Journal of Acquired Immune Deficiency Syndromes
3(Suppl. 1):S18–S23 © 1990 Raven Press, Ltd., New York

Risk Factors for Kaposi's Sarcoma in the Vancouver Lymphadenopathy–AIDS Study

Chris P. Archibald, Martin T. Schechter, Kevin J. P. Craib, Thinh N. Le, Bruce Douglas, Brian Willoughby, and *Michael O'Shaughnessy

*The Vancouver Lymphadenopathy–AIDS Study Group, St. Paul's Hospital and the Department of Health Care and Epidemiology, University of British Columbia, Vancouver, and *Bureau of Laboratories and Research, Federal Centre for AIDS, Department of National Health and Welfare, Ottawa, Canada*

Summary: In our ongoing cohort study of homosexual men, the ratio of new Kaposi's sarcoma (KS) cases to new opportunistic infections (OI) during the periods 1982–1985, 1986–1987, and 1988–1989 fell from 0.75 (9 KS:12 OI) to 0.57 (12 KS:21 OI) to 0.27 (4 KS:15 OI), respectively. To examine factors associated with the development of KS as compared to OI, we compared antecedent risk factors in 25 KS cases and 48 OI "controls." In univariate analyses, several classical HIV risk factors including numbers of sexual partners and receptive anal intercourse were higher in the KS than the OI group. The strongest associations were found with an elevated number of sex partners in high-risk areas (San Francisco, Los Angeles, and New York) in the 5 years prior to enrollment and with elevated use of nitrite inhalants. Logistic regression revealed the latter two variables and an elevated number of partners contacted in washrooms/parks to be significant, independent risk factors for KS relative to OI. Any or all of these variables could be related with early HIV infection. However, the association with early sexual contact in high-risk areas raises the more intriguing possibility that this variable is an indicator of an increased exposure either to a particular strain of HIV that is more pathogenic for KS, or, more likely, to a sexually transmitted KS cofactor that may have been more highly concentrated in these areas at this early point in the epidemic. The present study supports an independent association with use of nitrite inhalants, which could be hypothesized either to have an independent biologic effect on KS or to enhance the efficiency of transmission of the cofactor virus. **Key Words:** Kaposi's sarcoma—Homosexual men—Opportunistic infections—Human immunodeficiency virus.

Opportunistic infections (OI), particularly *Pneumocystis carinii* pneumonia (PCP), together with Kaposi's sarcoma (KS) remain the most frequent manifestations of acquired immune deficiency syndrome (AIDS) in North America. The factors that dictate why HIV infection leads to KS in some persons and to PCP or OIs in others are not well understood. Speculation about such factors has stemmed to a large degree from several intriguing features of the epidemiology of KS. It has long been observed, for example, that KS accounts for a much larger proportion of AIDS cases in homosexual/bisexual men than in other groups such as heterosexuals, hemophiliacs, and intravenous drug users (1). Furthermore, there has been a sharp decline

Address correspondence and reprint requests to Dr. M. T. Schechter at The Vancouver Lymphadenopathy–AIDS Study, St. Paul's Hospital, 1081 Burrard Street, Vancouver, B.C., Canada V6Z 1Y6.

in recent years in the proportion of KS among AIDS cases observed in several risk groups and settings (2–4).

The purpose of the present analysis was to examine factors associated with the development of KS as compared to OI in our ongoing cohort study of homosexual men. A case-control study design was used with the intent of generating hypotheses about cofactors for KS within this cohort study.

MATERIALS AND METHODS

The Vancouver Lymphadenopathy–AIDS study has been described in detail elsewhere (5,6). In summary, it is an ongoing prospective study of homosexual men who were recruited from six general practices in central Vancouver between November 1982 and February 1984. Members of the cohort make regular visits to their physicians, where a self-administered questionnaire is completed, a physical examination done, and blood drawn for immunologic and human immunodeficiency virus (HIV) antibody testing. Seroprevalent persons (SP; $n = 234$) are defined as those who entered the study seropositive for HIV antibody, and seroincident persons (SI; $n = 117$) as those who seroconverted after enrollment. Cases of AIDS were defined according to the criteria of the Centers for Disease Control (7) and were classified according to initial manifestation. All cases were confirmed through manual record linkage with the Canadian Federal Centre for AIDS national registry.

