Risk Patterns of Hodgkin’s Disease in Los Angeles Vary by Cell Type

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Abstract
Over the period 1972–1985, 2729 cases of Hodgkin’s disease were diagnosed in Los Angeles County, and 2492 were subclassified using the Rye classification. The occurrence of these cases was examined in relation to age, sex, race, place of birth, social class, occupation, and year of diagnosis. The pattern of nodular sclerosis occurrence conformed to expectations, supporting the polio model of etiology for this subtype. However, the risk pattern of mixed cell disease was quite distinct from that of nodular sclerosis, suggesting that the two may not share a common etiology. The pattern of lymphocyte predominance in Hodgkin’s disease, with a special prominence in younger blacks, resembled neither that of nodular sclerosis nor that of mixed cell disease. The cases of lymphocyte-depletion Hodgkin’s disease showed no distinctive epidemiological features, and its continued classification with nodular sclerosis and/or mixed cellularity can be justified solely by histological or biological evidence.

Introduction
Speculation regarding the etiology of Hodgkin’s disease has continued since it was described in 1832. The histopathology and symptomatology of HD are reminiscent of chronic infectious granulomatous disease, but the untreated clinical course is that of a malignancy. The bimodal age distribution of HD in the United States has suggested a heterogeneous etiology: at a minimum, one process in adolescents and young adults and another in the middle-aged and elderly (1). A heterogenous etiology is also suggested by the morphological variation of the surrounding tissue response, noted since the disease was first described (2). While the common feature linking these morphological variants has been the Reed-Sternberg cell, the putative neoplastic cell seen in all variations of HD, it may be specific to HD alone, since it is seen in other conditions, such as infectious mononucleosis and cytomegalovirus lymphadenitis (3).

In 1966, HD was reclassified into the four histological subtypes which now constitute the standard taxonomy (4): NS, MC, LP, and LD. The four histological subtypes differ not only in morphologic appearance, but in stage at diagnosis, survival (4–7), immunohistochemical profile (8), and the presence of demonstrable intracellular viral genome (9). Some have postulated that NS and MC represent different host responses to the same environmental challenge (7, 10–12). While the pattern of NS occurrence is familiar, the comparative epidemiology of the four subtypes has not been adequately described. We propose here to assess the epidemiological evidence supporting a common etiology by examining the pattern of HD occurrence in the multiethnic population of Los Angeles County.

Materials and Methods
The University of Southern California Cancer Surveillance Program, a population-based tumor registry, identified 2729 incident cases of HD from 1972 through 1985; 2492 (91%) of these were classified histologically according to the Rye Classification (4), as reflected by the 1970 International Classification of Diseases code system as follows: NS (9656, 9657); MC (9652); LP (9651); and LD (9653–9655). Of the 2492 classified cases, 50% were assigned to NS, 32% to MC, 10% to LP, and 8% to LD. Cases classified only according to the Jackson-Parker system and those without further subclassification are not included in the analysis to follow.

Information obtained on each case includes the age at diagnosis, sex, race/ethnicity, religion, census tract of residence, birthplace, and occupation. Racial/ethnic groupings include blacks, Asians (all groups combined), non-Spanish surnamed whites (hereafter referred to as whites), and Spanish-surnamed whites (Latinos). The list of Spanish surnames is a locally augmented version of the updated U.S. Bureau of the Census list (13). Smaller groups, including Pacific Islanders and Native Americans, have been excluded from the analysis of ethnicity. Each case is assigned to one of 5 levels according to the census tract of residence using a modification of the Hollingshead index; for this analysis the 5 levels have been collapsed into 3. A detailed list of religions has also been collapsed into 3 categories: Protestant, Catholic, and Jewish.

Annual incidence rates were calculated using sex, age, and projected year-specific denominators based on the 1980 United States Census, age-adjusted to the 1970 population distribution. Age and sex-specific populations of Latinos by birthplace were estimated using the 1980 census public use sample for Los Angeles County. Since

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3 The abbreviations used are: HD, Hodgkin’s disease; NS, nodular sclerosis; MC, mixed cellularity; LP, lymphocyte predominance; LD, lymphocyte depletion; PIR, proportional incidence ratio.
population size is not available by religion or social class, PIRs were computed, in the usual way, using the age-specific frequencies of all other cancers combined as the referent standard. Social class and religion were examined only between subgroups of whites; for purposes of constructing the figures which depict risk by these variables, the PIR for the referent, in each case the largest subclass and religion were examined only in whites; since the pattern of LP incidence parallels that of MC, but at a much lower level. LD is virtually nonexistent before about age 60. The incidence pattern of the subtypes in Los Angeles is similar to that for males, with the exception that the MC and LP curves are somewhat lower.

