Prevalence of hypercalcemia of malignancy among cancer patients in the UK: analysis of the Clinical Practice Research Datalink database

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A B S T R A C T

Background: The reported proportion of cancer patients who experience hypercalcemia of malignancy (HCM) ranges between 3% and 30%. HCM can be observed with any type of tumor and occurs most commonly in lung cancer, breast cancer and multiple myeloma. While HCM is a potentially fatal condition, the prevalence of HCM is not well defined.

Methods: Using the United Kingdom Clinical Practice Research Datalink, we identified adult cancer patients with recorded corrected serum calcium (CSC). Hypercalcemic patients (CSC >10.8 mg/dL) were classified into 4 CSC levels. We estimated annual prevalence of HCM overall, stratified by cancer type, and in patients with stage IV cancer.

Results: Among 37,442 cancer patients in 2003–2012 the prevalence of grade 1 HCM increased from 0.13% to 0.45% and the prevalence of HCM overall (grade 1 or higher) increased from 0.20% to 0.67% over the study period. Prevalence estimates varied across cancer type and were highest for lung cancer, multiple myeloma and patients with stage IV cancer.

Conclusion: We provide the first systematic analysis using a UK population-based data source to estimate number of cancer patients affected with HCM by grade. The increase in HCM prevalence over the 10-year study period is likely due to the increased recording of laboratory values, particularly comparing more recent data to 2003. Our findings suggest that HCM in general is not a common condition.

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1. Introduction

Hypercalcemia is a condition defined by a serum calcium level above the upper limit of the normal reference range. When hypercalcemia occurs in cancer patients during the course of the disease it is termed hypercalcemia of malignancy (HCM) and is the most frequent cause of hypercalcemia in a hospital patient population [1–3].

The primary etiology of HCM is increased bone resorption, which leads to elevated calcium concentrations in the extracellular fluid, and thus anti-bone resorptive therapies offer an appropriate therapeutic approach when hydration alone is ineffective in normalizing calcium values. HCM is clinically measured by grade, defined by corrected serum calcium levels, shown to correlate with symptom severity [4,5]. A gradual onset of symptoms is common with HCM because they may resemble symptomology of the underlying malignancy and its corresponding treatment [1]. Low grade HCM is characterized by general (e.g., dehydration, polyuria, polydipsia, fatigue, weakness, weight loss, bone pain) or gastrointestinal (e.g., nausea, vomiting, constipation, anorexia) symptoms, but the delayed diagnosis in patients presenting with nonspecific symptoms can result in increased morbidity and mortality. Patients with more severe hypercalcemia (grade 4 or higher, serum calcium >13.5 mg/dL) manifest neurological symptoms such as myopathy, confusion, delirium, and coma, requiring urgent intervention [1]. Current treatment for HCM is now available in the form of intravenous bisphosphonates and Denosumab, a fully human monoclonal antibody against RANKL [6].

The literature on the epidemiology of HCM is limited with significant variation in the reported prevalence (and definitions of prevalence). Reported proportions of patients with cancer who experience HCM range between 3% and 30% [7–10]. Although HCM generally occurs late in the course of malignancy, it is not necessarily associated with the prevalence of bone metastases [2]. Prevalence estimates can vary by tumor type, practice setting, geographic region, type of data source, and the precise definition or serum calcium level used to characterize HCM.
While HCM is a severe condition that can be fatal [7], the prevalence of HCM is not well defined. In this study, we aimed to estimate the prevalence of HCM by grade and tumor type using the Clinical Practice Research Datalink (CPRD), a population-based data source comprising electronic health records with laboratory data on patients in the United Kingdom (UK). In addition, we examined HCM trends over a recent time period (2003–2012), and provide annual prevalence of HCM in patients with stage IV cancer.

2. Methods

2.1. Data resource and study population

Data for this study were derived from the CPRD [11], which is housed and organized for research purposes at the Boston Collaborative Drug Surveillance Program. Briefly, the CPRD is an ongoing longitudinal database that has collected data from over 500 general practices in the UK since 1988. The CPRD currently contains information on more than 8 million patients, of which 3 million are currently active, with a cumulative follow-up time of more than 32 million person years. It covers approximately 6% of the UK population and has a representative age and sex distribution of the entire UK population. The information contained in electronic health records, includes patient demographics and characteristics, clinical diagnoses, drug prescriptions, consultant referrals, hospitalizations, and lab test results.

