Thyroid and renal cancers: A bidirectional association

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There is a deep interrelation between the thyroid gland and the kidney parenchyma, with dysfunction of the first leading to significant changes in renal metabolism and vice versa. Given the recognition of cancer as a systemic disease, the raise of thyroid tumors and the common association of several malignancies, such as breast cancer, prostate cancer, colorectal cancer, and other, with an increased risk of kidney disease, public health alert for these conditions is warranted. A systematic review of the current evidence on the bidirectional relationship between thyroid and renal cancers was conducted including 18 studies, highlighting patient’s characteristics, histology, time for secondary malignancy to develop from the first diagnosis, treatment, and follow-up. A total of 776 patients were identified; median age was 64 years (range: 7–76 years). Obesity and family history were identified as the most common risk factors, and genetic susceptibility was suggested with a potential strong association with Cowden syndrome. Controversy on chemo and radiotherapy effects was found, as not all patients were previously exposed to these treatments. Men were more likely to develop kidney cancer after a primary thyroid malignancy, with 423/776 (54%) experiencing renal disease secondarily. Median time after the first malignancy was 5.2 years (range: 0–20 years). With the advancement of current oncological therapy, the prognosis for thyroid cancer patients has improved, although there has been a corresponding rise in the incidence of multiple secondary malignancy within the same population, particularly concerning the kidney. Surgery can achieve disease-free survival, if surveillance follow-up allows for an early localized form, where radical treatment is recommended.

KEYWORDS
thyroid cancer, renal cancer, multiple cancer, cancer surveillance and screening, cancer risk

Abbreviations: ccRCC, clear cell renal cell carcinoma; CS, Cowden syndrome; PTC, papillary carcinoma of the thyroid; RCC, renal cell carcinoma; TC, thyroid cancer.
Introduction

Thyroid cancer (TC) is one of the most rapidly increasing malignancies in Western countries, with an annual incidence rate of 5.4% in men and 6.5% in women (1). Much of this rise is largely due to early detection using more sensitive diagnostic procedures, including Artificial Intelligence, performed for other medical reasons and able to identify incidental small thyroid nodules, otherwise missed (2–4). Certain risk factors for TC are female sex, family history of TC, radiation exposure, lymphocytic thyroiditis, and reduced iodine intake (5, 6). On the basis of the histological and the clinical behavior, TCs are divided into well differentiated and poorly differentiated; well differentiated TCs include the papillary and follicular histotypes (7). Surgery, either lobectomy or total thyroidectomy, represents the standard therapeutic approach for well differentiated TC; radioactive iodine therapy is recommended for high-risk patients (5). Ablation and active surveillance are of increasing importance in patients who refuse surgery or are unfit for.

Improvements in the detection of TC and therapeutic strategies have likewise resulted in a more favorable course for this disease. Because the mortality rates for TC remained stable at around 0.5 deaths per 100,000, the number of patients surviving is on the rise (8, 9).

On the other hand, renal cancer, or renal cell carcinoma (RCC), is the 9th common cancer in men and the 14th one in women. RCC frequently presents incidentally; in fact, it is asymptomatic in most cases. Therefore, the diagnosis of patients with localized renal cancer, which is potentially treatable only with surgery or ablation, is almost always accidental (10). Identified risk factors include male sex, smoking tobacco, obesity, and hypertension (10, 11). RCC comprises an heterogeneous group of histological subtypes: Clear cell renal cell carcinoma (ccRCC), papillary, and chromophobe are the most common solid RCC (11). Nephron-sparing surgery or partial nephrectomy has evolved as the standard of care in patients with localized RCC; ablation and active surveillance are traditionally alternatives for patients who are unfit for surgery (11).

Thyroid interrelation with the kidney is well known (12); on the one hand, this gland is necessary for renal cells growth and for the maintenance of hydro-electrolyte homeostasis; on the other hand, the kidney eliminates thyroid hormones and regulates their serum level. There is therefore a deep interrelation among the two organs, with thyroid dysfunction causing significant changes to renal metabolism and vice versa (13).

Cancer is a systemic disease, and many common cancers, such as breast cancer, prostate cancer, colorectal cancer, and other, are associated with an increased risk of kidney cancer development, especially within the first 5 years after their diagnosis (14). Because the risk of second cancers after the diagnosis of primary TC is elevated (15), too, the aim of this manuscript is to review the current state of knowledge on the interrelationship between thyroid and renal cancers.

Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) (16). The search was run in February 2022 across PubMed, Web of Science, and Scopus databases and was restricted to articles written in English only. References were cross-checked for additional relevant studies. The retrieved lists were exported to a reference manager (EndNote™) to eliminate duplicates, as shown in Figure 1.

Keywords “thyroid cancer” and “renal cancer” were used to include studies evaluating TC characteristics in patients previously affected by kidney cancer or kidney cancer characteristics in patients previously affected by TC. Reports of metastases were excluded from the analysis.

The research was performed by two independent investigators; subsequently, the results were compared and combined; in case of disagreement on the value of the selected
papers, an additional comparison was crucial in the decision-making process. Only published literature was included, and no date limits have been set. Only English language articles were included; reviews, editorials, and repeated or redundant manuscripts were excluded. Only registry analyses and retrospective studies, mostly case reports, were found and included in the present review.

Data extraction was performed thereafter, including the details of title, authors, date of publication, country, research design, patients’ characteristics, and outcomes.

A risk of bias assessment was performed using the Newcastle–Ottawa Scale quality assessment star system (Table 1), in which a paper is judged on the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or the outcome of interest for case control or cohort studies, respectively (24).

### Results

A total of 3,290 manuscripts were retrieved from the search; following exclusion based on title and abstract screening (n = 3,020) and after full text read (n = 48), the remaining studies included in the review were 18 (Table 2). The majority (11/18) were case reports. A total of 776/64,187 patients were identified.

### Patients’ characteristics

Median age was 64 years (range: 7–76 years). The association of thyroid and renal malignancies was more often observed in the male population. After evaluating the time between the two malignancies for all the studies included in the review, in no case, a significant difference was detected: The median interval

| Table 1 Newcastle–Ottawa Scale (NOS) quality assessment star system. |
|-------------------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| **COHORT STUDY**                                | Selection        | Comparability    | Outcomes         | Total            |
| Article                                         |                  |                  |                  |                  |
| Selection of nonexposed cohort                  |                  |                  |                  |                  |
| Representativeness of exposed cohort             |                  |                  |                  |                  |
| Ascertainment of exposure                       |                  |                  |                  |                  |
| Outcome not present at the start of the study   |                  |                  |                  |                  |
| Canchola et al. (17)                            | ☆                 | ☆                 | ☆                 | ☆                 | ☆                 | 9/9               |
| CASE CONTROL                                    |                  |                  |                  |                  |
| Article                                         | Selection        | Comparability    | Outcomes         | Total            |
| Case Definition                                 |                  |                  |                  |                  |
| Representativeness of the Cases                 |                  |                  |                  |                  |
| Selection of Controls                           |                  |                  |                  |                  |
| Definition of Controls                          |                  |                  |                  |                  |
| Comparator                                     |                  |                  |                  |                  |
| Ascertainment of Exposure                       |                  |                  |                  |                  |
| Murray, et al. (20)                             | ☆                 | ☆                 | ☆                 | ☆                 | ☆                 | 9/9               |
| Murray S, et al. (21)                           | ☆                 | ☆                 | ☆                 | ☆                 | ☆                 | 9/9               |
| Ngeow, et al. (22)                              | ☆                 | -                 | ☆                 | ☆                 | ☆                 | 7/9               |

