Risk Factors for Classical Kaposi's Sarcoma

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Background: **Classical Kaposi's sarcoma (KS) is a malignancy of lymphatic endothelial skin cells. Although all forms of KS are associated with the KS-associated herpesvirus (KSHV), classical KS occurs in a small fraction of KSHV-infected people. We sought to identify risk factors for classical KS in KSHV-infected individuals.** ***Methods:*** **Lifestyle and medical history data from case patients with biopsy-proven non-AIDS (non-acquired immunodeficiency syndrome) KS in Italy were compared by logistic regression analysis with data from population-based KSHV-seropositive control subjects of comparable age and sex. After KSHV immunofluorescence testing, randomly selected patients on the rosters of local physicians were identified as control subjects. Risk of KS was estimated by odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-sided.** ***Results:*** **From April 13, 1998, through October 8, 2001, we enrolled 141 classical KS case patients and 192 KSHV-seropositive control subjects of similar age (mean = 72 years for case patients and 73 years for control subjects) and sex (30% female case patients and 35% female control subjects). The strongest association was a reduced risk of KS with cigarette smoking (OR = 0.25, 95% CI = 0.14 to 0.45). Cigarette smoking intensity and duration could be evaluated for men, among whom the risk for KS was inversely related to the amount of cumulative smoking (P_{trend}<.001). KS risk decreased approximately 20% (OR = 0.81, 95% CI = 0.74 to 0.89) for each 10 pack-years reported, and it was decreased sevenfold (OR = 0.14, 95% CI = 0.07 to 0.30) with more than 40 pack-years. In multivariable analysis, a decreased KS risk was associated with smoking (OR = 0.23, 95% CI = 0.12 to 0.44); but an increased KS risk was associated with topical corticosteroid use (OR = 2.73, 95% CI = 1.35 to 5.51), infrequent bathing (OR = 1.85, 95% CI = 1.04 to 3.33), and a history of asthma (OR = 2.18, 95% CI = 0.95 to 4.97) or of allergy among men (OR = 2.59, 95% CI = 1.15 to 5.83) but not among women (OR = 0.09, 95% CI = 0.003 to 2.76). KS was not related to other exposures or illnesses examined.** ***Conclusion:*** **Risk for classical KS was approximately fourfold lower in cigarette smokers, a result that requires confirmation by other studies. Identification of how smoking affects KS risk may lead to a better understanding of the pathogenesis of this malignancy and interventions for its prevention. [J Natl Cancer Inst 2002; 94:1712–20]**

Classical Kaposi's sarcoma (KS), a malignancy of lymphatic endothelial cells of the skin *(1),* was originally described by Moritz Kaposi in 1872 *(2).* Violaceous classical KS lesions usually are slowly progressive, involving the skin of the feet and legs and to a lesser extent that of the hands and arms and frequently the lymph nodes draining those areas. It occurs predominantly among elderly people of Mediterranean or Jewish ancestry, particularly men. Clinically distinctive and more aggressive forms of KS were described between 1962 and 1981—endemic KS [in central and eastern Africa *(3)*], iatrogenic KS [among allograft recipients *(4)*], and epidemic KS [among persons with acquired immunodeficiency syndrome (AIDS) *(5)*]. In 1994, Chang et al. *(6)* discovered a previously unknown KS-associated herpesvirus (KSHV, also known as human herpesvirus 8) in virtually every KS lesion examined.

KSHV now is known to be the primary cause of all types of KS *(7),* but classical KS occurs in only a small fraction of KSHV-infected people. In the Mediterranean area, classical KS develops annually in only 0.03% of the KSHV-infected men older than age 50 years and in 0.01%–0.02% of the KSHV-infected women older than age 50 years *(8).* Thus, there must be strong cofactors affecting the risk of classical KS after KSHV infection. No highly pathogenic strain of KSHV has been identified *(9).* Genetic susceptibility is plausible, and the risk of classical KS was increased twofold with human leukocyte antigen (HLA) type DR5 in Sardinians *(10).* Evidence from Greek patients with classical KS suggests underlying immune activation is associated with this disease *(11).*

The current study is, to our knowledge, the first study to search generally for risk factors by comparing classical KS case patients to KHSV-infected control subjects.

