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Risk of Other Cancers following Kaposi's Sarcoma: Relation to Acquired Immunodeficiency Syndrome

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To evaluate the risk of another cancer among persons who initially developed Kaposi's sarcoma, the authors used data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute for the years 1973–1990. In persons under 70 years of age, 4,946 cases of Kaposi's sarcoma were observed during the period 1980–1990 (6,217 person-years of follow-up). On the basis of rates seen during the period prior to the epidemic of acquired immunodeficiency syndrome (AIDS), 169 cases were expected. Therefore, cases of Kaposi's sarcoma in this group were assumed to be AIDS-related, while cases occurring in older persons or during the 1970s were assumed to be non-AIDS-related. Rates were compared with the numbers of cases expected overall and by site on the basis of age-, sex-, and calendar year-specific rates from the SEER data. Among the 4,946 persons with AIDS-related Kaposi's sarcoma, the risk of developing non-Hodgkin's lymphoma through 1990 was increased 198-fold (95% confidence interval 169–232). However, the risk of all other cancers was only marginally increased (1.5-fold; 95% confidence interval 0.95–2.3), a risk that was probably biased upward because of ascertainment and misclassification. Among 491 persons with non-AIDS-related Kaposi's sarcoma, the relative risk of all cancers, including non-Hodgkin's lymphoma, was 0.9 (upper 95% confidence limit 1.2), and the risk of non-Hodgkin's lymphoma alone was 0.6 (upper 95% confidence limit 3.3). As of 1990, the risk of having another cancer following Kaposi's sarcoma was increased only in persons infected with human immunodeficiency virus, who were at high risk of non-Hodgkin's lymphoma but probably not of other cancers as a whole. *Am J Epidemiol* 1994;139:362–8.

acquired immunodeficiency syndrome; HIV; neoplasms; lymphoma, non-Hodgkin's; rectal neoplasms; sarcoma, Kaposi's

Kaposi's sarcoma is strongly associated with human immunodeficiency virus (HIV) infection, particularly in homosexual men (l), among whom the relative risk of developing Kaposi's sarcoma, a rare disease, has been estimated to be at least 100,000-fold higher than that in the general population (l). However, Kaposi's sarcoma can occur among persons who are not infected with HIV. In the period before 1980, prior to the epidemic of acquired immunodeficiency syndrome (AIDS), the US age-adjusted (1970 standard population) incidence was 2.9 and 0.7 per million per year in males and females, respectively (2). Most cases occurred in elderly persons. By 1989, however, the incidence of Kaposi's sarcoma among men aged 20–54 years had increased to 147 per million, and in the high-AIDS-

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Abbreviations: AIDS, acquired immunodeficiency syndrome; Cl, confidence interval; HIV, human immunodeficiency virus; SEER, Surveillance, Epidemiology, and End Results.

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risk area of San Francisco City/County, California, it was 1,967 per million (3).

For two reasons, we sought to determine the risk of a second primary cancer among persons who developed Kaposi's sarcoma. First, among persons who almost certainly had AIDS-related Kaposi's sarcoma, we wished to determine the risk of second cancers. Excess cancer risks due to HIV or its associated immunodeficiency in this group (most of whom would be HIV-infected homosexual men) should manifest as excess risks of second primary cancers. Second, we postulated that persons not HIV-infected who developed Kaposi's sarcoma might have an excess risk of second primary cancers, especially non-Hodgkin's lymphoma, a cancer known to be related to AIDS and other immunodeficiency conditions (l).

MATERIALS AND METHODS

We used data from nine US cancer registries participating in the Surveillance, Epidemiology, and End Results (SEER) program, which has monitored cancer incidence in about 10 percent of the US population since 1973 (3). Included in SEER areas were some groups living in areas with a high incidence of AIDS, such as San Francisco (4). To examine risk of second cancers in persons without HIV infection, we used data from Kaposi's sarcoma cases occurring in the pre-AIDS era (1973–1979) and data from more recent cases diagnosed in persons at least 70 years old.

