Use of Molecular Testing to Identify a Cluster of Patients with Polycythemia Vera in Eastern Pennsylvania

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Abstract

Background: The role of the environment in the origin of polycythemia vera has not been well documented. Recently, molecular diagnostic tools have been developed to facilitate the diagnosis of polycythemia vera. A cluster of patients with polycythemia vera was suspected in three counties in eastern Pennsylvania where there have long been a concern about environment hazards.

Methods: Rigorous clinical criteria and JAK2 617V>F testing were used to confirm the diagnosis of polycythemia vera in patients in this area. Participants included cases of polycythemia vera from the 2001 to 2005 state cancer registry as well as self- and physician-referred cases.

Finding: A diagnosis of polycythemia vera was confirmed in 53% of 62 participants using WHO criteria, which includes JAK2 617V>F testing. A statistically significant cluster of cases (P < 0.001) was identified where the incidence of polycythemia vera was 4.3 times that of the rest of the study area. The area of the cluster contained numerous sources of hazardous material including waste-coal power plants and U.S. Environmental Protection Agency superfund sites.

Interpretation: The diagnosis of polycythemia vera based solely on clinical criteria is frequently erroneous, suggesting that our prior knowledge of the epidemiology of this disease might be inaccurate. The JAK2 617V>F mutational analysis provides diagnostic clarity and permitted the confirmation of a cluster of polycythemia vera cases not identified by traditional clinical and pathologic diagnostic criteria. The close proximity of this cluster to known areas of hazardous material exposure raises concern that such environmental factors might play a role in the origin of polycythemia vera.

Introduction

Polycythemia vera is a chronic hematologic malignancy characterized by erythrocytosis, not infrequently leukocytosis and thrombocytosis, splenomegaly, and marrow hypercellularity. Patients exhibit a predisposition to develop vascular thrombosis and undergo evolution to myelofibrosis and acute leukemia (1, 2). Less than 10% of patients develop polycythemia vera-related myelofibrosis, a narrow failure state that may lead to transformation to acute leukemia in a small number of patients (<2% overall; refs. 1-3). Polycythemia vera is a member of a group of hematologic malignancies termed myeloproliferative disorders (MPD), which also include chronic myeloid leukemia, essential thrombocytemia, and primary myelofibrosis. These disorders are clonal in origin and are associated with hematopoietic progenitor hypersensitivity to cytokines (4).

Greater insight into the pathology of the MPD has occurred over the past 3 years with the discovery of an acquired point mutation in an intracellular kinase, JAK2, which plays a pivotal role in the cytokine regulation of hematopoiesis. The recurrent mutation in JAK2, consisting of a valine-to-phenylalanine change at position 617 (JAK2 617V>F) in the JH2 pseudokinase domain, occurs in >90% of patients with polycythemia vera and 50% of other MPD patients (either essential thrombocytemia or primary myelofibrosis; refs. 5-7). The implementation of molecular tests to detect JAK2 617V>F has revolutionized the manner by which physicians pursue the diagnosis of a MPD. The widespread availability of JAK2 617V>F testing has led to a revision of the diagnostic criteria for the MPD. This revision, which...
Polycythemia vera is more commonly diagnosed in older individuals (average age, 62.8 years) and in males (~60% of cases; refs. 1-3). Although JAK2 617V>F likely plays an important role in the development of the MPD, the factors that lead to the appearance of this specific somatic mutation in hematopoietic cells remain unclear. Family studies where members suffer from various forms of JAK2 617V>F-positive MPD provide evidence that genetic influences might favor the acquisition of the mutated form of JAK2 (10-12). Some early reports suggested that polycythemia vera was possibly associated with radiation and benzene exposures and among embalmers and petroleum refinery workers (13-15). These studies were limited by the size of the study populations and the diagnostic criteria used.

