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Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence

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To the Editor

Hypereosinophilic syndromes (HESs) include a heterogeneous group of diseases that have in common prolonged peripheral eosinophilia and organ damage in the absence of secondary causes for eosinophilia. Myeloproliferative (m-HES), lymphoproliferative, undefined, overlap, and associated variants of HES are now recognized,^{1,2} and new therapeutic approaches to each are evolving.³ Because no population-based data exist that address even such basic descriptive measures as incidence or prevalence, we examined a publicly available data source to evaluate the incidence of myeloproliferative HES/chronic eosinophilic leukemia and extrapolated from these data to estimate the incidence and prevalence of all HES.

The Surveillance, Epidemiology and End Results (SEER) program for cancer, funded by the National Cancer Institute, has been collecting data on HES since 2001 by using the International Classification of Diseases for Oncology, version 3, rubric of 9964/3 (HES including chronic eosinophilic leukemia), under the general category of chronic myeloproliferative disorders.⁴ The authors used SEER*stat software (<http://www.seer.cancer.gov/seerstat> version 6.4.4, Bethesda, Md, 2008) to calculate age-adjusted incidence in this group of patients; estimates from the literature were then used to extrapolate to the incidence of all HES.

Over the 5-year period (2001–2005), 131 incident cases in persons were reported in the SEER 17 area registries, resulting in a crude incidence of 0.035 per 100,000 and an age-adjusted rate of 0.036 per 100,000 person-years (95% CI, 0.030–0.042/100,000). There were 78 males and 53 females (age-adjusted rates, 0.044 and 0.027/100,000 person-years, respectively), and the male-to-female ratio was 1.47. Median age at diagnosis was 52.5 years, and rates increased with age to a peak in the range of 65 to 74 years (Fig 1).

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One caveat in considering these data on m-HES is the intervening recognition of the etiology (and new diagnostic testing) for myeloproliferative forms of HES as a result of the Fip1-like 1–platelet-derived growth factor receptor α fusion gene (*FIP1L1-PDGFR α*) chromosomal fusion.⁵ It is not recorded in the publicly available SEER data whether testing for *FIP1L1-PDGFR α* or other HES-related chromosomal fusions was done for the 131 patients. However, the majority had pathologic confirmation either through direct histologic examination (73%) or through a laboratory test or marker (15%), although no details are available in the public use database.

Does this age-adjusted incidence rate of 0.036 per 100,000 allow insight into the incidence of all HES? Gotlib and Cools⁶ reviewed the proportion of *FIP1L1-PDGFR α* ⁺ individuals in 8 series of patients with HES and concluded, given the various selection biases in the data, the true value probably lay between 10% and 20%. If m-HES accounts for as little as 10% or as much as 20% of all HES, projecting from the SEER incidence rate for m-HES/chronic eosinophilic leukemia (CEL) would imply an annual age-adjusted incidence rate for all HES of between 0.18 per 100,000 and 0.36 per 100,000 person-years. These estimates have to be considered as upper bounds because they assume that all cases in the 9964/3 category are *FIP1L1-PDGFR α* ⁺. Unfortunately, the proportion of cases that are positive for the gene versus CEL and other m-HES cannot be determined from the SEER data, but if it were assumed that the proportions were 10% *FIP1L1-PDGFR α* ⁺ m-HES and 90% other m-HES/CEL, it would necessitate lowering the incidence estimates proportionally, thus giving what is likely to be a lower bound for all HES of between 0.018 and 0.036 per 100,000 person-years.

What is the prevalence of all HES likely to be? Modern therapies for HES, including imatinib for m-HES, have rendered HES a chronic but rarely fatal disease. In an unpublished cohort of 49 French patients (18% of whom were m-HES), the 5-year, 10-year, and 15-year survival rates were 100%, 87%, and 66%, respectively (the last based on 3 deaths [2 in the m-HES subgroup] in 9 patients; Ackerman et al, personal communication, July 2009). Weibull survival curves were fit to these data under varying assumptions, and most predicted a median survival of approximately 17.5 years. Taking advantage of the relationship between prevalence as a product of incidence times duration of a chronic disease, this would imply, for the low bound of all HES incidence, 0.018 per 100,000/person-years $\times$ 17.5 years for a prevalence rate of 0.315 per 100,000 (0.000315%) and, for the upper bound, 6.3 per 100,000 (0.0063%). This upper bound is about 4 times the upper bound of a previous estimate (0.0007%–0.0017%) based on hospital discharges and a medical claims database⁷ and is within an order of magnitude of a clinical estimate from a textbook⁸ (incidence of 1 per 1,000,000 and prevalence of 1/100,000 or 0.001%).

Age-adjusted incidence rates for HES/CEL over the period 2001 to 2004 based on data from a subset of SEER registries and the nonoverlapping portions of the North American Association of Cancer Registries were both 0.03 per 100,000 person-years⁹; however, the SEER data included 5 girls with eosinophilia who were miscoded as having HES and therefore subsequently removed for the current estimate (Stevens, personal communication, November 2009, SEER Web Technical Support Information Management Services, Inc, seerweb@imsweb.com).

It should be noted that this survival estimate only partially reflects the improvements in modern therapeutic approaches to HES, including the introduction of imatinib and related receptor tyrosine kinase inhibitors to treat m-HES effectively. Improvements in survival will lead to an increased prevalence of HES in the near future until a new steady state is reached.

Currently in the United States, there are no International Classification of Diseases, Ninth Revision, codes that identify the varied forms of HES. Even the International Classification of Diseases, Ninth Revision, code for eosinophilia is rarely used by coders, as found by one of the authors (P.F.W.) in chart reviews of records of several large health maintenance organizations trying to assess the frequency of the Churg-Strauss syndrome. It seems likely that the great majority of the patients reported herein had m-HES although the authors have no way of knowing how many such patients may have been missed or improperly coded because referral patterns to the SEER database for HES are not currently known. Unfortunately, it is very unlikely that the other forms of HES or other eosinophilic diseases such as Churg-Strauss syndrome or eosinophil-associated gastrointestinal disease can be identified in any systematic manner in population-based data sets until specific codes are available.

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FIG. 1. Age-specific incidence per 100,000 for myeloproliferative HES/CEL in SEER, 2001 to 2005, by sex.