The possibility that an agent in addition to the human immunodeficiency virus (HIV) may contribute to the etiology of non-Hodgkin's lymphoma in persons with acquired immunodeficiency syndrome (AIDS) was studied using participants from the Multicenter AIDS Cohort Study (MACS) of homosexual and bisexual men enrolled in 1984–1985 and also in 1987–1991. A nested case-control analysis was conducted. The primary source of information on potential exposures and characteristics of the participants was the baseline study entry interview that was conducted prior to the development of AIDS. A total of 84 cases of non-Hodgkin's lymphoma were identified and compared with 527 participants who developed AIDS but had no evidence of cancer. The groups were similar for most sociodemographic characteristics as well as sexual activity and past history of antecedent illnesses. Although the non-Hodgkin's lymphoma cases reported less frequent use of recreational drugs and cigarettes compared with other persons with AIDS, these differences were not significant. Non-Hodgkin's lymphoma cases reported more frequent intake of aspirin during the week before the interview. However, there were no differences between the comparison groups for long-term aspirin intake or intake of other analgesics. The absence of any specific and strong association between non-Hodgkin's lymphoma and the various behavior-related activities and exposures considered in this analysis suggests that these factors are not related to a second agent in the etiology of HIV-induced non-Hodgkin's lymphoma. The possibility that a very common agent in this study population or that differences in the nature of the immune dysfunction resulting from HIV infection could act as a cofactor for HIV-induced non-Hodgkin's lymphoma cannot be excluded. Am J Epidemiol 1996;143:374-9.

acquired immunodeficiency syndrome; lymphoma, non-Hodgkin's; risk factors

Non-Hodgkin's lymphomas constitute a heterogeneous group of malignancies. Before the human immunodeficiency virus (HIV) epidemic, non-Hodgkin's lymphoma comprised 3 percent of all malignancies in the general population (1). Since 1960, there has been a 50 percent increase in non-Hodgkin's lymphoma incidence (2, 3).

The identified risk factors for non-Hodgkin's lymphoma include male sex, rural residence, occupational exposures to radiation and certain chemicals, a history of steroid use, hives and eczema, and chronic infectious diseases, especially tuberculosis and malaria (1, 4). Individuals with congenital and acquired immunodeficiencies are at greatly increased risk for non-Hodgkin's lymphoma. Compared with the general population, transplant recipients have a relative risk of 30-300 for non-Hodgkin's lymphoma and 1,000 for primary central nervous system lymphoma. Patients receiving allografts have a relative risk of over 100 for lymphomas (1, 5).

Between 3 percent and 10 percent of patients with acquired immunodeficiency syndrome (AIDS) (persons with AIDS) develop non-Hodgkin's lymphoma, usually as a high grade extranodal tumor. Compared with the general population, this results in a relative risk for AIDS patients of 60 for overall non-Hodgkin's
lymphoma, 360 in patients under age 20, and 1,000 for primary central nervous system and Burkitt’s lymphomas (6).

Most of the published reports on non-Hodgkin’s lymphoma in AIDS have been based on clinical case series and/or small studies. Some studies suggest that manifestation of non-Hodgkin’s lymphoma as an AIDS condition has recently increased. One reason postulated for this is that recent AIDS therapies allow persons with AIDS to survive longer and reach more severe levels of immunosuppression (7). Other reported associations for non-Hodgkin’s lymphoma in AIDS include hemophilia, white race, male sex, and a prior history of oral hairy leukoplakia or Kaposi’s sarcoma (8, 9). To date, the small size of most non-Hodgkin’s lymphoma series has permitted only demographic and existing laboratory data to be examined as potential risk factors. Other potential risk factors, if any, remain to be studied.

This is a nested case-control study of risk factors for non-Hodgkin’s lymphoma among AIDS cases in the Multicenter AIDS Cohort Study (MACS) population. The baseline interview database as well as data collected on some of the factors during semiannual follow-up visits was used. The analysis was aimed at identifying within the HIV-infected population factors that predispose to non-Hodgkin’s lymphoma.

