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Author(s): Chris P. Archibald, Martin T. Schechter, Thinh N. Le, Kevin J. P. Craib, Julio S. G. Montaner and Michael V. O'Shaughnessy

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Evidence for a Sexually Transmitted Cofactor for AIDS-Related Kaposi's Sarcoma in a Cohort of Homosexual Men

Chris P. Archibald,[1] *Martin T. Schechter,*[1] *Thinh N. Le,*[1] *Kevin J. P. Craib,*[1] *Julio S. G. Montaner,*[1] *and Michael V. O'Shaughnessy*[2]

We examined factors associated with the subsequent development of AIDS-related Kaposi's sarcoma in a cohort of 353 homosexual men infected with human immunodeficiency virus (HIV). Cumulative incidence curves for the development of Kaposi's sarcoma and opportunistic infection were stratified over a wide range of variables at enrollment, including those related to demographics, sexual behavior, illicit drug use, and medical history. We found no strong associations between any of these variables and the development of opportunistic infection, but two were related to Kaposi's sarcoma: use of nitrite inhalants (relative risk, 2.3; 95% confidence interval, 1.0–5.0) and high numbers of sexual contacts during the period 1978–1982 in the AIDS epidemic centers of San Francisco, Los Angeles, and/or New York (relative risk, 3.5; 95% confidence interval, 1.6–7.6). The latter variables remained independently associated with risk of Kaposi's sarcoma even after multivariate adjustment for a number of classical HIV risk factors. These results are consistent with the hypothesis that Kaposi's sarcoma is caused by a sexually transmitted cofactor that has remained more prevalent in the original epidemic centers. The effect of nitrites could be due to an independent biological mechanism or to enhancement of transmission of the cofactor. (Epidemiology 1992;3:203–209)

Keywords: AIDS, HIV, Kaposi's sarcoma, cofactor, sexually transmitted disease.

The causes of AIDS-related Kaposi's sarcoma are not known, although speculation about its etiology has arisen from several interesting features of its epidemiology. Kaposi's sarcoma occurs in a much greater proportion of AIDS cases in homosexual/bisexual men than in other risk groups,[1] and in recent years, there has been a notable decline in the proportion of Kaposi's sarcoma among AIDS cases.[2–4]

Recent overviews of the epidemiology of AIDS-related Kaposi's sarcoma in the United States, Europe, and Canada are consistent with the hypothesis that this disorder may have an as yet unidentified, sexually transmitted agent as a cofactor in addition to human immunodeficiency virus (HIV).[5–8] These studies, however, were based on national surveillance data and hence were unable to control for a number of potentially confounding variables. On the other hand, a study of a cohort of homosexual men in San Francisco that compared Kaposi's sarcoma cases with cases of AIDS presenting with other manifestations found no evidence to support such a hypothesis, and indeed found no differences between the two groups for a wide array of behavioral variables.[9] In this study, however, risk factors for Kaposi's sarcoma could not be differentiated from factors protective against other manifestations of AIDS.

The present analysis was conducted to examine factors associated with the subsequent development of AIDS-related Kaposi's sarcoma in our cohort of homosexual men.

Subjects and Methods

The Vancouver Lymphadenopathy-AIDS Study is a prospective study of homosexual men who were recruited from six general practices in Vancouver between November 1982 and February 1984.[10,11] Mem-

From the [1]Vancouver Lymphadenopathy-AIDS Study Group, Faculty of Medicine, University of British Columbia, and the B.C. Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, Canada; and the [2]Bureau of Laboratories and Research, Federal Centre for AIDS, Department of National Health and Welfare, Ottawa, Canada.

Address reprint requests to: Martin T. Schechter, Faculty of Medicine, University of British Columbia, 5804 Fairview Avenue, Vancouver, BC, Canada V6T 1Z3.