The analysis was that of an unmatched case-control study with KS acting as the cases and OI acting as the "controls." Variables from the enrollment questionnaire were analyzed in a dichotomous fashion. Continuous or ordinal variables were dichotomized a priori at a level based on previous studies (5,6) or, where published information was unavailable, on the median for that variable's distribution. Univariate analyses were based on the methods of Mantel and Haenszel (8). The odds ratio was used to measure the strength of the association of variables with KS relative to OI, and 95% confidence intervals were the test-based limits of Miettinen (9). Forward stepwise logistic regression was used to model the effects of several variables simultaneously. Unless stated otherwise, analyses are based on the SP and SI cohorts combined. All analyses were carried out using the Statistical Analysis System (SAS) (10).

RESULTS

As of July 1, 1989, a total of 82 cases of AIDS had been diagnosed in the cohort and later confirmed by the national registry. Only one case was identified by the registry that was not known to us. Of the 82 cases, 25 (20%) were KS, of whom 2 later went on also to develop PCP, and 48 (59%) were OI including 37 PCP and 11 other opportunistic infections (1 *Mycobacterium avium*, 10 candidiasis). One of the PCP cases went on later to develop KS. The remaining nine cases were excluded (seven lymphomas, one neurologic disease, and one progressive multifocal leukoencephalopathy). Thus, 73 cases were included in the present analysis: 25 KS and 48 OI. Four (16%) of the KS cases and 13 (27%) of the OI cases were seroincident. Ninety-eight percent of subjects were Caucasian. The mean age of the 73 subjects was 31.5 years: 32.4 years for the KS group and 31.0 years for the OI group. In terms of num-

TABLE 1. *Comparison of sexual practices at enrollment in cases later presenting as KS versus OI in a cohort of homosexual men*

Variable	No. (%) of KS cases	No. (%) of OI cases	Odds ratio (95% CI)	*p* Value
More than 20 male sexual partners in prior year	19 (76)	25 (52)	2.9 (1.0–8.4)	0.05
Sexual contacts in washrooms/parks[a]	7 (28)	5 (11)	3.3 (0.9–11.0)	0.06
Receptive anal intercourse[a]	19 (76)	26 (54)	2.7 (0.9–7.8)	0.07
Insertive fisting[b]	18 (72)	23 (48)	2.8 (1.0–7.8)	0.05
Receptive fisting[b]	11 (44)	11 (23)	2.6 (0.9–7.4)	0.06
Receptive oral–genital contact[a]	11 (44)	33 (69)	0.4 (0.1–1.0)	0.04
More than 20 male sex partners in high-risk areas in prior 5 years[c]	14 (56)	10 (21)	4.6 (1.6–13)	0.004

[a] More than 25% of sexual encounters included this practice.
[b] Ever vs. never.
[c] High-risk areas are San Francisco, Los Angeles, and New York.

bers of cases, the ratio of new KS cases to new OI cases during the periods 1982–1985, 1986–1987, and 1988–1989 fell from 0.75 (9 KS:12 OI) to 0.57 (12 KS:21 OI) to 0.27 (4 KS:15 OI), respectively.

Tables 1 and 2 present those sexual practice variables with evidence of an antecedent difference between KS and OI ($p < 0.1$). Elevated numbers of male sex partners, greater frequency of sexual contacts occurring in washrooms or parks, greater frequency of receptive anal intercourse, and receptive and insertive fisting appeared to be associated with KS. Receptive oral–genital contact was negatively associated with KS (Table 1). The strongest association was found with having an elevated number of sex partners in high risk areas (San Francisco, Los Angeles, and New York) in the 5 years prior to enrollment. Elevated use of nitrite inhalants was also found to be associated with KS (Table 2). In addition, there were weaker associations with prior histories of syphilis and herpes, and a negative association with a history of giardiasis.

