

## 1. Level of evidence once discussing the impact of published manuscripts.

Each of published manuscripts was listed as followed. And the level of evidence was classified by standard of OCEBM (Centre for Evidence-Based Medicine, University of Oxford, OCEBM).

**Table S1.** Standardized incidence ratios of thyroid cancer after breast cancer.

Study	Location(s)	Study Period	Mean Follow-Up Period (y)	Case(n)		SIR (95% CI)
				BC	TC	
Jin 2022	Korea	2002–2013	NA	3308	84	1.91 (1.47–2.49)
Cieszyńska 2022	Poland	1996–2014	6.3	10,832	53	4.27
Bright 2019	England, Wales	1971–2006	14.3	36,236	35	1.7 (1.2–2.4)
Huang	China	1999–2013	5.4	13,978	247	6.92 (6.03–8.29)
Corso 2018	Italy	1994–2010	NA	21,527	78	1.54 (1.23–1.92)
Silverman 2017	Israel	1990–2006	10	46,090	141	1.46 (1.20–0–1.71)
Jung 2017	Korea	1989–2014	NA	3344	44	2.29 (1.67–3.08)
Hung 2016	Taiwan	1997–2011	4.28	101,493	183	2.15 (1.85–2.48)
Molina-Montes 2013	Spain	1985–2007	6.4	5897	8	1.01 (0.02–2.01)
Mellemkjær 2011	Denmark, Finland, Norway	1943–2006	8.8	304,703	347	1.41
Lee 2008	Taiwan	1979–2003	5.4	59,001	45	1.42 (1.04–1.90)
Kirova 2008	France	1981–1997	10.5	16,705	20	0.87 (0.53–1.35)
Raymond 2006	USA (SEER) Europe, Canada,	1973–2000	NA	335,191	314	2.23
Mellemkjær 2006	Australia, Singapore	1943–2000	7.2	525,527	471	1.62
Soerjomataram 2005	Netherlands	1972–2000	6.6	9919	2	0.8 (0.1–3.3)
Sadetzki 2003	Israel	1960–1998	7.3	49,207	59	1.34 (1.03–1.72)
Levi 2003	Switzerland	1974–2998	6.4	9729	6	1.01 (0.37–2.20)
Tanaka 2001	Japan	1970–1994	8.6	2786	7	3.7 (1.5–7.6)
Huang 2001	Canada	1973–1993	6.8	194,798	140	1.2 (1.0–14)
Evans 2001	England	1961–1995	5.7	145,677	37	1.05
Rubino 2000	France	1973–1992	9.5	4416	4	2.2 (0.7–5.2)
Volk 1997	Slovenia	1961–1985	7.3	8791	10	2.5 (1.2–4.6)
Doherty 1993	Scotland	1954–1964	18	3926	4	2.33 (0.63–5.95)
Murakami 1987	Japan	1965–1982	5.7	9503	9	3.2 (1.5–6.1)
Teppo 1985	Finland	1954–1979	NA	26,617	22	1.95
Harvey 1985	USA	1935–1982	6.6	41,109	28	1.6
Schenker 1984	Israel	1960–1977	NA	12,302	33	1.7

Abbreviations: BC, breast cancer; CI, confidence interval; n, number of cases (studies with n < 1000 excluded); NA, data not available; TC, thyroid cancer; y, years.