METHODS

Case Patient Selection

We reviewed all cases of KS reported to the population-based cancer registries in Ragusa (Eastern Sicily) and Campania (Naples)

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See "Notes" following "References."

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and to the major referral centers in Sicily (the University of Palermo and the University of Catania) and Rome (San Gallicano Hospital and the Istituto Dermatopatico dell'Immacolata). Case patients were ineligible if they had AIDS; resided outside of Sicily, Lazio (including Rome), or Campania (including Naples); or lacked histologic confirmation [morphology code M9140/3 of the International Classification of Disease-Oncology *(12)*]. Project staff contacted each case patient by telephone to introduce the study.

Control Subject Selection

For our study, KSHV-seropositive control subjects of the same age and sex and from the same communities as the case patients were identified through and with the assistance of collaborating local, primary care physicians. Every person in Italy is assigned to a local, primary care physician. In Sicily, control subjects were obtained from the primary care physicians who had had a KS case patient. In Naples, control subjects were obtained from a large primary care group practice in the health districts of the cancer registry. In Rome, control subjects were obtained both from primary care physicians who had reported a KS case patient and from group practices representative of their communities.

Of all patients on the local physicians' rosters, up to 20 times as many potential control subjects as case patients were selected at random from each sex and age (±5 years or ⩾80 years of age) stratum. We anticipated 10%–15% KSHV seroprevalence among potential control subjects. Thus, a 20 : 1 ratio of potential control subjects to case patients was expected to yield twice as many KSHV-seropositive control subjects as case patients. At special sessions at each local physician's office, the study was explained to each potential control subject and, with written informed consent, blood was drawn for KSHV serology. Project staff contacted the KSHV-seropositive subjects to recruit them for the full study.

Institutional Review, Informed Consent, and Data and Specimen Collection

Institutional review boards at each institution reviewed and approved the protocol, forms, and process for obtaining written informed consent. KSHV test results were available on request but not routinely reported to individuals. Current understanding of KSHV, its distribution, and its relationship to KS was provided to all participants. Each participant was seen in a private setting, where a trained interviewer obtained written informed consent, questionnaire data, and laboratory specimens. The face-to-face interview questionnaire included demographic, occupational, sexual, and medical history, skin hygiene, alcohol use, and cigarette smoking. Smokers were those who reported smoking at least one cigarette per day for at least 1 year. On completion, the interviewer scored the cooperation of the respondent and the quality of the data on a four-point subjective scale. Four respondents (one case patient and three control subjects) were deemed to have provided unreliable data because of dementia or inebriation. Because exclusion of these four interviews had no substantive effect on the results, all collected data are presented herein.

KSHV Antibody Screening

Antibodies against KSHV antigens were detected in a 1 : 120 dilution of a patient's serum by an immunofluorescence assay, using the BCBL-1 cell line with and without induction by phorbol 12-tetradecanoate 13-acetate (TPA) *(13)*. All samples that tested KSHV-positive were blinded and retested, along with random samples that initially tested negative. Samples that produced disparate results (<4%) were retested again, and that result was considered final. All positive sera were also retested at the same dilution with the Molt4 cell line to exclude nonspecific cellular reactivity. Serum from control subjects that had antibody reactivity both with and without TPA induction was considered seropositive and included in the study. Serum from each case patient was tested likewise, and all sera were KSHV seropositive, except for serum from one case patient who lacked detectable antibodies without TPA induction.

Statistical Methods

Frequency distributions of questionnaire variables were used to compare classical KS case patients with KSHV-seropositive control subjects, first using contingency tables. Totals in the tables do not always sum to 141 KS case patients and 192 control subjects because of missing data. Continuous data were split at medians or in levels of approximately equal size. Corticosteroid medications were used by four routes (topical, inhalation, injection, and oral) examined by any use and by duration of use. Nonusers of corticosteroid medication were compared with high users (defined as those who used corticosteroid medication by at least three routes or orally for at least 2 years) and with low users (defined as all other corticosteroid users). Medication dose and brand could not be evaluated. Risk of classical KS, adjusted by sex, was estimated by the odds ratio (OR) and 95% confidence interval (CI) calculated by logistic regression. Statistically significant differences between sex strata were determined by the Breslow–Day test for homogeneity. Statistical significance of trends was tested with a 1-*df* Mantel–Haenszel χ^2 test. To examine the effect of KS survival on the association between smoking and KS risk, male KS case patients were stratified by time since diagnosis (<1, 1–5, and >5 years) and compared with male control subjects of similar age in each stratum. Logistic regression was used to evaluate the independence and mutual contributions of multiple variables by using liberal entry ($P<.20$) and stay ($P<.20$) criteria. The 95% CIs for logistic regression parameter estimates and linear combinations of these estimates were calculated from the variance–covariance matrix. All statistical tests were two-sided.