Polycythemia vera became reportable to state cancer registries in 2001. Registries typically collect data from various health-care providers, including hospitals, laboratories, and medical practitioners, and rely on a medical diagnosis from the attending physician. National Cancer Institute data from 2001 to 2004 provide an estimated incidence of polycythemia vera incidence in the United States of 1.0 (all incidence rates are reported as cases/100,000 persons/year).\(^5\) Before widespread JAK2 617V>F testing, reports of the incidence of polycythemia vera in smaller geographic areas such as communities, counties, and provinces within the United States and Europe ranged widely, from 0.02 to 2.8 (16-26). Pennsylvania law has required reporting of polycythemia vera to the state cancer registry by various medical providers since 2001; however, to date, only hospitals have reported polycythemia vera cases. Based on registry data from 2001 to 2003, Pennsylvania has an average annual polycythemia vera incidence rate of 1.5.\(^6\)

The Tamaqua area of eastern Pennsylvania includes the towns of McAdoo, Hometown, Still Creek, and Tamaqua and lies a few miles south of Hazleton at the nexus of Luzerne, Carbon, and Schuylkill counties (the year 2000 U.S. Census tricounty population = 528,388). The Tamaqua community has long been concerned about various potential environmental hazards in the area. These include areas of acid mine tailings and drainage, waste-coal power plants, and U.S. Environmental Protection Agency National Priorities Listing (Superfund) sites. At one of these latter sites, large quantities of industrial hazardous waste were placed directly into abandoned mine shafts.\(^7\) In 2004, community members and physicians in this area met with local and state officials to voice their concern over the high number of local residents reported to have rare cancers, including four residents with polycythemia vera on a single street. To address these concerns, the Pennsylvania Department of Health (PADOH) reviewed the 1996 to 2002 cancer incidence data for the three counties. PADOH released the results of this report in 2005, indicating a statistically significantly higher incidence of polycythemia vera in Luzerne and Schuylkill counties (3.01 and 3.42, respectively) compared with the overall state rate (1.5); rates for other reportable cancers in the tricounty area were not elevated.\(^8\) Because polycythemia vera reporting did not begin until 2001, PADOH extended the analysis to include 2003 to 2004 registry data. When the 2003 and 2004 data continued to indicate an overall increased incidence of polycythemia vera in Luzerne and Schuylkill counties, PADOH requested assistance from the Agency for Toxic Substances and Disease Registry to better characterize the situation.

The goals of the Agency for Toxic Substances and Disease Registry investigation were to locate all cases of polycythemia vera diagnosed in the three-county area from 2001 to 2005, confirm the polycythemia vera diagnosis using testing for JAK2 617V>F and existing medical records, and describe the characteristics of these individuals. This report describes the use of the JAK2 617V>F assay in the investigation and the challenges encountered performing epidemiologic studies of polycythemia vera in large patient populations.

Materials and Methods

Participants. Eligible participants included those who satisfied a diagnosis/time requirement (medical diagnosis of polycythemia vera from 2001 to 2005) and a residence requirement (residence in the tricounty area at diagnosis). Persons identified with polycythemia vera in the Pennsylvania state cancer registry and self- or physician-referred individuals with a medical diagnosis of polycythemia vera who were not included in the registry were also eligible. Polycythemia vera patients from the registry received an invitation by mail to participate, with a follow-up letter mailed to nonresponders after 2 weeks. Because only patient addresses were available from the registry, additional contact information was sought for all persons not responding to the second invitation using local telephone directories, Internet searches, and inquiries to the physicians of record. Media releases, which included toll-free telephone numbers to PADOH in Harrisburg and the Agency for Toxic Substances and Disease Registry in Atlanta, were issued to raise community awareness of the investigation and increase participation. All oncologists and hematologists in the tricounty area were contacted and encouraged to report any additional cases of polycythemia vera. Individuals not included in the registry were screened by an investigation team member to verify eligibility.

Case Investigation. Those who consented were interviewed in-person or by telephone by a field investigation team member who was trained to administer the questionnaire in a standardized, unbiased manner. Family members of deceased cases were asked to give interviews by proxy. The questionnaire included detailed information regarding socioeconomic and demographic characteristics; residence and employment history; exposures to various chemicals and hazards; smoking, drinking, and eating habits; and clinical symptoms and medical history. JAK2 617V>F testing was offered at no cost to all participants unless they have been shown previously to be JAK2 617V>F positive. Persons with a diagnosis of polycythemia vera who did not meet eligibility criteria were offered JAK2 617V>F testing as a public service and all test results were included in the diagnosis confirmation figures and the
questionnaire results. Deidentified blood samples were shipped to the University of Illinois at Chicago within 24 h of their collection according to the guidelines of the Institutional Review Board of the University of Illinois at Chicago. All samples were initially screened for the JAK2 617V>F mutation using PCR/direct sequencing (5% sensitivity), with negative samples being retested using allele-specific PCR (<0.5% sensitivity). Details of both mutational analysis methods were reported previously (27).