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bers of the cohort visit their physicians regularly for physical examinations, questionnaire completion, and serologic/immunologic testing. Seroincident persons (N = 119) were defined as those who became seropositive for HIV antibody after study enrollment, and seroprevalent persons (N = 234) were defined as those who were seropositive at the time of enrollment. AIDS cases were defined according to the criteria of the Centers for Disease Control,[12] and only cases manifesting as Kaposi's sarcoma or opportunistic infections were included for analysis (classified according to initial manifestation).

We used the product-limit method[13] to generate cumulative incidence curves for Kaposi's sarcoma and opportunistic infection in the seropositive cohort of 353 individuals. Individuals not undergoing the critical event (Kaposi's sarcoma or opportunistic infection) were considered no longer at risk at the time of first diagnosis of any other AIDS manifestation or as of October 1, 1990, if they remained AIDS-free. The index point or time zero for members of the seroincident cohort was taken to be the midpoint between the last seronegative and the first seropositive result. We have previously used immunologic parameters to estimate the index point in seroprevalent subjects.[14] In the present analysis, the index point for seroprevalent individuals was set at 18 months before enrollment, which was the median estimated index point. The entire analysis was repeated using each seroprevalent individual's estimated index point, but this led to no change in the conclusions. For that reason, only the results using an 18-month lead time assumption are shown.

Variables from the enrollment questionnaire covered a wide range of information on demographics, sexual behavior, medical history, and history of recreational drug use. They were analyzed in a dichotomous fashion to examine their association with the development of Kaposi's sarcoma or opportunistic infection. Ordinal or continuous variables were dichotomized *a priori* at a level based on previous studies[10,11,15] or, where published information was lacking, on the variable's median value. We used Cox regression analysis[16] to model the effects of several variables simultaneously on the development of Kaposi's sarcoma or opportunistic infection.

Results

A total of 99 cases of AIDS had been diagnosed in the cohort as of October 1, 1990. Of these, 28 (28%) had Kaposi's sarcoma, and 59 (60%) had opportunistic infection; of the latter, 44 had *Pneumocystis carinii* pneumonia, and 15 had other opportunistic infections (4 candidiasis, 4 *Mycobacterium avium* complex, 7 other). Two of the Kaposi's sarcoma cases later also developed *Pneumocystis*, and one of the *Pneumocystis* cases later developed Kaposi's sarcoma. The remaining 12 cases were excluded from analysis (7 lymphomas, 2 wasting syndromes, 3 other). Twenty-one (75%) of the Kaposi's sarcoma cases and 43 (73%) of the opportunistic infection cases occurred in seroprevalent subjects. The mean age at enrollment of the 87 individuals was 32.5 years: 33.5 for the Kaposi's sarcoma group, and 32.0 for the opportunistic infection group. Ninety-eight per cent of subjects were caucasian.

The cumulative incidence curves for Kaposi's sarcoma and opportunistic infection are shown in Figure 1. The product limit estimates for the cumulative incidence of Kaposi's sarcoma and opportunistic infection by 92 months were 9.3% (±1.7%) and 21.3% (± 2.6%), respectively. Curves for the development of Kaposi's sarcoma and opportunistic infection were separately stratified over variables from the enrollment questionnaire, and the results for selected variables are shown in Tables 1 and 2, respectively.

A number of variables were strongly associated with the development of Kaposi's sarcoma: elevated number of sexual contacts in San Francisco, Los Angeles, and/or New York in the 5 years before enrollment; increased use of nitrites; and receptive and insertive fisting. None of the baseline variables showed strong associations with the subsequent development of opportunistic infection (Table 2), although cumulative incidence was slightly higher among those frequently practicing insertive oral-anal contact and those infrequently practicing anal intercourse (insertive or recep-

