Cutaneous T-cell lymphoma (CTCL) refers to a group of lymphoproliferative disorders characterized by localization of T lymphocytes to the skin. The most common CTCL diagnosis is mycosis fungoides (MF).

Annual overall incidence of CTCL was 6.4 per million persons between 1973 and 2002, and 7.7 per million persons from 2001 to 2005. A consistent increase in incidence of CTCL has been regularly documented since the early 1970s. While the cause for this increase is not known, proposed reasons include a real increase in number of cases along with an improvement in physician detection and diagnostic changes. Increased incidence has been correlated with overall physician density and density of medical specialists.

We sought to measure changes in CTCL incidence trends and 5-year survival rates.

METHODS

Incidence data were derived from the 9 original registries of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI). Trend analysis was performed using the Joinpoint Regression Program provided by the NCI. Survival analysis was performed using the SeerSTAT statistical software of the NCI. The total number of cases of CTCL from 1973 to 2009 was 6230.

RESULTS

Overall CTCL incidence has stabilized since 1998 (95% CI, 1994-2002), with an annual percent change (APC) of 5.7% from 1973 to 1998 (95% CI, 4.9%-6.5%) and an APC of 0.1% from 1998 to 2009 (95% CI, −1.4% to 1.5%). Similar incidence stabilization patterns were found in subgroup analyses of race, sex, age, diagnosis, and registry. Five-year CTCL survival rates increased until 2004.

CONCLUSIONS AND RELEVANCE

The incidence of CTCL is no longer increasing. Causes for this trend change may include real incidence stabilization, stabilization of physician detection, or artifact.
Statistical Analysis

Data were analyzed using Stata SE, version 8 (StataCorp), and SEER*Stat, version 7.0.5 (National Cancer Institute) statistical software. Incidence rates were age-adjusted to the 2000 US standard population and are reported per million persons. Linear regression was used to evaluate incidence trends.

Trends for overall CTCL and subgroups of CTCL (age, sex, race, and registry) were analyzed using the Joinpoint Regression Program 4.0.1 (National Cancer Institute). The Joinpoint Regression Program uses permutation testing among other statistical methods to optimize standard errors and determine the number of times a trend changes. Owing to the relative rarity of CTCL, a log-linear model was applied to our data to enable reporting of an annual percent change instead of a fixed annual rate of change. A joinpoint year is defined as the year in which a statistically significant trend change was found. In cases when zero values were found for the dependent variable, which prevents the use of Joinpoint software to analyze trends, sensitivity analysis was performed.

Five-year relative survival rates were calculated using the actuarial method in SEER*Stat 7.0.5; cases with a missing or unknown cause of death were excluded from analysis. The period of survival was defined as the date of diagnosis to the date of last contact, death, or December 31, 2009.

Results

Overall CTCL Incidence

The total number of cases of CTCL from 1973 to 2009 was 6230. Per million persons, the annual age-adjusted incidence rate during this period was 7.5. Overall incidences and incidences by subgroups per 5-year period between 1973 and 2009 are reported in Table 1.

We observed a statistically significant stabilization of overall CTCL incidence (Figure). This change in incidence trend occurred in 1998 (95% CI, 1994-2002) (Table 2). Prior to 1998, overall CTCL incidence increased by 5.7% per year (95% CI, 4.9%-6.5%). Between 1998 and 2009, the annual percent change (APC) for CTCL was 0.1% (95% CI, −1.4% to 1.5%).

CTCL Subgroup Analysis

Subgroups of age, sex, race, and registry, when found to have a pattern of incidence stabilization, showed a steady increase in incidence until a joinpoint year, followed by an incidence rate that was not significantly different from 0. The joinpoint years, or years in which a statistically significant change in trend was found, vary as listed in Table 2.

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data were analyzed using Stata SE, version 8 (StataCorp), and SEER<em>Stat, version 7.0.5 (National Cancer Institute) statistical software. Incidence rates were age-adjusted to the 2000 US standard population and are reported per million persons. Linear regression was used to evaluate incidence trends. Trends for overall CTCL and subgroups of CTCL (age, sex, race, and registry) were analyzed using the Joinpoint Regression Program 4.0.1 (National Cancer Institute). The Joinpoint Regression Program uses permutation testing among other statistical methods to optimize standard errors and determine the number of times a trend changes. Owing to the relative rarity of CTCL, a log-linear model was applied to our data to enable reporting of an annual percent change instead of a fixed annual rate of change. A joinpoint year is defined as the year in which a statistically significant trend change was found. In cases when zero values were found for the dependent variable, which prevents the use of Joinpoint software to analyze trends, sensitivity analysis was performed. Five-year relative survival rates were calculated using the actuarial method in SEER</em>Stat 7.0.5; cases with a missing or unknown cause of death were excluded from analysis. The period of survival was defined as the date of diagnosis to the date of last contact, death, or December 31, 2009.</td>
</tr>
</tbody>
</table>
In our age group analysis, we found a consistent pattern of CTCL incidence stabilization for ages 0 to 54, 55 to 69, and 70 to 84 years. The joinpoint years and annual percent change from 1973 to the joinpoint year are listed in Table 2. No pattern of incidence stabilization was found in individuals 85 years or older. The CTCL incidence increased with age, a trend consistent with the literature. The highest CTCL incidence was found in those aged 70 to 84 years (Table 1).

