Risk of thyroid cancer in relatives of patients with medullary thyroid carcinoma by age at diagnosis

Mahdi Fallah1, Kristina Sundquist2 and Kari Hemminki1,2
1Division of Molecular Genetic Epidemiology, German Cancer Research Center, Im Neuenheimer Feld 580, 69120 Heidelberg, Germany
2Center for Primary Health Care Research, Lund University, Malmö, Sweden

Abstract

The familial risk of medullary thyroid carcinoma (MTC alone or as part of multiple endocrine neoplasms, MEN2A/MEN2B) is high, so we aimed to answer open questions about the lifetime cumulative risk of thyroid cancer (LCRTC at 0–79 years) among relatives of MTC patients by age and sex. For this nationwide study, a cohort of 3217 first-/second-degree relatives (FDRs/SDRs) of 389 MTC patients diagnosed in 1958–2010 in the Swedish Family-Cancer Database was followed for the incidence of thyroid cancer. The LCRTC in female relatives of patients with early-onset MEN2B (diagnosis age < 25 years) was 44–57%, representing 140–520 times increase over the risk in their peers without a family history of endocrine tumors (men: LCRTC = 22–52%, 320–750 times) depending on the number of affected FDRs/SDRs. The LCRTC in female relatives of patients with late-onset MEN2B (diagnosis age ≥ 25 years) was about 15–43% (men = 24%). The LCRTC among relatives of early-onset MTC-alone patients was 3–20%. The LCRTC among relatives of late-onset MTC-alone patients was 5–26%. The LCRTC in female relatives of MEN2A patients was 16–63% (men = 52%). The relatives of patients with early-onset MTC exhibited a high tendency to develop early-onset thyroid cancer. Simply available data on the number of FDRs and even SDRs affected with MTC and their age at diagnosis were quite informative for the estimation of the risk of thyroid cancer in probands. In settings where genetic testing is not available or affordable for all, evidence-based cumulative risks reported in this nationwide study may help physicians to identify very high-risk individuals.

Introduction

The incidence of thyroid cancer, the most common endocrine malignancy, continues to increase with over 213,000 new thyroid cancer cases being diagnosed in the world per year and 48,020 new cases in the USA (6.4% annual percentage increase during 1997–2008; Ferlay et al. 2010, Khan et al. 2010, Howlader et al. 2011). The familial risk of thyroid cancer is known to be highest among cancer sites (Goldgar et al. 1994), for which the increased risk extends beyond the nuclear family (Amundadottir et al. 2004). Medullary thyroid carcinoma (MTC) is the third most common thyroid neoplasm (3–10%) after papillary (50–80%) and follicular (10–40%) carcinomas (Hundahl et al. 1998, Boyle 2008, Pacini et al. 2010). A strong genetic component is known for medullary carcinoma, so that up to 25% of the cases are estimated to be heritable, caused by a gain-of-function germline mutation in the
RET proto-oncogene (multiple endocrine neoplasia (MEN) type 2A and MEN2B and familial MTC (FMTC)) with an autosomal dominant mode of inheritance (Negri et al. 2002, DeLellis et al. 2004, Nose 2011). Despite the rarity of these syndromes and MTC in general, early diagnosis is especially important, since MTC is a lethal disease if not promptly and appropriately treated (Sakorafas et al. 2008).

A limited number of population-based epidemiological studies have been able to quantify the familial risk of histological types of medullary and non-medullary carcinomas separately, but none had a large sample size to analyze the risk stratified by age and sex (Hemminki & Dong 2000, 2001, Hemminki et al. 2005) and none reported any clinically relevant absolute risk estimate (cumulative risk). One study on MTC has reported only parent–child familial risk (did not report the familial risk among siblings; Hemminki & Dong 2000), and another study has reported that relatives of less than half of 65 cases of MTC have concordant MTC (Hemminki & Dong 2001). Therefore, in this study, the latest updated version of the Swedish Family-Cancer Database (FCD) was used, which is an unbiased, high-quality nationwide family-cancer database, to be able to comprehensively quantify the familial risk ratio and, for the first time, cumulative risk of all MTC subtypes by age and sex.