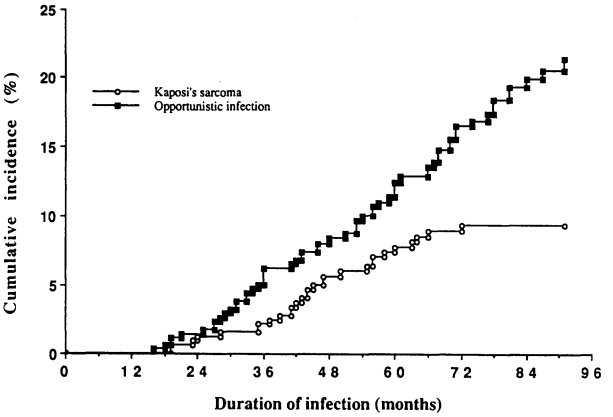

FIGURE 1. Kaplan-Meier curves for cumulative incidence of Kaposi's sarcoma and of opportunistic infection.

TABLE 1. Subsequent Incidence of Kaposi's Sarcoma Stratified by Baseline Risk Factors in a Cohort of Homosexual Men

Variable	Category	Cumulative Incidence (%)	Standard Error (%)
Sexual contacts*	≤20	5.8	1.6
	>20	20.4	4.9
No. of "hits" of nitrites in past month	≤20	6.6	1.7
	>20	16.2	4.2
Receptive fisting (lifetime)	Never	6.9	1.7
	Ever	16.9	4.5
Insertive fisting (lifetime)	Never	5.0	1.9
	Ever	14.1	2.9
No. of male sex partners in past year	≤20	7.6	1.9
	>20	12.4	3.4
Receptive anal intercourse (%)†	≤25	8.5	2.6
	>25	9.5	2.2
Insertive anal intercourse (%)†	≤25	5.8	2.4
	>25	11.1	2.3
Receptive oral-anal contact (%)†	≤25	9.3	2.0
	>25	8.7	3.4
Insertive oral-anal contact (%)†	≤25	9.2	1.9
	>25	9.3	4.0

* Sexual contacts in Los Angeles, San Francisco, or New York in the 5 years before enrollment.
† Percentage of sexual encounters during past year which included this practice.

TABLE 2. Subsequent Incidence of Opportunistic Infection Stratified by Baseline Risk Factors in a Cohort of Homosexual Men

Variable	Category	Cumulative Incidence (%)	Standard Error (%)
Sexual contacts*	≤20	22.0	3.0
	>20	20.4	5.5
No. of "hits" of nitrites in past month	≤20	22.3	3.0
	>20	20.9	5.5
Receptive fisting (lifetime)	Never	21.8	2.9
	Ever	20.8	5.8
Insertive fisting (lifetime)	Never	19.6	3.3
	Ever	24.0	4.1
No. of male sex partners in past year	≤20	22.7	3.3
	>20	19.3	4.3
Receptive anal intercourse (%)†	≤25	26.1	4.4
	>25	18.6	3.2
Insertive anal intercourse (%)†	≤25	28.3	5.1
	>25	18.1	3.0
Receptive oral-anal contact (%)†	≤25	21.4	3.0
	>25	22.6	5.4
Insertive oral-anal contact (%)†	≤25	19.5	2.8
	>25	30.9	6.6

* Sexual contacts in Los Angeles, San Francisco, or New York in the 5 years before enrollment.
† Percentage of sexual encounters during past year which included this practice.

tive). In addition, histories of other infectious diseases and of recreational drug use were not strongly associated with the development of either Kaposi's sarcoma or opportunistic infection (data not shown).

No important associations were found between the development of opportunistic infection and any of the measured baseline variables mentioned, using Cox regression (data not shown). The results of the Cox regression for Kaposi's sarcoma are shown in Table 3. The only variables associated with Kaposi's sarcoma were elevated numbers (>20) of sexual contacts in San Francisco, Los Angeles, and/or New York in the 5 years before enrollment (relative risk, 3.5; 95% confidence interval, 1.6–7.6) and the use of more than 20 "hits" of nitrites in the month before enrollment (relative risk, 2.3; 95% confidence interval, 1.0–5.0). For Kaposi's sarcoma, neither did the model improve nor were the coefficients for the sexual contact and the nitrite use variables significantly altered with the addition of any of the following variables to the Cox model: total number of sexual partners in the year before enrollment, frequency of insertive or receptive oral-anal or oral-genital contact, frequency of insertive or receptive anal intercourse, history of fisting, history of other infectious diseases, or use of recreational drugs.