We identified all patients in the CPRD, aged 18 or older, who had a diagnosis of cancer (except for non-melanoma skin cancers) and at least 1 post cancer diagnosis calcium and albumin laboratory value on the same day or 1 corrected serum calcium (CSC) during the years 2003 through 2012. Study patients were also required to have at least 1 year of history before the cancer diagnosis to identify incident cases. Patients with either a history of diagnosed hypercalcemia or hypercalcemia based on a CSC $\geq 10.8$ mg/dL from lab data, recorded more than 30 days prior to the cancer diagnosis were excluded (1% of the study population), while patients who experienced HCM within 30 days before the cancer diagnosis were included. We then identified all cancer patients in each year from 2003 through 2012 who had a code for a stage IV cancer on or after the first cancer date. See Appendix for Read diagnosis codes for stage IV cancer.

2.2. Hypercalcemia

HCM was defined according to CSC levels: CTCAE Grade 1 (ULN $\leq$ CSC $\leq 11.5$ mg/dL), grade 2 (11.5 $<$ CSC $\leq 12.5$ mg/dL), grade 3 (12.5 $<$ CSC $\leq 13.5$ mg/dL), and grade 4 (CSC $>13.5$ mg/dL) where CSC was calculated as CSC = $0.8 \times (4 - $ serum albumin $) +$ serum calcium [12] and ULN is upper limit of normal. We set the ULN to 10.8 mg/dL, a cutoff point commonly used to ascertain complete response to therapy [6]. We used the laboratory calculated CSC value present in the patient record to determine presence of hypercalcemia where available. Virtually all laboratory calculated values (99%) were the same as the value that we calculated using the serum calcium and serum albumin values present in the data using the formula described above. Where serum calcium plus serum albumin values were the only values present (10%) we used the calculated CSC values based on the formula described above to determine presence of hypercalcemia.

To validate the laboratory test results we first reviewed a random sample of 50 patients to ensure that we captured all laboratory test results recorded after their first cancer diagnosis. Then we reviewed a random sample of 50 patients with CSC values consistent with hypercalcemia to validate that they were correctly recorded, i.e., where all available calculated laboratory values were consistent with the values we calculated using the serum calcium and albumin values present on the same day. All sampled values appeared to be valid. Finally we manually checked the laboratory test results for patients with CSC values smaller than 5 mg/dL or greater than 20 mg/dL. If there were obvious data entry errors, we corrected them; otherwise we deleted these records. Validation checks were made to ensure accuracy of the test data and those with invalid values were excluded.

2.3. Statistical analysis

From among the cancer population, we identified all patients present in the database in each year from 2003 through 2012. These patients populated the denominators for annual prevalence. Patients who had a high CSC were placed in the numerator of the year in which the high CSC value was recorded. If more than one value was recorded in one year the highest value was used to calculate prevalence. We estimated the annual prevalence of HCM as the proportions of patients who had a CSC of $\geq 10.8$ mg/dL in a given year divided by the number of study cancer patients present in the database at any time during that year, and 95% confidence intervals (CI) using Byar’s method [13] overall and stratified by cancer type. Because there were patients in the population who had years of follow-up in which they had no calcium value recorded we estimated prevalence for each year by including patients in the numerator if they had a high CSC in that calendar year. For each year that there was no calcium data in the patient record and the patient was active in the CPRD we assumed that the CSC was normal. In the process of identifying HCM cases we identified some patients who had a Read code for hypercalcemia in a year where there were no recorded high CSC laboratory values. Therefore we conducted a sensitivity analysis to further estimate prevalence of any hypercalcemia where we included both HCM cases based on elevated CSC lab value $\geq 10.8$ mg/dL and those with a Read code only for hypercalcemia. For patients with stage IV cancer we calculated the annual prevalence with 95% CIs where the denominators contained all patients with stage IV cancer and the numerators were comprised of all stage IV patients who had a high CSC value recorded. We estimated prevalence first including only patients who had at least one serum calcium laboratory value in their record after the stage IV cancer code. We then estimated prevalence where all patients with a stage IV cancer diagnosis, including those with no serum calcium laboratory values, were included in the denominator. Because of the low number of patients with stage IV cancer we did not estimate the annual prevalence stratified by cancer type. All statistical analyses were carried out using SAS version 9.3 [SAS Institute, Cary, NC].