**Subjects and methods**

The Statistics Sweden maintains the Multi-generation Register that covers offspring born in or after 1932 along with their parents and siblings. This Register was linked to the Swedish Cancer Registry (1958–2010) to create the Swedish FCD, which is a unique resource in terms of size (world’s largest of its kind) and validity of data on family relationship and cancer. The nationwide cancer registry records all the cancer diagnoses (including thyroid cancer) in the country. The 2013 update of these data includes a total population of over 14.7 million individuals and more than 1.7 million cancer patients. The data are organized into child–mother–father triplets; the parents were registered at the time of birth of their child, allowing tracking of biological parents. For this study, we recoded ICD-7, Pathological Anatomic Diagnosis (PAD or C24/Hist), and ICD-O-2 codes to their corresponding ICD-10 and ICD-O-3 morphology codes. There was information on 405 MTC patients in the database. Information on 389 (215 women and 174 men) well-defined MTC patients (about 3% of all thyroid cancer patients in the database) and their first-/second-degree relatives (FDRs/SDRs, n=3217) was used for this study.

**Proband/MTC/MEN2A/MEN2B/MTC alone definitions**

In this paper, by probands we mean relatives (FDRs/SDRs) of a patient with MTC, for whom we estimate the familial risk. ICD-10 code C73 and ICD-O-3 morphology codes 8510–8511 and 8345–8347 were used to identify MTC cases. MEN2B cases (n=49) were defined as those with MTC and adrenal tumor without parathyroid tumor in the extended family (patients or any of their FDRs or SDRs). MEN2A cases (n=11) were defined as those with MTC (or unspecified thyroid cancer) and both parathyroid and adrenal tumors in the extended family. MTC-alone cases (n=329) were defined as those with MTC without any non-thyroid endocrine tumor (adrenal, parathyroid, pituitary, pancreatic insulinoma, or other specified endocrine gland tumors; ICD-10 codes C74–75 and C25.4) in the extended family. FMTC patients were defined as those with MTC alone and MTC alone in at least four FDRs or SDRs. Only 16 MTC cases that did not match our above-mentioned definitions were excluded (e.g. MTC+only endocrine tumors other than parathyroid or adrenal tumors).

**Statistical analyses**

Standardized incidence ratios (SIRs adjusted for sex, age, and period of diagnosis of thyroid cancer) were used to compare thyroid cancer risk in individuals with a family history of MTC with the risk in their peers without a family history of endocrine tumors (ICD-10 C73–75 or C25.4). Follow-up started for parents of the MTC cases at the birth of the MTC child and for others at birth, at immigration, or on 1st January 1961, whichever was latest. Follow-up was terminated on the date of death, at emigration, or on the date of study completion (31st December 2010). The SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from sex-, 5-year age group-, and period-specific (5-year bands) background incidence rates of thyroid cancer in those without a family history of endocrine tumors multiplied by the corresponding person-years for those with a family history of MTC in the study population. 95% CIs were calculated assuming a Poisson distribution. The SAS Software (by SAS Institute, Inc., Cary, NC, USA) version 9.3 was used for data analysis. For simplicity, SIRs >50 are rounded off to the nearest order of 10 (e.g. 667–670) in this paper and exact numbers are presented in the tables.

The lifetime cumulative risk (assumed to be 0–79 years, which is close to the average life expectancy in
Sweden, 81 years, and close to the maximum age of the second generation in the FCD, 78 years) was calculated based on the following formulas: age-specific annual incidence rate = number of cases for each 5-year age group divided by person-years of that age group (0–4, ..., 74–79); age-specific cumulative rate = $5 \times \text{age group-specific annual incidence rate}$; lifelong cumulative rate = sum of age-specific cumulative rates; and cumulative risk = $1 - \exp(-\text{cumulative rate})$. The 95% CIs for cumulative rate were calculated as follows: cumulative rate $\pm 1.96 \times 5 \times \text{root of sum of each contributing age-specific cumulative rate divided by its corresponding person-years}$. Then, the 95% CIs for cumulative rates were converted to 95% CIs for cumulative risks using a formula the same as the above. To avoid overestimation of cumulative risk due to ignorance of competing causes of death, in all the calculations, individual person-years were used, so that the person-year calculation was stopped in the year of death if the person had died during the study period.