Sex analysis showed a stabilization of CTCL incidence for both men and women. Annual percent change and joinpoint years are listed in Table 2. The male to female incidence rate ratio (IRR) has been approximately 2:1 in the past. We observed a statistically significant downward trend in the male to female IRR from 2.3 in the earliest period of 1973 to 1979 to 1.6 in the most recent period of 2005 to 2009 \( (P = .001) \).

Race analysis showed a stabilization of CTCL incidence for both blacks and whites; annual percent changes and joinpoint years are listed in Table 2. Blacks have consistently had a higher incidence of CTCL, but the ratio has changed erratically with no consistent trend. The black to white IRR for the most recent period of 2005 to 2009 was 1.28.

The diagnosis of MF alone also showed a stabilization of incidence, with a joinpoint year of 1984 (95% CI, 1981-1986). Prior to 1984, the APC was 7.8% (95% CI, 4.9%-10.7%), and after 1984, it was 0.5% (95% CI, 0.0%-1.0%). Trend changes in other CTCL diagnoses were not analyzed owing to a small number of cases. Age-adjusted incidence rates for MF are reported in Table 1.

Sensitivity analysis of all combinations of the 9 original registries after exclusion of any 2 showed a consistent stabilization of incidence. The highest CTCL incidence in both the earliest period and the most recent period was in San Francisco (Table 1). The incidence of CTCL between different registries within California varied significantly. Specifically, San Francisco had a much higher age-adjusted incidence rate in both 1992 and in 2009 than di San Jose. In 1992, the CTCL incidence in San Francisco was 13.4 per million persons (95% CI, 9.9-17.8 per million) compared with 4.3 per million persons in San Jose (95% CI, 1.8-8.5 per million). Similarly, in 2009, the CTCL incidence in San Francisco was 20.3 per million (95% CI, 16.3-24.9 per million) compared with 9.7 per million in San Jose (95% CI, 6.2-14.5 per million).

This pattern of stabilization was not seen in the 4 additional SEER registries from 1992 to 2009 when analyzed individually or when San Jose and Los Angeles were analyzed together. The incidence rates and populations of San Jose and Los Angeles combined made up 97% of the total population added to the SEER program in 1992.

Survival Analysis

In the earliest period of 1973 to 1980, overall CTCL survival was 71.5% (95% CI, 66.2%-78.8%). In the most recent period evaluated (1997-2005), overall CTCL survival was 78.3% (95% CI, 76.3%-81.3%). We found a statistically significant increase in 5-year survival rates from 1973 through 2004 \( (P = .01) \). However, we did not find any further statistically significant increase in survival after that period. The last year for which 5-year survival data were available was 2005.

Associated Factors

We evaluated correlations between CTCL incidence in whites and demographic characteristics of the 9 original registries between 1973 and 2009 and the 4 additional registries between 1992 and 2009. Consistent with prior report, CTCL incidence was correlated with median household income \( (r = 0.7, P = .01) \)
and median value of owner-occupied housing units \( r = 0.8, P < .001 \). Incidence of CTCL was also correlated with percentage of individuals who were foreign born \( r = 0.8, P = .001 \). Correlation of CTCL incidence with percentage of the population with a bachelor’s degree or higher was 0.6 \( P = .053 \). Incidence was not correlated with the percentage of the population with a high school diploma or higher education.

Discussion

We used comprehensive data from the original registries of the SEER program to evaluate temporal incidence trends in CTCL. A continuous increase in CTCL incidence has been documented since the early 1970s.2,6 We report a significant change in this trend. In recent years, incidence of overall CTCL has stabilized, a finding that is consistent across subgroups of race, sex, age, diagnosis, and location. This trend change has been previously reported. Bradford et al2 studied the SEER registries and noticed an apparent decrease in CTCL incidence from 2001 to 2005, a trend inconsistent with previous steady increases in incidence. Though the finding was not studied in detail or extensively over time, the authors suggested delayed identification and reporting as possible causes for the trend change.2

We propose that the cause of this trend change is multifactorial. Substantial improvements in medical care have been reported over the past few decades.7 Given the correlation between physician density and increased CTCL incidence, a proposed reason for a persistent increase in incidence in the past has been increased efficiency of physician detection.3 We suggest that improvements in physician detection may have stabilized as they approach a natural maximum, resulting in apparent incidence stabilization. A true increase in the number of cases has also been proposed in increasing CTCL incidence. Both improved physician detection and an increase in the true number of cases have been shown to be the primary causes of increased incidence in the cases of other malignant conditions such as thyroid cancer.8,9 Similarly, a true increase in the number of CTCL cases may indeed have contributed to a past increase in CTCL incidence. A corresponding true stabilization in the number of cases may play a role in our findings of CTCL incidence stabilization. If a true stabilization in CTCL incidence is present, the cause for it remains unknown.