The stars mean the grading according to the Newcastle-Ottawa scale.
| Article                        | Year | Type of study | Case | Sex | Age | Histology | Genetic syndrome | Risk factors | Thyroid cancer | Interval to second cancer | Conclusion                                                                 |
|-------------------------------|------|---------------|------|-----|-----|-----------|------------------|--------------|----------------|----------------------|---------------------------------------------------------------------------|
| Abdel-Rahman (14)             | 2017 | Case control  | 341/9861 | N/A | N/A | N/A       | N/A              | Treatment factors (radiation) Common etiology factors (smoking) Rare hereditary cancer syndromes | Primary | 5 years | Beyond 5 years, patients with primary thyroid cancer have an enhanced risk to develop a second primary kidney cancer. This link may be an expression of a particular genetic makeup determining patients’ susceptibility to both cancers. |
| Albores-Saavedra, et al. (25) | 2014 | Case report   | 2/2   | F   | 72  | 54        | Papillary urothelial carcinoma and PTC | N/A          | No specific risk factors were identified. | Second | 14 years | These malignant neoplasms do not apparently share similar risk factors. |
| Antonelli, et al. (18)        | 2012 | Case control  | 15/285 | N/A | N/A | N/A       | N/A              | No specific risk factors were identified. | Second | N/A    | The risk of development of a second neoplasm in patients with RCC increases with aging. |
| Canchola et al. (17)          | 2005 | Cohort study  | 16/10932 | F   | 55  | PTC and RCC not otherwise specified | N/A          | Obesity increases the risk of both thyroid and kidney cancer | Primary | 3 years | Increased surveillance is warranted for kidney cancer among women with thyroid cancer. |
| Carhill et al. (19)           | 2014 | Case control  | 117/23514 | N/A | N/A | Papillary thyroid carcinoma (85%) and ccRCC (79%) | N/A          | Genetic susceptibility, implication of clinical therapy | N/A     | 6 years | The association between thyroid and kidney cancer needs further investigation. |
| Oh, et al. (26)               | 2015 | Case report   | 1/1   | M   | 50  | ccRCC and PTC | N/A          | Family history of thyroid cancer | Synchronous | 0       | No specific risk factor or genetic syndrome were identified. |
| Atta, et al. (27)             | 2016 | Case report   | 1/1   | F   | 76  | ccRCC and PTC | No mutations were detected | Family history of colon, lung, kidney and thyroid cancer. | Primary | 14 years | No genetic mutation was detected, despite the family history. |
| Kim, et al. (15)              | 2020 | Case report   | 1/2   | M   | 22  | Chromophobe RCC and PTC | Cowden syndrome (CS) | Family history of kidney and thyroid cancer. | Primary | 12 years | Thyroid neoplasmia and RCC are minor diagnostic criteria for CS. |
| Klain, et al. (28)            | 2021 | Case report   | 1/2   | M   | 64  | ccRCC and PTC | N/A          | No specific risk factors were identified. | Second | 20 years | No specific risk factor or genetic syndrome were identified. |
| Ma, et al. (29)               | 2014 | Case report   | 1/1   | F   | 35  | cRCC+ SFT and PTC + follicular thyroid carcinoma | N/A          | Negative family history of neoplasia | Synchronous | 0       | No specific risk factor or genetic syndrome were identified. |
| Malchoff et al. (30)          | 1999 | Family report | 31/31 | N/A | N/A | Papillary renal carcinoma and PTC | Mutation of a gene that maps to 1q21 | No specific risk factors, except for | N/A     | N/A    | Familial association of PTC with papillary renal neoplasmia defines a distinct familial tumor syndrome. |

(Continued)
between first and second cancer was 5.2 years (range: 0–20 years).

Most patients presented a TC as first primary malignancy (423 out of 776; 54%), and 110 patients (14%) developed a TC as second primary malignancy; a renal tumor was synchronous in only six patients out of 776 (0.78%).

**Histopathological characteristics**

With regards to histology, the papillary phenotype of TC was found in all patients. Sporadic cases of follicular carcinoma (29) and medullary (32) thyroid carcinoma have also been identified; however, both of them were also associated with a papillary thyroid carcinoma. On the contrary, with regards to renal carcinoma, a greater variety was observed concerning histology. In the series evaluated, the most represented type was ccRCC; however, sporadic cases of other renal malignancy cases were also reported, namely, urothelial (25), chromophobic (34), and papillary renal carcinoma (30).

**Sex**

With regard to TC, female sex was universally identified as a risk factor (17, 20); on the contrary, male sex is associated to the
development of RCC (17). From the report by Van Fossen et al. (23), female TC patients had a twofold increase in the prevalence of a subsequent renal cell cancer (23), and female renal cell cancer patients had a 1.5-fold increase in the prevalence of TC; male patients with TC had 4.5-fold prevalence increase of subsequent RCC, and male patients with RCC had an increased threefold prevalence of subsequent TC. Male sex emerged as a risk factor of association between thyroid and kidney cancers (18).

Common identified risk factors

Identified common risk factors between thyroid and kidney cancers are few (19, 25), with obesity remaining a unique denominator to develop malignancy in general and in particular for these two; see Figure 2. Family history (29) of both cancers is also well recognized, and as previously mentioned, male sex as well as aging increased the risk to develop both cancers and, in particular, RCC (18).

Although radiation exposure is a known risk factor for the development of neoplasms and, in particular, for TC, no correlation between radiotherapy and the development of both TC and renal cancer was identified in any of the studies included in the review. Murray et al. (21) observed, in fact, that only 35% of patients with TC and an additional primary cancer, whether it is RCC or not, reported radiation exposure in their medical history. Given the recognized increased risk of TC following other primary malignancies, particularly RCC, it seems unlikely that the increased incidence could be due to the carcinogenic effect of radiations (14).

