3	4	1	15

FIRST TUMOUR	AGE CLASSES						TOTAL
	60-64	65-69	70-74	75-79	80-84	85-89	
COLON				1			1
LARINX			1				1
SKIN	1	1			2		4
BLADDER						1	1
LNH		2	1				3
TOTAL	1	3	2	1	2	1	10

according to generally accepted histology and morphology parameters [16]. Furthermore, as a criterion of differential diagnosis between KS and CKS, all Kaposi's sarcoma cases included in the study, underwent a blood test for HIV infection after collecting patients' written informed consent. At moment of hospital admission, all subjects were also carefully interviewed about previous transplant and/or immunosuppressive therapy; all information were recorded in the case-history. The tumours were classified as multiple according to the International Agency Cancer Research (IARC) rules [17]. The crude rates were computed using the cases number and the official estimated population of province in the considered period (1992-2001), and adjusted on the European standard population by

means of the direct standard method (EAR = European Adjusted Rates). Finally the Rate of multiple tumours was calculated, using the person/year rate of KS and all other multiple tumours, during the period 1992-2001.

To analyze the time trend for cancer rates, we carried out a "join-point" analysis, a model where several different trend lines are connected together [18]. We tested which one between different join-point models including from 0 to 2 join-points, with a maximum of three line segment allowed, could fit well the data. The analysis was performed with the Joinpoint 2.5 software provided by the National Cancer Institute:

[www-ccps.nci.nih.gov/SRAB/joinpoint](http://www-ccps.nci.nih.gov/SRAB/joinpoint).

TABLE 3. RATE OF MULTIPLE TUMOURS IN KS AND IN ALL OTHER TUMOURS PER 1000.

	KS MALE	ALL TUMOURS MALE	KS FEMALE	ALL TUMOURS FEMALE
MULTIPLE TUMOURS	15	890	3	415
PERSON/YEARS	865.35	94000	394.08	81000
RATE	18.49	9.47	5.08	5.13
C.I.-LOWER	11.33	8.87	1.27	4.66
C.I.-UPPER	30.18	10.11	20.29	5.65
R.R.	1.95		0.99	

NOTE: C.I., confidence interval; R.R., relative risk.

### 3. RESULTS

From 1992 to 2001, 151 KS cases were diagnosed. Considering the clinical epidemiological forms, we found 139 CKS cases, 10 AIDS-associated cases and 2 KS developed in patients undergoing an immunosuppressive therapy. Among KS patients, the males were 106 and the females 45; for all of them, the histological examinations were available and cancer diagnosis of each case was confirmed on pathology report. In our series, six cases of KS AIDS-associated among males aged 25-39 as well as four cases AIDS-associated and two cases who underwent immunosuppressive therapy after kidney transplant among females aged 20-34 were observed. The incidence is particularly high in males aged 70 years and over. The frequency, crude, specific and EAR are reported in TABLE 1.

Among patients with multiple tumours, fifteen

(14%) out 106 male patients had a KS as a first cancer whereas ten (9%) of them had KS as a second cancer (TABLE 2). Overall, we found 890 (7.3%) malignant multiple tumours out of 12,188 cancer diagnoses in males and 415/9,710 (4.3%) in females. Therefore, the relative risk (RR) of multiple tumours in KS is 1,95 for males and 0,98 for females (TABLE 3) for all tumours.

Among males, KS was increasing until 1997 before registering an inverted trend; among females, KS incidence is still increasing (TABLE 4).

### 4. DISCUSSION

The classic Kaposi's sarcoma (KS) mostly affects individuals over 60 years old; sometimes, it occurs in 40-50 year-old peoples. After the AIDS spread, an increasing number of younger people was involved. In North Sardinia, both specific and standardized rates of classic KS are higher than in other areas from North Italy [8] as well as from other Italian regions [9].

In a study previously conducted within our region, incidence of KS was found at a rate lower than that here presented [19]. However, the previous study was based on data collected during a precedent shorter observation period (five years, from 1987 to 1991) in comparison to that of the present study (ten years, from 1992 to 2001). These findings seem to suggest an increased KS incidence during the recent years. Considering the KS trend, we found a decrease of disease incidence among males (starting from 1998) and a steadily increased incidence among females (starting from 1996). In the last thirty years, two changes have been registered in this population: the ageing of people which

TABLE 4. TREND OF KAPOSI'S SARCOMA.

SEX	NO. PER YEAR (AVERAGE)	EAR PER YEAR (AVERAGE)	TREND 1	TREND 2	TREND 3
			RANGE OF YEARS	RANGE OF YEARS	RANGE OF YEARS
M	10.6	3.93	0 (1992-94) - 0.175	1 (1995-97) - 0.710	2 (1998-01) - 0.861
F	4.5	1.41	0 (1992-96) + 0.683	1 (1997-99) - 0.006	2 (2000-01) + 0.10

did not develop the malaria disease, and the transformation of social and economic conditions (moving from the agriculture to industry, with a more evident involvement of females in industrial work). These changes could somehow influence the trend of disease, although some authors did not find any association with the occupational risk [20].