No associations were detected for a number of variables including sexual contact with a person with AIDS, insertive and receptive oral–anal contact, insertive oral–genital contact, and insertive anal intercourse. With regard to other infectious diseases, we found no differences with respect to prior histories of gonorrhea, nonspecific urethritis, venereal warts, pubic lice, scabies, mononucleosis, hepatitis, amebiasis, or "gay bowel syndrome." It is noteworthy that neither total prior duration of nitrite use nor use of a number of illicit drugs, including cocaine, amphetamines, heroin, lysergic acid diethylamide (LSD), or methylenedioxyamphetamine (MDA), were different in the KS and OI groups.

All variables with evidence of an association with KS in the univariate analysis ($p < 0.1$) were used to develop a multiple logistic regression model; the final model is shown in Table 3. Significant independent risk factors for KS relative to OI as the manifestation of AIDS (conditional on the development of AIDS) were an elevated proportion of sexual partners who were contacted in public washrooms/parks, an elevated number of sexual contacts in high-risk areas in the 5 years prior to enrollment, and increased nitrite use in the month before enrollment. These effects persisted and remained stable even after adjustment for date of AIDS diagnosis and for serologic status at enrollment.

TABLE 3. *Final logistic regression model*

Variable	β[a]	Relative risk	*p* Value[b]
>25% of contacts in public washrooms or parks	2.18	8.85	0.023
>20 sexual contacts in high-risk areas in prior 5 years[c]	1.57	4.81	0.016
>20 "hits" of nitrites in prior month	1.50	4.48	0.019

[a] Estimated regression coefficient in logistic regression model.
[b] Level of significance in the final multivariate model.
[c] High-risk areas are San Francisco, Los Angeles, and New York.

In an attempt to control for duration of HIV infection, we restricted the analysis of the three independently significant variables to only seroincident cases recognizing that the sample size was thereby reduced from 73 to 17 (4 KS, 13 OI). Neither elevated proportion of partners contacted in public washrooms/parks nor elevated numbers of partners in high-risk areas in the 5 years prior to enrollment remained significantly associated with KS. For example, 1 of 4 KS cases and 1 of 13 OI cases reported 20 or more sexual contacts in high-risk areas in the prior 5 years (Fisher's $p = 0.43$). The limited statistical power must be recognized here. Increased nitrite use in the prior month, however, was associated with KS: 3 of 4 KS cases reported more than 20 "hits" in the month before enrollment compared to only 1 of 13 OI cases (Fisher's $p = 0.019$).

TABLE 2. *Comparison of other risk factors at enrollment in AIDS cases later presenting as KS versus OI in a cohort of homosexual men*

Variable	No. (%) of KS cases	No. (%) of OI cases	Odds ratio (95% CI)	*p* Value
>20 "hits" of nitrites in prior month	13 (57)	14 (30)	3.0 (1.1–8.3)	0.04
History of syphilis[a]	11 (44)	12 (25)	2.4 (0.8–6.5)	0.09
History of herpes[a]	10 (40)	10 (21)	2.5 (0.9–7.3)	0.08
History of giardiasis[a]	1 (4)	10 (24)	0.14 (0.02–0.9)	0.04

[a] Ever vs. never.

To examine trends in nitrite use, we computed the proportions of seropositives reporting high use (20 or more "hits" in the previous month) at each questionnaire cycle. As seen in Table 4, there was a clear trend of declining use. In the first cycle (median date of April 1983), 29% of seropositives reported high nitrite use; by the eighth cycle (median date of February 1988), this had fallen steadily to only 3%. To rule out any possible survivorship bias, we removed from this analysis at all time points any persons who subsequently developed AIDS and observed essentially the same results regarding declining use. As well, similar trends were observed in the seronegative cohort.

