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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Association of Thyroid, Breast and Renal Cell Cancer: A Population-based Study of the Prevalence of Second Malignancies

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ABSTRACT

Background. Analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results data has shown that the incidence of thyroid cancer is higher in patients with a preexisting malignancy and that the incidence of other malignancies is higher in patients with thyroid cancer. The purpose of this study was to evaluate the prevalence of a second malignancy in patients treated for thyroid, breast or renal cell cancer and determine what associations, if any, exist between these cancers.

Methods. This study utilized the novel data system, Explorys, as its population base. Patient cohorts were constructed using ICD-9 codes, and prevalence rates were obtained for each cancer. Rates of second malignancy were obtained and compared to the baseline prevalence for a particular malignancy.

Results. Female thyroid cancer patients had a 0.67- and twofold increase in prevalence of a subsequent breast and renal cell cancer. Female breast and renal cell cancer patients had a twofold and 1.5-fold increase in the prevalence of thyroid cancer, respectively. Male patients with thyroid cancer had a 29- and 4.5-fold increase in prevalence of subsequent breast and renal cell cancer. Male patients with breast and renal cell cancer had an increased prevalence of subsequent thyroid cancer, 19- and threefold, respectively.

Conclusions. Our study demonstrated a bidirectional association between thyroid, breast and renal cancer in both male and female patients. This may have important implications for patient follow-up and screening after treatment of a primary cancer.

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In the last decade, the incidence of thyroid cancer has increased by 34 % in women and 17 % in men and the annual percentage increase of thyroid cancer is higher than any other malignancy.[1,2] On January 1, 2009, in the US there were ~496,901 people alive with a history of thyroid cancer, 108,920 men and 387,981 women.[1] Thyroid cancer is now the fifth most common cancer in women.[3]

According to Surveillance, Epidemiology and End Results (SEER) Cancer Registry data, the cumulative incidence of developing a second malignancy in a patient with thyroid cancer is 16 % at 25 years.[4] There are reports suggesting that a unidirectional or bidirectional association may exist between thyroid, breast and renal cell cancer.[4–26] A unidirectional association is defined as a one-way relationship between two cancers; that is, having a primary cancer increases the relative risk of a subsequent cancer, but the converse is not true. A bidirectional association implies a two-way or reciprocal relationship between two cancers regardless of which cancer occurred first. Each primary malignancy can increase the relative risk of developing a second malignancy. Breast cancer is the most common second primary cancer among thyroid cancer survivors, followed by renal cell cancer.[7]

The purpose of this study was to evaluate the prevalence of a second malignancy in patients treated for thyroid, breast, or renal cell cancer and determine if either a unidirectional or bidirectional association exists between malignancies.

METHODS

A novel population-based data system, Explorys, Inc. (Cleveland, OH; http://www.explorys.com), was used to evaluate the prevalence and possible reciprocal association of thyroid, breast and renal cell cancer. Explorys is a commercially available analytics platform that standardizes statistically deidentified inpatient and ambulatory data from the electronic medical record systems of a network of participating provider organizations to form the Explorys "universe." At the time we prepared this article, the following institutions were utilizing Explorys: Cleveland Clinic Foundation, MetroHealth Medical Center, Summa Health System and University Hospitals of Cleveland in northeast Ohio; Medstar Health in Washington, DC, St. Joseph Hospital System in Southern California and Lancaster General Health in Pennsylvania which accounts for the 11,541,080 patients in this study. Data are securely imported through the electronic medical record and can be followed longitudinally for research purposes and outcomes. Because all of the data are deidentified, the study was exempt from institutional review board approval. On average, each patient has an electronic medical record covering 1,040 days (range 1–4,539 days over 12 years from 1999 to 2011). Explorys is a dynamic system with an ever-increasing population number as more patients, hospitals and health care systems are incorporated into the universe. A Population Explore application allows investigators to explore and retrieve information and save it as a static cohort for research purposes.

Cohorts of patients with thyroid, breast, renal cell and bladder cancer were created using this application. Bladder cancer was used as a control cohort since there is no previously identified association with thyroid cancer.[12,25] Cohorts were constructed by entering demographic criteria and ICD-9 codes to search 11,541,080 individual patient records. The following ICD-9 codes were used to identify the cohorts: 193, primary malignant neoplasm of the thyroid; 174 and 175, primary malignant neoplasm of the female and male breast, respectively; 189.0, primary malignant neoplasm of the kidney; and 188, malignant tumor of the bladder. Prevalence rates across the universe were obtained for thyroid, breast, renal cell and bladder cancer and were further stratified by gender. This data was saved as a static cohort to maintain the same patients throughout the study period.

Each cancer cohort was queried to look for the development of subsequent malignancies. To capture a secondary cancer after a primary cancer, a preexisting exclusion group was added as a criterion to exclude patients with an individual cancer diagnosis (thyroid, breast, renal cell or bladder cancer) prior to the primary cancer. This allowed us to determine the number of patients with each primary cancer who subsequently developed a secondary cancer (Table 1). The prevalence of second malignancies was determined and was compared to the baseline prevalence of that particular malignancy in the universe (Figs. 1, 2, 3a, b).

