Abstract. Background/Aim: Second primary tumors (SPTs) often occur, either synchronous or metachronous. Struma ovarii is a rare ovarian tumor represented by thyroid tissue in the ovary. Among other factors, production of thyroid hormones by the tumor or a shared genetic predisposition can further influence the development of SPTs. The occurrence of SPT, either synchronous or metachronous, following a long follow-up, has never been considered extensively. Patients and Methods: We analyzed the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2011 to follow-up all the cases of malignant struma ovarii in an effort to calculate the occurrence of SPT in this cohort of patients. Results: We identified 21 patients with malignant struma ovarii in the period between January 1973 and December 2011. In a follow-up period of 219.57 person-years, 3 patients had SPT. One patient had synchronous thyroid sclerosing carcinoma, 1 patient had metachronous papillary adenocarcinoma with a latent time of 7 years and 1 patient had synchronous salivary ductal carcinoma. Conclusion: Up to date, only thyroid synchronous tumors have been reported in the literature. A synchronous and a metachronous thyroid tumor, plus a synchronous salivary gland tumor, were found. A significant association between malignant struma ovarii and thyroid/salivary gland cancer is herein demonstrated.

Synchronous and Metachronous Malignancies After Malignant Struma Ovarii in the SEER Database

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The database contains information on patient demographics, primary cancer site, histology, methods of diagnostic confirmation, treatment regimens (including surgery and radiation therapy) and year of death. Institutional Review Board approval was not required for this study as the SEER database is free of any sensitive patient information or identifiers.

The SEER 9 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound and Utah. Data are available for cases diagnosed from 1973 and later for these registries with the exception of Seattle-Puget Sound and Atlanta. The Seattle-Puget Sound and Atlanta registries joined the SEER program in 1974 and 1975, respectively.

We used the SEER*Stat software (18) to estimate the incidence of SPT in the struma ovarii cases.

For the identification of SPTs, SEER takes account of histology, site, laterality and time since initial diagnosis to identify multiple primary cancers (19, 20).

In the distinction between synchronous and metachronous SPT, we used the widely-accepted criteria established by Warren and Gates (21) as follows: synchronous tumors were defined as second primary tumors that were diagnosed within 6 months of the first primary tumor; metachronous cancers were defined as those that were detected after an interval of more than 6 months.

The SEER*Stat software (18) gives also the ratio between observed/expected (O/E) cases, calculating significance levels with the Fisher’s exact test.

A p-value less that 0.05 was considered statistically significant.

Results

We identified 21 patients with malignant struma ovarii in the period between January 1973 and December 2011. In a follow-up period of 219.57 person-years, 3 patients had SPT (Table I).

One patient had synchronous thyroid sclerosing carcinoma, 1 patient had metachronous papillary adenocarcinoma with a latent time of 7 years and 1 patient had synchronous salivary ductal carcinoma.

All patients had surgery of the primary site without subsequent radiotherapy.

The O/E ratio to the general population was 41.88 for thyroid cancers and 344.10 for salivary gland tumors, both of them resulted to be statistically significant (Table II).

The risk of all solid tumors, in general, was not augmented when compared to the general population (Table II).

Discussion

We found a significant association between malignant struma ovarii and thyroid/salivary gland cancer.

Up until now, only thyroid synchronous tumors have been reported in the literature (9, 14-16). We found a synchronous and a metachronous thyroid tumor, plus a synchronous salivary gland tumor.

The current, generally accepted, main theories have proposed the co-occurrence of struma ovarii and thyroid cancer as a mutagenic trigger causing independent genetic events (14).

The risk of further primary cancers might be due to persisting effects of genetic and behavioural risk factors, long term side-effects of chemo- and radiotherapy, as well as increased diagnostic sensitivity.

We suppose that a common genetic mutagen can affect different body sites to develop similar tumoral mutations. One can also speculate that the thyroid hormonal production by the ovarian tumor can further influence the development of other tumors in the subsequent years. Treatment for struma ovarii involves surgical resection due to the risk of malignant degeneration or hyperthyroidism.

Due to the rarity of thyroid cancer arising within struma ovarii, optimal management has not yet been defined (16). Surgical management of the primary tumor and the thyroid gland, as well as the potential indications for adjuvant treatment, have not been standardized.