The age-specific incidence of thyroid cancer among relatives of MEN2/MTC-alone patients peaked at age 15–19 years in this study and dropped at age 25–29 years and again increased with some other drops due to small sample size in older ages. Therefore, we used the cutoff age of 25 years to distinguish between early-onset and late-onset familial thyroid cancers.

**Ethics**

The Lund regional Ethics Committee approved the study protocol.

**Results**

The lifetime cumulative risk of thyroid cancer (LCRTC) among individuals without a family history of any endocrine tumor was 0.4% in women and 0.2% in men. The familial risks of MTC by subtype of MTC (MEN2B/MTC alone/MEN2A), age at diagnosis (<25 or $\geq$ 25 years), number (1 or $\geq$ 2) and type of relationship (FDR or SDR only) of affected relatives, and proband’s age and sex were as follows:

**Multiple endocrine neoplasia type 2B**

The LCRTC in female FDRs of patients with early-onset MEN2B (diagnosis age <25 years) was 55% (Table 1), which represents about 420-fold increase over the risk in their peers without a family history of endocrine tumors (men: LCRTC = 42%, about 750-fold). An interesting finding was that in the absence of MEN2B in young FDRs, the presence of MEN2B in young SDRs was also associated with an increased LCRTC in probands (one affected SDR 41–44% and $\geq$ 2 SDRs 52–55%, depending on sex). The LCRTC in relatives of patients with late-onset MEN2B (diagnosis age $\geq$ 25 years) was generally high, but lower than the risk in relatives of early-onset MEN2B patients (one FDR 21%, $\geq$ 2 FDRs 43%, and SDRs 8–13%).

**MTC alone**

The LCRTC in female FDRs of patients with MTC alone diagnosed at young ages (<25) was 30% (Table 2), which represents about 180-fold increase over the risk in their peers without a family history of endocrine tumors (men: LCRTC = 10%, about 210-fold). When there were one or more SDRs with early-onset MTC alone in a family, the LCRTC in other relatives was 2–6%, depending on proband’s sex and age. The LCRTC in relatives of patients with MTC alone diagnosed at older ages ($\geq$ 25) was generally higher than the population risk, but lower than the risk in relatives of early-onset MTC-alone patients (one FDR 6% in women and 4% in men).

**Multiple endocrine neoplasia type 2A**

The LCRTC in FDRs of patients with MEN2A was 40%, representing about 290-fold increase over the risk in their peers without a family history of endocrine tumors (Supplementary Table 1, see section on supplementary data given at the end of this article).

**Risk trend by age**

The age-specific cumulative risk of thyroid cancer (CRTC) by family history of MEN2B is shown in Fig. 1 (upper panels). In general, the CRTC in a proband with a family history of MEN2B at younger ages (<25) started to increase at younger ages, while the CRTC when a relative was diagnosed with MTC at older ages started to increase at older ages. A similar pattern was observed for the CRTC in relatives of MTC-alone patients (lower panels, Fig. 1). More detailed information on the CRTC of MEN2A/MEN2B/MTC alone is given in Supplementary Tables 2, 3 and 4, see section on supplementary data given at the end of this article.

**Discordant cancer sites**

Among all the non-endocrine discordant cancers, only the risk of colorectal cancer (SIR = 3.2, 95% CI = 1.1–7.6, $n = 5$)
Table 1  SIRs and CRs of thyroid cancer in relatives (proband) of MEN2B patients

<table>
<thead>
<tr>
<th>Patients info</th>
<th>n</th>
<th>SIR</th>
<th>95% CI</th>
<th>CR% 95% CI</th>
<th>n</th>
<th>SIR</th>
<th>95% CI</th>
<th>CR% 95% CI</th>
<th>n</th>
<th>SIR</th>
<th>95% CI</th>
<th>CR% 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>229</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>224</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>224</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>9</td>
<td>79 (30-218)</td>
<td>21 (0-9-26)</td>
<td>10</td>
<td>66 (10-218)</td>
<td>21 (0-9-26)</td>
<td>10</td>
<td>66 (10-218)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>212</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>212</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>212</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>258</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>258</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>258</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>118</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>118</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>118</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>90</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>90</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>90</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>130</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>130</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>130</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>58</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>58</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>58</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at MEN2B diagnosis ≤25 years</td>
<td>229</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>229</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>229</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>9</td>
<td>79 (30-218)</td>
<td>21 (0-9-26)</td>
<td>10</td>
<td>66 (10-218)</td>
<td>21 (0-9-26)</td>
<td>10</td>
<td>66 (10-218)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>212</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>212</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>212</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at MEN2B diagnosis &gt;25 years</td>
<td>258</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>258</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>258</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>9</td>
<td>79 (30-218)</td>
<td>21 (0-9-26)</td>
<td>10</td>
<td>66 (10-218)</td>
<td>21 (0-9-26)</td>
<td>10</td>
<td>66 (10-218)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>258</td>
<td>158 (315-317)</td>
<td>21 (0-9-26)</td>
<td>258</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td>258</td>
<td>154 (153-317)</td>
<td>21 (0-9-26)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDR, first-degree relative; SDR only, second-degree relative with no affected FDR; bold type standardized incidence ratio (SIR), 95% CI did not include 1.00. Italic numbers represent cumulative risk (CR). CR at 25–79 years was reported for proband’s age ≥25 years and CR at 0–79 years for ‘all’ ages.