Results

Age- and Sex-specific Rates. Annual age-adjusted incidence rates for HD (all reported cases combined) are slightly lower among Los Angeles County residents than elsewhere in the United States (1). Because the age-specific incidence pattern is so clearly divided into modes before and after age 45, most noncontinuous variables were examined separately for cases aged 0–44 years and those 45 and older.

NS and MC are the most common morphologies in both males and females (Fig. 1). In males, the bimodal age-specific HD incidence curve consists of a younger age mode, primarily composed of NS, and an older age mode, made up mostly of MC. Peak NS incidence occurs in the adolescent and young adult years, declining thereafter. Each of the other subtypes shows the gradual rise in incidence after middle age typical of most neoplasms. The rate of MC, which comprises most of these older cases, increases gradually; by age 75, it exceeds the peak rate of NS in young adults.

The pattern of LP incidence parallels that of MC, but at a much lower level. LD is virtually nonexistent before age 50, and the rate rises to converge with that for NS at about age 60. The incidence pattern of the subtypes in females is similar to that for males, with the exception that the MC and LP curves are somewhat lower.

Racial/Ethnic Pattern. Three different patterns of NS incidence can be seen (Fig. 2): one common to blacks and whites; one common to immigrant Latinos and Asians; and one seen in U.S.-born Latinos, which is
intermediate between these two. In whites and blacks, incidence peaks between ages 15 and 44 but remains low at earlier and later ages. Blacks experience a slightly higher incidence of NS than whites in childhood but a lower incidence in young adulthood. The NS incidence peak seen in young adult whites is significantly higher at that age than in the other groups and is the highest age-specific rate of Hodgkin’s disease seen in any racial group at any age.

In immigrant Latinos and in Asians, there is a stepwise increase with age, with the highest rates in the elderly; immigrant Latino children experience NS rates similar to those of black children, whereas NS is virtually absent in Asian children under 15.

U.S.-born Latinos have a pattern of NS which is intermediate between the other two: a low incidence in childhood which triples in early adulthood and remains at this higher level throughout life. Thus, in young adults, whites are the group in which NS occurs most frequently, whereas in the elderly that distinction is held by Latinos, at a level significantly above that in whites.

In contrast to that of NS, the pattern of MC incidence varies little by ethnicity or race; incidence increases stepwise with age and peaks in the elderly in each group. In the age group 15–44, whites have significantly higher rates of MC than other groups, as they do for NS at that age.

Whites generally experience increasing incidence of both LD and LP with age, although there is a small mode of LD incidence in young adult males (Fig. 3). A similar pattern is evident in blacks, except that it is LP incidence which is elevated in young adults. Because of the small numbers of cases of these two subtypes, immigrant and native Latinos have been combined; they experienced less LP, but perhaps slightly more LD after 45, than whites. Both LP and LD were notably lacking in Asians; only three cases were diagnosed during the study period.

Social Class. Variation in NS rates by social class is restricted to the age group 10 to 24 (Fig. 4). At this age, NS incidence increases stepwise with social class; levels are 1.5 times greater in the high than in the low social class group. A correlation between social class and MC incidence is evident in this same age group, and again after age 45, but it is in the reverse direction; incidence decreases stepwise with increasing social class. Young children of high social class have very low rates of both NS and MC.

It should be noted that in young white adults in Los Angeles, the correlation between social class and the combined incidence of all cancers (the referent for the PIR) is direct, as it is for NS. It is likely that comparisons based on PIRs have slightly underestimated the strength of the direct correlation of NS and slightly overestimated the strength of the inverse correlation to MC risk.
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The incidence of NS increased in the males and females (Fig. 6) of each racial and ethnic group, especially in whites, although rates have been relatively stable in males since 1983. MC rates have been generally stable, although in the years 1975–1977, an extra eight or nine cases, of disparate age and place of residence, inexplicably but temporarily doubled the incidence in Latino males. If anything, a slight decreasing trend is seen for LD (Fig. 7). For LP, the secular trend varies by race/ethnicity and sex; a modest decrease has occurred for whites and Latinos of both genders, whereas black males have experienced a modest increase in incidence, and black females a lesser increase, over the same period.