To examine the cancer risk that follows Kaposi's sarcoma presumed to be AIDS-related, we used Kaposi's sarcoma cases that occurred in persons under 70 years of age from 1980 through 1990. The cutoff age of 70 years was chosen to minimize the likelihood of having included AIDS-related Kaposi's sarcoma in the group of persons considered to have non-AlDS-related Kaposi's sarcoma. Data on nonmelanoma skin cancers and carcinoma in situ were not available. Because of the high risk of non-Hodgkin's lymphoma in AIDS patients, we expected the incidence of non-Hodgkin's lymphoma following AIDS-related Kaposi's sarcoma to be increased, and we examined the incidence of other second primaries separately from that of non-Hodgkin's lymphoma.

To reduce ascertainment biases, only cancer diagnoses made more than 2 months after the primary Kaposi's sarcoma diagnosis were considered second primaries. Follow-up continued from 2 months after the date of Kaposi's sarcoma to the date of death, the date of the second primary, the date of last follow-up, or December 31, 1990, whichever was earliest. We divided follow-up into the first year (2 months to 1 year) and total years of follow-up (2 months to end date) because of uncertainty about the completeness of follow-up in later years, particularly among a potentially mobile population of homosexual men with AIDS. The expected numbers of cancers were based on sex-, age-, and calendar year-specific incidence rates in the entire SEER population and the number of person-years at risk for each group (5). Ninety-five percent confidence intervals were computed from the Poisson distribution.

RESULTS

AIDS-related Kaposi's sarcoma

Before 1980, the SEER program recorded 80 incident cases of Kaposi's sarcoma among persons under 70 years of age and 132 incident cases among older persons. In the 1980s (1980–1990), 279 cases were observed in older persons (table 1). If the ratio found between younger and older persons in the pre-AIDS period (80:132) had been maintained during the 1980s, 169 cases of Kaposi's sarcoma in persons under age 70 years would have been expected in this period, while 4,946 cases were observed. Since almost all (4,777/4,946 or 97 percent) of the Kaposi's sarcoma cases occurring in people under age 70 years during the 1980s were probably related to AIDS, we assumed that this group had AIDS-related Kaposi's sarcoma.

Other data are consistent with this assumption. Among persons under age 70

TABLE 1. Numbers of persons diagnosed with Kaposi's sarcoma from 1973 to 1990, by SEER* registry, age group, and race

Registry	Age group‡ (years)	Time period†	
		1973–1979	1980–1990
San Francisco/ Oakland, California	<70	22	3,461
	≥70	38	65
Connecticut	<70	20	212
	≥70	30	72
Metropolitan Detroit, Michigan	<70	17	167
	≥70	28	67
Hawaii	<70	1	118
	≥70	5	9
Iowa	<70	1	24
	≥70	8	16
New Mexico	<70	7	68
	≥70	6	14
Seattle/Puget Sound, Washington	<70	8	410
	≥70	11	22
Utah	<70	0	44
	≥70	1	3
Metropolitan Atlanta, Georgia	<70	4	442
	≥70	5	11
Total	<70	80	4,946
	≥70	132	279

* SEER, Surveillance, Epidemiology, and End Results.
† By period, 5.2 percent were black in 1973–1979, compared with 6.9 percent in 1980–1990.
‡ By age group, 7.0 percent were black among persons aged <70 years, compared with 4.1 percent among persons aged ≥70 years.

years who developed Kaposi's sarcoma, 99.4 percent were men in the AIDS era, whereas only 77.5 percent were men in the pre-AIDS era. Furthermore, the average age of the Kaposi's sarcoma patients under age 70 years in the AIDS era—38.2 years—was typical of AIDS cases and was considerably lower than the average age of Kaposi's sarcoma patients under age 70 in the pre-AIDS era (57.5 years). The average follow-up interval was also shorter in the AIDS-related Kaposi's sarcoma cases than in the other Kaposi's sarcoma cases (1.26 and 4.89 years, respectively), reflecting the high mortality associated with AIDS.