Polycythemia Vera Case Definition and Confirmation of Diagnosis. A panel of medical experts was used to (a) establish a rigorous case definition using diagnostic criteria for polycythemia vera similar to those defined recently by WHO (8, 9) and (b) evaluate cases with questionable/incomplete records or ambiguous test results. Confirmation of the polycythemia vera diagnosis was based on a positive JAK2 617V>F result and evidence of erythrocytosis in the medical record. In the absence of a positive JAK2 617V>F result, the WHO criteria were used to establish the diagnosis.

Statistical Analysis. The questionnaire data were analyzed using SAS version 9.1 and EPI-INFO 2002 version 3.3.2. The confirmed addresses of cases at diagnosis were evaluated for possible geographic associations using geospatial software (ESRI ArcGIS version 9.2). Age- and sex-adjusted polycythemia vera rates were calculated for both zip codes and census tracts in the three counties to evaluate general patterns of polycythemia vera incidence. Standardized rate ratios were then determined for each zip code/census tract compared with the entire tricounty area. Cluster analysis was done using SaTScan, a geospatial software tool developed by the National Cancer Institute for cluster detection.® SaTScan systematically compares rates in different sized potential clusters with the tricounty rate to determine the most probable cluster. Rate ratios were calculated for the identified cluster area by comparing the polycythemia vera rate inside the area with those in the remainder of the tricounty area and the total tricounty area. The approximate binomial probability of finding the specified number of cases in the cluster area was calculated via a Poisson distribution. This probability establishes the likelihood of the cluster being a random event based on the total number of confirmed cases in the tricounty area.

Environmental Analyses. Although this was not designed to be an etiologic study, the relationship between case locations and known hazardous sites was examined in response to community concerns. The Pennsylvania Department of Environmental Protection and the U.S. Environmental Protection Agency provided geospatial data sets of known hazardous material sources in the tricounty area. These included Superfund sites and other hazardous waste areas, industrial emissions, coal mining operations, and radiation sources. The source locations were compared with the high-rate polycythemia vera areas using ArcView GIS Software (version 9).

Results
A total of 97 individuals from the tricounty area were listed in the 2001 to 2005 cancer registry at the time of the investigation. The final 2005 registry data, which were not released until after the investigation concluded, contained 7 additional polycythemia vera patients. Of the 97 original registry patients, 36 consented to an interview, and in two instances, relatives agreed to act as a proxy for a deceased patient (overall response rate = 39%). The remaining 30 people from the registry could not be found, declined to participate (16 people), or were deceased (13 people). The registry participation rate was similar throughout the tricounty area. Thirty-four non registry polycythemia vera patients (28 self-referred and 6 physician-referred) were also interviewed; however, 7 of these individuals did not satisfy the residency requirement and 3 others were not diagnosed within the survey period. This resulted in 24 eligible nonregistry participants and a total participant population of 62 (Table 1). The participants’ average age was 65 ± 13 years and 60% were male. Participants were predominantly White and of mixed European descent.

Confirmation of Polycythemia Vera Diagnosis. Fifty-two participants provided blood specimens for JAK2 617V>F analysis. A total of 27 (52%) of these specimens were positive for the JAK2 617V>F mutation. Five other participants were reported to be JAK2 617V>F positive in their medical record. A diagnosis of polycythemia vera was confirmed in 53% (33 of 62) of the participants (32 JAK2 617V>F positive and 1 JAK2 617V>F negative). Five of the ineligible self-referred patients also submitted blood specimens and all were JAK2 617V>F positive. These individuals were prior residents of the tricounty area diagnosed with polycythemia vera during 2001 to 2005 who were not residents at the time of diagnosis. The polycythemia vera diagnosis was not confirmed in 29 participants: the expert panel determined that 17 (27% overall) had secondary polycythemia and 12 (19% overall) had insufficient data in their medical records to make a diagnosis of polycythemia vera. Four of the latter group were JAK2 617V>F negative, but the medical records contained some evidence supportive of