The prevalence of a second malignancy was also determined separately for male and female patients and was compared to the total male and female patients in the universe. Gender data was missing in ~5,300 patients and they were excluded from the analysis. In order to help ensure patient data deidentification and security, it is the practice of Explorys, Inc. to round patient numbers to the nearest tenth in the database. This practice was instituted in order to ensure HIPAA compliance for small cohorts of patients with a rare cancer or disease who could potentially be reidentified by a health care provider. Larger cohorts of patients are rounded to the nearest tenth in order to maintain consistency throughout the system.

In order to validate the larger population database, an internal control utilizing the Explorys system was conducted on active patients, defined as patients with a documented encounter in a participating network organization within the past 3 years and a diagnosis of thyroid, breast, renal cell or bladder cancer. These active patients also had 3 or more years of documented follow-up to evaluate the prevalence of a second malignancy (Table 2), which is important since newer patients to the system may not have had time to develop a second malignancy.

RESULTS

At the time of this study, there were 11,541,080 patients in the Explorys universe, 6,308,430 (55 %) female (F) subjects and 5,228,040 (45 %) male (M) subjects. A total of 15,940 patients had a diagnosis of thyroid cancer, for an overall prevalence of 0.1 % (12,210 F, 0.2 %, 3,720 M, 0.1 %); 74,650 patients had breast cancer, for an overall prevalence of 0.6 % (73,510 F, 1.2 %, 510 M, 0.01 %); 20,400 patients had renal cell cancer, for an overall prevalence of 0.2 % (7,810 F, 0.1 %, 12,590 M, 0.2 %); and 21,070 patients had bladder cancer, for an overall prevalence of 0.2 % (5,610 F, 0.1 %, 15,460 M, 0.3 %).

Female Patients

When we looked at our female patients specifically, of the 12,210 female patients with thyroid cancer, 240 (2.0 %) developed breast cancer, 20 (0.2 %) had a subsequent renal cell cancer and 20 (0.2 %) had a subsequent bladder cancer. This is compared to only 1.2, 0.1 and 0.1 % of all

TABLE 1 Cancer Prevalence Rates: Baseline prevalence of primary cancers in the Explorys database "universe" compared to prevalence of secondary cancers

Primary cancer type	Total # male/ female patients	Total # of pateints (universe)	% Baseline prevalance	Male patients only	Total # of male patients	% Baseline prevalence	Female patients only	Total # of female patients	% Baseline prevalence
Thyroid	15,940	11,541,080	0.10 %	3,720	5,228,040	0.10 %	12210	6,308,430	0.20 %
Breast	74,650	11,541,080	0.60 %	510	5,228,040	0.01 %	73510	6,308,430	1.20 %
Renal	20,400	11,541,080	0.20 %	12,590	5,228,040	0.20 %	7810	6,308,430	0.10 %
Bladder	21,070	11,541,080	0.20 %	15,460	5,228,040	0.30 %	5610	6,308,430	0.10 %
Primary to second cancer	Total # male/ female patients with secondary cancer	Total number primary cancer	% Prevalance secondary cancer	# Male patients secondary cancer	Total # males with primary cancer	% Prev secondary cancer	# Female patients secondary cancer	Total # of females with primary cancer	% Prevalence secondary cancer
Thyroid:breast	250	15,940	1.60 %	10[a]	3,720	0.30 %	240	12,210	2.00 %
Thyroid:renal	60	15,940	0.40 %	40	3,720	1.10 %	20	12,210	0.20 %
Thyroid:bladder	40	15,940	0.30 %	20	3,720	0.50 %	20	12,210	0.20 %
Bladder:thyroid	30	21,070	0.10 %	20	15,460	0.10 %	20	5,610	0.40 %
Bladder:renal	740	21,070	3.50 %	520	15,460	3.40 %	220	5,610	3.90 %
Bladder:breast	210	21,070	1.00 %	30	15,460	0.20 %	180	5,610	3.20 %
Breast:thyroid	340	74,650	0.50 %	10[a]	510	2.00 %	330	73,510	0.40 %
Breast:renal	310	74,650	0.40 %	20	510	3.90 %	290	73,510	0.40 %
Breast:bladder	250	74,650	0.30 %	30	510	5.90 %	220	73,510	0.30 %
Renal:breast	250	20,400	1.20 %	10[a]	12,590	0.10 %	220	7,810	2.80 %
Renal:thyroid	80	20,400	0.40 %	50	12,590	0.40 %	40	7,810	0.50 %
Renal:bladder	770	20,400	3.80 %	530	12,590	4.20 %	240	7,810	3.10 %

