Cancer of unknown primary (CUP): does cause of death and family history implicate hidden phenotypically changed primaries?

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Background: Cancer of unknown primary (CUP) is diagnosed at the metastatic stage. We aimed to identify hidden primary cancers in CUP patients by comparison with cancers in family members. We take use of the fact that the cause of death in CUP patients is often coded as the cancer in the organ of fatal metastasis.

Patients and methods: Forty-one thousand five hundred and twenty-three CUP patients were identified in the Swedish Family-Cancer Database, and relative risks (RRs) were calculated for cancer in offspring when family members were diagnosed with CUP and died of the cancer diagnosed in offspring.

Results: The RR for lung cancer in offspring was 1.85 when a family member was diagnosed with CUP and died of lung cancer. Significant familial associations were found for seven other cancers. Many familial associations were also significant when offspring CUP patients died of the cancer diagnosed in family members.

Conclusions: The cause of death after CUP diagnosis frequently matched the cancer found in a family member, suggesting that the CUP had originated in that tissue. The metastasis had probably undergone a phenotypic change, complicating pathological tissue assignment. These novel data suggest that some CUP cases are phenotypically modified primary cancers rather than cancers of unknown primaries.

Key words: cancer of unknown primary (CUP), cancer prevention, epidemiology

introduction

Cancer of unknown primary site (CUP) accounts for some 2%–5% of all cancers in developed countries and, because of its aggressiveness, for a higher percentage of cancer deaths [1–3]. By definition, CUP patients are diagnosed with metastatic disease and the primary tumors cannot be found despite rigorous efforts [4–7]. The diagnostic work-up for identifying the tissue of origin is extensive because it forms the basis of oncological treatment of metastatic cancer. New and powerful identification methods include immunohistochemical (IHC) panels, gene expression profiling arrays and advanced imaging techniques [6–11]. When the primary site is found, many cancer registries replace CUP diagnosis by the primary cancer [1]. The new methods for tissue identification are the likely reason for the recent declining incidence rates for CUP [1]. Even autopsies fail to identify primary tumors in a large proportion of cases; when found, these include cancers of the lung, pancreas, colorectum, liver, stomach, kidney, ovary and others [12–15].

The enigmatic pathogenesis of CUP is a challenge to cancer biology and therapeutic practice [4, 11, 15, 16]. The absence of a primary tumor has been explained in a number of ways, including its small size, dormancy or involution [11, 12, 15, 17]. In addition to the immunological and apoptotic mechanisms of halting tumor growth, data have accumulated on roles of senescence, microenvironment and tumor stem cells in the process of metastasis [18–22]. These new data may add plausibility to earlier speculation that CUP may present an unusual primary tumor mimicking metastatic disease, probably derived from embryonic rest cells or adult stem cells [15, 17]. Importantly, better understanding of the pathobiology of CUP might thus provide new insights into general mechanisms of metastasis. A striking parallel could be the lessons learned in general cancer biology from rare hereditary cancer syndromes.

In a recent study on the Swedish Family-Cancer Database, we demonstrated familial clustering of CUP and the association of CUP with many other cancers, especially in organs with suspected hidden primaries [23]. Accordingly, CUP often occurred in family members of patients with lung, colorectal, liver, ovarian, kidney and some other cancers.
Familial clustering of these cancers suggested that the primary site in CUP was the one which showed the high familial risk, i.e. one of the above sites. In the present study, we analyze the familial clustering further by taking advantage of the fact that CUP is the only cancer for which death certificates give the site of fatal organ metastasis as the cause of death; for any other cancers, the primary cancer is given as the cause of death. Importantly, death certificates are of high quality in Sweden because 85% of cancer patients die in hospitals and for over 90% of cancer deaths, the related hospital records have been the basis on which the death certificate was issued [24, 25]. The primary cancer in one family member was used to analyze the risk for fatal metastatic cancer in the other family member diagnosed with CUP. Surprisingly, the sites were concordant for many cancers: for example, CUP patients were at risk of dying of lung cancer when their family members were diagnosed with lung cancer. These data imply that, for many CUP patients, the hidden primary resides or had resided in the organ where the metastases were detected and evaded pathological tissue identification through some phenotypic change.

