To evaluate incidence rates (IRs) of classic Kaposi's sarcoma (CKS) in Italy after the spread of AIDS, we distinguished CKS from AIDS-related KS (AKS) using an 'ad hoc' record linkage procedure between 15 Cancer Registries (CRs) (21% of the Italian population) and the national AIDS Registry. Between 1985 and 1998, 874 cases of CKS and 634 cases of AKS were diagnosed in the study areas. CKS accounted for 16 and 27% of KS cases below 55 years of age in men and women, respectively, but for 91 and 100% of those above age 55. The IRs for CKS were 1.0/100 000 in men and 0.4/100 000 in women, but they varied between 0.3 in Umbria and 4.7 in Sassari in women. IRs of CKS in both genders were stable between 1985–1987 and 1993–1998. In Northern and Central CRs the IR (adjusted for age and gender) for CKS was 0.5 in individuals born in the same area, but 1.6 in individuals born in Southern Italy or in the Islands (rate ratio ¼ 3.2) suggesting that KS-associated herpesvirus, the cause of KS, is acquired early in life.

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Before the AIDS epidemic, Kaposi’s sarcoma (KS) occurred sporadically in Europe, most notably in elderly men of Mediterranean or Middle Eastern origin (classic KS, CKS) (Franceschi and Geddes, 1995). Some increase in incidence was reported in the 1960s and 1970s and attributed to the increase in immunosuppressive treatment (e.g. corticosteroid use) (Dictor and Attewell, 1988).

Since the 1980s, consequent on the AIDS epidemic, KS incidence has increased in all Western countries (Dal Maso et al., 1999), mainly due to the high frequency of AIDS-associated KS (AKS) among HIV-infected homosexual and bisexual males (IARC, 1996). KS-associated herpesvirus (KSHV or human herpesvirus type 8, HHV8) is recognised as the necessary, though not sufficient, cause of all clinical variants of KS (Moore and Chang, 1998; Iscovich et al., 1994; Geddes and Attewell, 1998). Automatic linkage procedures...
(Franceschi et al., 2003) provide a powerful tool to distinguish KS from AKS in populations where Cancer Registries (CRs) and HIV/AIDS Registries both exist (Guttmann-Yassky et al., 2003), and we applied this approach in our Italian study.

**MATERIALS AND METHODS**

CKS and AKS were distinguished using the record-linkage procedure of Cancer and AIDS Registries Linkage (CARL) study (Dal Maso et al., 2003). Several independent CRs, covering a population of 11.6 million (21% of the total Italian population), have produced accurate KS incidence rates (IRs) for the mid-1990s (Parkin et al., 2002; Zanetti et al., 2002). They covered the ‘North-East network’, including the Friuli-Venezia Giulia region and the provinces of Trento and Alto Adige, the regions of Romagna and Umbria, part of the Veneto region, the municipality of Turin, the provinces of Biella, Genoa, Varese, Parma, Modena, Ferrara, Macerata, Florence and Prato, Sassari and Ragusa. CRs varied in size, ranging from populations of approximately 190,000 to 2 million, as well as in the number of registration years available (Parkin et al., 2002; Dal Maso et al., 2003).

AIDS notification in Italy started in 1982 and has been mandatory since 1986. By the end of the year 2000, 47,503 AIDS cases had been recorded according to the clinical standard definitions (Istituto Superiore di Sanità, 2003). CRs and RAIDS are linked by first and last name, and by date of birth. Satisfaction of the name-date algorithm requires: (a) that the records are identical for at least one critical field; and (b) that the other two critical fields, if not identical, differ only in prescribed ways. Personal identifiers are removed during linkage procedures; thus, the staff of each registry is blinded to which persons have been linked. SALI has been shown to have a very high sensitivity and specificity in the Italian AIDS registry (RAIDS) and CRs are linked by first and last name, and by date of birth. Satisfaction of the name-date algorithm requires: (a) that the records are identical for at least one critical field; and (b) that the other two critical fields, if not identical, differ only in prescribed ways. Personal identifiers are removed during linkage procedures; thus, the staff of each registry is blinded to which persons have been linked. SALI has been shown to have a very high sensitivity and specificity in the Italian context, and it is available upon request (Dal Maso et al., 2001a).