We cannot exclude that our findings may be due to artifact. One major limitation to the study of CTCL over time is change in ICD-O coding. The diagnoses that fall under CTCL as a group have been redistributed several times in the past few decades, with the most recent change in ICD-O coding applied to CTCL cases starting in 2001.10 Coding changes have resulted primarily in shifts of distribution of CTCLs among subcategories instead of major insertions or deletions. However, the joinpoint year for overall CTCL incidence stabilization as well as for each of the subgroups analyzed tended to be near 2001 (Table 2). It is thus possible that ICD-O coding changes may have contributed to our findings. Apparent stabilization of MF incidence has been reported in the past5; redistribution in ICD-O coding has been considered the reason for that finding.1

Delayed reporting is another important limitation to our results, as Bradford et al2 have suggested. The SEER program allows for a 2-year delay in report of cancer cases. However, Clegg et al22 suggest that up to 17 years would be required for more than 99% of cancer cases to be reported and that delayed reporting is a primary cause of apparent stabilization in cancer incidence trends. In the case of CTCL, however, for diagnoses made between 1975 and 1994, there was minimal if any reporting delay overall.23 While we do not have specific evidence on delayed reporting since that time, this finding makes it unlikely that delayed reporting played a primary role in our findings.

Incidence of CTCL in men has been higher than that in women since at least 1973, with a male to female ratio of roughly 2:1.24 The ratio decrease we reported appears to be due to a faster rate of increase in female CTCL incidence, which has quadrupled between 1973 and 2009, compared with male CTCL incidence, which tripled during that period.

Incidence varied greatly by geographic location. Of note, we reported that 2 registries in California, San Jose and San Francisco, had drastically different age-adjusted incidences both in the past and in the most recent period, though they are located within 50 miles of each other. Access to and utilization of health care may play a role in these differences. Incidence has been correlated with high physician density. We confirmed that other indices of socioeconomic status such as median family income and median home value are correlated with CTCL incidence.1 Further analysis of hospitalization rates or insurance rates in those diagnosed with CTCL may be informative in evaluation of confounding by access to health care. We did not confirm previously reported correlation of incidence with population density10 or with percentage of population with a bachelor’s degree or higher education level,1 although we did find a trend toward higher education level.

It has been previously suggested that the high incidence of CTCL in San Francisco follows an incidence trend observed in other HIV-related cancers such as non-Hodgkin lymphoma and Kaposi sarcoma.1-5,14 Atypical cutaneous lymphoproliferative disorder, a term used to describe a lymphoproliferative disorder that closely mimics MF clinically and histopathologically, has been reported in association with human immunodeficiency virus (HIV).15,16 However, MF itself is not a known complication of HIV. In addition, unlike the HIV-related cancers, a previous case-control study failed to find an increased risk for CTCL among never-married men.1,17,18 Thus, while an association has been suggested, it is unlikely that HIV plays a role in the geographical variation in incidence we report. The heterogeneity in CTCL incidence rates among the registries provides an avenue for further research. We presented associations that suggest a role for socioeconomic factors in geographical variation in CTCL incidence, but further investigation is required to identify specific causes for these differences.

A substantial and steady increase in survival from CTCL has been reported from 1973 to 1992, but advanced age and black race were associated with poorer survival.19 We confirmed a continued increase in survival through 2004 but not after that. Analysis of more recent data is necessary to deter-
mine true temporal trends in CTCL survival. We did not evaluate survival for MF separately because a previous analysis demonstrated that MF diagnoses may have been subject to misclassification to “cutaneous lymphoma, NOS” over the years. Incidence of MF in Connecticut dropped from 6.7 to 1.0 per million persons from the 1981-1991 period to the 1992-2002 period, and cutaneous lymphoma, NOS incidence increased from 0.2 to 8.5 per million persons during that same period. Therefore, survival rates are better discussed for CTCL as a group.

Our population-based study provides an update in CTCL epidemiology and suggests a major trend change in CTCL incidence in the United States. The cause of this trend change remains unknown, though it may include a stabilization of improvements in physician detection, true stabilization of incidence, and artifact.

REFERENCES