RESULTS

From April 13, 1998, through October 8, 2001, 141 case patients with classical KS and 192 KSHV-seropositive control subjects were enrolled. Twenty-five eligible KS case patients and 43 KSHV-seropositive potential control subjects could not be enrolled because of refusal (20 case patients, 32 control subjects), serious underlying illness (five case patients, 10 control subjects), or unsatisfactory phlebotomy (one control subject). The enrolled case patients and control subjects had similar distributions of age (mean = 72 years for case patients and 73 years for control subjects) and sex (30% female case patients and 35% female control subjects; Table 1). Across the four sites, control/case ratios ranged from 1.04 to 1.75, in part reflecting the KSHV seroprevalence rates in these populations. At the time of the interview, 87 (62%) of the 141 case patients had KS lesions at multiple dermal sites, 21 (15%) had lesions at one

Table 1. Characteristics of case patients with classical Kaposi's sarcoma (KS) and control subjects with KS-associated herpesvirus (KSHV) infection

Characteristic	KS case patients (n = 141)	KSHV control subjects (n = 192)
Sex, No. of males/No. of females (% female)	99/42 (30)	125/67 (35)
Mean age at interview, y (range)	72 (29–92)	73 (45–91)
Mean age at KS diagnosis, y (range)	65 (16–88)	NA*
No. enrolled in each region (%)		
Western Sicily	48 (34)	84 (44)
Eastern Sicily	43 (30)	54 (28)
Rome	27 (19)	28 (15)
Naples	23 (16)	26 (14)

*NA = not applicable.

dermal site, 31 (22%) had no current lesion, and two (1.4%) had missing data.

Socioeconomic status, as determined by years of education and availability of indoor plumbing in the childhood home, was not associated with KS risk (Table 2). KS risk also was not associated with childhood home factors, including numbers of residents, in total and by age group, and number of people who shared the participant's bedroom. A small increase in KS risk was associated with having more than two older siblings (OR = 1.56, 95% CI = 0.99 to 2.45).

History of frequent or prolonged dirt on the skin during adulthood did not differ between case patients and control subjects. An increased KS risk was moderately but not statistically significantly associated with bathing or showering less than the median of twice per week (OR = 1.43, 95% CI = 0.91 to 2.27). Number of lifetime sexual partners differed greatly by sex but was unrelated to KS risk (Table 2).

Cigarette smoking was associated with a statistically significantly reduced risk of KS (OR = 0.25, 95% CI = 0.14 to 0.45). Among men, 59% of the case patients and 86% of the control subjects were current or former smokers. Among men, more intensive smoking (packs per day) and especially more cumulative smoking (pack-years) were associated with an even lower risk (P_{trend}<.001 for each; Table 3). The risk for KS decreased

Table 2. Risk factors for case patients with classical Kaposi's sarcoma (KS) compared with control subjects with KS-associated herpesvirus (KSHV) infection, stratified by sex