Discussion

The risk patterns described above are based on rather large samples, and in general, the differences found are between subcategories of patients who have been diagnosed in institutions of comparable size and reputation, with histological classification by pathologists of comparable training and philosophy. Of course, any analysis based on divergent interpretations of subtle histological criteria must overcome errors of misclassification, and the distinctions between morphological variants of HD are especially subtle (18, 19). However, there is no reason to expect that such errors would be systematic with respect to the variables examined in this study; thus any bias introduced by classificational error would tend to obscure, not artificially produce, distinctions. To evaluate one source of such bias, we examined all cases coded under the rubric “HD, not otherwise specified” (International Classification of Diseases for Oncology code 9650) to see if such cases, essentially classified by default, were preferentially represented among those of any specific race, sex, age group or hospital of diagnosis. We could only conclude that HD not otherwise specified was designated more often in extreme old age at all hospitals, in all races, and in both sexes. This may indicate inadequate attention given to tumors of the elderly by surgeons or pathologists, or it might represent a true ambiguity in the histology of tumors of older people, but it does not suggest a major source of error.

Our observations suggest the hypothesis that the morphological subtypes of HD represent distinct entities with partial, if not complete, differences in etiology. The strikingly different age-, race-, and sex-specific incidence patterns seen for each subtype are also difficult to reconcile with the alternative hypothesis that each subtype represents a stage in the natural history of a single syndrome.

We have previously reported that NS incidence is higher in whites than in coreident blacks or Latinos and that neither the distinct mode of incidence nor the direct link with social class seen for NS in young adult whites is evident for the other subtypes combined (20). The same pattern of peak NS incidence in early adulthood and the positive correlation with social class among cases aged 0–34 years has been reported in England (21), and the same distinctions by histological subtype with respect to secular trend and race have been reported in the United States (16, 22, 23). Direct comparison with most other

Religion. Among whites, Jews are at higher risk of MC both before and after age 45 and are at much higher risk of NS before age 45 than Catholics or Protestants (Fig. 5). Protestants experience a lower risk of both NS and MC after age 45 than either Jews or Catholics.

Occupation. The occupational pattern of cases by histological subtype was examined with special attention to links that have been previously reported (17): woodworking (carpenters, cabinet makers, furniture workers); chemicals (chemists, chemical engineers, janitors, farmers, gardeners, hairdressers); high-voltage electricity (linemen, electricians, electrical engineers); and childhood infections (physicians; dentists; nurses; dental assistants; preschool, primary, and secondary teachers; and recreation and childcare workers). In most of these categories the expected number of cases or fewer was observed, and the pattern according to both cell type and exposure group of occupations was inconsistent. Table 1 presents results for the standard occupational categories, together with those positive results seen for specific occupations according to whether or not a priori concerns had been raised. For only one occupation (male gardeners) could as many as 5 additional cases in 14 years be attributed to the occupation. Note that each finding, including this one, can be adequately explained by chance; in effect, comparisons have been made within the cells defined by 4 subtypes, 2 genders, and over 500 occupations. These results are presented only because of the widespread interest in specific occupations.

Secular Trend. The estimated risk for nodular sclerosis and mixed-cell Hodgkin’s disease by religion, Los Angeles County whites, 1972–1985. Frequencies for Catholic, Protestant, and Jewish patients, respectively, for nodular sclerosis HD, at age 0–44, 188, 353, and 110; and at age 45+, 56, 106, and 29; for mixed-cell HD, at age 0–44, 46, 84, and 31; and at age 45+, 59, 114, and 46. At age 0–44, the risk for Jewish patients was significantly greater than for others at 0.05 for nodular sclerosis; at age 45+, risk for Jewish patients was significantly greater than for others at 0.05 for mixed cell.