Table 1. Registry and nonregistry participants, polycythemia vera status, and nonparticipants

<table>
<thead>
<tr>
<th></th>
<th>Registry</th>
<th>Nonregistry</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total eligible</td>
<td>104*</td>
<td>24</td>
<td>128</td>
</tr>
<tr>
<td>Actual</td>
<td>38</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>Polycythemia vera status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>18</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Not polycythemia vera</td>
<td>11</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Insufficient data</td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Nonparticipants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused</td>
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<td>—</td>
<td>16</td>
</tr>
<tr>
<td>Deceased</td>
<td>13</td>
<td>—</td>
<td>13</td>
</tr>
<tr>
<td>Not found</td>
<td>30</td>
<td>—</td>
<td>30</td>
</tr>
</tbody>
</table>

*Includes 7 cases added to the registry after the investigation was completed.

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polycythemia vera. The demographics of the confirmed polycythemia vera cases were similar to those of the nonconfirmed participants, except that the latter group contained more men (80%) and was younger (average age = 53 years). The diagnosis of polycythemia vera was confirmed in 18 of 38 (47%) registry participants (11 males and 7 females). Of the remaining 20 registry participants, 11 were determined not to have polycythemia vera and 9 individuals lacked sufficient data to satisfy the diagnostic criteria. The diagnosis status of registry and nonregistry participants appears in Table 1.

**Questionnaire.** Confirmed polycythemia vera cases were more likely than nonconfirmed participants to have splenomegaly, whereas those in the nonconfirmed group were more likely to report shortness of breath and/or a history of smoking \((P < 0.05, \text{ Fisher’s exact test for both})\). No other significant differences in home- or job-related exposures, eating or drinking habits, recreational activities, or medical history were observed between the two groups. Confirmed cases moved infrequently and remained at a residence nearly twice as long as those found not to have polycythemia vera (23.1 versus 13.6 years; \(P < 0.001, \text{ two-tailed} \ t \text{ test})\). Ten of the 11 registry participants found not to have polycythemia vera resided in northern Luzerne County.

**Spatial Analyses.** Initially, standardized rate ratios were calculated for each census tract and zip code in the three counties using the confirmed polycythemia vera cases found in the investigation as well as all cases from the registry with confirmed or unknown polycythemia vera status. The high-rate zip code areas identified were not in good agreement with the high-rate census tracts due to the arbitrary nature of these area units and the relatively small number of polycythemia vera cases in each area. Additionally, the registry standardized rate ratios did not agree with the confirmed cases standardized rate ratios. SaTScan was then used to analyze the addresses at diagnosis of the 33 confirmed cases. A single statistically significant cluster \((P < 0.001)\) was identified near the geographic center of the three counties, with Hazleton and Tamaqua at the north and south borders, respectively (area T; Fig. 1). A possible secondary cluster was also identified; however, it did not contain enough cases to achieve statistical significance (area P). The incidence of polycythemia vera in the cluster area (area T) is 4.3 times higher than the rest of the tricounty area (95% confidence interval, 2.2-8.5; Table 2). Based on the Poisson distribution, the probability of finding \(\geq 15\) cases in area T and 18 cases in the remainder of the tricounty area is 1 in \(2.2 \times 10^5\). The probability of the cluster being a random event based on the total number of confirmed

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Polycythemia vera cluster areas (areas P and T), U.S. Environmental Protection Agency Superfund sites, and local waste-coal power plants in Carbon, Luzerne, and Schuylkill counties of Pennsylvania.
Environmental Analyses. Several hazardous material exposure sources were found in or near the high-rate areas of polycythemia vera. For example, 7 of the 16 waste-coal power plants in the United States are located in or within a few miles of the high-rate areas. Emissions from these plants, which began operations in the early 1990s, are characterized by fine particulate matter, various heavy metals, and complex hydrocarbons, including polycyclic aromatic hydrocarbons (28). Seven U.S. Environmental Protection Agency Superfund sites are contained within the two high-rate areas (Fig. 1). Currently, these sites are inactive and are contained or in the process of remediation by state and federal agencies. Environmental sampling conducted over the past 5 years does not suggest that people are currently exposed to hazardous chemicals. Before 1990, environmental exposure data are not available; therefore, past exposures cannot be assessed.