Among AIDS patients, association of KS with other tumours (particularly, immunoblastic lymphoma) has been widely described [10]. Conversely, a risk of a second primary tumour after classic KS is still controversial [11-13]. In our experience during ten years of observation, we found that males patients with KS present a significant risk (RR 1,95) of multiple tumours. Association with AIDS and immunosuppressive therapy clearly indicates that a deregulation of the immunological system may be involved in KS pathogenesis. However, this hypothesis alone is not able to fully explain the differences between sexes and the risk of carcinoma as a second primary tumour in patients with KS. Further studies in larger collections of patients with different geographical origins are thus awaited.

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#### REFERENCES

- [1] ANTMAN K AND CHANG Y [2000] Kaposi's sarcoma. *N Engl J Med* 342: 1027-1038.
- [2] MOORE PS, BOSHOF C, WEISS RA AND CHANG Y [1996] Molecular mimicry of human cytokine response pathway genes by KSHV. *Science* 274: 1739-1744.
- [3] RADKOV SA, KELLAN P AND BOSHOF C [2000] The latent nuclear antigen of Kaposi's sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells. *Nat Med* 6: 1121-1127.
- [4] FRANCESCHI S AND GEDDES M [1995] Epidemiology of classic Kaposi's sarcoma, with special reference to Mediterranean population. *Tumori* 8: 308-314.
- [5] BIGGAR RJ, HORM J, FRAUMENI JF JR, GREENE MH AND GOEDERT JJ [1984] Incidence of Kaposi's sarcoma and mycosis fungoides in the United States including Puerto Rico, 1973-81. *J Natl Cancer Inst* 73: 89-93.
- [6] GRULICH AE, BERAL V AND SWERDLOW AJ [1992] Kaposi's sarcoma in England and Wales before the AIDS epidemic. *Br J Cancer* 66: 1135-1137.
- [7] COTTONI F, DE MARCO R AND CERIMELE D [1985] Kaposi's sarcoma in Northeast Sardinia. An epidemiologic, geographic and statistical study. In: CERIMELE D (EDITOR), *Kaposi's Sarcoma*. Rome: SP Medical and scientific book, pp. 19-28.
- [8] ASCOLI V, BELLI S, BENEDETTI M, TRINCA S, RICCI P AND COMBA P [2001] High incidence of classic Kaposi's sarcoma in Mantua, Po Valley, Northern Italy (1989-1998). *Br J Cancer* 85: 379-382.
- [9] GEDDES M, FRANCESCHI S AND BARCHIELLI A [1994] Kaposi's sarcoma in Italy before and after the AIDS epidemic. *Br J Cancer* 69: 333-336.
- [10] ENGELS EA, ROSENBERG PS AND GOEDERT JJ [2001] Cancers associated with Kaposi's sarcoma (KS) in AIDS: A link between KS herpesvirus and immunoblastic lymphoma. *Br J Cancer* 85: 1298-1303.
- [11] BIGGAR RJ, CURTIS RE, COTE TR, RABKIN CS AND MELBYE M [1994] Risk of other cancers following Kaposi's sarcoma: Relation to acquired immunodeficiency syndrome. *Am J Epidemiol* 139: 362-368.
- [12] ISCOVICH J, BOFFETTA P AND BRENNAN P [1999] Classic Kaposi's sarcoma as a first primary neoplasm. *Int J Cancer* 80: 173-177.
- [14] ISCOVICH J, MOFFETTA P, WINKELMANN R AND BRENNAN P [1999] Classic Kaposi's sarcoma as a second primary neoplasm. *Int J Cancer* 80: 178-182.
- [15] BUDRONI M, CESARACCIO R, PIRINO D, SECHI O, MAMELI G, PALMIERI G, COSSU A, MANCA A, LISSIA A AND TANDA F [2002] The Sassari Cancer Registry (1993-1997). In: PARKIN DM, WHELAN SL, FERLAY J, TEPPLO L AND THOMAS DB (EDITORS), *Cancer Incidence in Five Continents*, vol. VIII. Lyon: International Agency for Research on Cancer Press, pp. 380-381.
- [16] BUDRONI M AND TANDA F [2004] Registro Tumori della Provincia di Sassari. Anni 1992-2001. *Epidemiologia in Sardegna* 8: 37-47.
- [17] LEVER WF AND SCHAUMBURG-LEVER G [1990] Kaposi's sarcoma. In: LEVER WF AND SCHAUMBURG-LEVER G (EDITORS), *Histopathology of the Skin*. Philadelphia: Lippincott, pp. 704-707.
- [18] PERCY C, VAN HOLTEN V AND MUIR C [1990] *International Classification of Diseases for Oncology*. Geneva: World Health Organization, p144.
- [19] KIM H-J, FAY MP AND FEUER EJ [2000] Permutation tests for joinpoint regression with applications to cancer rates.

Statistics in Medicine 19: 335-351.

- [20] COTTONI F, DE MARCO R AND MONTESU MA [1996] Classical Kaposi's sarcoma in northeast Sardinia. An overview from 1977 to 1991. Br J Cancer 73: 1132-1134.
- [21] COTTONI F, MASALA MV AND BUDRONI M [1997] he role of occupation and past history of malaria in the etiology of classic Kaposi's sarcoma: a case control study in north-east Sardinia. Br J Cancer 76: 1518-1520.

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