Second primary malignancy risk after primary thyroid cancer: A systematic review and meta-analysis
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Thyroid cancer is the most common endocrine malignancy and generally comes with an excellent prognosis.

Primary treatment of thyroid cancer is based on thyroidectomy with or without adjuvant radioiodine (RAI) therapy depending on histological information and pathologic stage.

Trends of use of RAI are nowadays decreasing according to the recent published guidelines of DTC treatment as survival rate of patients at low risk seems not to be influence by the use of RAI (Augen et al, 2016).

Second primary malignancies (SPM) after primary thyroid cancer have been reported in several studies.

The relative contribution of shared genetic and environmental risk factors versus late effects of RAI treatment to these risks is still debated.

### Results

**Risk compared to the general population**
- SIR pooled = 1.24 (95% confidence interval [CI], 1.16-1.31)
- SIR men = 1.29 (95% CI 1.14-1.45), SIR women = 1.15 (95% CI, 0.98-1.35)
- Increased SIRs for 17 out of 25 site-specific SPMs
- Highest increased SIRs observed for:
  - Salivary gland: SIR = 6.0, 95% CI 2.74-11.48
  - Adrenal gland: SIR = 5.4, 95% CI 1.67-17.99
  - Leukaemia: SIR = 1.94, 95% CI 1.60-2.35

**Treatment by RAI**
- 7 out of 8 studies showed increased risks in the treated group with highest activities.
- No pooled RR could be obtained due to the lack of comparable categories of delivered activities.

### Objectives

This systematic review and meta-analysis aims to synthesize the published studies on SPM risk among thyroid cancer survivors and to provide site-specific SPM risk estimates.

**Specifically**
- Review of published data
- Ascertain the overall risk associated

**Material and methods**

- Systematic review has been performed according to PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) guidelines ( Liberati A 2009).
- English epidemiological studies (cohort and case-control) including at least 200 thyroid cancers (except for paediatric thyroid cancer >100 cases) and published between 1975 and 2019 were retrieved from online databases.
- The main outcome considered was standardized incidence ratio (SIR) of SPM following thyroid cancer diagnosis. Analyses of risk by site, gender, and 151I treatment status were also performed.
- Random effect model was used to estimate pooled risk (DerSimonian and Laird 1986).
- Statistical analysis were performed with STATA software.

### Table 1 : Characteristics of the selected studies

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Study type (Origin of data)</th>
<th>Study period</th>
<th>No. of patients (% women)</th>
<th>Specific characteristics</th>
<th>Mean (median) age at FTC</th>
<th>Mean (median) time (yr) between FTC and SPM/minimum latency period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rademaker 2009, France, Italy, and Sweden</td>
<td>Cohort (hospital and cancer reg)</td>
<td>1984-1997</td>
<td>5841 (71)</td>
<td>RA</td>
<td>15/2</td>
<td>5/0 (9)</td>
</tr>
<tr>
<td>Sandeep 2006, Europe, Canada, Australia and Singapore</td>
<td>Cohort (Cancer registry)</td>
<td>1943-1998</td>
<td>300 (74)</td>
<td>RA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Verhoef 2004, Netherlands</td>
<td>Cohort (Hospital)</td>
<td>1981-1997</td>
<td>2821 (70)</td>
<td>RA</td>
<td>45.5</td>
<td>6.7/9.7</td>
</tr>
<tr>
<td>Fakhfakh 2011, Iran</td>
<td>Cohort (Hospital)</td>
<td>1984-2004</td>
<td>973 (75)</td>
<td>RA</td>
<td>74.7</td>
<td>7/5.6</td>
</tr>
<tr>
<td>Lung 2012, Hong Kong</td>
<td>Cohort (Hospital)</td>
<td>1971-2009</td>
<td>895 (83)</td>
<td>RA</td>
<td>Exclusion of patients (N=96) or EBT (N=94)</td>
<td>46.4</td>
</tr>
<tr>
<td>Alsopplau 2015, Saudi Arabia</td>
<td>Cohort (Hospital)</td>
<td>2000-2012</td>
<td>823 (86)</td>
<td>RA</td>
<td>(50)</td>
<td>6/4.5/0.5</td>
</tr>
<tr>
<td>Choi 2015, Korea</td>
<td>Cohort (Cancer registry)</td>
<td>1995-2010</td>
<td>1784 (86)</td>
<td>RA</td>
<td>45.7</td>
<td>5/3</td>
</tr>
<tr>
<td>Sie 2015, Korea</td>
<td>Cohort (Health care)</td>
<td>2008-2013</td>
<td>3114 (82)</td>
<td>RA</td>
<td>Leukaemia outcome</td>
<td>48</td>
</tr>
<tr>
<td>Tang 2016, Taiwan</td>
<td>Cohort (Health registry)</td>
<td>1997-2014</td>
<td>2025 (89)</td>
<td>RA</td>
<td>&gt; 20 yrs at FTC diagnosis</td>
<td>46.6</td>
</tr>
<tr>
<td>Secco 2016, Brazil</td>
<td>Cohort (hospital)</td>
<td>1979-2009</td>
<td>413 (88)</td>
<td>RA</td>
<td>(44.6)</td>
<td>2/11</td>
</tr>
</tbody>
</table>

**Abbreviations:** FTC = first thyroid cancer; SPM = second primary malignancy; RA = radioiodine; NA = not available.

### Conclusion

Thyroid cancer survivors are at increased risk of SPMs compared with the general population.

Analyses by treatment suggest that RAI may highly contribute to this risk, but pooled analyses were not possible based on available data.

More research is needed to better characterize the risk of SPMs from RAI, including the shape and magnitude of the dose-response relationship, ideally in large studies with precise estimates of the absorbed doses to target organs.