Although many chemotherapeutic agents are known to be carcinogenic, the patients have not undergone chemotherapy, and it is therefore not possible to evaluate the carcinogenic effects of these drugs.

Genetic syndrome

TC is associated with a heterogeneous pattern of genetic mutations involving the mitogen-activated protein kinase (MAPK) pathway (6). The main genetic mutations are represented by the oncogenes RAS and BRAF; in particular, BRAFV600E is present in about half of the PTCs (35).

Excluding the familial forms of medullary thyroid carcinoma, such as familial medullary thyroid carcinomas and multiple endocrine neoplasia (MEN), the familial forms of thyroid carcinoma are numerous and can be divided into syndromes with a prevalence of non-thyroid neoplasms and syndromes with a prevalence of TC. The first group includes also familial adenomatous polyposis, Cowden syndrome (CS), Werner syndrome, Carney complex, and Pendred syndrome; the second group includes pure familial papillary thyroid carcinoma with or without oxyphilia and familial papillary thyroid carcinoma with papillary RCC or with multinodular goiter (36).

There are also numerous genetic alterations involved in the development of RCC, in particular, the most important mutations involving the tumor-suppressor Von Hippel-Lindau (VHL), observed in about 80% of ccRCC (9). Hereditary forms of RCC include von Hippel-Lindau syndrome, hereditary papillary RCC, Birt-Hogg-Dube syndrome, hereditary leiomyomatosis, and tuberous sclerosis (11).

The link between thyroid and kidney cancer may be an expression of genetic makeup that increases patients’ susceptibility to both malignancies (26, 27). Although this
Thyroid carcinoma is one of major diagnostic criteria for development of a variety of tumors, both benign and malignant tumor suppressor gene. This syndrome is associated with the Phosphatase and tensin homolog (PTEN)-hamartoma tumor syndrome, a disorder caused by a germline mutation of PTEN, a tumor suppressor gene. This syndrome is associated with the development of a variety of tumors, both benign and malignant (11): Thyroid carcinoma is one of major diagnostic criteria for CS, whereas RCC is part of the minor criteria.

PTEN mutation, even in the absence of the CS, was identified as risk factor (22), with Integrin αvβ6 positively expressed in multiple primary cancer, among which TC and RCC (31). The genetic mutation 1q21 (30) was identified in forms where PTC was associated to papillary renal neoplasia tumors, highlighting in this way a peculiar familial tumor syndrome (Table 2).

**Time of second cancer occurrence**

According to the analysis of the data presented in Table 2, the median interval between first and second cancer was 5.2 years (range: 0–20 years), with no substantial difference in the time interval considering one or the other cancer as the first presented.

**Treatment and follow-up**

For both thyroid and kidney cancers, treatment of choice was represented by surgical excision (28), with no differences if they were primary, synchronous, or second malignancies. In most cases, the selected patients were affected by localized neoplasms; thus, no need for systemic therapy was required. Furthermore, as they were detected at an early stage, surgery had a curative effect. In case of synchronous malignancy, radical nephrectomy first and then total thyroidectomy with lymphadenectomy were carried out (33).

In general, management of PTC remained equivalent, regardless of whether or not the patient had a synchronous or antecedent non-thyroidal neoplasia (21).

In most of the reported cases, the second cancer was identified during follow-up, except for the few cases of synchronous tumors, for which the pre-operative investigations made it possible to identify the second neoplasm at an earlier stage (33). In consideration of the increased risk of developing a second tumor after the primary cancer, all the authors recommended to keep this risk in mind during the follow-up of thyroid and kidney malignancies.

**Discussion**

The present review evaluated the association between thyroid and renal cancers, regardless of which cancer occurred first, highlighting that each primary thyroid or renal malignancy increases the relative risk of subsequent malignancy in the remnant organ of the survived patients. This applies to both sexes, particularly relevant in men (23), even if other reports document an increase only in treated female TCs (37).

Although there is a risk of a second primary tumor following primary invasive neoplasms and, specifically, there is a reciprocal association between thyroid and renal cancers, the estimated risk for the development of both cancers is low, with an incidence of about 1% according to Van Fossen et al. (23) For this reason, it is not considered necessary to include diagnostic screening tests in the follow-up of these neoplasms, compared with what is already foreseen for general population. If a more targeted preventive screening is deemed appropriate (7, 38, 39) in the presence of additional risk factors, ultrasound scans of the neck and kidneys may be indicated.