Figure 2 shows Kaplan-Meier curves for Kaposi's sarcoma stratified by the two variables shown to be independently important in multivariate analysis: number of sexual partners in San Francisco, Los Angeles, and/or New York and use of nitrite inhalants. The *upper panel* of Figure 2 shows the increased risk of Kaposi's sarcoma associated with high numbers of sexual contacts in these three cities. The *lower panel* illustrates the risk associated with nitrite use. The cumulative incidence curves for opportunistic infection stratified over these same two variables were virtually indistinguishable (Figure 3).

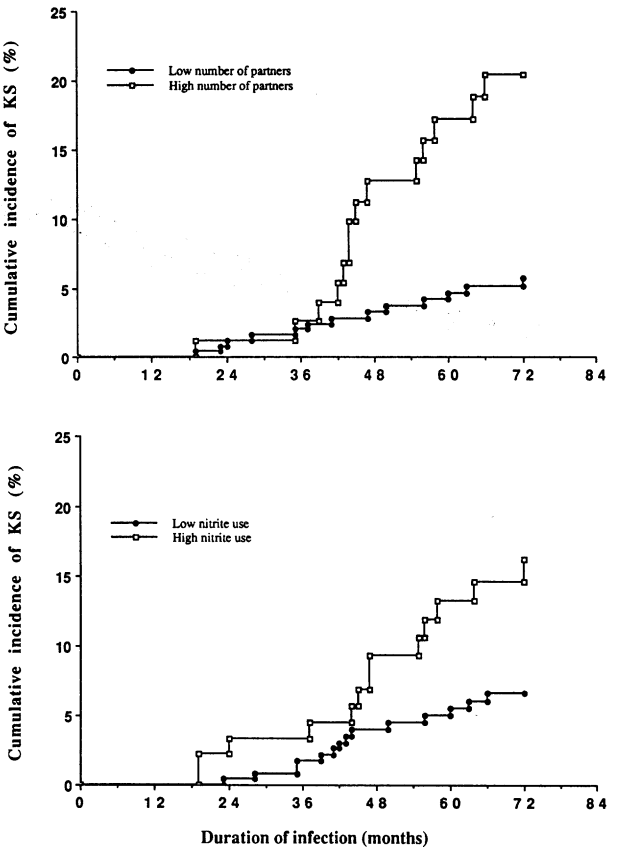

FIGURE 2. Kaplan-Meier curves for cumulative incidence of Kaposi's sarcoma (KS) stratified in the *upper panel* by high (>20) and low (≤20) numbers of sexual partners in San Francisco, Los Angeles, and/or New York in the 5 years before enrollment and in the *lower panel* by high (>20 "hits") and low (≤20 "hits") use of nitrite inhalants in the month before enrollment.

Discussion

There has been a marked decrease in the proportion of Kaposi's sarcoma among AIDS cases in the U.S., Canada, and Europe, and this decline appears to be occurring at similar rates in different risk groups and in different settings.[1,2,5–7] This relative decrease in Kaposi's sarcoma may be partly explained by our finding that the absolute risk of developing Kaposi's sarcoma in this cohort has declined dramatically over time. Our follow-up procedures make it unlikely that this decline is due to selective underreporting of Kaposi's sarcoma, nor does it appear to be due to any acceleration in the

TABLE 3. Final Cox Regression Model for Cumulative Incidence of Kaposi's Sarcoma

Variable	Relative Risk	95% Confidence Interval
Sexual contacts*	3.5	1.6–7.6
Use of nitrite inhalants†	2.3	1.0–5.0

* More than 20 sexual contacts in Los Angeles, San Francisco, or New York in the 5 years before enrollement.
† More than 20 "hits" of nitrites in the month before enrollment.