We also used death certificate data on AIDS as an underlying cause of death. However, AIDS information became available to the SEER registries only after January 1, 1987. Among the 2,316 Kaposi's sarcoma patients under 70 years old who died in 1987–1990 and for whom the cause of death was recorded, 1,970 (85.1 percent) had AIDS listed as the underlying cause of death. We believe that additional patients with AIDS-related Kaposi's sarcoma will have died without having AIDS coded on the death certificate. Among 90 Kaposi's sarcoma patients aged >=70 years who died in 1987–1990, three (3.3 percent) had AIDS listed as the underlying cause of death. Thus, in the great majority of patients under 70 years old, Kaposi's sarcoma appeared to be related to AIDS.

Among persons with AIDS-related Kaposi's sarcoma, the risk of developing any second primary cancer was substantially increased (table 2). In the first year (3,026 person-years), 92 second primaries were observed, while 5.2 cases were expected (observed/expected = 17.6). During all of the years of follow-up (6,217 person-years), 191 second primaries were observed, while 15.8 were expected (observed/expected = 12.1). Of the second cancers that occurred, 168 (88 percent) were non-Hodgkin's lymphoma, whereas less than one case was expected to occur in all of the years of follow-up. The incidence of non-Hodgkin's lymphoma was 239-fold (95 percent confidence interval (CI) 191–299) greater than expected in the first year and 198-fold (95 percent CI 169–232) greater overall.

Other than non-Hodgkin's lymphoma, 10 second primary cancers were reported in persons with AIDS-related Kaposi's sarcoma in the first year of follow-up, while 4.9 cases were expected (observed/expected = 2.0; 95 percent CI 0.96–3.7). With complete follow-up, 23 other second primaries occurred, while 14.9 were expected (observed/expected = 1.5; 95 percent CI 0.95–2.3). During the first year, cancers other than non-Hodgkin's lymphoma included anal or anorectal cancer (n = 2), lung cancer (n = 2), and one case each for the testis, brain, skin (melanoma), and conjunctiva and Hodgkin's disease (plus one unspecified). Beyond the first year, cancers reported at

TABLE 2. Risk of second cancers in persons with Kaposi's sarcoma, 1973-1990*

	Follow-up period					
	2-12 months			All years		
	Obs†	Exp†	O/E†	Obs	Exp	O/E
AIDS†-related Kaposi's sarcoma‡ (4,946 persons at risk)						
		3,026 PY†			*6,217 PY*	
All cancers	92	5.2	17.6 (14.2–21.8)‖	191	15.8	12.1 (10.5–13.9)
All cancers, excluding non-Hodgkin's lymphoma	10	4.9	2.0 (0.96–3.7)	23	14.9	1.5 (0.95–2.3)
Non-Hodgkin's lymphoma	82	0.3	239.3 (191–299)	168	0.8	198.3 (169–232)
Non-AIDS-related Kaposi's sarcoma§ (491 persons at risk)						
		368 PY			*2,401 PY*	
All cancers	8	8.7	0.9 (0.4–1.8)	50	56.5	0.9 (0.7–1.2)
All cancers, excluding non-Hodgkin's lymphoma	8	8.6	0.9 (0.4–1.8)	49	54.9	0.9 (0.7–1.2)
Non-Hodgkin's lymphoma	0	0.3		1	1.6	0.6 (0.02–3.3)

* Data are from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. Expected numbers of cases were derived from age-, sex-, and calendar year-specific SEER rates.

† AIDS, acquired immunodeficiency syndrome; Obs, no. observed; Exp, no. expected; O/E, observed/expected; PY, person-years at risk.

‡ AIDS-related Kaposi's sarcoma was defined as Kaposi's sarcoma diagnosed in persons of either sex aged <70 years during the period 1980–1990.

§ Non-AIDS-related Kaposi's sarcoma was defined as Kaposi's sarcoma diagnosed before 1980 or in persons aged ≥70 years during the period 1980–1990.

‖ Numbers in parentheses, 95 percent confidence interval.

additional sites were cancers of the lung (*n* = 3), prostate (*n* = 2), and bladder (*n* = 2) and one case each for the colon, liver, larynx, testis, and connective tissue (plus one unspecified). Except for the anal cancers (one squamous cell cancer of the anus and one cloacogenic carcinoma) and the conjunctival cancer (squamous cell carcinoma) in the first year, none of the rates observed for cancers other than non-Hodgkin's lymphoma significantly exceeded rates expected at specific sites.