*Example: CR of thyroid cancer at 25–79 years in a man (proband) with a family history of early-onset MEN2B (diagnosis age <25 years) only in his mother (1 FDR) is 20%, representing a 23-fold higher risk than the risk in his peers without a family history of endocrine tumors.
Table 2  SIRs and CRs of thyroid cancer in relatives (proband's) of MTC-alone patients

<table>
<thead>
<tr>
<th>Family history of MTC alone</th>
<th>Sex</th>
<th>Age (years)</th>
<th>n</th>
<th>SIR</th>
<th>95% CI</th>
<th>CR%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td></td>
<td>27</td>
<td>24</td>
<td>(16-35)</td>
<td>8</td>
<td>(5-11)</td>
</tr>
<tr>
<td></td>
<td>&lt;25</td>
<td></td>
<td>9</td>
<td>239</td>
<td>(109-45-4)</td>
<td>3</td>
<td>(1-5)</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td></td>
<td>18</td>
<td>17</td>
<td>(10-26)</td>
<td>5</td>
<td>(3-8)</td>
</tr>
<tr>
<td>Women</td>
<td>All</td>
<td></td>
<td>19</td>
<td>23</td>
<td>(14-36)</td>
<td>10</td>
<td>(5-14)</td>
</tr>
<tr>
<td></td>
<td>&lt;25</td>
<td></td>
<td>5</td>
<td>161</td>
<td>(5-2-376)</td>
<td>3</td>
<td>(0-6)</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td></td>
<td>14</td>
<td>18</td>
<td>(10-30)</td>
<td>7</td>
<td>(3-11)</td>
</tr>
<tr>
<td>Men</td>
<td>All</td>
<td></td>
<td>8</td>
<td>27</td>
<td>(12-5-3)</td>
<td>6</td>
<td>(2-10)</td>
</tr>
<tr>
<td></td>
<td>&lt;25</td>
<td></td>
<td>4</td>
<td>608</td>
<td>(16-155-8)</td>
<td>3</td>
<td>(0-6)</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
<td></td>
<td>4</td>
<td>14</td>
<td>(4-35)</td>
<td>3</td>
<td>(0-6)</td>
</tr>
</tbody>
</table>

Age at MTC diagnosis

<table>
<thead>
<tr>
<th>Age at MTC diagnosis</th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>≥25</td>
<td>15</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>

Note: FDR, first-degree relative; SDR, second-degree relative; bold type standardized incidence ratio (SIR), 95% CI did not include 1.00. Italic numbers represent cumulative risk (CR). CR at 25–79 years was reported for proband's age ≥ 25 years and CR at 0–79 years for 'all' ages.

Example: CR of thyroid cancer at 25–79 years in a man (proband) with a family history of late-onset MTC alone (diagnosis age ≥ 25 years) only in his mother (1 FDR) is 3%, representing a 14-fold higher risk than the risk in his peers without a family history of endocrine tumors.
was significantly increased when a FDR had MEN2B (data not shown), which can be a chance finding. No case of non-medullary thyroid cancer was found among the relatives of MTC patients.

Discussion

The unique resource of the Swedish FCD enabled us to study the familial risk of MTC as part of MEN2 syndromes (type A and B) or MTC alone and to provide sex- and age-specific estimates for cumulative risk by family history status and age at diagnosis of relatives.