Discussion

This is the first report describing use of testing for the JAK2 617V>F mutation to evaluate clinically diagnosed polycythemia vera cases in a population setting. Only 47% (18 of 38) of the polycythemia vera participants in the cancer registry were confirmed compared with 59% (20 of 34) of those reported outside of the registry. Nearly half (15 of 33) of the confirmed eligible cases were not reported to the state cancer registry but were found through intensive case ascertainment efforts. Despite limitations inherent in this type of retrospective investigation, the findings indicate a geographic cluster of polycythemia vera occurred within three counties located in eastern Pennsylvania.

Before the identification of the JAK2 617V>F mutation, the diagnosis of polycythemia vera was based on the implementation of a wide array of clinical and laboratory variables, which were imprecise in providing a definitive diagnosis in individual patients or were employed in a suboptimal fashion (1). The recent advent of a molecular assay for JAK2 617V>F has provided previously unachievable diagnostic clarity for polycythemia vera (8, 9). The value of this new tool is underscored by the conclusions of our expert panel who determined that, based on the established case definition, 53% (20 of 38) of the participants reported to the state (in the registry) as having polycythemia vera either did not have polycythemia vera or there was insufficient information available to make this diagnosis. These findings are similar to those reported by other authors who have used the JAK2 617V>F mutational analyses to validate historically diagnosed polycythemia vera cases (5, 29). The resulting overestimation of the true polycythemia vera incidence rate caused by these misclassifications, however, is opposed by the underreporting of polycythemia vera to the registry. Many polycythemia vera patients are not hospitalized, and because the state cancer registry is primarily dependent on hospitals for data collection, these individuals were not included in the registry. This investigation identified more misclassified registry polycythemia vera cases (20 cases) than unreported cases of JAK2 617V>F-positive polycythemia vera (15 cases). Similar misclassifications likely exist among the 66 nonparticipants found in the registry. Selection bias is common in studies of this type; however, it is unlikely that large numbers of unidentified, diagnosed polycythemia vera cases exist in the tricounty area because of the extensive media coverage and the cooperation of local hematologists/oncologists. The net result is a registry containing a falsely high number of reported polycythemia vera cases. These findings indicate that both state and national polycythemia vera incidence rates generated using cancer registry information collected in a similar fashion are likely to be unreliable as comparison rates or as the basis for statistical associations between polycythemia vera and potential risk factors. Until the problems of misclassification and underreporting can be reconciled, epidemiologic studies of polycythemia vera will require the integration of outpatient and hospital case ascertainment data with JAK2 617V>F testing, a diagnostic armamentarium that establishes the diagnosis and incidence of polycythemia vera with a much greater degree of certainty.

In the current investigation, comprehensive case-finding methods and a newly discovered diagnostic biomarker were used to confirm the polycythemia vera diagnosis in 33 individuals. Polycythemia vera incidence rates calculated for zip codes and census tracts were not in good agreement as variations in the population and/or size or these areas can both result in misleading analyses and lack specificity in defining discrete high-rate areas. The SaTscan analysis, which is less affected by these arbitrary area boundaries, identified a single cluster of polycythemia vera.

Table 2. Incidence of polycythemia vera in the Tamaqua cluster (area T) compared with the rest of the tricounty area and the entire tricounty region

<table>
<thead>
<tr>
<th>Area</th>
<th>Population* (% total)</th>
<th>Confirmed eligible cases</th>
<th>Polycythemia vera incidence rate †</th>
<th>Area T rate ratio ‡ (95% confidence interval)</th>
<th>Area T Poisson probability ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>86,482 (16)</td>
<td>15</td>
<td>3.47</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rest of tricounty</td>
<td>441,906 (84)</td>
<td>18</td>
<td>0.81</td>
<td>4.3 (2.2-8.5)</td>
<td>2.8 (1.7-4.5)</td>
</tr>
<tr>
<td>Total tricounty</td>
<td>528,388 (100)</td>
<td>—</td>
<td>—</td>
<td>1 in 22.2 × 10⁶</td>
<td>1 in 2.0 × 10⁷</td>
</tr>
</tbody>
</table>