Thirty-two cases of Kaposi's sarcoma were reported in women under 70 years of age in the AIDS era. None of those women were reported as having another cancer during the follow-up period (98 person-years).

Non-AIDS-related Kaposi's sarcoma

We considered 491 cases of Kaposi's sarcoma to be non-AIDS-related. Among the 212 Kaposi's sarcoma patients whose illness was diagnosed before 1980, few would have been infected with HIV. Those 279 Kaposi's sarcoma patients aged >=70 years who presented for treatment during the AIDS era could have included persons who were HIV-infected. Although the number of people in this group increased from 18.8 cases per year in the pre-AIDS era to 25.4 cases per year in the 1980s, the population under surveillance also increased. Furthermore, the AIDS epidemic probably increased clinical interest in Kaposi's sarcoma, which may have contributed to the rising frequency of this diagnosis. However, both the average age (81.1 years) and the male:female sex ratio (183:86 or 2.1:1) of older persons in the 1980s were similar to those among older persons in the pre-AIDS era (79.8 years and 95:37 or 2.6:1, respectively), suggesting that the groups were relatively similar and probably included few HIV-infected individuals.

Among the persons with non-AIDS-related Kaposi's sarcoma, there were 368 person-years of follow-up in the first year

and a total of 2,401 person-years of follow-up for all years (table 2). Because age at diagnosis was much higher in this group (average age = 72.8 years), the expected number of cancers was much larger than that in the group that developed AIDS-related Kaposi's sarcoma (average age = 38.2 years). In the first year after Kaposi's sarcoma diagnosis, eight second primaries were observed, while 8.7 were expected (observed/expected = 0.9, 95 percent CI 0.4–1.8). Using all years of follow-up, 50 second primaries were observed, while 56.5 were expected (observed/expected = 0.9; 95 percent CI 0.7–1.2). Stratification by age group (<70 years vs. >=70 years), time period (1973–1979 vs. 1980–1990), and sex yielded similar results.

One case of non-Hodgkin's lymphoma was observed following non-AIDS-related Kaposi's sarcoma, while 1.6 cases were expected (observed/expected = 0.6; 95 percent CI 0.02–3.3). This case occurred in an elderly woman during the pre-AIDS era. Two cases of multiple myeloma were diagnosed, one in the first year and one later. The excess incidence seen in our study (0.7 cases expected overall) was not statistically significant. Both cases occurred in women during the period 1973–1979.

DISCUSSION

Previous attempts to assess cancer risk in HIV-infected persons have relied on either cohorts of subjects known to be HIV-infected with relatively few cancer outcomes (6, 7) or large studies in which demographic data (sex, age, marital status, and area) were used to identify populations likely to have a high HIV infection rate (8, 9). These studies revealed the excess relative risk of at least 100-fold for non-Hodgkin's lymphoma in populations at risk for AIDS (10). Excesses of other types of cancers have not been easily documented, although they have been much discussed.

In this study, we found the excess risk of non-Hodgkin's lymphoma—239-fold in the first year and 198-fold overall—to exceed previous estimates, probably because we better identified a subset of persons who were highly likely to have had AIDS. This relative risk can only be applied to those who had Kaposi's sarcoma during the course of their AIDS illness, weighing it heavily towards homosexual men. We cannot exclude the possibility that persons with AIDS-related Kaposi's sarcoma are at higher risk of non-Hodgkin's lymphoma than persons presenting with other AIDS illnesses, but we note that persons with non-AIDS-related Kaposi's sarcoma do not have an excess risk of non-Hodgkin's lymphoma.

In contrast to non-Hodgkin's lymphoma, the overall excess of other cancers was only marginally significant: 1.5-fold, with the upper 95 percent confidence limit being 2.3-fold. Thus, among persons with AIDS, the excess risk of all cancers other than non-Hodgkin's lymphoma is low.