3. Results

There were 37,442 patients in the CPRD who had a first cancer diagnosis during the years 2003 through 2012 and who had at least one serum calcium laboratory value plus one serum albumin value recorded on the same day on or after the day of the first cancer diagnosis, or one calculated CSC. The median number of CSC test results during a median 59 months of follow up was 2 (interquartile range 1–4). Age, sex, year of cancer diagnosis, and cancer type are provided in Table 1. Slightly more patients were female (52%) and most were between ages 50 and 89 years (88%). As expected, the most common cancer type was prostate cancer in men (38%) and breast cancer in women (43%).

3.1. Prevalence of hypercalcemia

Annual prevalence of hypercalcemia by year and CSC level for all cancers combined are shown in Table 2. Most HCM cases were grade 1 (CSC between 10.8 and 11.5 mg/dL). The prevalence of
Table 1
Age, sex, calendar year and cancer type distribution of the cancer population CPRD 2003–2012 (N=37,442).

<table>
<thead>
<tr>
<th>Age</th>
<th>Males: N=18,010 (%)</th>
<th>Females: N=19,432 (%)</th>
<th>Total: N=37,442 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&lt;20)</td>
<td>(&lt;20)</td>
<td>(&lt;20)</td>
</tr>
<tr>
<td></td>
<td>7 (0.04)</td>
<td>5 (0.03)</td>
<td>12 (0.03)</td>
</tr>
<tr>
<td></td>
<td>20–29</td>
<td>61 (0.34)</td>
<td>277 (1.43)</td>
</tr>
<tr>
<td></td>
<td>30–39</td>
<td>183 (1.02)</td>
<td>766 (3.94)</td>
</tr>
<tr>
<td></td>
<td>40–49</td>
<td>578 (3.21)</td>
<td>2097 (10.79)</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>2034 (11.29)</td>
<td>3727 (19.18)</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>5117 (28.41)</td>
<td>4908 (25.26)</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>6679 (37.81)</td>
<td>4616 (23.86)</td>
</tr>
<tr>
<td></td>
<td>80–89</td>
<td>3124 (17.35)</td>
<td>2724 (14.02)</td>
</tr>
<tr>
<td></td>
<td>90+</td>
<td>227 (1.26)</td>
<td>292 (1.50)</td>
</tr>
<tr>
<td>Year of cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>2047 (11.37)</td>
<td>2452 (12.62)</td>
<td>4499 (12.02)</td>
</tr>
<tr>
<td>2004</td>
<td>2323 (12.90)</td>
<td>2484 (12.78)</td>
<td>4807 (12.84)</td>
</tr>
<tr>
<td>2005</td>
<td>2185 (12.13)</td>
<td>2518 (12.96)</td>
<td>4703 (12.56)</td>
</tr>
<tr>
<td>2006</td>
<td>2244 (12.46)</td>
<td>2421 (12.46)</td>
<td>4665 (12.46)</td>
</tr>
<tr>
<td>2007</td>
<td>2215 (12.30)</td>
<td>2282 (11.74)</td>
<td>4497 (12.01)</td>
</tr>
<tr>
<td>2008</td>
<td>2032 (11.28)</td>
<td>2180 (11.22)</td>
<td>4212 (11.25)</td>
</tr>
<tr>
<td>2009</td>
<td>1853 (10.29)</td>
<td>1927 (9.92)</td>
<td>3780 (10.10)</td>
</tr>
<tr>
<td>2010</td>
<td>1547 (8.59)</td>
<td>1581 (8.14)</td>
<td>3128 (8.35)</td>
</tr>
<tr>
<td>2011</td>
<td>1074 (5.96)</td>
<td>1132 (5.83)</td>
<td>2206 (5.89)</td>
</tr>
<tr>
<td>2012</td>
<td>490 (2.72)</td>
<td>455 (2.34)</td>
<td>945 (2.52)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>822 (4.56)</td>
<td>669 (3.44)</td>
<td>1491 (3.98)</td>
</tr>
<tr>
<td>Breast</td>
<td>56 (0.31)</td>
<td>8284 (42.63)</td>
<td>8340 (22.27)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2038 (11.32)</td>
<td>1832 (9.43)</td>
<td>3870 (10.34)</td>
</tr>
<tr>
<td>Prostate</td>
<td>7075 (39.28)</td>
<td>–</td>
<td>7076 (18.90)</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>220 (1.22)</td>
<td>177 (0.93)</td>
<td>397 (1.06)</td>
</tr>
<tr>
<td>Renal</td>
<td>285 (1.58)</td>
<td>232 (1.19)</td>
<td>517 (1.38)</td>
</tr>
<tr>
<td>Other solid</td>
<td>5788 (32.14)</td>
<td>6706 (34.51)</td>
<td>12,493 (33.37)</td>
</tr>
<tr>
<td>Other hematologic</td>
<td>1726 (9.58)</td>
<td>1532 (7.88)</td>
<td>3258 (8.70)</td>
</tr>
</tbody>
</table>