Fig. 5. Estimated risk for nodular sclerosis and mixed-cell Hodgkin’s disease by religion, Los Angeles County whites, 1972–1985. Frequencies for Catholic, Protestant, and Jewish patients, respectively, for nodular sclerosis HD, at age 0–44, 188, 353, and 110; and at age 45+, 56, 106, and 29; for mixed-cell HD, at age 0–44, 46, 84, and 31; and at age 45+, 59, 114, and 46. At age 0–44, the risk for Jewish patients was significantly greater than for others at 0.05 for nodular sclerosis; at age 45+, risk for Jewish patients was significantly greater than for others at 0.05 for mixed cell.
Table 1. Frequency and proportional incidence ratio* of Hodgkin's disease by sex, occupation, and cell type, Los Angeles County, 1972-1985

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Positive findings for specific occupations*

A priori concern

- Male chemists: 3 cases
- Male aircraft mechanics: 4 cases
- Male physicians: 8 cases
- Male carpenters: 4 cases
- Male gardeners: 5 cases

No a priori concern

- Male accountants: 11 cases
- Male civil engineers: 0 cases
- Male salesmen/clerks: 5 cases
- Male structural metal craftspersons: 3 cases
- Male checkers, inspectors: 2 cases
- Male cooks: 3 cases
- Male police officers: 6 cases
- Female social worker: 3 cases
- Female bank tellers: 5 cases
- Female salespersons/clerks: 4 cases

* For ages 20–64, age-adjusted to the 1970 U.S. population. Standard (PIR = 100) = all reported occupations.

* Criterion: at least 5 cases with PIR of >1.50.

Studies is difficult because others have usually examined either total HD incidence or the simple frequency of subtypes (1, 11, 24–31). There has been one other attempt to compare incidence by subtype and race/ethnicity: a comparison between blacks and whites based on nationwide Surveillance, Epidemiology, and End Results cases (22). There, as in Los Angeles, whites have significantly higher NS and MC rates than blacks.

Registry-based studies in Latin America (24) and in New Mexico (28) have found relatively higher rates of HD in Hispanic children and lower rates in adolescents/young adults compared to whites (24, 32, 33), but age-specific rates for Latinos by subtype have not been reported. In Los Angeles, immigrant Latinos display the pattern described in Latin America, but U.S.-born Latinos do not. Asians and Jews are generally comparable with respect to social class and education level, and yet Asians have low rates of all subtypes of HD, as reported elsewhere (34–38), even lower than those reported for immigrant Latinos, while Jews have consistently high rates.

There have been many allegations that risk from HD may be increased on account of occupation. The cases reported here derive from an economy larger and more diversified than that of most countries, and occupations...
have been assigned at the time of diagnosis rather than after death. We have examined those occupations previously linked to HD (17), those which entail exposure to industrial processes, to toxic chemicals, to various infections, and to potential reservoirs of infection. While our findings are compatible with modest increases associated with both previously suspected and unsuspected occupations, we have found no individual occupations at unequivocally high risk and no consistent occupational pattern of risk. It seems unlikely that occupation plays a major role in the etiology of any form of HD in a city the size of Los Angeles.

The race- and sex-specific secular trends reported here, in particular the increasing incidence of NS, are consistent with those reported elsewhere (16). The increasing incidence of LP among blacks has also been noted elsewhere (22).

Similarities between the risk patterns of NS and those of paralytic polio in the prevaccine era have led to speculation that NS may be a rare sequela of a relatively late infection with some common agent that is usually contracted in childhood (14, 25, 27, 29, 39, 40). According to this etiologic model, protected conditions, higher social class, and fewer siblings available to serve as virus reservoirs result in exposure at a later age to viruses such as Epstein-Barr virus, which, like polio and varicella-zoster, results in asymptomatic or mild infections when contracted in childhood (14, 25, 27, 29, 39, 40). The intermediate rates of U.S.-born Latinos can be explained if disease were to result from the late reactivation of a dormant virus, as does herpes zoster (shingles), a reactivation of varicella-zoster virus from the dorsal root ganglia (40). Another possibility is that NS in younger age groups is at least partially distinct etiologically from NS at older ages. A major morphological variant of NS, with a cellular "phase," has been described and is particularly common at advanced ages (5). The clinical picture and the survival rate of NS-cellular phase resembles MC more than NS not otherwise specified (5), and some maintain that it more properly should be classed with HD-MC (6), also more common at older ages.

Several aspects of the NS risk pattern are consistent with this polio model. Lower childhood and higher adolescent/young adult rates in whites, direct correlation with social class in young adults, higher risk for young Jewish adults, and equal rates among males and females all support this model of NS etiology (20, 21, 25, 29, 30, 32). The pattern of NS incidence among immigrant Latinos in Los Angeles (higher risk in childhood, lower risk as young adults relative to whites) is similar to that seen for polio in economically disadvantaged populations (40). The intermediate rates of U.S.-born Latinos can be explained by the variation among them; some were born to families who had recently immigrated, and some were born into acculturated families which were identical in all respects to those of other white natives.