DISCUSSION

The epidemiology of AIDS-associated KS is unique in several respects. This illness occurs predominantly in homosexual men and is found to a far lesser degree in heterosexuals, hemophiliacs, and intravenous drug users with AIDS (1,2; T. A. Peterman, unpublished data). Among homosexual men, the proportion of cases accounted for by KS in blacks is one-half of that for whites and Hispanics (T. A. Peterman, unpublished data). There has been a marked decrease in the proportion of KS among AIDS cases from about one-third of the first 1,000 cases reported in the U.S. to only one-tenth of the 11,000 cases reported between January and August 1987. This decline appears to be occurring at similar rates in different risk groups and different settings (1,2; T. A. Peterman, unpublished data). A similar decrease has been observed in our cohort that, based on our follow-up procedures, cannot easily be attributed either to selective underreporting of KS or to increasing recognition of other AIDS illnesses.

The reasons for these unique features of KS are unknown, but a number of theories have been advanced to explain the development of KS in HIV infection. Most of the attention has been focused on three putative cofactors: cytomegalovirus (CMV), genetic predisposition, and volatile nitrite inhalants. Excellent reviews of each of these factors can be found in accompanying articles at this Symposium (W. L. Drew, unpublished data; and 11,12). We conducted the present analysis to generate hypotheses about the development of KS as compared to OI in our ongoing cohort study of homosexual men.

TABLE 4. *Use of nitrite inhalants in the seropositive cohort by questionnaire*

Questionnaire cycle (Median date)	Percentage reporting >20 hits in previous month
Q1 (April 1983)	29
Q2 (December 1983)	28
Q3 (September 1984)	28
Q4 (March 1985)	23
Q5 (September 1985)	12
Q6 (June 1986)	8
Q7 (January 1987)	3
Q8 (February 1988)	3

According to the univariate analysis, there was evidence of associations of several variables with the development of KS relative to OI. These included high numbers of sexual partners in high-risk areas in the 5 years before enrollment, elevated numbers of lifetime male sexual partners, increased frequency of anal-receptive intercourse and both insertive and receptive fisting, high proportion of contacts in washrooms/parks, and elevated use of nitrites in the month before enrollment. These represent a profile of behaviors associated with high risk for HIV. Since the enrollment questionnaires were completed in all cases before the diagnosis of AIDS with a median interval between enrollment and diagnosis of 46 months, one cannot attribute these differences to recall bias. Three variables were significantly associated with a decreased risk of KS relative to OI in univariate analyses ($p < 0.05$): swallowing semen, a history of giardiasis, and frequent receptive oral-genital contact. While these variables could conceivably be linked to cofactors that promote the development of OI, they more likely appear to be protective simply by virtue of a negative correlation with practices such as receptive anal intercourse. Indeed, these three protective variables did not appear to be significant when adjusted in the logistic regressions.

In multivariate analyses, three variables were significantly and independently related to the development of KS: a high proportion of sexual partners met in public washrooms/parks, an elevated number of sexual partners in high-risk areas in the 5 years before enrollment, and increased use of volatile nitrites in the month before enrollment. Other studies have found the following factors to be related to KS: intensity of nitrite use (13–15) and a number of sexual behaviors such as receptive anal intercourse (13), increased number of bathhouse partners (13), frequent rectal douches (16), and a large number of sexual partners (15).

Methodological problems in assessing risk factors

for AIDS progression in cohort studies are well known. A fundamental problem is that duration of infection, which is unknown in seroprevalent populations, can have a significant confounding effect (17). Indeed, any variable that is associated with earlier infection will automatically appear to act as a cofactor for increased risk of AIDS progression within a given time interval if duration of infection cannot be taken into account. Studies of selective KS cofactors are made even more complex by the overlay of the secular decline of KS. Any variable such as early HIV infection (or its surrogates) that favored progression to AIDS earlier in the epidemic may automatically appear to be associated with KS relative to OI because of the greater relative occurrence of KS at these earlier times. Given the fact that a slightly greater proportion of the KS group was seropositive at enrollment (85 vs. 73%), it is possible that the KS group was infected earlier with HIV than the OI group. If so, then one must address the possibility that some or all of the three variables differentiating the KS and OI groups are simply confounded with earlier HIV infection. However, if these variables are surrogates for early infection, it is difficult to explain why they all remained significant in the multivariate analysis.