Pelvic management includes unilateral cystectomy as main procedure. Eventually, the surgeon can decide to perform unilateral salpingo-oophorectomy or total abdominal hysterectomy with bilateral salpingo-oophorectomy, depending on the grade of the tumor and the patient’s fertility wellness. When extra-ovarian extension or distant metastases are present, total thyroidectomy may be performed to facilitate radioactive iodine (RAI) therapy.

The role of thyroidectomy and RAI in localized, non-metastatic struma ovarii thyroid cancer is not well-defined, since the natural history of the disease is not yet well-known (22). The few studies available about follow-up of struma ovarii have showed an overall good prognosis and a low percentage of recurrence of well-differentiated thyroid cancer arising in struma ovarii (16, 23), even if very aggressive forms have been described (24).

Our finding of two second primary thyroid tumors coincidentally or after struma ovarii, reinforces the side of an aggressive management comprehending a thyroidectomy (25). The association with a salivary gland tumor is new and further studies are needed to assess the relationship between these two tumors. There seems to be little evidence of the direct relationship between the function of the thyroid gland and the salivary glands from experiments in rats and mice (26, 27). Thyroid diagnostic imaging at the time of the diagnosis of struma ovarii is very important in order to find any other synchronous tumor present in other locations or any metastases. This can be performed by $^{125}$I-positron emission tomography/computed tomography (PET/CT). Magnetic resonance (MR) imaging and ultrasound (US) are useful to unearth pathological structures located in soft tissues (28-30). In addition, a check-up for synchronous salivary gland tumor could be of certain importance.

In our opinion, the extension of surveillance for a longer follow-up period should be carefully evaluated in every patient affected by struma ovarii, in search of subsequent development of thyroid cancers or other tumors after struma ovarii.
Table I. Second primary tumor (SPT) after struma ovarii identified.

<table>
<thead>
<tr>
<th>SPT</th>
<th>Year/Age at diagnosis of struma ovarii</th>
<th>Year/Age at diagnosis of SPT</th>
<th>Person-time calculated of the event</th>
<th>Person-years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid (papillary adenocarcinoma)</td>
<td>1984/45</td>
<td>1991/50</td>
<td>7.25</td>
<td>219.57</td>
</tr>
<tr>
<td>Thyroid (non-encapsulated sclerosing carcinoma)</td>
<td>2003/54</td>
<td>2003/55</td>
<td>0.08</td>
<td>219.57</td>
</tr>
<tr>
<td>Salivary gland (infiltrating duct carcinoma)</td>
<td>2010/52</td>
<td>2010/52</td>
<td>0.42</td>
<td>219.57</td>
</tr>
</tbody>
</table>

Table II. Incidence analysis of second primary tumor (SPT) in various body sites in comparison to the expected incidence in the general population.

<table>
<thead>
<tr>
<th></th>
<th>Observed</th>
<th>Expected</th>
<th>O/E</th>
<th>CI 95% (lower-upper)</th>
<th>Excess risk</th>
<th>Persons at risk</th>
<th>Person-years at risk</th>
<th>Mean person-years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>3</td>
<td>1.24</td>
<td>2.42</td>
<td>0.5-7.07</td>
<td>80.19</td>
<td>21</td>
<td>219.57</td>
<td>10.46</td>
</tr>
<tr>
<td>All sites excluding non-melanoma skin</td>
<td>3</td>
<td>1.24</td>
<td>2.43</td>
<td>0.5-7.09</td>
<td>80.35</td>
<td>21</td>
<td>219.57</td>
<td>10.46</td>
</tr>
<tr>
<td>All solid tumors</td>
<td>3</td>
<td>1.13</td>
<td>2.65</td>
<td>0.55-7.74</td>
<td>85.02</td>
<td>21</td>
<td>219.57</td>
<td>10.46</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>1</td>
<td>0</td>
<td>344.10</td>
<td>8.71-1,917.19</td>
<td>45.41</td>
<td>21</td>
<td>219.57</td>
<td>10.46</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td>0.05</td>
<td>41.88</td>
<td>5.07-151.3</td>
<td>88.91</td>
<td>21</td>
<td>219.57</td>
<td>10.46</td>
</tr>
</tbody>
</table>

O/E, Observed/expected; CI, confidence interval.

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Conflicts of Interest

None.

References


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