The present study was restricted to people who: (1) were diagnosed at age 55 or above. Between 1985 and 1998, 874 CKS and 634 AKS were reported to Italian CRs (Table 1). The age distribution of CKS was similar for men and women, the median age was 72 years (range 18 – 95), and only 119 (14%) occurred in persons below age 55. Conversely, AKS occurred at a median age of 36 (range 19 – 83) and only 49 (8%) were diagnosed at age 55 or above.

With respect to site of cancer presentation, skin predominated in both CKS (88%) and AKS (86%) but skin of the leg and hip was more frequently involved in CKS than in AKS (Table 1). In total, 10% of AKS was diagnosed in the lip, oral cavity, pharynx and digestive organs compared to only 3% of CKS. Figure 1 shows the age-specific IRs of CKS and all KS in all Italian study areas in the period 1985 – 1998. It is noteworthy that in Italy CKS accounted for 91.0 and 100% of new cases of KS, respectively, in men and women aged 55 years or older in Italy, but only 15.7 and 26.9%, respectively, below that age. No significant correlation emerged between IRs of CKS and AKS in different areas (Spearman coefficient, r = –0.16 in men and 0.38 in women, data not shown).

Table 2 shows CKS IRs by gender and place of residence. Overall, the IRs were 0.98/100,000 men and 0.41/100,000 women. However, a wide heterogeneity emerged, with IRs between 0.3 in Umbria (Central Italy) to 4.7 in Sassari (Sardinia, Southern Italy) in men, and between 0.1 in Parma (Northern Italy) to 1.7 in Sassari

| ICD 10; Site of presentation | Classic KS | (%)a | AIDS-related KS | (%)a |
|----------------------------|------------|------|----------------|------|
| C00–C14; lip, oral cavity and pharynx | 9 | (1.4) | 29 | (5.6) |
| C15–C26; digestive organs | 9 | (1.4) | 20 | (3.9) |
| C30–C39; respiratory and intrathoracic organs | 5 | (0.8) | 2 | (0.4) |
| C44; skin | 551 | (88.2) | 444 | (86.2) |
| C44.1–6; skin of face, scalp, neck, trunk, arm and shoulder | 128 | (23.2) | 160 | (36.0) |
| C44.7; skin of leg and hip | 301 | (54.6) | 68 | (15.5) |
| C44.8–9; skin, other or not specified | 122 | (22.2) | 216 | (48.6) |
| C49; connective, subcutaneous and other soft tissue | 27 | (4.3) | 10 | (1.9) |
| C51–C68; genital and urinary organs | 15 | (2.4) | 5 | (1.0) |
| Other and ill-defined sites | 9 | (1.4) | 5 | (1.0) |
| C80; unknown primary site | 249 | | 119 | |

aUnknown primary site excluded from the calculation.

**RESULTS**

Between 1985 and 1998, 874 CKS and 634 AKS were reported to Italian CRs (Table 1). The age distribution of CKS was similar for men and women, the median age was 72 years (range 18 – 95), and only 119 (14%) occurred in persons below age 55. Conversely, AKS occurred at a median age of 36 (range 19 – 83) and only 49 (8%) were diagnosed at age 55 or above.

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in women (Table 2). Central Italy showed the lowest IRs while, in Northern Italy, the IRs in Ferrara were similar to those in Ragusa (Sicily) and significantly higher than those in nearby areas in both genders. Three-fold higher IRs were found in the two CRs from Southern Italy, mainly on account of particularly elevated IRs in Sassari.

A high positive correlation \( r = 0.66 \) between IRs in men and women emerged. Thus, male-female ratios were generally between 2.0 and 2.5 in most of the areas, despite some probability of random variation.

The association of place of birth and CKS was evaluated in Northern and Central CRs (Table 3). Among CKS cases in Northern and Central Italy, the IR was 0.5 for individuals born in the same area, while it was 1.6 for individuals born in Southern Italy or in the Islands (RR = 3.2; 95% CI: 3.2 – 3.3). The RRs for individuals born in the South or in the Islands were particularly elevated in the North-East (7.0) and Umbria (9.5), but close to unit in Ferrara (1.7) and Varese (1.6).

Figure 2 shows trends in the CKS incidence and, for comparison purposes, for all KS in the seven CRs that had been active since 1985. CKS IRs in men slightly increased between 1985 – 1987 (IR = 0.7) and 1988– 1992 (1.0) but did not change thereafter (1.1 in 1993–1998). In women, the IRs were between 0.3 and 0.4 throughout the considered period. By contrast, consequent to the steady increase of people with HIV/AIDS, the incidence of all KS increased from 1.1 and 0.3 in 1985 – 1987 to 2.9 and 0.6 in 1993–1998 in men and women, respectively.