With reference to nitrites, there are a number of points that argue against their role as simple surrogates for early HIV infection. First, there appears to be a specificity to nitrites since we found no other illicit drug to be associated with KS, while use of other drugs has previously been associated with infection at entry into this cohort (5). Second, if nitrites are a marker for early infection, one might expect the duration of nitrite use also to be associated with KS but it was not. Third, the nitrite effect persisted despite adjustment for early sexual contacts in high-risk areas, a variable that at least in part is probably related to early infection. Finally, one would not expect an association between nitrites and KS in the seroincident subgroup if nitrites are related to KS merely by virtue of their association with early infection.

There are several cautions that must be raised with regard to this study. First, the relatively small sample size makes interpretation of negative findings tenuous. This is particularly so for the analysis restricted to the small number of seroincident cases. On the other hand, the demonstration of three significant independent variables in a study of only 73 subjects is impressive and suggests that the associations are strong. Second, sexual practices and other behaviors such as nitrite use have clearly changed with time so that the use of risk factor information at enrollment will undoubtedly have led to some degree of misclassification. However, we felt that to use later information as well would risk not only confounding general secular trends but also protopathic effects in which behaviors are influenced by disease progression rather than the reverse.

In summary, we have found a recent decrease in incidence of KS in our cohort, which is consistent with other reports and that we believe is not artifactual. We have also demonstrated three significant independent variables to be associated with KS relative to OI. With regard to nitrite inhalants, it does not appear that these are acting simply as a surrogate for early infection but this cannot be ruled out entirely. We believe that the present data support an association between nitrites and KS. Whether this is through a direct biologic effect or through association with exposure to another KS cofactor remains open.

Even more interesting than this nitrite effect is our finding of an association of KS with those men who had elevated numbers of sexual contacts in San Francisco, Los Angeles, and New York in the 5 years prior to their enrollment (corresponding roughly to the period 1978–1983). Although early sexual contact in high-risk areas could simply be acting as a surrogate marker for early HIV infection, the more intriguing possibility is raised that this variable is an indicator of an increased exposure either to a particular strain of HIV that is more pathogenic for KS, or, more likely, to a sexually transmitted KS cofactor that may have been more highly concentrated in these areas at this early point in the epidemic.

To complete this speculation, one might postulate the existence of a viral KS cofactor perhaps related to CMV. This virus would rarely be transmitted by blood, blood products, or shared needles but would be sexually transmissible in the same manner as HIV although with a far lesser degree of efficiency. This virus would have been present in the homosexual community along with HIV but because of the lower efficiency would have primarily infected those with the greatest degree of risk behaviors early in the epidemic. This would account for our finding that at enrollment, KS cases reported greater numbers of partners and more frequent receptive anal intercourse and fisting than the OI controls. As well, because of the lower transmission

efficiency, spread of the cofactor virus would have been curtailed earlier in the epidemic than the spread of HIV due to behavior change and so may have remained more highly concentrated in the original epidemic centers. This would help to explain not only our association with early sexual contact in those areas, but the report of Peterman et al. of a general geographic association of KS with those areas (T. A. Peterman, unpublished data). If this cofactor virus was much more prevalent at earlier points in the epidemic and for a relatively short time, then birth cohorts whose period of maximal sexual activity coincided with the period of maximal prevalence of the virus would have had greater exposure to the cofactor. This could explain the birth cohort effect observed by M. A. Chiasson (unpublished data) and the higher prevalence of KS in homosexual men aged 25–44 years than in younger or older men reported by T. A. Peterman (unpublished data). Use of nitrite inhalants could be hypothesized either to have an independent biologic effect on KS or, more likely, to enhance the efficiency of transmission of the cofactor virus perhaps by known effects on the vasculature. Both the declining use of nitrites we and others have reported as well as the widely documented changes in sexual behavior that would have had an earlier effect on spread of the cofactor virus than on HIV can serve to explain the decline in KS that we have all observed. At the very least, we conclude that the epidemiology of AIDS-related KS remains enigmatic and more study is required to unravel its undoubtedly complex etiology.

