



## A STUDY OF ADULT T-CELL LEUKEMIA/LYMPHOMA INCIDENCE IN CENTRAL BROOKLYN

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**Adult T-cell leukemia/lymphoma (ATL), a rare outcome of infection with human T-lymphotropic virus (HTLV-I), is endemic in central Brooklyn, which has a large Caribbean migrant population. Previous studies have suggested that HTLV-I prevalence in central Brooklyn may be similar to that recorded in the Caribbean islands. We established a pilot 1-year surveillance program to identify cases of ATL in 7 of 10 hospitals serving the residents of 18 zip codes of central Brooklyn with a combined population of 1,184,670. Of the 6,198 in-patient beds in the catchment area, approximately 83% were covered. Twelve incident cases of ATL were ascertained, all among persons of Afro-Caribbean descent, indicating an annual incidence in African-Americans in this community of approximately 3.2/100,000 person-years. Unexplained hypercalcemia was the most useful screening method, identifying 3 of 5 patients not referred for possible ATL by a local hematologist. The female:male ratio was 3:1. The age pattern was different from that reported in the Caribbean Basin and closer to the pattern seen in Japan. Our study supports evidence that HTLV-I infection and ATL are endemic in central Brooklyn and suggests that a more intensive surveillance program for this disease coupled with intervention efforts to reduce HTLV-I transmission are warranted. *Int. J. Cancer* 80:662–666, 1999.**

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Adult T-cell leukemia/lymphoma (ATL) is an aggressive, chemotherapy-resistant malignancy that is the most devastating result of infection with human T-lymphotropic virus (HTLV-I) (Takatsuki *et al.*, 1977). The lifetime risk of an HTLV-I-infected individual developing ATL has been estimated at 3% to 5% (Murphy *et al.*, 1989), perinatal infection apparently being more important in the pathogenesis of this disease than infection acquired later in life (Cleghorn *et al.*, 1995). Prevention of infection is a much more effective means of disease control than treating established disease; therefore, identification of endemic areas of HTLV-I infection is an appropriate target of cancer prevention and control programs. ATL is a useful marker disease for the identification of HTLV-I-endemic areas (Levine *et al.*, 1988, 1994b), and since our case series (Dosik *et al.*, 1988) and seroprevalence studies (Dosik *et al.*, 1992) suggested that central Brooklyn could be an area where HTLV-I is endemic, we evaluated the incidence of ATL in central Brooklyn by developing a population-based surveillance study involving those areas where ATL cases and HTLV-I infection had been documented. In addition to providing data for the evaluation of possible cancer detection and counseling programs in central Brooklyn, this

project was developed as a pilot for other areas of the United States where ATL cases appear to be concentrated and where HTLV-I infection may be endemic, such as southern Florida (Harrington *et al.*, 1991, 1995; Levine *et al.*, 1994b).

### MATERIAL AND METHODS

#### Identification of patients

A surveillance system was established for 18 zip codes in central Brooklyn, which were centered around the 10 hospitals serving the area (Fig. 1). The targeted population was known to utilize the local hospitals, and affected patients were unlikely to be seen in hospitals outside of our surveillance. All 10 area hospitals were contacted, and 7, comprising 82.7% of the 6,198 in-patient beds serving the Brooklyn community, participated in a case-identification study. Potential cases were ascertained through physician referral, by review of all new in-patients and out-patients and through hospital records with diagnosed hematological malignancy, unexplained leukocytosis or unexplained hypercalcemia (no parathyroid abnormalities, dehydration, etc.). Any patient identified by these criteria was given full information about the study. A blood sample was drawn from those who gave informed consent for a screening assay to detect HTLV-I antibody (Fujirebio, Tokyo, Japan). A positive screening test resulted in the patient's entry into the second phase of the study, which included the collection of detailed clinical and demographic data by interview and chart review. All sera were subsequently tested by a battery of serological assays to determine the specificity of the screening result (see below). Each hospital entered into the study was monitored for 1 year.