These findings are potentially biased in several ways. Because screening at the time of AIDS diagnosis might accelerate diagnoses of cancers to within the first 2 months, rates in the first year following AIDS diagnosis could be underestimated. In addition, patients with AIDS-related Kaposi's sarcoma may move from the site of their initial diagnosis to other hospitals and caregivers, which could make recording of second malignancies more difficult. Persons with AIDS could also provide fictitious names and develop second cancers or die without this information being linked to cancer registry data. In a follow-up study linking non-Hodgkin's lymphoma records in AIDS registries to those in cancer registries in California, Florida, New Jersey, and Atlanta, Georgia, we have found cancer registry data to be about 85 percent complete (Cote et al., unpublished data; because these registries were generally not within the SEER network, the data may not be quite analogous to those in this study). These biases would underestimate the rates of non-Hodgkin's lymphoma. However, ascertainment bias associated with being under close medical supervision is also likely, although this may be offset by the reluctance of physicians and patients to pursue cancer diagnoses aggressively.

Probably more serious is misclassification of those cancers coming to diagnosis. Histologies may be erroneous, resulting in miscoding of Kaposi's sarcoma, a cancer which can occur at almost any site. In addition, relative to other cancers, non-Hodgkin's lymphoma was so frequent that only a minor amount of misclassification of this disease (e.g., as Hodgkin's disease) could lead to increased rates of those cancers. Thus, some of this slight excess risk of cancers other than non-Hodgkin's lymphoma may be artifactual.

Finally, other lifestyle variables could increase the risk of cancer among homosexual men above background rates for reasons other than HIV or its associated immunodeficiency. In a study conducted during the 1970s, before the onset of the AIDS epidemic, rates of anal cancer were fourfold higher among homosexual men than in the general male population (11). In addition, homosexual men may have more exposure to other carcinogens than the general population. For example, in several cohort studies, HIV-seroconverting participants tended to smoke more cigarettes (12, 13).

Among persons unlikely to be HIV-infected who developed Kaposi's sarcoma, we found no significant excess of cancer overall (observed/expected = 0.9) or of non-Hodgkin's lymphoma (observed/expected = 0.6). In a study comparing patients hospitalized with Kaposi's sarcoma to the general population, a 20-fold excess risk of non-Hodgkin's lymphoma was estimated (14). Such an excess is inconsistent with the results of the present study. The only study comparable to ours was conducted in Sweden (15). Among 529 non-AIDS-related Kaposi's sarcoma cases, the authors found no excess of all cancers but a significant excess (a 2.3-fold increase) of "lymphoma" (including eight cases of non-Hodgkin's lymphoma, three cases of Hodgkin's disease, and two multiple myelomas). While we did not find an elevated risk of non-Hodgkin's lymphoma in patients with non-AIDS-related Kaposi's sarcoma (0.9-fold), the Swedish result is not beyond the upper limit of the broad confidence intervals in our findings (95 percent CI 0.02–3.3). Although it was not statistically significant in our study, the finding of two cases of multiple myeloma in the non-AIDS-related patients may be of interest, because the Swedish investigators observed an excess incidence (two cases) of multiple myeloma in their study (15).

In summary, while the risk of non-Hodgkin's lymphoma following Kaposi's sarcoma that was presumed to be AIDS-related was increased 230-fold in the first year and 198-fold overall, the incidence of other cancers was increased only 2.0-fold in the first year and 1.5-fold overall. For all cancers other than non-Hodgkin's lymphoma, the lower confidence limit of the relative risk included 1.0 (95 percent CI 0.95–2.3). However, small increased risks of specific types of cancer could be present or could emerge if survival increases dramatically. In this study, the average length of follow-up in the cases assumed to have AIDS-related Kaposi's sarcoma was only 1.26 years. In addition, risks could be increased in groups such as women, children, or persons exposed to HIV by routes other than homosexual activity.

Assessing the risk of cancers other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with HIV infection and its related immunodeficiency will require the study of very large numbers of persons at risk, since the incidence of those cancers is so low. Furthermore, if excess risks are found, evaluation of each case will be required in order to limit misclassification. Persons with Kaposi's sarcoma who are not infected with HIV have no excess risk of non-Hodgkin's lymphoma or of other cancers combined.

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