Acknowledgment: This work was supported by the Federal Centre for AIDS and by the National Health Research Development Programme of the Department of National Health and Welfare of Canada through an operating grant (#6610-1389-AIDS) and through a National Health Research Scholar Award to Dr. Schechter. The authors are indebted to colleagues in the AIDS Care Group at St. Paul's Hospital and to Bonnie Devlin and Pam Merrick for their research assistance.

REFERENCES

1. Haverkos HW, Drotman DP, Morgan M. Prevalence of Kaposi's sarcoma among patients with AIDS. *N Engl J Med* 1985;312:1518.
2. Des Jarlais DC, Stoneburner R, Thomas P, Friedman SR. Declines in proportions of Kaposi's sarcoma among cases of AIDS in multiple risk groups in New York City. *Lancet* 1987;2:1024–5.
3. Selik RM, Starcher ET, Curran JW. Opportunistic diseases reported in AIDS patients: frequencies, associations, and trends. *AIDS* 1987;1:175–82.
4. Rutherford GW, Schwarcz SK, Lemp GF, et al. The epidemiology of AIDS-related Kaposi's sarcoma in San Francisco. *J Infect Dis* 1989;159:569–72.
5. Jeffries E, Willoughby B, Boyko WJ, et al. The Vancouver Lymphadenopathy–AIDS study: 2. Seroepidemiology of HTLV-III antibody. *Can Med Assoc J* 1985;132:1373–7.
6. Schechter MT, Boyko WJ, Douglas B, et al. The Vancouver Lymphadenopathy–AIDS study: 6. HIV seroconversion in a cohort of homosexual men. *Can Med Assoc J* 1986;135: 1355–60.
7. Centers for Disease Control. Revision of the CDC surveillance case definition of acquired immunodeficiency syndrome. *MMWR* 1987;36:(suppl 1S):3S–14.
8. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies. *JNCI* 1959;22:719–48.
9. Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976;103:226–35.
10. *Statistical Analysis System*, Version 5. Cary, NC: SAS Institute, 1985.
11. Mann DL, Murray C, O'Donnell M, Blattner WA, Goedert JJ. HLA antigen frequencies in HIV-1-related Kaposi's sarcoma. *J Acq Immun Def Synd* 1990;3(suppl. 1):S51–S55.
12. Haverkos HW. Nitrite inhalant abuse and AIDS-related Kaposi's sarcoma. *J Acq Immun Def Synd* 1990;3(suppl. 1):S47–S50.
13. Haverkos HW, Pinsky PF, Drotman DP, Bregman DJ. Disease manifestation among homosexual men with acquired immunodeficiency syndrome: a possible role of nitrites in Kaposi's sarcoma. *Sex Transm Dis* 1985;12:203–8.
14. Mather-Wagh U, Mildvan D, Senie RT. Follow-up at 4 ½ years on homosexual men with generalized lymphadenopathy. *N Engl J Med* 1985;313:1542–3.
15. Osmond D, Moss AR, Bachetti P, Volberding P, Barre-Sinoussi F, Chermann J-C. A case-control study of risk factors for AIDS in San Francisco. Presented at the First International Conference on AIDS, Atlanta, 1985.
16. Goedert JJ, Biggar RJ, Melbye M, et al. Effect of T4 count and cofactors on incidence of AIDS in homosexual men infected with human immunodeficiency virus. *JAMA* 1986; 257:331–4.
17. Schechter MT, Craib KJP, Le TN, et al. Progression to AIDS and predictors of AIDS in seroprevalent and seroincident cohorts of homosexual men. *AIDS* 1989;3:347–53.