#### Verification of surveillance efficacy

To evaluate the completeness of our surveillance, we compared our ascertained cases with those identified by the New York State Cancer Registry. Since the early 1990s, the New York State Cancer Registry has histologically confirmed 83% of reported cases, 3.4%

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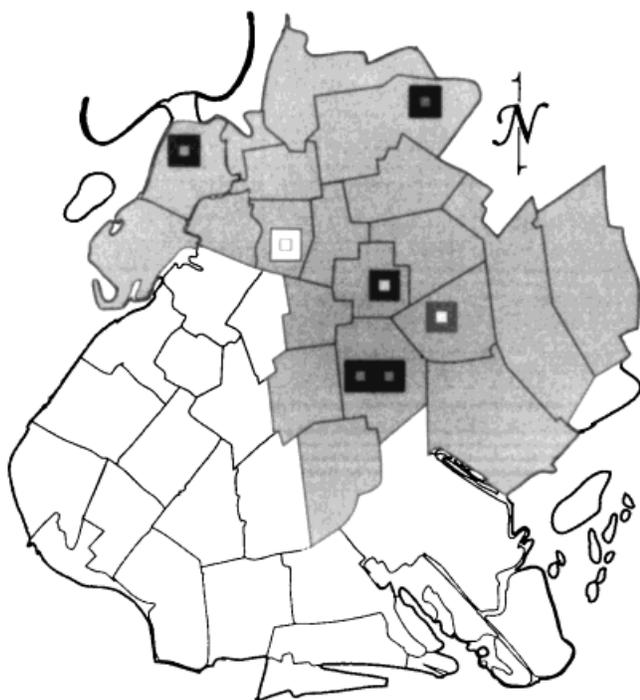


FIGURE 1—Map of Brooklyn demonstrating the zip code areas (shaded) included in our study area.

being confirmed as a malignancy but not further classified. Death certificate diagnosis with tumor type was utilized for 5%, and the remaining 8.6% were classified as malignancy, type not specified. To evaluate the completeness of surveillance at King's County Hospital, tissue blocks were obtained on all lymphoma cases between 1988 and 1993. Histology and immunophenotype were reviewed and the 10 T-cell lymphomas were evaluated for the presence of HTLV-I, thus documenting which cases were and were not ATL.

### Laboratory tests

All sera were initially screened for HTLV-I antibody in Brooklyn by the particle agglutination assay (Fuji-ribo). Sera with positive results were confirmed by an enhanced Western blot analysis, testing for reactivity to both *gag*(p24) and recombinant *env*(rgp21e) antigens at the Retrovirus Laboratory, Frederick Cancer Research and Development Center. Serotyping to distinguish HTLV-I from HTLV-II was performed using ELISA. The presence of HTLV-I infection in tissue blocks was determined by PCR. DNA was extracted from each of the 10 T-cell lymphomas by scraping 5-mm-thick histological sections of formalin- or Bouin's-fixed paraffin tissue blocks. DNA was amplified using PCR and primers specific for the *env* and *pol* regions of HTLV-I proviral DNA. Adequate DNA was amplified in 8 cases.

### Review of New York State Cancer Registry database to validate our ATL surveillance system

To evaluate the efficacy of our ATL surveillance system, leukemia and lymphoma cases with diagnosis dates within a 6-month period beginning July 1, 1992 (the start of the surveillance project), were abstracted. Cases were restricted to persons residing in neighborhoods with zip codes in our catchment area. The listing was further restricted to hematological malignancies with ICD site codes 200.0–208.9. Finally, cases with reported malignancies of B-cell phenotype were excluded. Information for cases included

hospital where the malignancies were first diagnosed, gender and ethnicity.