	Males		Females		
Variable	No. of case patients (n = 99)	No. of control subjects (n = 125)	No. of case patients (n = 42)	No. of control subjects (n = 67)	Odds ratio (95% CI)*
Low education†	67	83	17	40	0.77 (0.44 to 1.10)
Childhood home‡					
No indoor toilet	49	54	18	27	1.25 (0.81 to 1.95)
No indoor faucet	54	77	23	32	0.90 (0.58 to 1.41)
>7 total residents	36	46	14	35	0.79 (0.51 to 1.25)
>4 young residents	53	75	22	41	0.74 (0.47 to 1.17)
>2 older residents	45	52	18	30	1.12 (0.72 to 1.74)
>3 in bedroom	37	48	17	23	1.07 (0.68 to 1.68)
No. of siblings					
0–2	19	27	5	11	1.00 (referent)
3 or 4	28	40	16	14	1.31 (0.68 to 2.51)
5 or 6	31	28	8	20	1.31 (0.67 to 2.55)
>6	21	30	11	22	1.01 (0.51 to 1.99)
Birth order§					
>2 older siblings	49	39	13	26	1.56 (0.99 to 2.45)
>2 younger siblings	33	56	20	33	0.72 (0.46 to 1.12)
Skin hygiene‖					
Often very dirty	66	88	15	19	1.01 (0.63 to 1.62)
More dirty than neighbors	53	61	20	23	1.35 (0.87 to 2.10)
Bathe or shower <2 times/week	49	72	14	38	1.43 (0.91 to 2.27)
No. of lifetime sexual partners¶					
Low	24	26	29	50	1.00 (referent)
Medium	26	41	7	11	0.80 (0.43 to 1.47)
High	42	52	—	—	0.88 (0.44 to 1.74)*
Cigarette smoking					
None	40	18	39	57	1.00 (referent)
Current or former**	58	107	2	10	0.25 (0.14 to 0.45)

*Adjusted for sex by logistic regression. Analysis of high number versus low number of sexual partners was limited to males. If not stated, referents complement the variable presented, such as more than low education, presence of an indoor toilet, up to seven total residents, and skin about as dirty as that of neighbors. CI = confidence interval.

†Low education defined as up to 4 years of schooling for females and up to 5 years for males.

‡Primary residence from ages 5–10 years. Young residents are aged 0–15 years; older residents are aged 16 years and older.

§Birth order indicates the number of older siblings. The first, second, and third child have less than or equal to two older siblings, all children after the third have more than two older siblings. To reflect family size, data also are presented with respect to number of younger siblings.

‖"Often very dirty" = lifetime exposures in which the respondent's skin was "very dirty for at least 4 hours on at least 100 occasions." "More dirty than neighbors" relates to occupations held for at least 10 years and whether the respondent's skin got more, less, or about as dirty as the skin of neighbors of the same sex who had other types of occupations. "Bathing and showering" relates to usual habits during adult life.

¶Lifetime sexual partners categorized as low (1–4 for males, 1 for females), medium (5–20 for males, >1 for females), or high (>20, males only).

**At least one cigarette per day for at least 1 year.

Table 3. Risk of classical Kaposi's sarcoma (KS) among males compared with male control subjects with KS-associated herpesvirus (KSHV) infection, by smoking intensity and cumulative smoking, stratified by survival

	No. of case patients*	No. of control subjects	Odds ratio (95% CI)	P_{trend}†
All male KS case patients				
Cigarette smoking				
Total	98	125		
None	40	18	1.00 (referent)	
⩽1 pack/day	42	63	0.30 (0.15 to 0.59)	
>1 pack/day	16	44	0.16 (0.07 to 0.36)	<.001
⩽40 pack-years	38	44	0.39 (0.19 to 0.79)	
>40 pack-years	20	63	0.14 (0.07 to 0.30)	<.001
Male KS case patients diagnosed within 1 year of interview				
Cigarette smoking				
Total	17	22		
None	7	2	1.00 (referent)	
⩽1 pack/day	7	12	0.17 (0.03 to 1.04)	
>1 pack/day	3	8	0.11 (0.01 to 0.84)	.036
⩽40 pack-years	8	5	0.46 (0.07 to 3.14)	
>40 pack-years	2	15	0.04 (0.004 to 0.33)	.002
Male KS case patients diagnosed 1–5 years before interview				
Cigarette smoking				
Total	47	60		
None	19	8	1.00 (referent)	
⩽1 pack/day	23	34	0.28 (0.11 to 0.76)	
>1 pack/day	5	18	0.12 (0.03 to 0.42)	.001
⩽40 pack-years	19	24	0.33 (0.12 to 0.93)	
>40 pack-years	9	28	0.14 (0.04 to 0.41)	<.001
Male KS case patients diagnosed more than 5 years before interview				
Cigarette smoking				
Total	32	41		
None	14	6	1.00 (referent)	
⩽1 pack/day	10	23	0.19 (0.06 to 0.63)	
>1 pack/day	8	12	0.29 (0.08 to 1.06)	.06
⩽40 pack-years	10	13	0.33 (0.09 to 1.02)	
>40 pack-years	8	22	0.16 (0.04 to 0.55)	.004

*One KS case patient lacked date of diagnosis, and a second lacked date of interview. Thus, in the analyses stratified by interval of survival from diagnosis to interview, the male KS case patients sum to 96. The 99th male case patient lacked smoking data.