The familial risk is usually presented as a risk ratio (e.g. SIR), which needs to be converted to absolute risk to be meaningful in clinical practice. This is the first time that the CRTC in relatives of MTC patients is additionally presented in a nationwide cohort study. Cumulative risk is an absolute risk measure, tangible to clinicians and patients and their family members. The CRTC in women with one FDR affected with early-onset MEN2B was
already about 30% by age 25 years (men 28%; lifetime risk: about 55% in women and 42% in men, much higher than that in the general population (LCRTC <0.5%)). When MEN2B was diagnosed at older ages, the LCRTC (17–24%), especially CRTC (6–7%) at 0–24 years, was substantially lower than that of early-onset MEN2B. The same pattern (high risk of developing early-onset cancer when relatives had early-onset MTC and relatively lower risk of early-onset cancer in relatives of late-onset MTC patients, although still higher than the risk in the general population) could be observed in one FDR with MTC alone too. On the one hand, these may suggest that the age at diagnosis of thyroid cancer in individuals may be to some extent predetermined by the age at diagnosis of MTC in their relatives. On the other hand, the tendency for concordant age at diagnosis might partly be due to the difference in average age at diagnosis between different subtypes of MTC (MTC alone at older ages and MEN2B and MEN2A at younger ages) and concordant familial association of these MTC subtypes, although the role of more intensive earlier surveillance among relatives of early-onset MTC patients could not be ruled out.

Although SIRs (risk ratios) for men were usually higher than those for women, the LCRTC generally remained higher in women than in men with MEN2/MTC-alone patients in their family (Fig. 1). This is in line with the higher risk of thyroid cancer in women (0–74 years cumulative risk =0.47%) in the general population than in men (0.15%) (Ferlay et al. 2010).

The present study, which is the largest yet published, benefited from the nationwide cohort with unbiased data on family history of cancers. However, the histological type used in older periods of time (less specific codes) in such a long follow-up study may not be as accurate as that used in recent years (e.g. MTC could have been coded as unspecified thyroid cancer before 1985). This in turn could be the source of a potential bias toward the under-estimation of SIRs only for concordant histological types. We tried to rectify this potential bias by reporting the risk of thyroid cancer (medullary, non-medullary, and unspecified thyroid cancer before 1985). This in turn could be the source of a potential bias toward the under-estimation of SIRs only for concordant histological types. We tried to rectify this potential bias by reporting the risk of thyroid cancer (medullary, non-medullary, and unspecified together) in relatives of known medullary cases. We counted individuals with unspecified thyroid cancers as MEN2A if they had a personal or family history of both parathyroid and adrenal tumors because these few highly likely MEN2A cases exhibited a familial risk that was very similar to that exhibited by those with well-defined MEN2A (MTC and parathyroid and adrenal tumors). Statistically significant sex- and age-specific SIRs, however, consistently showed a high familial risk in line with the pattern of overall results (internally validated), which is in favor of unbiased estimates, although one should also consider the CIs when it comes to the application of results in clinical practice.

In conclusion, simply available data on the number of FDRs and even SDRs affected with MTC and their age at diagnosis were quite informative for the estimation of the risk of thyroid cancer in probands. The relatives of patients with early-onset MTC exhibited a high tendency to develop early-onset thyroid cancer. This may suggest that age at diagnosis of thyroid cancer in individuals is to some extent predetermined by age at diagnosis of MTC in their relatives. In settings where genetic testing is not available or affordable for all, evidence-based cumulative risks in this nationwide study may help physicians to identify very high-risk individuals.

**Supplementary data**

This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-13-0021.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

**Funding**

This work was supported by the Swedish Council for Working Life and Social Research and the German Cancer Aid. The funding sources had no role in any stage of this study.

**Author contribution statement**

K Hemminki and M Fallah were responsible for study concept and design; K Sundquist was responsible for study material provision; M Fallah carried out data analysis; M Fallah and K Hemminki were involved in study result interpretation and manuscript writing; and all authors commented on the manuscript and gave final approval for the manuscript.

**References**


Goldgar DE, Easton DF, Cannon-Albright LA & Skolnick MH 1994


Received in final form 23 July 2013
Accepted 7 August 2013
Made available online as an Accepted Preprint 8 August 2013