grade 1 HCM increased from 0.13% to 0.45% between 2003 and 2012. However, the annual prevalence of grades 2, 3 and 4 HCM were stable over the study period. During the study period, we estimated that the prevalence of grade 1 or higher HCM was stable over the study period. During the study period, we estimated that the prevalence of grade 1 or higher HCM ranged between 0.20% and 0.67%; grade 2 or higher from 0.07% to 0.26%; grade 3 or higher, 0.02% to 0.09%; and grade 4, 0.02% to 0.06%. When we stratified by cancer type (Fig. 1) we found HCM prevalence estimates were highest for lung cancer, multiple myeloma, and renal cancer though it should be noted that multiple myeloma and renal cancer are rare and the prevalence estimates were based on small numbers. Prevalence estimates for all other cancers were much lower.

In 2012, no more than 2% of cancer patients experienced HCM (HCM grade 1 or higher ranged from 0.48% to 2.01%), with highest proportions observed for individuals with lung cancer or multiple myeloma, followed by breast, colorectal, and renal cancer cases (Fig. 2).

3.2. Sensitivity analyses

When we included HCM cases identified by a Read code in the numerators, the prevalence of HCM increased by 4–27% with a range between 0.24% and 0.76% in 2003–2012 (Table 3), compared to 0.20% to 0.67% in the main analysis (Table 2).

3.3. Prevalence of hypercalcemia in patients with stage IV cancer

We identified 3484 individuals (9.3%) in the cancer population who had a diagnosis consistent with stage IV cancer that was recorded on or after the date of the original cancer diagnosis. Among them, 2390 cases had at least one serum calcium lab value in their record after the stage IV cancer code. In order, there were 53 cases whose diagnosis was recorded at the time of death (stage IV cancer was noted at death, and who therefore did not contribute to the analysis. The prevalence of HCM was higher among the stage IV cancer patients with annual prevalence estimates across all cancers ranging from 1.46% to 2.74% (Table 4). The prevalence of HCM in stage IV cancer was approximately 4-fold higher than the overall prevalence for cancer patients diagnosed with any stage, with some variation by year where the prevalence of HCM among stage IV to all stages decreased over the study period.

4. Discussion

Hypercalcemia is a serious metabolic complication of malignancy whose prevalence has not been quantified systematically. This study is unique and provides estimates of prevalence based on a population of 37,442 individuals diagnosed with cancer during...
the years 2003–2012 in the UK using CPRD data. We estimated that the prevalence of grade 1 HCM increased from 0.13% in 2003 to 0.45% in 2012 and the prevalence of HCM overall (grade 1 or higher) increased from 0.20% to 0.67% over the study period.