However, Latinos and Asians both experience peak NS incidence at an older age, a fact which is hard to reconcile with the polio model. Such a pattern could be explained if disease were to result from the late reactivation of a dormant virus, as does herpes zoster (shingles), a reactivation of varicella-zoster virus from the dorsal root ganglia (40). Another possibility is that NS in younger age groups is at least partially distinct etiologically from NS at older ages. A major morphological variant of NS, with a cellular "phase," has been described and is particularly common at advanced ages (5). The clinical picture and the survival rate of NS-cellular phase resembles MC more than NS not otherwise specified (5), and some maintain that it more properly should be classed with HD-MC (6), also more common at older ages.
The risk pattern seen for MC in Los Angeles is completely different from that seen for NS; risk is higher among immigrant Latino children and increases stepwise with age in all groups. Males have twice the rate of females. MC incidence is linked to lower, not higher social class, yet Jews of all ages are at increased risk. MC is recognized to be the most common subtype in Latin Americans (35, 41-43), in developing countries generally (26, 32, 33, 35, 42, 43), and in U.S. Latinos (18, 20, 26, 28).

This pattern with respect to age, gender, social class, and religion is consistent with, if not characteristic of, the patterns of non-Hodgkin’s lymphomas. The special link to young Latinos, particularly those born in developing countries, may additionally suggest an infectious process, but a process more prevalent under conditions of poverty and one in which the incidence of symptomatic disease increases as the host ages, possibly reflecting an aging immune system. Thus tuberculosis, rather than polio, might be more appropriate to consider as a model for the etiology of MC. It may also be pertinent that MC is reported to be the most common HD subtype seen in acquired immunodeficiency disease patients (41).

Our findings do not preclude the possibility that NS and MC represent different host responses to the same agent, with the specific manifestations determined by the timing of infection and the immune status at the time of infection, but we believe it to be more parsimonious to postulate that the two syndromes are caused by unrelated agents. There is little direct correlation between the two levels of risk, and only in relation to social class in young adults are the syndromes inversely correlated.

Further evidence bearing on this point can be obtained from the geographical distribution of the two syndromes as reflected by international registry data for populations of non-Asian origin (35) (Fig. 8). For the purposes of this graph, registries from “developed” countries included those from North America and Northern and Western Europe, while those from Eastern Europe, Latin America, and West and South Asia were considered to be from “developing” countries. NS incidence (as represented by the highest 5-year age-specific incidence of HD between the ages 15 and 35) seems related to the level of economic development, and there is more variation in age-adjusted MC incidence in either strata of development between the male populations, but no indirect correlation, and no strong or consistent direct correlation is apparent for either gender or for either stratum of development. Thus the risk factors for these two syndromes seem independent, offering no support for the hypothesis that young-adult NS and life-long MC represent alternative responses to the same challenge.

LP and LD are only one-fourth as common as NS or MC, and the patterns are harder to characterize; the most distinctive pattern is the generic increase with age seen with many neoplasms. In fact, the patterns of both LP and LD are as similar to those of non-Hodgkin’s lymphomas as they are to NS or MC.

Only LP shows any distinctive features, both in relation to blacks. The significance of the increasing LP incidence in blacks and the excess in young black men is not clear, and it should be followed closely in the future, perhaps with a careful distinction between “nodular” and “diffuse” LP. Molecular biologists have recently presented evidence that LP is fundamentally different from the other subtypes; Epstein-Barr virus has been recovered from NS, MC, and LD but not LP tumors (9), and B-cell antigens have been detected more often in the Reed-Sternberg cells from LP cases, whereas T-cell antigens have been detected more often from NS and MC cases (8).

Finally, LD represents a small fraction of HD, and its pattern of occurrence has little in common with the other subtypes. It shows no distinctive epidemiological features and may actually represent a combination of misclassified T-cell non-Hodgkin’s lymphomas (36, 44), chemotherapy and radiation changes superimposed upon other subtypes (2), and, possibly, a component of true end-stage HD (2, 6, 45).

In summary, the dramatically different risk patterns of the different HD subtypes support the hypothesis that the morphological heterogeneity seen represents etiological heterogeneity.

References
Risk Patterns of Hodgkin’s Disease in Los Angeles and Cell Type


Risk patterns of Hodgkin's disease in Los Angeles vary by cell type.

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