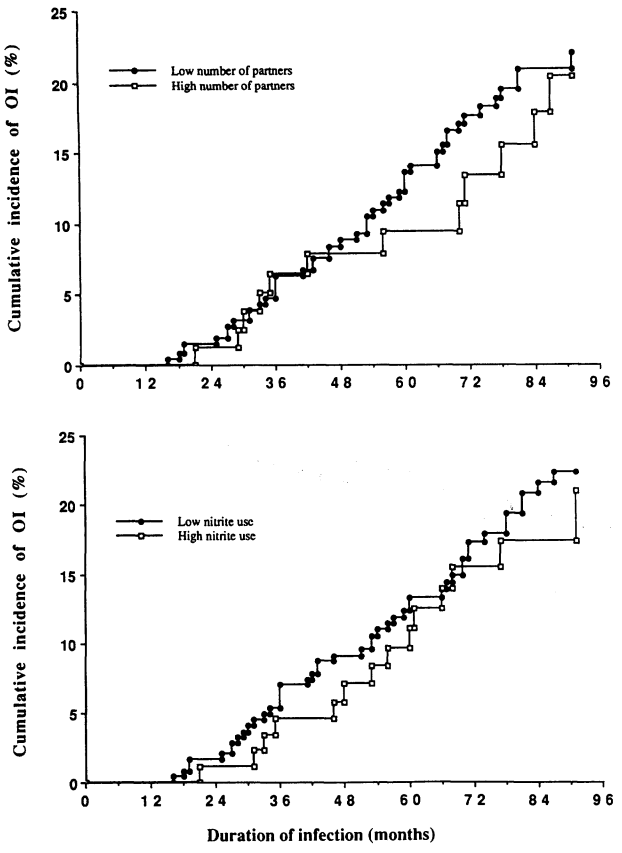

FIGURE 3. **Kaplan-Meier curves for cumulative incidence of opportunistic infection (OI) stratified in the *upper panel* by high (>20) and low (≤20) numbers of sexual partners in San Francisco, Los Angeles, and/or New York in the 5 years before enrollment and in the *lower panel* by high (>20 "hits") and low (≤20 "hits") use of nitrite inhalants in the month before enrollment.**

accrual of cases manifesting with illnesses other than Kaposi's sarcoma.

A number of methodologic issues in this study need to be addressed. First, the use of risk factor information from the enrollment questionnaire may have led to some misclassification, since sexual practices and other behaviors have changed with time. To use later information, however, would risk confounding by general secular trends and by the possibility of disease development influencing behavior. Second, the duration of HIV infection can have a confounding effect in cohort studies that assess risk factors for the development of AIDS. If the duration of infection is not taken into account, then variables associated with earlier infection will automatically appear as cofactors for the development of AIDS within a given time interval. The analyses presented here, however, accounted for each individual's estimated date of seroconversion.

In this study, we found no variables that were strongly associated with the development of opportunistic infection. On the other hand, we found two variables that were independently and strongly associated with an increased risk of Kaposi's sarcoma in multivariate analysis: namely, an elevated number of sexual partners in high-risk areas (San Francisco, Los Angeles, and/or New York) in the 5 years before enrollment and increased use of nitrites in the month before enrollment. At first glance, it is tempting to ascribe the role of these variables as surrogates of general life-style factors, perhaps related to earlier HIV infection. If this were so, however, one would also expect associations to be present for opportunistic infections, which was not the case.

We have previously published a study of antecedent risk factors in those developing Kaposi's sarcoma compared with those developing opportunistic infection which found associations with these variables.[17] This previous study, however, was a retrospective analysis that compared Kaposi's sarcoma cases with opportunistic infection cases and did not take into consideration the large number of seropositive but AIDS-free individuals at risk. Therefore, variables showing a positive association with Kaposi's sarcoma in this earlier analysis could be either risk factors for Kaposi's sarcoma or factors protective against other manifestations of AIDS. Furthermore, specificity for one type of AIDS manifestation, as found in the present analysis, can only be detected by studying risk factors for AIDS-defining illnesses individually. We view the specificity of the associations for Kaposi's sarcoma found in the present analysis as compelling evidence of a real biological association.