†P_{trend} for none, ⩽1 pack/day, >1 pack/day; and for none, ⩽40 pack-years, and >40 pack-years. All statistical tests were two-sided.

approximately 20% (OR = 0.81, 95% CI = 0.74 to 0.89) for each 10 pack-years reported. With more than 40 pack-years, the OR for KS was 0.14 (95% CI = 0.07 to 0.30) (Table 3).

The effect of survival on the relationship between smoking and KS risk was considered further (Table 3). Among incident case patients (i.e., the 17 men who were interviewed within 1 year of KS diagnosis), current or former smokers had an OR for KS of 0.14 (95% CI = 0.02 to 0.82), and those with more than 40 pack-years of cumulative smoking had an OR of 0.04 (95% CI = 0.004 to 0.33) (Table 3). The OR associated with smoking was reduced nearly as much for the 47 men whose KS was diagnosed 1–5 years before interview (OR = 0.23, 95% CI = 0.09 to 0.58) and for the 32 men whose KS was diagnosed more than 5 years before interview (OR = 0.22, 95% CI = 0.07 to 0.67). Similarly, the statistically significant trend of lower KS risk associated with more cumulative pack-years of cigarette smoking was independent of the interval between KS diagnosis and date of interview. Smoking was too uncommon among women (5% of case patients and 15% of control subjects) to analyze smoking intensity, cumulative exposure, or effect of survival.

KS risk was not associated with drinking beer or liquor (OR = 1.03, 95% CI = 0.64 to 1.67) or wine (OR = 1.37, 95% CI = 0.76 to 2.47) at least monthly. Risk of KS also was not associated with the intensity and cumulative amounts of beer, liquor, and wine consumption (data not shown).

KS was not associated with histories of sexually transmitted diseases, arthritis, colitis, diabetes, cirrhosis, cardiovascular disease, or renal disease (Table 4). With allergies, the risk of KS was statistically significantly elevated among men (OR = 2.78, 95% CI = 1.39 to 5.54) and statistically nonsignificantly reduced among women (OR = 0.36, 95% CI = 0.11 to 1.18; interaction with sex P = .002). An elevated risk of KS was associated with a history of asthma (OR = 2.34, 95% CI = 1.12 to 4.91). Statistically nonsignificant elevated risks for KS from sparse data were associated with a history of gout (OR = 2.13, 95% CI = 0.74 to 6.15) and benign prostate disease (OR = 2.16, 95% CI = 0.59 to 7.90). History of non-KS cancers was not statistically significantly associated with reduced KS risk among case patients (OR = 0.77, 95% CI = 0.34 to 1.73). Among the case patients, four reported a non-KS, nonmelanoma skin cancer; three reported uterine cancer; and one each reported breast cancer, bladder cancer, and leukemia. Malignancies among the control subjects included three each of uterine, breast, colorectal, and bladder cancers; two each of lung and prostate cancers; and one each of gastric cancer and leukemia. No case patient or control subject had received an organ transplant.

Table 4. History of medical conditions among case patients with classical Kaposi's sarcoma (KS) compared with matched control subjects with KS-associated herpesvirus (KSHV) infection