Primary tumors of the lung and breast [2,7,8] and multiple myeloma [9] are the most common hypercalcemia-associated malignancies in the United States and Europe, followed by head and neck, kidney, and ovary cancers. HCM occurs less frequently in patients with colorectal and prostate cancers [7,9], and the incidence is relatively low, estimated to be 15 cases per 100,000 person-years, among patients with malignant tumors [9,14,15]. Prevalence of HCM in the current study also varied across cancer type and was highest for lung cancer and multiple myeloma, consistent with literature reports. Individuals diagnosed

**Fig. 1.** Annual prevalence (%) of HCM (CSC ≥10.8 mg/dL) by tumor type in the CPRD 2003–2012.

**Fig. 2.** Prevalence (%) of HCM by tumor type in 2012.
Table 3
Comparison of prevalence (%) of hypercalcemia of malignancy (HCM) and impact of inclusion of patients with read code for HCM in CPRD 2003–2012.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cancer patients</th>
<th>CSC ≥10.8 mg/dL</th>
<th>Prevalence (95% CI)</th>
<th>CSC ≥10.8 mg/dL or a diagnosis of hypercalcemia</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HCM cases</td>
<td></td>
<td>HCM cases</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>4499</td>
<td>9</td>
<td>0.20 (0.09, 0.38)</td>
<td>11</td>
<td>0.24 (0.12, 0.44)</td>
</tr>
<tr>
<td>2004</td>
<td>9283</td>
<td>31</td>
<td>0.33 (0.23, 0.47)</td>
<td>39</td>
<td>0.42 (0.30, 0.57)</td>
</tr>
<tr>
<td>2005</td>
<td>13,836</td>
<td>63</td>
<td>0.46 (0.35, 0.58)</td>
<td>66</td>
<td>0.48 (0.37, 0.61)</td>
</tr>
<tr>
<td>2006</td>
<td>18,161</td>
<td>77</td>
<td>0.42 (0.33, 0.53)</td>
<td>86</td>
<td>0.47 (0.38, 0.58)</td>
</tr>
<tr>
<td>2007</td>
<td>22,066</td>
<td>98</td>
<td>0.44 (0.36, 0.54)</td>
<td>109</td>
<td>0.49 (0.41, 0.60)</td>
</tr>
<tr>
<td>2008</td>
<td>25,317</td>
<td>122</td>
<td>0.48 (0.40, 0.58)</td>
<td>137</td>
<td>0.54 (0.45, 0.64)</td>
</tr>
<tr>
<td>2009</td>
<td>27,770</td>
<td>129</td>
<td>0.46 (0.39, 0.55)</td>
<td>152</td>
<td>0.55 (0.46, 0.64)</td>
</tr>
<tr>
<td>2010</td>
<td>29,169</td>
<td>164</td>
<td>0.56 (0.48, 0.66)</td>
<td>180</td>
<td>0.62 (0.53, 0.71)</td>
</tr>
<tr>
<td>2011</td>
<td>29,082</td>
<td>169</td>
<td>0.58 (0.50, 0.68)</td>
<td>182</td>
<td>0.63 (0.54, 0.72)</td>
</tr>
<tr>
<td>2012</td>
<td>27,240</td>
<td>182</td>
<td>0.67 (0.57, 0.77)</td>
<td>206</td>
<td>0.76 (0.66, 0.87)</td>
</tr>
</tbody>
</table>