The present data indicate that for homosexual men in Vancouver, elevated sexual exposure in the primary AIDS epidemic centers for North America (San Francisco, Los Angeles, and New York) in the 5 years before enrollment (roughly the period 1978–1982) was associated with approximately a fourfold increase in the risk of Kaposi's sarcoma. One immediate possibility is that these men were exposed to a particular strain of HIV in these areas that is more pathogenic for Kaposi's sarcoma. This hypothesis, however, does not explain the paucity of Kaposi's sarcoma among AIDS risk groups other than homosexual men.

It is our view that the most plausible explanation for the present findings and for the curious epidemiologic patterns of AIDS-related Kaposi's sarcoma is the exist-

ence of a sexually transmitted Kaposi's sarcoma cofactor that increases the likelihood of Kaposi's sarcoma in the presence of HIV infection. We hypothesize that this cofactor was more prevalent in the primary AIDS epidemic centers, explaining the higher proportion of cases with Kaposi's sarcoma in these areas.[5,7] As we have previously speculated,[17] this Kaposi's sarcoma cofactor would be sexually transmitted in the same manner as HIV, but with less efficiency. Thus, changes in sexual behavior would have had an earlier effect on spread of the cofactor than on HIV because of the lower efficiency of transmission. The cofactor would thus have remained concentrated in the primary AIDS centers. In this way, men who traveled from a secondary epidemic center such as Vancouver to these primary areas and had increased sexual contact there acted as a form of migrant group who took on the higher risk of the centers where the sexual contact occurred. Such an explanation would also account for the recent finding by Beral *et al*[8] that AIDS-related Kaposi's sarcoma in Britain was more common among men whose likely source of HIV infection was the United States or Africa.

In a study of a cohort of homosexual men in San Francisco, Lifson *et al*[9] examined a large number of variables pertaining to sexual behavior, history of infectious disease, and recreational drug use and found none that were associated with Kaposi's sarcoma cases relative to other AIDS manifestations. These findings could be explained by the fact that San Francisco was one of the primary centers of the AIDS epidemic in North America. If the Kaposi's sarcoma cofactor was more prevalent in San Francisco, members of a homosexual cohort in that city may be more homogeneous with respect to exposure to the putative cofactor. Even so, one would expect individuals with greater degrees of sexual activity to be more likely to be exposed to the agent. The Kaposi's sarcoma cases in the San Francisco study did have greater numbers of sexual partners and more frequently engaged in receptive anal intercourse than the non-Kaposi's sarcoma cases, but the confidence intervals were broad.[9] Our cohort study was conducted in a population from a secondary AIDS epidemic center. One might therefore speculate that, in our cohort, there was a greater heterogeneity in degree of exposure to the putative Kaposi's sarcoma cofactor and that this exposure took place mainly in primary epidemic centers. Thus, the degree of exposure could be measured by the number of sexual contacts in these primary centers during the 5 years before enrollment.

The association between Kaposi's sarcoma and nitrite use in our data could be due to a direct biological effect of nitrites on the development of AIDS-related Kaposi's sarcoma, a theory that has been under consideration since the start of the AIDS epidemic.[18] It is also possible that the use of nitrites may enhance transmission of the Kaposi's sarcoma cofactor via their known effects of vasodilation and/or loss of sexual inhibition.[19]

Evidence from this prospective analysis of risk factors for Kaposi's sarcoma in a cohort of homosexual men supports the theory that Kaposi's sarcoma has a sexually transmitted cofactor in addition to HIV. A similar conclusion has been reached by authors examining national AIDS surveillance data in the U.S., Canada, and Europe.[5-8] The fact that two types of studies using very different approaches have reached the same conclusion offers considerable consistency to this hypothesis.

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