To estimate the number of expected ATL cases in the catchment annually, we counted the number of leukemia or lymphoma cases excluding known B-cell malignancies for patients residing in our catchment that were reported to the registry. Of these diagnoses compatible with ATL, 27 were reported to the registry during the first 6 months, for an anticipated annual total of 54 cases. Of these potential ATL cases, we estimated from previous work in Caribbean populations (Cleghorn *et al.*, 1995) that 50% of non-Hodgkin's lymphoma (NHL) malignancies would be of T-cell phenotype. Thus, we would expect 27 cases of T-cell leukemia and lymphoma annually for our catchment. Finally, based on present findings from our own surveillance of T-cell malignancies in central Brooklyn, we would expect 12/30, or 40%, of these T-cell malignancies to be HTLV-I-associated, for a total of 11 expected cases of ATL annually. Since our surveillance identified a virtually identical number of ATL cases (12 cases), we used 12 as the expected incidence for incidence calculations.

### Estimates of population at risk for ATL and expected ATL incidence

A sensitivity analysis was conducted to produce a range of estimated ATL incidence rates as a function of varying numbers of persons at risk in our catchment area. The number of total illegal Afro-Caribbean immigrants in New York City was estimated to be 398,000 (Warren, 1995). The proportion of illegal Afro-Caribbean immigrants residing in central Brooklyn was considered to be at least 50% but no more than 90%. To these estimates, we added 176,000 Afro-Caribbean residents in the catchment (by zip code) who were counted as part of the 1990 US Census and were likely to be immigrants registered with the US Immigration and Naturalization Service or US citizens. These totals were adjusted to reflect the percentage of the Afro-Caribbean population in the catchment that was adult and at risk for ATL; these percentages varied from 50% to 90%.

Finally, ATL incidence was calculated over the range of estimated adult Afro-Caribbean persons at risk. Incidence rates were assumed to be distributed as Poisson random variables, and 95% confidence intervals were calculated accordingly.

## RESULTS

Thirty patients were identified with either hematological malignancies, unexplained leukocytosis or unexplained hypercalcemia. Of these 30 cases, 12 incident cases of HTLV-I-associated ATL were identified (40% of putative cases identified by screening). Eight of the ATL cases were referred by hematologists as possible ATL, 3 were identified by abstracting the clinical chemistry and patient record logs for unexplained hypercalcemia and 1 patient was identified by reviewing the pathology log for NHL cases. Demographic and clinical features are shown in Table I. The mean age at presentation was 47.5 years, and all cases were of Afro-Caribbean descent. In this series, unusual clinical findings included the absence of skin lesions and a 3:1 female:male ratio. Hypercalcemia proved to be a useful means of detecting cases; 3 of the 4 patients not referred to the study by practicing hematologists were identified by elevated serum calcium levels.

Age-specific ATL incidence among female African-Americans residing in the catchment area indicated increasing rates with age (Table II). A yearly incidence rate of 13.9/100,000 [95% confidence interval (CI) 3.9–24.0/100,000] was estimated for women 60 to 69 years of age. Although numbers from the present study are small, the shape of the age-specific incidence curve is reminiscent of the pattern for Japanese women, with the highest rates observed during the 6th to 7th decade of life (Tajima, 1990). This pattern of maximum incidence rate in older persons does not seem to parallel rates reported for Jamaica and Trinidad (Murphy *et al.*, 1989) (Table III). For the combined incidence in Jamaica and Trinidad, significant rates of ATL have been observed among the youngest