**patients and methods**

The research dataset used in this study was the most recent update of the Family-Cancer Database, which is a subset of the national MigMed2 dataset at the Center for Primary Health Care Research, Lund University, Malmö. The database was created by linking the Multigeneration Register, created by Statistics Sweden covering offspring born after 1932 and their parents, with the Swedish Cancer Registry (1958–2008) [26]. Death causes were obtained from the Swedish Causes of Death Register. Data on family relationships were obtained from the Multigeneration Register, where children born in 1932 and later are registered with their biological parents as families. Thus, the individuals in the database can be divided into the first generation. The Swedish Cancer Registry is based on compulsory reports of diagnosed cases, with a close-to-complete coverage of cancers nationwide. The family history of concordant cancers was defined through parental and sibling probands. The database includes >12 million individuals and 1.1 million cancers from 1958 to 2008. The offspring generation of the database had a maximal age of 76 years, while the age of the parental generation was not limited. Tumors were identified according to the seventh revision of International Classification of Diseases (ICD-7). Any subsequent codes were translated into ICD-7 terminology in order to ensure consistency for follow-up of incidence trends. Each person was monitored from 1 January 1958 to diagnosis of cancer or date of emigration or end of the follow-up period, 31 December 2008, whichever came first. The risk of cancer was estimated for offspring given cancer in their parents, siblings or either. Relative risks (RR) were calculated using Poisson regression (PROC PHREG, SAS version 9.2; SAS Institute). The data were adjusted for age (5-year bands), sex and period (10-year bands). Data are shown only for cancer sites when at least two familial cases were found in offspring.

The study was approved by the Ethics Committee at Lund University.

**results**

We cover two generations, parents (no age limit) and offspring (maximal age 76 years). According to Table 1, a total of 301 762 cancers were diagnosed in the offspring population. Of these, 6717 were CUP patients, but only 1420 of these died with CUP as the underlying cause of death. All offspring cancer deaths after CUP numbered 5272; lung cancer was the most common cause, with 994 deaths. The parental population showed 984 422 cancers and 29 656 cancer deaths after CUP; lung cancer deaths numbered 4823.

We calculated all familial risks for various cancers in offspring given death from the same cancer after diagnosis of CUP in parents or siblings. Offspring can thus be considered cases and parents or siblings as probands. In Table 2, familial risks were analyzed for cancers in offspring when their parents, siblings or either were diagnosed with CUP and died of the same cancer as the one diagnosed in offspring; i.e. RR for offspring cancer ‘X’ given death in that cancer in a proband

### Table 1. Numbers of diagnosed cancers in offspring and parents and numbers of cancer deaths after cancer of unknown primary (CUP)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Number of diagnosed cancers</th>
<th>Cancer deaths after CUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Offspring</td>
<td>Parents</td>
</tr>
<tr>
<td>CUP</td>
<td>6717</td>
<td>34 806</td>
</tr>
<tr>
<td>Stomach</td>
<td>3955</td>
<td>39 912</td>
</tr>
<tr>
<td>Colorectum</td>
<td>23 623</td>
<td>120 589</td>
</tr>
<tr>
<td>Liver</td>
<td>3799</td>
<td>27 606</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4319</td>
<td>28 298</td>
</tr>
<tr>
<td>Lung</td>
<td>16 178</td>
<td>82 119</td>
</tr>
<tr>
<td>Breast</td>
<td>57 185</td>
<td>149 579</td>
</tr>
<tr>
<td>Ovary</td>
<td>8010</td>
<td>26 254</td>
</tr>
<tr>
<td>Prostate</td>
<td>35 994</td>
<td>162 694</td>
</tr>
<tr>
<td>Kidney</td>
<td>6750</td>
<td>31 595</td>
</tr>
<tr>
<td>Melanoma</td>
<td>20 372</td>
<td>40 384</td>
</tr>
<tr>
<td>Nervous system</td>
<td>17 648</td>
<td>35 865</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>4399</td>
<td>10 169</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10 406</td>
<td>33 113</td>
</tr>
<tr>
<td>Other</td>
<td>82 407</td>
<td>161 439</td>
</tr>
<tr>
<td>All</td>
<td>301 762</td>
<td>984 422</td>
</tr>
</tbody>
</table>
who was diagnosed with CUP. Lung cancer showed the largest number of familial cancers and significant RRs when parents (RR 1.37), siblings (3.16) or either (1.85) had died of lung cancer after CUP diagnosis. Ovarian cancer was also increased according to all proband categories, with an overall RR of 2.35. The overall RR was additionally increased for CUP (1.12), stomach (1.21), colorectal (1.36), liver (1.84), pancreatic (2.03), breast (1.71), prostate (1.57), kidney (1.18), nervous system (1.66) and thyroid (8.85) cancers and for melanoma (2.28).