MATERIALS AND METHODS

Study population

The MACS prospectively studies the natural history of HIV infection among homosexual and bisexual men from four metropolitan areas of the United States: Baltimore-Washington, Chicago, Pittsburgh, and Los Angeles. From April 1984 through March 1985, 4,954 homosexual and bisexual men were enrolled; 634 additional men were enrolled from April 1987 through September 1991. Among these 5,588 men, 2,190 men were seropositive for HIV at entry as determined by enzyme-linked immunosorbent assay confirmed by Western blot, and 488 others have subsequently seroconverted for HIV by January 1995. More information on the MACS study design is provided elsewhere (10).

For this analysis, AIDS and AIDS illnesses are defined by the 1987 CDC definition (11) and are determined by active and passive surveillance with confirmation by physicians and/or medical records. For the current analysis, the 84 incident cases of non-Hodgkin’s lymphoma during the follow-up period constitute the case group, while 527 cases of AIDS with no diagnosis of a malignancy, the control group. In addition, the cases were compared with 1,639 HIV-seropositive individuals with no AIDS-defining illness at the time of the analysis. Considering that the results with the latter group of comparison were similar to those with the comparison with the 527 AIDS controls, this paper will present the results of the first set of analyses only. Of the 84 incident non-Hodgkin’s lymphoma cases, non-Hodgkin’s lymphoma was the initial AIDS outcome in 37 participants, while 47 cases were diagnosed with non-Hodgkin’s lymphoma after some other initial AIDS outcome, 15 of whom were identified with non-Hodgkin’s lymphoma at autopsy. Of the non-Hodgkin’s lymphoma diagnoses, 60 were confirmed by biopsy, cytology, and/or autopsy, and 24 cases were based on self-reports or clinical information, pending receipt of copies of laboratory or pathology records.

Covariates

Comparisons were based on the data obtained at the baseline interview, which was prior to the development of AIDS outcome. At study entry, MACS participants were asked about their lifetime history of infections including sexually transmitted diseases. They also reported on the types and frequency of particular sexual activities, the total number of sexual partners, and the use of recreational drugs during the previous 2 years. A copy of the detailed baseline questionnaire is available upon request. Peripheral blood counts of CD4+ lymphocytes were obtained by flow cytometry as described elsewhere (12).

Analysis

In this study, the 84 non-Hodgkin’s lymphoma cases were compared with the 527 controls. Following selection of the variables of interest, frequency distributions were conducted, and a number of primary variables were defined based upon previous knowledge of the epidemiology of non-Hodgkin’s lymphoma and HIV infections. Also, special scores were developed that would summarize a particular pattern of activity or exposure. Thus, scores were developed for different types of sexual activity, recreational drug use, and infections. The components of these scores were the positive responses to the various questions related to these activities. For example, a recreational drug use score of 5 would mean five positive responses by the interviewee to five questions about the use of five specific drugs.

Multivariate logistic regression models were used to study potential confounding and interactions. Individual covariates and groupings of variables were included in these models according to scoring systems developed in the univariate analysis.
RESULTS

As a first step in the analysis, background characteristics of the non-Hodgkin's lymphoma cases and controls with AIDS but no malignancy were compared. These groups were similar with respect to age, race, and ethnic origin. The comparisons did not reveal any significant differences by education, occupation, and study site. Univariate analyses of the baseline characteristics of the case and control groups revealed that there were no significant differences between the study groups with respect to any sexual activity (table 1). Also, there were no differences between the study groups as to antecedent infections (table 2) or conditions previously reported to be associated with non-Hodgkin's lymphoma, such as rheumatoid arthritis (1). A review of some of the serologic markers for antecedent infection in the cases and controls did not reveal any additional significant findings.

As seen in table 3, comparison of the study groups by the history of use of various recreational drugs revealed that non-Hodgkin's lymphoma cases, in general, reported less use of such drugs, but the differences were not statistically significant. This was also reflected in the comparison of cumulative drug summary scores. Those with non-Hodgkin's lymphoma reported using a lower number of these drugs. However, there was no gradient in the odds ratios with an increasing number of these drugs. Nevertheless, there were no significant differences when these comparisons were made for aspirin intake, there were no differences between the study groups as to the use of these medications. Non-Hodgkin's lymphoma cases reported significantly more aspirin intake than did the controls in the 7 days prior to the date of baseline interview (table 4). However, there were no significant differences when these comparisons were made for aspirin use for the longer term and for other analgesics.