Table 4
Annual prevalence (%) of HCM in the CPRD 2003–2012. Among stage IV cancer population with ≥1 serum calcium laboratory value after their stage IV cancer diagnosis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of stage IV cancer patients</th>
<th>CSC ≥10.8 mg/dL</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>76</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2004</td>
<td>206</td>
<td>4</td>
<td>1.94 (0.52, 4.97)</td>
</tr>
<tr>
<td>2005</td>
<td>329</td>
<td>9</td>
<td>2.74 (1.25, 5.19)</td>
</tr>
<tr>
<td>2006</td>
<td>507</td>
<td>12</td>
<td>2.37 (1.22, 4.13)</td>
</tr>
<tr>
<td>2007</td>
<td>677</td>
<td>12</td>
<td>1.77 (0.91, 3.10)</td>
</tr>
<tr>
<td>2008</td>
<td>823</td>
<td>20</td>
<td>2.43 (1.48, 3.75)</td>
</tr>
<tr>
<td>2009</td>
<td>956</td>
<td>14</td>
<td>1.46 (0.80, 2.46)</td>
</tr>
<tr>
<td>2010</td>
<td>1070</td>
<td>20</td>
<td>1.87 (1.14, 2.89)</td>
</tr>
<tr>
<td>2011</td>
<td>1114</td>
<td>17</td>
<td>1.53 (0.89, 2.44)</td>
</tr>
<tr>
<td>2012</td>
<td>1077</td>
<td>25</td>
<td>2.32 (1.50, 3.43)</td>
</tr>
</tbody>
</table>

with renal cancer experienced HCM at relatively high proportions with the exception of more recent years. Overall, women diagnosed with breast cancer did not have higher prevalence compared with patients with other tumor types. Prevalence estimates were higher for patients with stage IV cancer ranging from 1.46% to 2.74%.

Prevalence of grade 1 HCM increased over the study period. This could be due to the increased recording of laboratory values particularly in the later years compared to 2003. CPRD data are based on general practice electronic health records and as such are subject to improvement in data recording practices of the general practitioners (GPs). The capability to directly download laboratory data into patient records was not available until the early 2000s and has increased over time.

Interestingly, and in contrast with all cancer stages, annual prevalence estimates of HCM associated with stage IV cancer patients were approximately constant over time, averaging 2% over the entire study period. It is possible that laboratory records associated with advanced cancer are more completely captured in the database relative to all other cancers.

The prevalence of HCM calculated in the CPRD data is lower than the prevalence estimated in a recent analysis of data from a large electronic health records database of patients treated at outpatient hematology/oncology practices across the United States [16]. The higher prevalence estimates derived from outpatient visits in the United States were specific to the oncology practice setting and captured a higher median number of serum calcium/albumin tests per patient than measured in the general practice setting of the CPRD. Despite different populations and practice settings, both studies reported the highest prevalence of HCM among patients diagnosed with lung cancer and multiple myeloma, and lowest prevalence for prostate cancer patients. The differences between studies were greater where the numbers of patients with cancer and hypercalcemia were small reflecting the instability of the estimates. It should be noted that we estimated prevalence by year using the highest HCM grade in that year, thus prevalence of the lower grade HCM may have been underestimated.

This study was conducted in a UK population-based data resource that includes data on all individuals registered with selected GPs, and thus includes HCM cases identified from a general patient population rather than a hospital or registry population. While the population-based nature of this study is a strength, the study also has several limitations. First, patients who had a Read code for hypercalcemia but no CSC value were not included in the primary analyses for this study because we were not able to evaluate their HCM grade. To evaluate the potential impact on the prevalence due to missing HCM cases, we identified those with a Read code for hypercalcemia and re-calculated the prevalence. The prevalence of HCM was higher with the additional cases but the difference was small. Second, these results were limited to patients who had recorded laboratory values for serum calcium and serum albumin (or CSC) thus we have likely missed some patients with elevations in calcium. 37,442 (14.8%) out of 253,508 people in the cancer population had at least one test for serum hypercalcemia. It is possible that in cancer patients GPs do not routinely record individual cancer related complications, in particular those based on hospital findings. Further, values were not recorded in each calendar year thus we did not always know when CSC values returned to normal. Third, lung cancer may have been under reported in the CPRD. One explanation for this is that there was no good treatment available for lung cancer and some of these patients may have died in hospital very soon after diagnosis. Thus it is possible that some information on the diagnosis of lung cancer was not transmitted to primary care. However, levels of concordance between cancer registries and the CPRD were reported to be reasonably high [17], missing some lung cancer cases therefore should not have materially affected the study results. Finally, cancer staging data are not available in the CPRD thus information on the stage IV cancer subset was identified through Read codes for secondary or metastatic cancers. It is thus likely that we missed some stage IV cancer patients in this sub analysis.