**DISCUSSION**

Our study is one of the first attempts (Guttman-Yassky et al, 2003) to describe the epidemiology of CKS in a large population after the huge increase of KS caused by the AIDS epidemic (Dal Maso et al, 2001b). A many-fold higher incidence of CKS, compared to

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**Table 2** Observed (Obs) cases, standardised incidence rates (IR), and 95% confidence intervals (CI) of classic Kaposi’s sarcoma by gender in 15 Italian Cancer Registries, 1985–1998

| Cancer registry | Male | Female |
|-----------------|------|--------|
| **North of Italy** | | |
| Turin           | 86   | 1.22 (0.98 – 1.51) | 35   | 0.43 (0.30 – 0.59) |
| Biella          | 2    | 0.44 (0.05 – 1.60) | 5    | 0.90 (0.28 – 2.14) |
| Genoa           | 72   | 1.17 (0.91 – 1.48) | 16   | 0.24 (0.14 – 0.39) |
| Varese          | 59   | 1.24 (0.94 – 1.60) | 28   | 0.53 (0.35 – 0.76) |
| North East      | 28   | 0.66 (0.44 – 0.96) | 16   | 0.32 (0.18 – 0.53) |
| Veneto          | 59   | 0.75 (0.57 – 0.97) | 30   | 0.32 (0.21 – 0.45) |
| Parma           | 23   | 0.65 (0.41 – 0.97) | 5    | 0.13 (0.04 – 0.30) |
| Modena          | 37   | 0.97 (0.68 – 1.33) | 24   | 0.59 (0.38 – 0.88) |
| Ferrara         | 38   | 1.68 (1.18 – 2.31) | 23   | 0.90 (0.57 – 1.36) |
| Romagna         | 38   | 0.70 (0.49 – 0.96) | 26   | 0.44 (0.29 – 0.64) |
| **Centre of Italy** | | |
| Macerata        | 6    | 0.45 (0.16 – 0.98) | 3    | 0.23 (0.04 – 0.70) |
| Florence        | 54   | 0.63 (0.47 – 0.83) | 29   | 0.30 (0.20 – 0.44) |
| Umbria          | 5    | 0.26 (0.08 – 0.61) | 4    | 0.18 (0.05 – 0.46) |
| **Total, North and Centre** | 507 | 0.88 (0.81 – 0.96) | 244 | 0.38 (0.33 – 0.43) |
| **South of Italy** | | |
| Sassari         | 60   | 4.69 (3.57 – 6.04) | 20   | 1.65 (1.00 – 2.55) |
| Ragusa          | 28   | 1.47 (0.98 – 2.13) | 15   | 0.92 (0.51 – 1.52) |
| **Total, South** | 88   | 2.81 (2.25 – 3.46) | 35   | 1.23 (0.85 – 1.71) |
| **Total, Italy** | 595  | 0.98 (0.90 – 1.06) | 279  | 0.41 (0.36 – 0.46) |

*Age-standardised (per 100 000 population) according to Italian population, 1991. *Computed according to Poisson distribution.
A relatively high incidence of CKS was confirmed in the present study for the 1985–1998 period and the evidence of a broad within-country variation in both genders was expanded. The new CR in Sardinia, one of the only two available in the South and Islands, confirmed previous reports (Santarelli et al., 2004) and showed a four-fold excess, compared to North (Ascoli et al., 2003) and Central Italy, where the majority of CRs are concentrated. However, high rates of CKS are also recorded in some areas in the North, notably in Ferrara, in the delta of the Po (Parkin et al., 2002).

The reasons for such variations in CKS are not well understood. In our present study, we showed that the incidence of CKS was mainly determined by place of birth but not by the place of living. Being born in the South of Italy was associated with a three-fold increased risk of CKS among individuals who lived in the North and Centre. The massive waves of migration from the rural South to industrial towns in the North, such as Genoa, Turin and Varese during the last century probably account for the moderate excess of CKS in the corresponding CRs compared to the national average.