**Table S2.** Standardized incidence ratios of breast cancer after thyroid cancer.

Study	Location(s)	Study Period	Mean Follow-Up Period (y)	Case(n)		SIR (95% CI)
				BC	TC	
Jin 2022	Korea	2002–2013	NA	39	3949	1.67 (1.15–2.43)
Bright 2019	England, Wales	1971–2006	NA	170	6215	1.3 (1.1–1.5)
Lu 2013	Taiwan	1976–2006	7	102	19,068	1.42 (1.16–1.72)
Kim 2013	U.S.A	1973–2008	NA	1041	52,103	1.13 (1.06–1.20)
Consorti 2011	Italy	1996–2009	6.2	7	75	3.58 (1.14–8.37)
Mellemkjær 2006	Europe, Canada, Australia, Singapore	1943–2000	NA	552	NA	1.31 (1.21–1.43)
Verkooijen 2006	Netherlands	1985–1999	10.6	5	282	1.52 (0.46–3.18)
Berthe 2005	France	1960–1998	8	12	875	1.19 (0.62–2.08)
Rubino 2003	France, Italy, Sweden	1934–1995	13	128	6841	1.3 (1.0–1.5)
Adadj 2003	France	1934–1955	12	48	2365	1.3 (1.0–1.7)
Sadetzki 2003	Israel	1960–1998	9.4	4911	70	1.07 (0.84–1.34)
Hemminki 2001	Sweden	1958–1996	NA	113	19,281	1 (0.8–1.2)
Edhemovic 1999	Slovenia	1971–1993	5.2	4	894	1.12 (0.31–2.87)
Dottorini 1995	Italy	1960–1993	8	10	694	2
Glanzman 1992	Switzerland	1960–1988	14.5	5	298	1.9 (0.6–4.5)
Hall 1991	Sweden	1950–1975	16	24	1955	1.46
Johns 1989	U.S.A	1975–1985	2.7	5	115	8.9
Edmonds 1986	England	NR	11.2	6	258	2.37
Osterlind 1985	Denmark	1943–1980	5.9	11	1351	0.96 (0.76–1.20)
Ron 1984	USA	1935–1978	8	24	1618	1.89

Abbreviations: BC, breast cancer; CI, confidence interval; n, number of cases (studies with n < 1000 excluded); NA, data not available; TC, thyroid cancer; y, years.

**Table S3.** Level of evidence about Thyroid cancer and Breast cancer.

Study	Level of evidence	Year
Ron E et al. <sup>1</sup>	3	1984
Osterlind, A., et al. <sup>2</sup>	3	1985
Edhemović, I., et al. <sup>3</sup>	3	1998
Evans, H. S., et al. <sup>4</sup>	3	2001
Soerjomataram, I., et al. <sup>5</sup>	3	2005
Langballe, R., et al. <sup>6</sup>	3	2011
Mellemkjaer, L., et al. <sup>7</sup>	3	2006
Kim, C., et al. <sup>8</sup>	3	2013
Nielsen, S. M., et al. <sup>9</sup>	1	2016

**Table S4.** Level of evidence about Thyroid Hormone and Breast cancer.

Study	Level of evidence	Year
Tran, T et al. <sup>10</sup>	1	2020
Kapdi, C rt al. <sup>11</sup>	3	1976
Tosovic, A., et al. <sup>12</sup>	3	2012
Hellevik, A. I., et al. <sup>13</sup>	2	2009

Journy, N. M. Y., et al. <sup>14</sup>	2	2017
Kim, E. Y., et al. <sup>15</sup>	2	2019
Søgaard, M., et al. <sup>16</sup>	2	2016
Kuijpers, J. L. P., et al. <sup>17</sup>	2	2005
Ortega-Olvera, C., et al. <sup>18</sup>	4	2018
Bach, L., et al. <sup>19</sup>	4	2020
Freitas, Paula Andréa V. C. J et al. <sup>20</sup>	4	2016
Chen, S., et al. <sup>21</sup>	1	2021

Table S5. Level of evidence about Estrogen and Thyroid cancer.

Study	Level of evidence	Year
Sun, L.-M., et al. <sup>22</sup>	2	2020
Messuti, I., et al. <sup>23</sup>	3	2014
Kim, M., et al. <sup>24</sup>	2	2021
Rosenblatt, K. A., et al. <sup>25</sup>	3	2009

Table S6. Level of evidence about Autoimmune thyroid disease and Breast cancer.

Study	Level of evidence	Year
Ito, K et al. <sup>26</sup>	4	1975
Giani, C., et al. <sup>27</sup>	4	1996
Smyth, P. P., et al. <sup>28</sup>	4	1998
Turken, O., et al. <sup>29</sup>	4	2003
Giustarini, E., et al. <sup>30</sup>	4	2006
Jiskra, J., et al. <sup>31</sup>	4	2007
Graceffa, G., et al. <sup>32</sup>	3	2021
Kuijpers, J. L. P., et al. <sup>17</sup>	2	2005
Hedley, A. J., et al. <sup>33</sup>	3	1981
Pan, X.-F., et al. <sup>34</sup>	1	2020
Szychta, P., et al. <sup>35</sup>	4	2013

Table S7. Level of evidence about Oncogenic effects of the therapies for primary cancer.