TABLE I – INCIDENT CASES OF ATL IN CENTRAL BROOKLYN SURVEILLANCE STUDY

Patient ID	Hospital	Date of ATL diagnosis <sup>1</sup>	Age at diagnosis (years)	Ethnicity	Gender	Country of birth	Surveillance method	Initial diagnosis	Presenting features
BK1000	Brookdale	07/10/92	64	B	M	Jamaica	Hematologist	UTI, R/O ATL	Hypercalcemia, leukocytosis
BK1001	Interfaith	07/16/92	52	B	F	Trinidad	Hematologist	R/O ATL, Cholecystitis	Hypercalcemia, leukocytosis
BK1006	Brooklyn	08/12/92	49	B	F	Trinidad	Hematologist	R/O ATL	Hypercalcemia, lymphadenopathy
BK1009	Brooklyn	10/15/92	57	B	F	Grenada	Hematologist	Lymphoma	Abdominal lymphoma
BK1012	Interfaith	08/17/92	61	B	F	St. Vincent	Hematologist	Lymphoma	Loss of vision, leukocytosis
BK1014	Interfaith	12/22/92	39	B	F	Panama	Hematologist	R/O ATL	Leukocytosis, lymphadenopathy
BK1016	Brooklyn	01/27/93	63	B	F	Grenada	Hypercalcemia	Dyspnea, pneumonia	Hypercalcemia
BK1017	St. Mary's	01/25/93	26	B	F	Barbados	Hypercalcemia	HIV <sup>+</sup> , R/O NHL	Hypercalcemia
BK1019	Interfaith	10/11/92	41	B	F	Barbados	Hematologist	NHL	Lymphadenopathy, hypercalcemia
BK1021	Brooklyn	06/24/93	39	B	F	Trinidad	Pathology log	R/O ATL	Lymphadenopathy, hypercalcemia
BK1022	Brooklyn	08/23/93	40	B	M	Trinidad	Hypercalcemia	?Sarcoidosis	Lymphadenopathy, hypercalcemia
BK1026	King's County	12/28/93	39	B	M	Trinidad	Hematologist	R/O lymphoma	Lymphadenopathy, leukocytosis

<sup>1</sup>Positive HTLV-I serology plus diagnosis of hematological malignancy. ATL, Adult T-cell leukemia/lymphoma; UTI, urinary tract infection; NHL, non-Hodgkin's lymphoma; B, black; R/O, rule out.

TABLE II – AGE-SPECIFIC INCIDENCE RATE (IR) FOR WOMEN BY 10-YEAR INTERVAL

Age (years)	Expected numbers <sup>1</sup>	At risk	IR and 95% CI
20–29	1.2	73,453	1.6 (0–4.5) <sup>2</sup>
30–39	2.4	72,707	3.3 (0–7.5)
40–49	2.4	56,202	4.3 (0–9.7)
50–59	2.4	40,936	5.8 (0–13.2)
60–69	2.4	29,956	13.9 (3.8–24.0)

Crude IR among women: 3.6 (1.4–5.8).—Crude IR for both men and women: 2.8 (1.3–4.3).—<sup>1</sup>Expected numbers determined from actual numbers and the percentage of coverage.—<sup>2</sup>All IRs are per 100,000 per year.

adults (ages 20 to 29), but these are equivalent to the ATL incidence we observed in our catchment. ATL incidence in the Jamaican and Trinidad populations increases until age 50 to 59, when it declines.

A comparison of our cases with those identified by the New York State Cancer Registry revealed that we had identified virtually all cases predicted from the registry data (12 vs. 11 predicted cases). The corresponding estimates of incidence among adult Afro-Caribbean residents from the sensitivity analysis ranged from 2.5 to 6.4/100,000 person-years (Table IV). Given our “best guess” estimates that 70% of Afro-Caribbean immigrants reside in central Brooklyn and that of these 70% are adults, we would expect the annual ATL incidence to be 3.8/100,000 person-years (95% CI 2.6–5.0/100,000 person-years).

In the study of lymphoma cases at King's County Hospital, only 1 of the 8 T-cell lymphomas proved to be HTLV-I-positive. Both the *env* and *pol* regions of HTLV-I proviral DNA were amplified by PCR. This patient (BK1026) had already been identified by our surveillance methods.

#### DISCUSSION

This population-based study confirmed that central Brooklyn is an endemic area for ATL and showed unexpected features of the disease, particularly the absence of skin manifestations, a high female:male ratio and possibly the age pattern.