Comparison with other countries is hampered by the difficulty in distinguishing CKS and AKS. IRs for all KS, in the second half of the 1990s, are available from 186 registries for 57 countries (Parkin et al., 2002). These range, in men, from less than 0.5/100 000 in most CRs in Asia and Northern Europe, relatively spared by the AIDS epidemic, to 16.7/100 000 in non-Hispanic Whites in San Francisco, California and 50.8/100 000 in Harare, Zimbabwe (Parkin et al., 2002). Apart from Italy, recent population-based CKS IRs are only available for Israeli Jews. After excluding AKS cases, Guttman-Yassky et al. (2003) reported for 1960–1998 a CKS incidence of 2.1/100 000 for men and 0.8/100 000 for women, standardised using the world standard population. Using the same standard population, the IRs for Italy (0.6 in men and 0.2 in women) was lower than in Israel, but in Sardinia (2.6 in men and 0.6 in women) was similar to Israel. Substantial variations in the incidence of CKS were shown in Israel by country of origin, with approximately two-fold higher IRs among Jews from Iraq, Morocco, and Romania compared to Jews who were born in Israel (Guttman-Yassky et al., 2003).

Our findings from Italy suggest substantial stability of CKS incidence between 1985 and 1998, as in Israel in the same period, when various Israeli subpopulations were taken into consideration (Guttman-Yassky et al., 2003). A male-to-female ratio of 2-to-3 is also similar in Italy and Israel.

Table 3. Observed (Obs) cases of classic Kaposi’s sarcoma, standardised incidence rates (IR)*, rate ratio and 95% confidence intervals (95% CI) by place of birth and place of residence among individuals of both genders in 12 Northern and Central Italian Cancer Registries, 1985–1998.

| Place of birth                  | South and Islands* | North and Centre* |
|--------------------------------|--------------------|-------------------|
|                                | Obs    | IR    | Obs    | IR    | Rate Ratio† (95% CI) |
| North of Italy                 |        |       |        |       |                    |
| Turin                          | 85     | 2.08  | 34     | 0.37  | 5.6 (5.1–6.1)       |
| Biella                         | 0      | 0.00  | 7      | 0.78  | 0.0                 |
| Genoa                          | 31     | 1.26  | 55     | 0.48  | 2.3 (2.0–2.5)       |
| Varese                         | 19     | 1.18  | 61     | 0.75  | 1.6 (1.4–1.8)       |
| North East                     | 12     | 2.66  | 29     | 0.38  | 7.0 (5.5–8.9)       |
| Veneto                         | 13     | 2.65  | 73     | 0.52  | 5.1 (4.3–6.2)       |
| Parma                          | 4      | 1.27  | 23     | 0.34  | 3.8 (2.0–7.0)       |
| Modena                         | 10     | 2.19  | 50     | 0.75  | 2.9 (2.2–3.9)       |
| Ferrara                        | 2      | 2.30  | 59     | 1.33  | 1.7 (0.6–4.9)       |
| Romagna                        | 6      | 1.82  | 56     | 0.53  | 3.4 (2.3–5.1)       |
| Centre of Italy                |        |       |        |       |                    |
| Florence                       | 25     | 1.00  | 54     | 0.31  | 3.2 (2.8–3.6)       |
| Umbria                         | 3      | 1.30  | 5      | 0.14  | 9.5 (3.2–28.0)      |
| Total, North and Centre        | 210    | 1.56  | 506    | 0.48  | 3.2 (3.2–3.3)       |

*Standardised by age and gender (per 100 000 population) according to Italian population, 1991. †Computed according to Poisson distribution. Information is not available for Macerata Cancer Registry and is missing for 26 CKS cases. *South and Islands includes Basilicata, Puglia, Campania, Calabria, Sicily and Sardinia. *North and Centre includes Valle d’Aosta, Piedmont, Liguria, Lombardy, Trentino-Alto Adige, Veneto, Friuli-Venezia Giulia, Emilia-Romagna, Tuscany, Lazio, Umbria, Marche, Abruzzo and Molise. South and Islands vs North and Centre.
Despite some limitation of available data, the seroprevalence of KSHV antibodies in various geographic areas is correlated with the frequency of KS not associated to AIDS. The seroprevalence of KSHV antibodies is more than 25% in Africa and below 10% in the United States and Europe (Whitby and Boshoff, 1998). Substantial variations, consistent with those reported here for CKS incidence, were also found between Italian regions, with seroprevalence below 10% in certain areas of the North (Calabrò et al, 1998; Whitby et al, 1998) but higher than 30% in the Islands of Sicily and Sardinia (Calabrò et al, 1998; Perna et al, 2000; Santarelli et al, 2001; Serraino et al, 2001).