Study	Level of evidence	Year
Ron, E., et al. <sup>36</sup>	3	1998
Metso, S., et al. <sup>37</sup>	2	2007
Ryödi, E., et al. <sup>38</sup>	2	2015
Kitahara, C. M., et al. <sup>39</sup>	3	2019
Melo, D. R., et al. <sup>40</sup>	3	2015
Silva-Vieira, M., et al. <sup>41</sup>	3	2017
Lin, C.-Y., et al. <sup>42</sup>	3	2016
Ko, K.-Y., et al. <sup>43</sup>	3	2015
Shim, S. R., et al. <sup>44</sup>	1	2021
de Groot, S., et al. <sup>45</sup>	4	2015
Kailajärvi, M., et al. <sup>46</sup>	4	2000

Kumar, N., et al. <sup>47</sup>	2	2004
Khan, M. A., et al. <sup>48</sup>	2	2015
Mortezaee, K., et al. <sup>49</sup>	1	2019
Rahu, K., et al. <sup>50</sup>	3	2013
Ivanov, V. K., et al. <sup>51</sup>	3	2002
Schaapveld, M., et al. <sup>52</sup>	3	2015
Grantzau, T., et al. <sup>53</sup>	2	2013
Akin, M., et al. <sup>54</sup>	3	2014
Choi, S. H., et al. <sup>55</sup>	2	2021
Darvish, L., et al. <sup>56</sup>	1	2018
Grantzau, Trine et al. <sup>57</sup>	1	2016
Reinertsen, K. V., et al. <sup>58</sup>	3	2009
Sechopoulos, I et al. <sup>59</sup>	4	2012
Yuan, M.-K., et al. <sup>60</sup>	4	2014

Table S8. Level of evidence about Genetic predisposition.

Study	Level of evidence	Year
Mucci, L. A., et al. <sup>61</sup>	2	2016
Zheng, G., et al. <sup>62</sup>	3	2017
Ngeow, J., et al. <sup>63</sup>	2	2014
Bennett, K. L., et al. <sup>64</sup>	4	2010

Table S9. Level of evidence about other factors and Breast cancer.

Study	Level of evidence	Year
Neuhouser, M. L., et al. <sup>65</sup>	2	2015
Ewertz, M., et al. <sup>66</sup>	3	2011
Engeland, A., et al. <sup>67</sup>	3	2006
Kitahara, C. M., et al. <sup>68</sup>	3	2012
He, Q., et al. <sup>69</sup>	4	2019
Hwang, Y., et al. <sup>70</sup>	4	2016
Rinaldi, S., et al. <sup>71</sup>	2	2012
Kim, H. J., et al. <sup>72</sup>	3	2013
Park, Y. M. M., et al. <sup>73</sup>	2	2021
Wang, T., et al. <sup>74</sup>	2	2021

## 2. Search criteria:

**Search statement:** ((Thyroid Neoplasms"[Mesh]) OR (((Thyroid Carcinoma\*) OR (Thyroid Cancer\*)) OR (Thyroid Neoplasm\*))) AND ((Breast Neoplasms"[Mesh]) OR (((((Breast Malignant Tumor\*[Title/Abstract]) OR (Breast Cancer\*[Title/Abstract])) OR (Breast Malignant Neoplasm\*[Title/Abstract]))) OR (Mammary Cancer\*[Title/Abstract]))) OR (Mammary Carcinoma\*[Title/Abstract])) OR (Breast Carcinoma\*[Title/Abstract]))

**Database:** Pubmed

**Time limit:** from the earliest literature archived to Sept. 30th, 2022

**Literature type:** abstract, book, dataset, reference materials were excluded

After an electronic search of PubMed was conducted in September 2022 for literature published in English. 6749 literatures were found and the duplicates were removed. Then two researchers screened the title and abstract and selected relevant literatures respectively. Finally, after reading full text of interested literatures of each parts, we wrote manuscript and cited these literatures. The following terms were used, and relevant articles were considered as well: (thyroid cancer\*), (breast cancer\*), (genetic), (obesity), (second primary cancer).

### 3. Cowden Syndrome and Cowden Syndrome-like

OMIM graphical views of phenotype-gene relationships is in PDF file named OMIM\_graphics.