Non-Hodgkin lymphoma was increased when parents were affected (2.80).

The analyses were carried out in reverse order, i.e. familial risks were analyzed for offspring CUP patients would die of a defined cancer when their parents, siblings and either were diagnosed with the same cancer (Table 3). It should be noted that the follow-up ceased at CUP diagnosis in offspring. The analyses were completely independent of those shown in Table 2 when parents were affected, but for siblings, the affected pairs were the same; the small differences in case numbers were due to the number of affected siblings in each family (two or three). Offspring risks were increased for CUP when the cause of death in parents was pancreatic (1.92) or lung (1.81) cancer. These, and liver and kidney cancer deaths and melanoma deaths, were also increased when parents or siblings were affected.

discussion

Our previous family study suggested that CUP is associated with cancers of organs commonly thought to be the origins of hidden primaries, such as liver, lung, ovarian and kidney cancers [23]. The present results take this one stage further and show that in all common cancers, including prostate cancer that rarely harbors CUP primaries, the cause of death after CUP was frequently the same as that diagnosed in a familial member. The evidence can be considered strong if at least two independent analyses showed an increased risk; completely independent analyses were those considering any parental proband data or sibling data but the latter could be counted one only. Thus, the data were strongest for lung cancer with three independent associations and for pancreatic and ovarian cancers, each with two associations. CUP, colorectal, liver, breast, prostate, kidney, nervous system and thyroid cancers and melanoma and non-Hodgkin lymphoma, each showed a single independent significant association, and thus, the likelihood of a chance finding cannot be excluded. However, for breast, prostate (Table 2) and kidney (Table 3) cancers and for melanoma (Tables 2 and 3), the overall associations (parent or sibling) were also significant. Of note, as CUP is a disease of older people with a median age of 71 years in Sweden, the case numbers in the offspring generation (maximal age of 76 years) were small, thus decreasing the likelihood of detection of familial cancers of old age (Table 3) [3, 27].

Melanoma was not relevant in a site-specific analysis but it offered a proof-of-principle in showing a sibling risk of 3.76 and 3.86 in the present study (Tables 2 and 3), somewhat higher than the RR of 2.94 for incident melanoma between siblings in the Family-Cancer Database [28]. In fact, even the other observed familial risks of ~2.0 in the present study were not different, and some were even higher, compared with those found for incident cancers [29]. The equally high familial risks between incidence and death certificate data attest to the high quality of diagnostic data available to the death registrar; the reason being the access to the relevant hospital records in almost all cases for persons who died of cancer [24, 25]. The results on melanoma offer an important point about the coding practice of the death registrar. Metastatic melanomas are diagnosed in a number of organs in CUP patients,
including various lymph nodes, brain and liver [3]. However, the histological designation, rather than the affected organ system, was that which the death registrar was able to record and which obviously requires access to an up-to-date patient journal.

The present data on some common CUP metastatic sites suggest that the primary tumors in fact reside or resided in these organs. The accumulating gene expression profiling and IHC data often report that primaries may reside in organs other than those biopsied for metastasis [9–11, 15]. However, the large majority of these studies are focused on CUP populations with relatively good survival, because tissue of origin identification may not benefit patients with a survival prognosis of only a few months, including those with pancreatic, liver and lung metastases [3]. Many gene expression studies thus have large numbers of patients with nodal metastasis, with relatively favorable survival times of 1 year or more [30–34]. For all CUP patients, the median survival is ~3 months in population-based studies catching all patients [2, 3]. In some tissue of origin studies that have included patients with metastatic liver, pancreatic and lung cancers, the tissue identification at these sites has often failed because of assumed dedifferentiation and phenotypic changes [9, 30, 35, 36]. The conclusion from the cited literature is that many of the published tissue of origin identification studies have recruited CUP patients with a relatively benign disease, for which the primary tumor may reside in another organ and for which the present study would not show familial risks.