Four major categories of ATL have been characterized: the acute or prototypic type, lymphoma type, chronic type and smoldering

type (Shimoyama *et al.*, 1991). A feature of the natural history of this disease is for the more benign types to evolve into the more aggressive types. Acute ATL is an aggressive mature T-cell lymphoma with frequent leukemic involvement (80% of cases) and characteristic pleomorphic polylobulated cells, hypercalcemia (50% of cases) and cutaneous involvement (40% of cases ranging from maculo-papular rashes to tumorous lesions). Organ and extranodal involvement are common. Lymphoma-type ATL shares many features with acute ATL, but it is distinguishable by the absence of peripheral leukemic involvement. Chronic ATL presents as T-cell chronic lymphocytic leukemia, and a substantial proportion of cases have cutaneous involvement; nodal or extranodal involvement is rare and hypercalcemia is absent. Smoldering ATL resembles mycosis fungoides/Sézary syndrome with cutaneous involvement presenting as erythema or as infiltrative plaques or tumors, and Pautrier's micro-abscesses may be observed.

The distribution of subtypes appears to vary by geography (Levine *et al.*, 1994a). Thus, in Japan, the majority of cases present with leukemic manifestations, but in the Caribbean most cases are initially lymphoma type. All patients conformed to the definition of ATL as suggested by an international study group (Levine *et al.*, 1994a) and, more specifically, were of the lymphoma type as defined by Shimoyama *et al.* (1991). In general, ATL presents a decade earlier in the Caribbean than in Japan (Manns *et al.*, 1993). The age pattern in our group was much closer to that reported in Japan (Tajima, 1990) than to those in Jamaica and Trinidad (Murphy *et al.*, 1989; Cleghorn *et al.*, 1995), suggesting that environment, rather than genetics, may be responsible for this feature of ATL, but a cautious interpretation is necessary because of the small number of cases. Less interpretable but also of interest is the absence of skin manifestations at the onset of disease compared with their presence reported in 35% to 39% of Jamaican cases (Cleghorn *et al.*, 1990; Gibbs *et al.*, 1987; Hanchard *et al.*, 1990) and the high (3:1) female:male ratio (75% of cases compared with 50% in Jamaica and Trinidad). It is possible that this gender difference reflects a female preponderance among Caribbean immigrants, but we do not have data to support this hypothesis.

Our project demonstrated that an effective surveillance program could be implemented in an inner-city population and that incident cases could be identified. A variety of screening techniques were employed, including a full-time study physician monitoring all hospitals since many physicians working in inner-city hospitals are

**TABLE III** – COMPARISON OF ATL INCIDENCE RATES (IR) IN BROOKLYN AND THE CARIBBEAN

Age (years)	Brooklyn <sup>1</sup> number (IR)	Population distribution number (%)	Jamaica and Trinidad <sup>2</sup> number (IR)	Population distribution <sup>3</sup> number (%)
20–29	1 (0.8)	131,795 (26%)	18 (3.8)	476,426 (34%)
30–39	3 (2.4)	127,358 (25%)	17 (6.0)	285,556 (20%)
40–49	3 (3.1)	97,011 (19%)	13 (6.4)	203,350 (14%)
50–59	2 (2.9)	69,462 (14%)	13 (7.5)	174,057 (12%)
60+	3 (3.6)	83,870 (16%)	8 (3.0)	266,291 (19%)
Total	12 (100%)	509,496 (100%)	69 <sup>2</sup> (100%)	1,405,680 (100%)

<sup>1</sup>Incidence rates per 100,000 person-years. –<sup>2</sup>T-cell HTLV-I + NHL as proxy for ATL. –<sup>3</sup>Caribbean data from Cleghorn *et al.* (1995).

**TABLE IV** – SENSITIVITY ANALYSIS FOR ESTIMATING ATL INCIDENCE

Estimated Afro-Caribbean illegal immigrants (percent total in NYC) <sup>1</sup>	Estimated total Afro-Caribbean immigrants (including 176,000 reported to US Census)	ATL incidence per 100,000 person-years among adult Afro-Caribbean residents in central Brooklyn by percent of adults in population (estimated adult population at risk)				
		50%	60%	70%	80%	90%
358,000 (90)	534,000	4.5 (267,000)	3.8 (320,000)	3.2 (373,000)	2.8 (427,000)	2.5 (481,000)
318,000 (80)	494,000	4.9 (247,000)	4.1 (296,000)	3.5 (346,000)	3.0 (395,000)	2.7 (445,000)
278,000 (70)	454,000	5.3 (227,000)	4.4 (272,000)	3.8 (318,000)	3.3 (363,000)	2.9 (409,000)
238,000 (60)	414,000	5.8 (207,000)	4.8 (248,000)	4.1 (290,000)	3.6 (331,000)	3.2 (373,000)
199,000 (50)	374,000	6.4 (187,000)	5.4 (224,000)	4.6 (262,000)	4.0 (299,000)	3.6 (337,000)