#### 3.1 Phenotypic Series:

Location	Phenotype	Inheritance	Phenotype mapping key	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
<a href="#">3q26.32</a>	<a href="#">Cowden syndrome 5</a>		3	<a href="#">615108</a>	<a href="#">PIK3CA</a>	<a href="#">171834</a>
<a href="#">10q23.31</a>	<a href="#">Cowden syndrome 4</a>		3	<a href="#">615108</a>	<a href="#">KLLN</a>	<a href="#">612105</a>
<a href="#">10q23.31</a>	<a href="#">Lhermitte-Duclos disease</a>	AD	3	<a href="#">615108</a>	<a href="#">PTEN</a>	<a href="#">601728</a>
<a href="#">10q23.31</a>	<a href="#">Cowden syndrome 1</a>	AD	3	<a href="#">158350</a>	<a href="#">PTEN</a>	<a href="#">601728</a>
<a href="#">14q32.33</a>	<a href="#">Cowden syndrome 6</a>		3	<a href="#">615109</a>	<a href="#">AKT1</a>	<a href="#">601728</a>
<a href="#">14q32.33</a>	<a href="#">?Cowden syndrome 7</a>	AD	3	<a href="#">615109</a>	<a href="#">SEC23B</a>	<a href="#">610512</a>

#### 3.2 Clinical Synopsis:

##### INHERITANCE

- Autosomal dominant

##### GROWTH

###### Weight

- Obesity, increased risk of

##### HEAD & NECK

###### Head

- Progressive macrocephaly

###### Face

- 'Birdlike' facies (uncommon)
- Hypoplastic mandible (uncommon)
- Hypoplastic maxilla (uncommon)

###### Ears

- Hearing loss

#### *Eyes*

- Cataract
- Angioid streaks
- Myopia

#### *Mouth*

- Microstomia
- High-arched palate
- Scrotal tongue
- Oral papillomas

## **CARDIOVASCULAR**

#### *Vascular*

- Vascular anomalies (50% of patients)
- Intracranial developmental venous anomalies

## **CHEST**

#### *Ribs Sternum Clavicles & Scapulae*

- Pectus excavatum

#### *Breasts*

- Virginal hyperplasia
- Fibrocystic breast disease
- Gynecomastia in males
- Breast fibroadenomas

## **ABDOMEN**

#### *Gastrointestinal*

- Hamartomatous polyps
- Colonic diverticula

## **GENITOURINARY**

#### *External Genitalia (Male)*

- Hydrocele
- Varicocele

#### *External Genitalia (Female)*

- Vaginal cysts
- Vulvar cysts

#### *Internal Genitalia (Female)*

- Ovarian cysts
- Leiomyomas

## SKELETAL

*Spine*

- Scoliosis
- Kyphosis

## SKIN, NAILS, & HAIR

*Skin*

- Multiple facial papules
- Acral keratoses
- Palmoplantar keratoses
- Multiple skin tags
- Facial trichilemmomas
- Subcutaneous lipomas

## NEUROLOGIC

*Central Nervous System*

- Seizure
- Intention tremor
- Lhermitte-Duclos disease
- Mental retardation, mild to moderate (in 12%)
- Psychomotor delay, mild to moderate
- Cerebellar gangliocytoma manifesting as seizure and tremor

## ENDOCRINE FEATURES

- Goiter
- Thyroid adenoma
- Hyperthyroidism
- Hypothyroidism
- Thyroiditis
- Enhanced insulin sensitivity

## IMMUNOLOGY

- Primary immunodeficiency (in some patients)
- Recurrent infections (in some patients)
- Opportunistic infections (in some patients)
- Hypogammaglobulinemia (in some patients)
- Lymphopenia (in some patients)
- Inverted CD4/CD8 T cell ratio (in some patients)
- Decreased memory B cells (in some patients)
- Decreased class-switched B cells (in some patients)

## **NEOPLASIA**

- Breast cancer
- Ovarian carcinoma
- Cervical carcinoma
- Uterine adenocarcinoma
- Thyroid cancer (follicular cell)
- Transitional cell carcinoma of the bladder
- Meningioma
- Mucosal neuromas

## **MISCELLANEOUS**

- Symptoms usually occur in adults
- Skin lesions are fully penetrant by second decade
- Skeletal abnormalities are variable
- Allelic to Bannayan-Riley-Ruvalcaba syndrome ([153480](#)), which has an earlier age at onset
- Approximately 80% of CS patients have PTEN mutations

## **MOLECULAR BASIS**

- Caused by mutation in the phosphatase and tensin homolog gene (PTEN, [601728.0001](#))

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- Cancer Receiving or Not Receiving  $^{131}\text{I}$  Treatment: A Nationwide Population-Based Cohort Study. *J Nucl Med*. 2016;57(5):685-690.
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