How do we reconcile the present findings? First, we have to refute the assumption that a cancer diagnosis in a relative would somehow influence the registered cause of death in another relative. According to our previous study, a large majority of familial cancers were diagnosed after the parents had died of that cancer; for example in lung cancer, the percentage was 85 [29]. Even for siblings diagnosed at an old age, the influence is unlikely. Why does the histology of the metastatic biopsy not reveal that the tumor may be derived from that organ? We can only speculate: as the organ has been able to control the growth of the primary, the tumor had to undergo extensive phenotypic changes in order to escape the control. Whether epithelial–mesenchymal transition or other partially overlapping microenvironmental or immunological mechanisms are involved, or whether CUP expresses embryonic or stem cell characteristics, remains to be resolved in the future [15, 17–22].

Immuoediting is becoming a widely understood phenomenon in cancer progression, with parallels to CUP [37]. The immune system may be able to consecutively eradicate recognizable clones, thus editing out immunogenic features eventually resulting in a poorly immunogenic or immunosuppressive clone. In the case of CUP, the entire primary tumor may have been eradicated, except for a metastatic clone. It is easy to envision a ‘stealth clone’ remaining ‘under the radar’ for extended periods, perhaps acquiring additional pro-survival features and thus gaining an eventual growth advantage. This pattern of behavior would be compatible with the high median age of CUP diagnosis: eventual outgrowth could be assisted by the declining vigilance of the aging immune system. There could be a link between immunoediting and the histopathological CUP phenotype. The edited metastatic CUP may show immunological tissue characteristics which are difficult to recognize using diagnostic pathology, which is much dependent—especially in problem cases—on IHC antibodies which recognize defined epitopes [30, 35, 38]. If epitopes recognizable by antibodies have been immunoedited, it is no surprise that they cannot be detected in the immunopathology laboratory. The immunoediting hypothesis is not in contradiction of the cancer initiating stem cell hypothesis, as, e.g. mesenchymal stem cells have been proposed to have immune suppressive properties [39]. Lastly, we need to point out that the strongest effects were noted for lung, liver, pancreatic and ovarian cancers, all of which are tumors with a poor prognosis. In less aggressive cancers, the metastatic progression may be slower, less visible to the immune system and therefore less likely to be immunoedited, resulting in easier pathological diagnosis.

### Table 3. Relative risks (RRs) for offspring to develop CUP and die of a site-specific cancer when a family member was diagnosed with that cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Deaths in offspring</th>
<th>Cases in parents</th>
<th>Cases in siblings</th>
<th>Cases in parents or sibs</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUP</td>
<td>1420</td>
<td>34</td>
<td>11</td>
<td>45</td>
<td>1.31 (0.96–1.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>74</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>2.23 (0.23–21.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectum</td>
<td>303</td>
<td>19</td>
<td>7</td>
<td>26</td>
<td>1.26 (0.74–2.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>475</td>
<td>17</td>
<td>3</td>
<td>20</td>
<td>2.07 (1.22–3.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>526</td>
<td>17</td>
<td>5</td>
<td>22</td>
<td>2.07 (1.16–3.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>994</td>
<td>64</td>
<td>44</td>
<td>108</td>
<td>2.22 (1.65–2.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>82</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>1.26 (0.71–2.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>255</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>1.65 (0.68–3.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>17</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1.91 (0.70–5.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>79</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>3.01 (1.37–6.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>327</td>
<td>6</td>
<td>11</td>
<td>17</td>
<td>2.53 (1.46–4.38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold type indicates that the 95% CIs do not include 1.00.

RRs adjusted for age (<35, 35–39, …, 70+), sex, period (<2000, 2000 +), region and socioeconomic status (five groups).

#RRs adjusted for age (<50, 50–54, …, 70+), sex, period (<2000, 2000 +) and socioeconomic status (five groups).

CI, confidence interval; CUP, cancer of unknown primary.
In conclusion, the present data on CUP patients with fatal metastases provide evidence, based on familial links, that the hidden primary resided in the organ where metastases were found. The failure of histopathological tissue of origin identification suggests that phenotypic changes in the primary tumor allowed it to be disguised as metastases. The immunologically modified ‘stealth’ phenotype could explain the extraordinary aggressiveness of CUP. Taken together, these data suggest that many of the fatal CUP cases are in fact phenotypically modified primary cancers rather than cancers of unknown primary origin.

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disclosure

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references