*Based on 2000 U.S. Census.
†Rate per 100,000 persons/year.
‡Ratio of rate in cluster area/rate in the rest of the tricounty area or the entire tricounty area.
§Probability of ≥15 cases occurring in area T based on rest of tricounty rate and total tricounty rate.
significant cluster \(P < 0.001\) of confirmed polycythemia vera cases (area T) where the incidence was more than four times that of the rest of the tricounty area. The unknown status of 78 eligible participants (66 registry patients who did not participate and 12 participants who were not classified) adds a possible unquantifiable uncertainty to these calculations and analyses. In addition, other as-yet unreported polycythemia vera patients may exist in the tricounty area. Because it is likely that these groups contain polycythemia vera patients who satisfy the investigation’s case definition, the incidence rates calculated using only the confirmed cases represent the most conservative estimate of the actual number of cases present in this area. Any additional polycythemia vera cases, depending on their number and location, could alter the size and position of the observed polycythemia vera cluster and potentially identify other clusters. A rigorous set of analyses was done using various diagnosis confirmation rates for the 78 patients of unknown polycythemia vera status, including the unlikely assumption that all were true polycythemia vera. Although these analyses are beyond the scope of this article, in every scenario, the area T cluster retained statistical significance.

The reasons for the elevated incidence of this disease are unknown. In the analysis of cancer incidence in the tricounty area done by PADOH, the incidence of other hematologic malignancies including the other MPD such as chronic myeloid leukemia, essential thrombocytopenia, and primary myelofibrosis was reported not to be increased. Further investigations are, however, planned to confirm these data. Our investigation was conducted to properly characterize cases in the area, not to systematically examine risk factors for illness. Identifying such factors requires a different and more rigorous study design. Additional work, which includes assessment of possible contaminant exposures and the inclusion of an appropriate comparison population, is necessary to evaluate potential hypotheses. None of the cluster-area cases were related, and their ethnicity/ancestry was similar to the population of the investigation area. The probability that the cluster is a random occurrence is also very low (\(~ 1 \text{ in } 2,000\)). Although there are numerous environmental challenges in the area, any role for specific hazards is hypothetical. The geographic areas of concern are associated with both Superfund sites and waste-coal power plants. However, aside from proximity, there is at present no direct evidence to indicate that these sources played a role in the current polycythemia vera cluster. Recent reports suggest that polycyclic aromatic hydrocarbons might potentially contribute to the generation of polycythemia vera and thus a cluster such as the one seen in this geographic area (30-35). These compounds constitute ubiquitous environmental contaminants, are potent carcinogenic and immunotoxic agents, and are also present in waste-coal emissions and at most of the Superfund sites associated with area T. The aryl hydrocarbon receptor, for which polycyclic aromatic hydrocarbon serves as a ligand, is present in the cytoplasm of human hematopoietic stem and progenitor cells (30-32). This might serve as a potential target for environmental contaminants, leading to a multistep process culminating in the development of a hematologic malignancy such as polycythemia vera (31-35). Suggestions of a specific environmental cause for this cluster are, however, purely hypothetical because the development of polycythemia vera has not been previously associated with exposure to any particular substance. Furthermore, this investigation was not designed to examine any such associations, which require a more rigorous study design. Additional research, which involves assessment of possible environmental contaminant exposures and the inclusion of an appropriate comparison population, is necessary to evaluate these hypotheses.

The use of existing data sources to evaluate disease incidence is both convenient and practical. However, the validity of this approach is questionable for diseases that lack clear diagnostic markers and/or do not require inpatient treatment. We found high rates of misclassified and unreported cases of polycythemia vera in the current investigation but employed active case-finding and a biological marker to identify a cluster of polycythemia vera, which would not have been found using the traditional methods. To our knowledge, this is the first report of a polycythemia vera cluster and carries major implications for cancer registries and reporting agencies, the medical research community, and the residents of the cluster area. Until reporting systems are improved and diagnostic accuracy can be assured by registries, epidemiologic studies of diseases such as polycythemia vera will require the use of comprehensive case-finding methods and rigorous case definitions based on molecular diagnostic testing.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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