A bidirectional association between thyroid and renal cancers can be explained by shared genetic and/or common environmental risk factors including recognized etiological factors (i.e., smoking and obesity), or rare genetic syndromes predisposing to both events and regardless of the use of any forms of radiation treatment (14). Furthermore, individuals who develop both thyroid and renal carcinomas may represent a unique subset of cancer patients (19). TC is associated with a number of genetic mutations leading to a different aggressive behavior. BRAF and RAS rearrangements remain the principal onco genes, although other mutations, namely, TERT promoter and in TP53, as well as PIK3CA–PTEN–AKT–mTOR pathway and SWI–SNG complex (40), synergistically concur to worse outcomes and can be used in tumor prognostication (41). In the case of medullary carcinoma, RET mutation is commonly identified, supporting a distinct clonal origin in the case of a coexisting papillary tumor, as different cellular types might be affected simultaneously (42, 43).

The majority of renal carcinomas are sporadic, and numerous are the genetic alterations involved; in particular, the most important mutations involve the tumor-suppressor VHL, observed in about 80% of ccRCC (9). A genetic predisposition accounts for around 4% of the incidence of this malignancy; namely, in people affected by von Hippel-Lindau disease, hereditary papillary renal cancer, hereditary leiomyomatosis and renal cancer, and Birt-Hogg-Dube syndrome. Other studies have also proposed possible genetic correlations between thyroid and renal cancers; Malchoff et al. (30) identified a distinct familial tumor syndrome linked to a germline mutation in chromosome...
1q21 and characterized by a familial association of papillary
TC, nodular thyroid disease, and papillary renal neoplasia.
TC of follicular origin and renal cancer have also been found
with greater frequency in CS, a hereditary cancer syndrome
associated with a germline mutation in PTEN (44) and
characterized by the presence of multiple hamartoma and
dermatologic manifestations such as acral keratosis and facial
trichilemmomas. For CS, thyroid carcinoma is one of the
major diagnostic criteria, whereas RCC is part of the
minor criteria.

Interestingly, as our review reported, the phenomenon of
increased genetic instability and reduction of tumor immunity
in multiple cancer patients was confirmed by the case of the
woman with medullary, papillary, and RCC (32), a very rare
combination, where even if the patient had no previous
endocrine history, her mother was affected by breast cancer,
another disease deeply connected to TC (4, 45–47) and the
brother presented with RCC, too. A triple malignant tumor was
also reported in a male of the same age with thyroid, kidney,
and colon being affected (31), demonstrating common
expression paths with integrin avß6 in multiple primary
cancers. A bidirectional association between thyroid and renal
cancers has been identified and can be explained by shared
genetic and common environmental risk factors. Even if there is
an association, the coexistence of primary thyroid and RCC is rare.
The standard treatment for both thyroid and kidney cancers
remains surgery, which does not need to be associated with
adjuvant therapies in the early stages, and the follow-up does not
require special attention from clinicians or screening tests, except in
cases of known genetic syndromes.

Of note, the incidence of RCC in patients with known
PTEN mutations is rare (44). In fact, the association between kidney
cancer and PTEN mutations is not supported by many studies
and may not be as well-documented as previously believed.

Conclusions

As for TC, the advancement of diagnostic methods has led to an
early treatment and an improvement in prognosis; in the same way,
for kidney cancer, the increase in the diagnosis of neoplasms in the
early stages has led to an increased survival; therefore, there has
been a corresponding rise in the incidence of multiple primary
cancers. A bidirectional association between thyroid and renal
cancers has been identified and can be explained by shared
genetic and common environmental risk factors. Even if there is
an association, the coexistence of primary thyroid and RCC is rare.
The standard treatment for both thyroid and kidney cancers
remains surgery, which does not need to be associated with
adjuvant therapies in the early stages, and the follow-up does not
require special attention from clinicians or screening tests, except in
cases of known genetic syndromes.

Data availability statement

The original contributions presented in the study are
included in the article. Further inquiries can be directed to the
 corresponding author.

Author contributions

Conceptualization: MB, EL, SS and DP. Methodology: MB,
SS, FF, AL, DT, MA and MV. Investigation and Data
curation: EL, DP, VC, VD, EB and SU. Writing—original draft
preparation: MB and EL. Writing—review and editing: MB,
EL, SS, DP, FF, AL, DT, MA, MV, VC, EB and SU. Supervision:
SS, DP, FF, SU and AL. All authors contributed
to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the
absence of any commercial or financial relationships that could
be construed as a potential conflict of interest.
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