Medical history	No. of case patients (n = 141)	No. of control subjects (n = 192)	Odds ratio (95% CI)*
Allergies	31	31	1.54 (0.88 to 2.70)†
Male	27	16	2.78 (1.39 to 5.54)
Female	4	15	0.36 (0.11 to 1.18)
Asthma	20	13	2.34 (1.12 to 4.91)
Bronchitis or emphysema	37	49	1.08 (0.65 to 1.79)
Other pulmonary disease	7	7	1.44 (0.49 to 4.24)
Cardiovascular disease	65	87	1.05 (0.67 to 1.64)
Crohn's or ulcerative colitis	13	18	1.06 (0.50 to 2.27)
Other gastrointestinal disease	23	34	1.17 (0.44 to 3.16)
Liver cirrhosis	19	22	1.34 (0.69 to 2.61)
Renal disease	27	33	1.19 (0.67 to 2.10)
Prostate hypertrophy or prostatitis	8	7	2.16 (0.59 to 7.90)
Sexually transmitted disease	17	20	1.18 (0.58 to 2.38)
Diabetes mellitus	25	34	1.03 (0.58 to 1.84)
Thyroid disease	4	5	0.93 (0.16 to 5.22)
Other endocrine disease	3	4	0.98 (0.21 to 4.45)
Arthritis	18	26	0.97 (0.50 to 1.85)
Gout	9	6	2.13 (0.74 to 6.15)
Other musculoskeletal	61	84	1.04 (0.66 to 1.64)
Cancer, excluding KS	10‡	18‡	0.77 (0.34 to 1.73)

*Adjusted for sex by logistic regression, except for prostate disease and separate strata for males and females with allergies. Referent groups are the subjects who did not report the particular condition (e.g., no reported allergy, no reported cardiovascular disease). CI = confidence interval.

†Breslow–Day test for homogeneity of odds ratios, P = .002, with reduced KS risk for females and increased KS risk for males with a history of allergies, as shown. All statistical tests were two-sided.

‡One case patient and two control subjects reported more than one non-KS malignancy.

Use of any corticosteroid medication was associated with a small but statistically significantly increased KS risk (OR = 1.61, 95% CI = 1.02 to 2.52; Table 5). Risk of KS was further analyzed by route and duration of corticosteroid use. Fourteen case patients reported having used a topical corticosteroid to treat their KS lesions. Excluding these patients, topical corticosteroid use was still associated with an increased risk (OR = 2.44, 95% CI = 1.33 to 4.47), although the risk was not higher with more prolonged use (Table 5). KS risk also was elevated with use of an oral corticosteroid for up to 2 years (OR = 2.17, 95% CI = 0.94 to 5.01) but not for longer than 2 years (OR = 1.17, 95% CI = 0.45 to 3.05). The use of corticosteroid injections and inhalations did not differ between case patients and control subjects (Table 5). Use of inhaled and other nontopical corticosteroid medications did not confound or have statistically significant interactions with the associations of asthma and of allergies among men with KS risk (data not shown). Combining routes and duration of corticosteroid use in a hierarchy, a 1.48-fold increased KS risk was associated with low use, and a 2.05-fold increased KS risk was associated with high use (P_{trend} = .03; Table 5).

Adjusted for age and sex, the following four variables were independently associated with KS risk by multivariable logistic regression modeling (Fig. 1): history of cigarette smoking (OR = 0.23, 95% CI = 0.12 to 0.44), use of topical corticosteroid medication (excluding topical treatment of KS lesions; OR = 2.73, 95% CI = 1.35 to 5.51), infrequent bathing or showering (OR = 1.85, 95% CI = 1.04 to 3.33), and history of asthma (OR = 2.18, 95% CI = 0.95 to 4.97). In an alternative but more complex model, asthma was replaced by two other variables, history of allergy and a sex–allergy interaction term. In this more complex model, an increased KS risk was statistically significantly associated with allergies for men (OR = 2.59, 95% CI = 1.15 to 5.83), but a decreased KS risk was statistically nonsignificantly associated with allergies for women (OR = 0.09, 95% CI = 0.003 to 2.76). KS risk also was associated with smoking, topical corticosteroid use, and bathing, as in the simpler model (Fig. 1). No other interaction or confounding was found, and the associations with KS could not be explained by use of inhaled or other nontopical corticosteroid medications. The risk estimates were robust and not substantially altered by adding study site, numbers of siblings, or other variables to the regression model. Separate models (data not shown) for the two principal geographic areas, Sicily and Rome/Naples, yielded similar results.