DISCUSSION

The current study takes advantage of a nested case-control approach within the prospective follow-up of MACS and has a large non-Hodgkin's lymphoma case group not likely to exist in other longitudinal studies. Although type II error is possible, we believe that the risk factors studied here would have likely been identified had they been major risk factors for non-Hodgkin's lymphoma. Except for genital herpes, the upper limit of all 95 percent confidence intervals for odds ratios was always less than 3, and these upper limits were usually less than 1.50.

The primary comparison of this analysis was between the cases of non-Hodgkin's lymphoma and other AIDS patients in order to identify specific features that distinguish the non-Hodgkin's lymphoma group. Such differences from the other persons with AIDS could suggest the identification of specific factors that are involved in the etiology of non-Hodgkin's lymphoma. Except for perhaps aspirin, there were no significant differences between the study groups as to known or potential risk factors for non-Hodgkin's lymphoma.

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In general, non-Hodgkin’s lymphoma cases were less exposed to recreational drugs and cigarettes compared with other persons with AIDS, but these differences were small. The only significant observation in these and other comparisons was the finding of a history of higher intake of aspirin during the 7 days prior to interview within the non-Hodgkin’s lymphoma group (odds ratio = 1.70, 95 percent confidence interval 1.04–2.79). In a population-based case-control study of prior medication use and health history among non-HIV-infected cases and controls, Bernstein and Ross (13) observed that non-Hodgkin’s lymphoma cases reported more long-term use of aspirin and other pain relievers than did neighborhood controls. This difference was statistically significant for the females only. The lack of consistency of this observation within the current study as well as in the various subgroups studied by Bernstein and Ross casts doubt on whether this association is of etiologic significance.

In the absence of any specific and strong associations between non-Hodgkin’s lymphoma and the various behavioral and suspected agents that were considered in this analysis, it seems unlikely that a cofactor related to sexual behavior or drug use is involved in the etiology of non-Hodgkin’s lymphoma in persons with AIDS. However, as all of our participants were sexually active and most used drugs, we could therefore miss a cofactor that is highly prevalent in this population. Our previously reported findings of important differences in behavioral patterns and past infections between case and control groups in a study of Kaposi’s sarcoma in the same population speak against such a possibility (14).

A comparison of baseline CD4 levels and CD4 levels within 6 months prior to AIDS between the non-Hodgkin’s lymphoma group and the control group of persons with AIDS with no cancer did not reveal any major differences in these levels. Recently,
Yawetz et al. (15) reported elevated serum levels of soluble CD23 prior to the appearance of AIDS-associated non-Hodgkin's lymphoma within the MACS study population. They believed that soluble CD23 was a B-cell activation and differentiation marker. They hypothesized that B-cell hyperstimulation, in particular the chronic stimulation of B cells to undergo isotype switching associated with HIV infection, may play an important role in the pathogenesis of non-Hodgkin’s lymphoma. If our findings are correct along with this hypothesis, that suggests that no cofactors other than immunosuppression are involved with this isotype switching.

More recently, Chang et al. (16) identified herpes virus-like DNA sequences in HIV-related Kaposi’s sarcoma. The specificity of this DNA code to Kaposi’s sarcoma tissue from individuals with different manifestations of the condition suggests a definite role for this agent in the pathogenesis of Kaposi’s sarcoma. The same group has also reported similar herpes virus-like DNA sequences from eight of 193 non-Hodgkin’s lymphoma specimens from persons with AIDS (17). All eight patients who were positive for the DNA sequences had body cavity-based lymphomas. In contrast to the studies of Kaposi’s sarcoma, additional investigations are needed to establish the specificity of these herpes virus-like DNA sequences in a subtype of non-Hodgkin’s lymphoma.

Although the current study did not provide any leads to a specific etiology of non-Hodgkin’s lymphoma in persons with AIDS, it allowed us to test a number of general hypotheses as to the specific risk factors involved in this condition. It is important to repeat this study in other populations of persons with AIDS. A case-control study based on clinical case material selected from a broader representation of persons with HIV infection may allow us the identification of additional factors that may be of significance in the etiology of non-Hodgkin’s lymphoma in persons with AIDS.

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