Previously, the prevalence of HCM was thought to range between 3% and 30% among cancer types [7,18]. However, estimates of HCM prevalence can only be reliably ascertained from serum calcium (and albumin) laboratory values. These types of patient-level laboratory data reside in electronic health records, such as found in the CPRD data in our study. We provide the first systematic analysis using a population-based data source to estimate the number of cancer patients affected with HCM by grade and year in a 10-year study period. Our findings suggest that HCM in general is not a common condition.
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Authorship contribution

S. Jick participated in the conception and design of the study, and contributed to data analysis. L. Li contributed to study design and conducted analyses. V.M. Gastanaga participated in the conception and design of the study, and contributed to data analysis and interpretation. A. Liebe participated in the conception and design of the study, and contributed to data analysis and interpretation. All authors participated in revisions of the manuscript draft for intellectual content. S. Jick is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix. Read diagnosis codes for Stage IV cancer

B56.00 Secondary and unspecified malignant neoplasm of lymph nodes
B56.11 Lymph node metastases
B5600 Secondary and unspec malig neop lymph nodes head/face/neck
B560000 Secondary and unspec malig neop of superficial parotid LN
B560100 Secondary and unspec malignant neoplasm mastoid lymph nodes
B560200 Secondary and unspec malig neop superficial cervical LN
B560300 Secondary and unspec malignant neoplasm occipital lymph node
B560400 Secondary and unspec malig neop deep parotid lymph nodes
B560500 Secondary and unspec malig neop submandibular lymph nodes
B560600 Secondary and unspec malig neop of facial lymph nodes
B560700 Secondary and unspec malig neop submental lymph nodes
B560800 Secondary and unspec malig neop anterior cervical LN
B560z00 Secondary unspec malig neop lymph nodes head/face/neck NOS
B561.00 Secondary and unspec malig neop intrathoracic lymph nodes
B561000 Secondary and unspec malig neop internal mammary lymph nodes
B561300 Secondary and unspec malig neop ant mediastinal lymph nodes
B561400 Secondary and unspec malig neop post mediastinal lymph nodes
B561500 Secondary and unspec malig neop paratracheal lymph nodes
B561600 Secondary and unspec malig neop superfic tracheobronchial LN
B561700 Secondary and unspec malig neop inferior tracheobronchial LN
B561800 Secondary and unspec malig neop bronchopulmonary lymph nodes
B561900 Secondary and unspec malig neop pulmonary lymph nodes
B562.00 Secondary and unspec malig neop intraabdominal lymph nodes
B562000 Secondary and unspec malig neop coeliac lymph nodes
B562200 Secondary and unspec malig neop inferior mesenteric LN
B562300 Secondary and unspec malig neop common iliac lymph nodes
B562400 Secondary and unspec malig neop external iliac lymph nodes
B562z00 Secondary and unspec malig neop intraabdominal LN NOS
B563.00 Secondary and unspec malig neop axilla and upper limb LN
B563000 Secondary and unspec malig neop axillary lymph nodes
B563200 Secondary and unspec malig neop infracavicular lymph nodes
B563300 Secondary and unspec malig neop pectoral lymph nodes
B564.00 Secondary and unspec malig neop inguinal and lower limb LN
B564000 Secondary and unspec malig neop superficial inguinal LN
B564100 Secondary and unspec malig neop deep inguinal lymph nodes
B564z00 Secondary and unspec malig neop of inguinal and leg LN NOS
B565.00 Secondary and unspec malig neop intrapelvic lymph nodes
B565300 Secondary and unspec malig neop sacral lymph nodes
B56y00 Secondary and unspec malig neop lymph nodes multiple sites