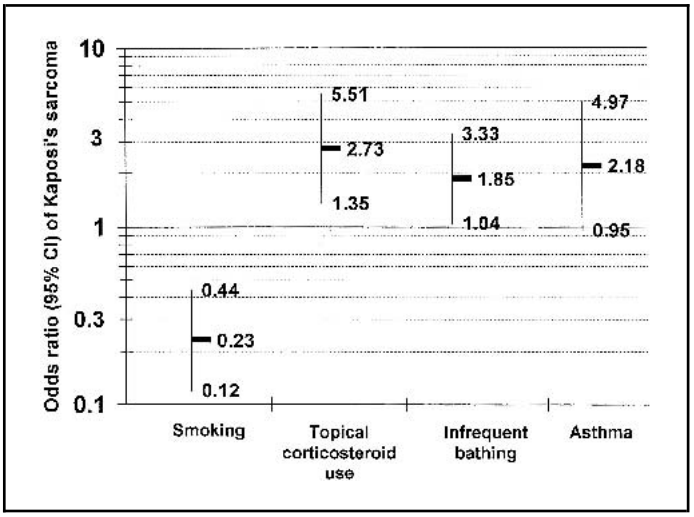

Fig. 1. Adjusted odds ratios (and 95% confidence intervals [CIs]) of classical Kaposi's sarcoma from the multivariable logistic regression model. The model included age and sex (data not shown), as well as current or former smoking, use of topical corticosteroid medication, bathing or showering less than twice per week, and history of asthma.

Table 5. History of corticosteroid medication use among case patients with classical Kaposi's sarcoma (KS) compared with matched control subjects with KS-associated herpesvirus (KSHV) infection

Use of corticosteroids	No. of case patients (n = 141)	No. of control subjects (n = 192)	Odds ratio (95% CI)*
Any by any route	66	74	1.61 (1.02 to 2.52)
Topical for any duration	30†	22	2.44 (1.33 to 4.47)
No topical	93	165	1.00 (referent)
Topical for up to 2 years	14	8	3.05 (1.23 to 7.56)
Topical for more than 2 years	13	7	3.39 (1.30 to 8.83)
Oral for any duration	24	24	1.45 (0.78 to 2.69)
No oral	112	165	1.00 (referent)
Oral for up to 2 years	15	10	2.17 (0.94 to 5.01)
Oral for more than 2 years	8	10	1.17 (0.45 to 3.05)
Inhalation, any	32	34	1.36 (0.79 to 2.34)
Injection, any	19	24	1.08 (0.56 to 2.07)
Hierarchy‡			
No corticosteroid use	64	116	1.00 (referent)
Low use	50	61	1.48 (0.91 to 2.39)
High use	15	13	2.05 (0.92 to 4.59)

*Adjusted for sex by logistic regression. CI = confidence interval.

†Excludes 14 case patients who reported treatment of KS lesions with topical corticosteroids. Numbers do not sum to totals because of missing data.

‡High = corticosteroids used by at least three routes or orally for more than 2 years. Topical treatment of KS lesions was excluded. P_{trend} = .03. All statistical tests were two-sided.

DISCUSSION

The strength of this study is the comparison of classical KS case patients and KSHV-infected persons without KS, an approach that avoids confounding by risk factors associated with KSHV infection rather than tumor development. We found that decreased KS risk was substantially and statistically significantly associated with a history of cigarette smoking. The risk was reduced fourfold (OR = 0.25) among people who were current or former cigarette smokers and sevenfold (OR = 0.14) among men who smoked more than 40 pack-years.

Previously, HIV-infected homosexual men in the United States who smoked were found to have a reduced risk of AIDS-associated KS that was statistically significant, albeit of lesser magnitude (OR = 0.4), than what we found *(14)*. In Uganda, tobacco use was not associated with AIDS-associated or endemic KS *(15,16)*.

If the prevalence of smoking is indeed low among KS patients, then smoking-related diseases should be reduced in this population. In support of this hypothesis is a striking absence of lung cancer among classical KS patients from Israel, Sweden, and New York *(17–19)*. In the American population, patients with predominantly classical KS (diagnosed after age 70 years or before 1980) had a markedly reduced risk of lung cancer (OR = 0.27, 95% CI = 0.06 to 0.80; Rabkin CR and Goedert JJ: unpublished data from the Surveillance, Epidemiology, and End Results [SEER][1] U.S. cancer registries).