<sup>1</sup>NYC, New York City.

not familiar with the presenting manifestations of ATL (Welles *et al.*, 1998) and health-care workers are frequently overwhelmed with other medical emergencies. The importance of identifying ATL cases, however, goes beyond current management and involves patient and family counseling since it has been shown that perinatal virus infection and the risk of developing ATL are minimized if a seropositive pregnant woman is advised not to breast-feed for more than 3 months (Hino *et al.*, 1985, 1987). Our results indicate that continuation of this type of surveillance project coupled with the counseling of families could have a significant impact on the control of HTLV-I in the United States.

However, using reasonable estimates of adult Afro-Caribbean persons at risk for developing ATL (Table IV) and estimating an incidence of 11 cases during 1 full year of surveillance, we identified virtually all expected ATL cases in central Brooklyn. The corresponding incidence rate among adult (70% of total residents) Afro-Caribbean catchment residents, 3.8/100,000 person-years (95% CI 2.6–5.0), is in agreement with previously published studies (Murphy *et al.*, 1989; Cleghorn *et al.*, 1995).

Our estimated ATL incidence rate among adult Afro-American residents in the catchment and estimates of incidence among adult Afro-Caribbean immigrants from sensitivity analyses are statistically similar to previous estimates (Murphy *et al.*, 1989; Cleghorn *et al.*, 1995). However, several assumptions were made which could potentially introduce error into estimates among Afro-American residents. We assumed incidence to be constant over the calendar year, thus yielding an expected total had we conducted surveillance for a full calendar year. Furthermore, we assumed complete ascertainment of adult African-Americans within the catchment during the 1990 US Census, while this assumption is probably flawed in practice. Our sensitivity analyses incorporated several simplifying assumptions, all estimates from previously published research and our own experience: the number of expected HTLV-I-associated T-cell NHL cases came from our previous work on ATL incidence in a Caribbean population with endemic HTLV-I infection. The number of Afro-Caribbean persons at risk comprised the US Census estimates and other published work on illegal immigrant populations in New York City. Finally, the percentage of this population being adult ( $\geq 20$  years of age) and at risk comes from our own experience working with immigrant US populations.

However, despite all sources of error, estimated ATL incidence paralleled previously published rates in the Caribbean. This would be expected if immigration to the United States was not related to HTLV-I infection status. We expect this is the case since patients with ATL had resided in the catchment area well before the onset of disease.

Our pathology-based study at King's County Hospital indicated that our ascertainment of HTLV-I-associated lymphomas was probably complete, but we were unable to evaluate completeness of ascertainment in those with only leukemic manifestations. The identification of 12 new patients in this 1-year pilot surveillance project confirms, however, that HTLV-I infection is an important public health problem in central Brooklyn.

The review of the New York State Cancer Registry database revealed that within the community hospitals where we conducted ATL surveillance we ascertained all ATL cases diagnosed in the first 6 months of our project. Thus, our algorithm for detection of ATL using both clinical and laboratory criteria was sufficiently sensitive. In summary, the agreement of our findings with reported cases from hospitals within our catchment demonstrates that our method of surveillance is highly effective and can serve as a prototype in areas with significant numbers of immigrants from countries with endemic HTLV-I infection. Regarding the precise incidence of ATL in Brooklyn and the unexpected findings of a 3:1 female predominance, an age pattern closer to that in Japan compared to the Caribbean Basin and the absence of skin lesions, we emphasize that we are reporting on a small number of cases compared to reports on well-documented endemic areas over a much longer period of time.

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