Although sexual transmission is chiefly implicated in the high prevalence of KS among homosexual and bisexual men (Moore and Chang, 1998), other transmission routes have yet to be fully elucidated. KSHV is shed in saliva, like other viruses of the Herpes family (Wojcicki, 2003), and nonsexual transmission has been suggested to be the major route of transmission in Africa, where the infection is common in children (Mbulaiete et al, 2003). Our findings concerning the importance of birth place, independently of place of residence, also suggest that in Italy early acquisition of KSHV infection is, or was, common in the middle-aged or elderly individuals with CKS in the present study. The excess of CKS in some Italian areas where wetlands and swamps are widespread (e.g. the Po delta, where Ferrara is located, and part of Sardinia) may have different explanations (Ascoli et al, 2001). These include a link between KS and malaria (Geddes et al, 1995) or, rather than malaria itself, the high-density of particular haematophagous insects (e.g. malaria vector Anopheles, black flies, sand flies, biting midges and mosquitoes). The practice of applying saliva to children’s bite sites to relieve the itching and scratching may represent an efficient route of KSHV transmission (Coluzzi et al, 2003). Extensive land reclamation up to the 1960s and DDT-spraying in the early 1950s in malaria-endemic areas of Italy should have reduced this type of KSHV transmission (Coluzzi et al, 2003), but did not seem to have yet produced a decline of CKS, a disease chiefly of the elderly. Genetically increased susceptibility to KSHV infection and KS development in some Mediterranean populations, including those from Southern Italy, is also a possibility (Iscovich et al, 2000).

The significance of our findings depends on the accurate distinction of CKS from other neoplasms and KS variants. The majority (96%) of CKS reported here were histologically confirmed and, therefore, misclassification with sarcomas other than KS or with skin cancer can be ruled out. Misclassification of some AKS as CKS is of greater concern but should not account for our findings. AIDS registration in Italy is nationwide and has been shown to be almost complete (Ajdaicic-Gross et al, 2001). Moreover, in Italy, HIV-testing is routinely performed in patients with KS and CR staff reviewed medical records of all CKS cases. In very few KS (2%), not matched with RAIDS, HIV-positivity or history of illnesses typically related to HIV or AIDS were found. Few cases of KS would have arisen because of severe iatrogenic immune suppression but, in the three CRs that systematically collected details of organ transplantation, only 3% of KS unrelated to AIDS had occurred in organ recipients.

In conclusion, between 1985 and 1998 in Italy, CKS accounted for 97% of all KS in elderly people (≥65 years) and a non-negligible fraction (42%) of KS in men between 39 and 64 years. Presently, there is no evidence that the improvements in the standard of living in Italy over the last decades are causing a decline in this disease. Separation of CKS from AKS will be important in studies of the disease, especially now that HIV-positive individuals may live into old age.

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Appendix

*Cancer and AIDS Registry Linkage Study*: Pierluca Piselli (INMI ‘L Spallanzani’, Rome); Claudia Braga, Gary Clifford (IARC Lyon, France); Massimiliano Oggiano (Registro Tumori della Provincia di Sassari); Carmela Nicita (Registro Tumori Ragusa); Paolo Contiero (Registro Tumori Lombardia – Provincia di Varese); Stefano Rosso (Registro Tumori Piemonte, Torino); Maria Elisa Artioli (Registro Tumori della Provincia di Modena); Maria Antonietta Orengo (Registro Tumori Ligure, Genova); Pier Carlo Vercellino (Registro Tumori della Provincia di Biella); Loris Zanier (Registro Tumori del Friuli-Venezia Giulia); Fabio Vittadello (Registro Tumori dell’Alto Adige); Rosa Vattioni (Registro Tumori della Romagna, Forlì); Carmen Fiorella Stocco (Registro Tumori del Veneto, Padova); Eugenio Paci (Registro Tumori Toscano, Firenze); Lidia Serventi (Registro Tumori della Provincia di Parma); Franco Pannelli (Registro Tumori Provincia di Macerata, Camerino); Maria Gentilini (Registro Tumori della Provincia di Trento); Francesco La Rosa (Registro Tumori Umbro); Valerio Ramazzotti, Maurilio Natali (Registro Tumori di Popolazione della Provincia di Latina); Mario Fusco, Maurizio Montella (Registro Tumori della Provincia di Napoli); Stefano Boros (Istituto Superiore di Sanità, Roma)