B562.00 Secondary and unspec malig neop lymph nodes NOS
R4M23.00 Lymphoma stage IV
B57.00 Secondary malig neop of respiratory and digestive systems
B57.11 Metastases of respiratory and/or digestive systems
B57.12 Secondary carcinoma of respiratory and/or digestive systems
B570.00 Secondary malignant neoplasm of lung
B571.00 Secondary malignant neoplasm of mediastinum
B572.00 Secondary malignant neoplasm of pleura
B573.00 Secondary malignant neoplasm of other respiratory organs
B574.00 Secondary malignant neoplasm of small intestine and duodenum
B574000 Secondary malignant neoplasm of duodenum
B574z00 Secondary malig neop of small intestine or duodenum NOS
B575.00 Secondary malignant neoplasm of large intestine and rectum
B575000 Secondary malignant neoplasm of colon
B575100 Secondary malignant neoplasm of rectum
B575z00 Secondary malig neop of large intestine or rectum NOS
B576.00 Secondary malig neop of retroperitoneum and peritoneum
B576000 Secondary malignant neoplasm of retroperitoneum
B576100 Secondary malignant neoplasm of peritoneum
B576200 Malignant ascites
B577.00 Secondary malignant neoplasm of liver
B577z11 Liver metastases
B577y00 Secondary malignant neoplasm of other digestive organ
B573.00 Secondary malig neop of respiratory or digestive system NOS
BS8.00 Secondary malignant neoplasm of other specified sites
BS8.11 Secondary carcinoma of other specified sites
BS8.00 Secondary malignant neoplasm of kidney
BS8.00 Secondary malignant neoplasm of other urinary organs
BS8.00 Secondary malignant neoplasm of ureter
BS8.10 Secondary malignant neoplasm of bladder
BS8.00 Secondary malignant neoplasm of urethra
BS8.00 Secondary malignant neoplasm of other urinary organ NOS
BS8.00 Secondary malignant neoplasm of skin
BS8.00 Secondary malignant neoplasm of skin of neck
BS8.00 Secondary malignant neoplasm of skin of trunk
BS8.00 Secondary malignant neoplasm of skin of shoulder and arm
BS8.00 Secondary malignant neoplasm of skin of hip and leg
BS8.00 Secondary malignant neoplasm of skin of breast
BS8.00 Secondary malignant neoplasm of skin of arm
BS8.00 Secondary malignant neoplasm of other part of nervous system
BS8.00 Secondary malignant neoplasm of bone and bone marrow
BS8.00 Secondary malignant neoplasm of ovary
BS8.00 Secondary malignant neoplasm of adrenal gland
BS8.00 Secondary malignant neoplasm of other specified sites
BS8.00 Secondary malignant neoplasm of breast
BS8.00 Secondary malignant neoplasm of uterus
BS8.00 Secondary malignant neoplasm of vagina
BS8.00 Secondary malignant neoplasm of vulva
BS8.00 Secondary cancer of the vulva
BS8.00 Secondary malignant neoplasm of prostate
BS8.00 Secondary malignant neoplasm of penis
BS8.00 Secondary malignant neoplasm of tongue
BS8.00 Secondary malignant neoplasm of cervix uteri
BS8.00 Secondary cancer of the cervix
BS8.00 Secondary malignant neoplasm of testis
BS8.00 Secondary malignant neoplasm of epididymis and vas deferens
BS8.00 Secondary malignant neoplasm of other specified site NOS
BS8.00 Secondary malignant neoplasm of other specified site NOS
BS9.00 Malignant neoplasm of unspecified site
BS9.00 Disseminated malignancy NOS
BS9.11 Carcinomatosis
BS9.00 Malignant neoplasms of independent (primary) multiple sites
BS9.00 Malignant neoplasm of unknown site
BB0.00 Malignant neoplasm; metastatic
BB03.11 Malignant neoplasm
BB13.00 Malignant carcinoma; metastatic; NOS
Byu200 [X]2ndry + unspcf malignant neoplasm lymph nodes/multi regions
Byu300 [X]Secondary malignant neoplasm/oth + unspcf respiratory organs
Byu400 [X]Secondary malignant neoplasm/oth + unspcf digestive organs
Byu500 [X]2ndry malignant neoplasm/related + oth + unspf urinary organs
Byu600 [X]2ndry malignant neoplasm/oth + unspcf parts/ nervous system
Byu700 [X]Secondary malignant neoplasm of other specified sites

References