Smoking has myriad effects that could influence the risk of KS. Hoover et al. *(14)* postulated that an effect of smoking on inflammatory cytokines might lower the risk of AIDS-associated KS. This is an attractive hypothesis, given that inflammatory cytokines and growth factors have potent effects on the recruitment of KSHV-infected cells into tissue sites and induction of KSHV replication leading to local dissemination of the infection *(20,21).* Some cytokines and growth factors are altered in smokers or *in vitro* by smoke extracts *(22–24),* although the interactions are complex and not well defined. Perhaps activation of these immunologic and inflammatory pathways also are related to the apparently higher risk of KS that we observed for people with asthma and men with allergies.

Case–control studies are subject to bias. Of greatest concern for our study is the possibility of participation bias; that is, if control subjects who smoked were disproportionately enrolled. We sought an unbiased sample of control subjects from the rosters of the local physicians, but we cannot rule out the possibility that smokers might have been more willing than nonsmokers to be tested for KSHV antibodies and to enroll as control subjects. The prevalence of smokers in Italy has been well quantified by stratified random sampling and face-to-face interviews. In 1995, 76% of men and 19% of women ages 65–74 years reported that they were current or former smokers *(25).* The prevalence of smokers among our control subjects was lower than expected among females (15%) but higher than expected among males (86%). Hypothetically, if there were no smokers among the 25 men who did not enroll as control subjects, our male smoking prevalence would have been 71%, and the risk of KS for smokers would have been reduced twofold (OR = 0.52, 95% CI = 0.32 to 0.86) rather than the fourfold that we estimated from the participants.

Survival bias is inevitable in a prevalent case–control study, because an exposure such as smoking may differentially affect survival and the risk of disease development. The lower risk of KS among smokers, particularly long-term heavy smokers, did not differ between case patients with incident KS who were recently diagnosed and those who had survived the disease for more than 5 years (Table 3). Although based on only 17 case patients with incident KS, this suggests, but by no means proves, that survival bias had little effect on our results. What cannot be excluded is recall bias among case patients, especially for variables such as use of topical corticosteroid medication. Overall, however, recall bias appears to have been small, as illustrated by the similar past medical histories of case patients and control subjects (Table 4).

Skin hygiene or skin disease may affect the risk of classical KS. Based on Ziegler's proposal *(26)* that endemic KS results from localized immune deficiency in the extremities resulting from chronic exposure of the skin to volcanic soil, Montella et al. *(27)* noted that risk of classical KS was twofold higher among people born near Mount Vesuvius than among people born in neighboring areas. In Uganda, delayed-type hypersensitivity skin reactions were diminished in the legs and feet compared with the arms of endemic KS patients *(28).* Our finding that KS risk was increased with use of topical corticosteroid medication supports the hypothesis that inflammatory or immunologic events in the skin are critical to the development of classical KS. Because the risk was not clearly related to duration of medication use, the dermatitis and not its treatment may be the link to KS. The KS risks that we observed for asthmatics and for men with allergies, which were a bit ambiguous but not confounded by use of nontopical corticosteroid medications, suggest an intrinsic proclivity for developing KS.

Prolonged working or walking in river or lake water was associated with increased risks of AIDS-associated and endemic KS in Uganda *(15,16).* We could not evaluate prolonged exposure to dirty water in Italy, but we found no differences between case patients and control subjects in frequent or prolonged dirt on the skin. We did, however, find a higher KS risk with infrequent bathing or showering. This association with bathing was not statistically significant in univariate analysis. However, as skin hygiene was an *a priori* hypothesis, bathing frequency was included in the multivariable model and was found to have a statistically significant 1.85-fold association with KS risk.

Finally, although KSHV can be transmitted to children, perhaps via saliva *(29,30),* and among adults, probably via sexual activity *(31,32),* our case patients and control subjects had nearly identical histories of household crowding, birth order, and sexual activity. Thus, the route of and age at KSHV infection may not have strong effects on the risk of classical KS.

In summary, we found that the risk of classical KS was increased approximately fourfold for nonsmokers, an observation that requires corroboration in another population. Our findings should in no way be interpreted as an endorsement of smoking, because the many serious complications of smoking far outweigh its effect on classical KS, which remains a rare outcome of KSHV infection even among male nonsmokers. Understanding how smoking affects KS risk may lead to a better understanding of the pathogenesis of this malignancy and to interventions for its prevention.

APPENDIX

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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