Prev prevalence

[a] Numbers rounded to the nearest 10th to maintain compliance within Explorys

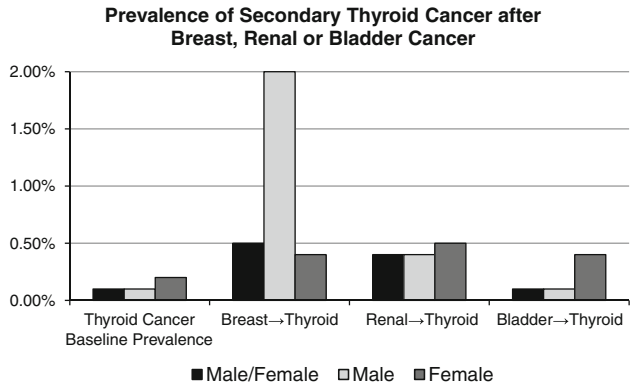


FIG. 1 Thyroid Cancer Baseline Prevalence compared to Secondary Thyroid Cancer after Breast, Renal or Bladder Cancer

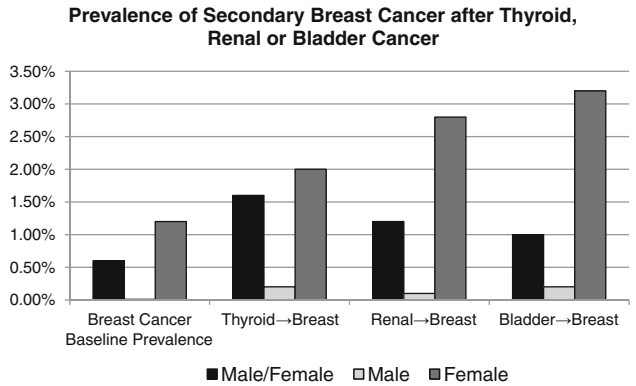
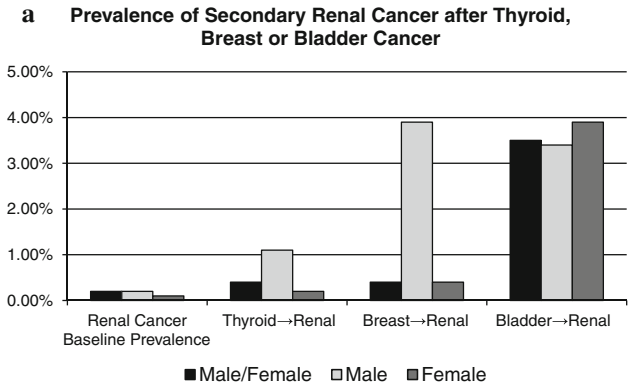


FIG. 2 Breast Cancer Baseline Prevalence compared to Secondary Breast Cancer after Thyroid, Renal or Bladder Cancer



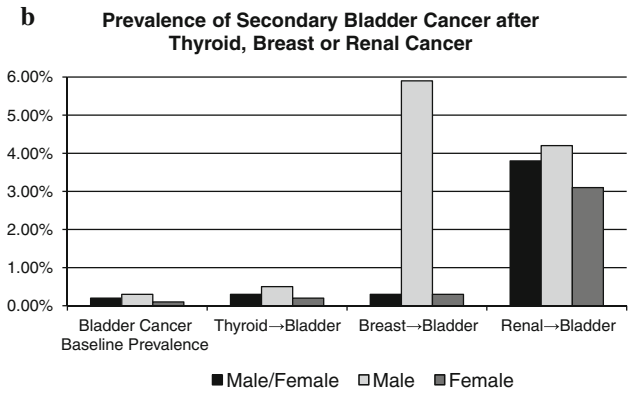


FIG. 3 **a** Renal Cancer Baseline Prevalence compared to Secondary Renal Cancer after Thyroid, Breast or Bladder Cancer. **b** Bladder Cancer Baseline Prevalence compared to Secondary Bladder Cancer after Thyroid, Breast or Renal Cancer

female patients in the universe for these 3 malignancies. Of the 73,510 female patients with breast cancer, 330 (0.4 %) developed thyroid cancer, 290 (0.4 %) subsequently developed renal cell cancer and 220 (0.3 %) developed bladder cancer compared to 0.2, 0.1 and 0.1 % of female patients in the universe. Of the 7,810 female patients with a history of renal cell cancer 220 (2.8 %) developed breast cancer, 40 (0.5 %) had a subsequent thyroid cancer and 240 (3.10 %) had a subsequent bladder cancer compared to 1.2, 0.1 and 0.1 % of female patients in the universe. Of the 5610 female patients with bladder cancer, 20 (0.4 %) developed thyroid cancer, 220 (3.9 %) developed renal cell cancer and 180 (3.2 %) developed breast cancer, compared to 0.2, 0.1 and 1.2 % of female patients with these malignancies in the universe.

Male Patients

Of the 3720 male patients with thyroid cancer, 10 (0.3 %) developed a subsequent breast cancer, 40 (1.1 %) developed a subsequent renal cell cancer and 20 (0.5 %) developed a subsequent bladder cancer compared to 0.01, 0.2 and 0.3 % respectively, for all male patients in the universe. Of the 510 male patients with breast cancer, 10 (2.0 %) developed thyroid cancer, 20 (3.9 %) subsequently developed renal cell cancer and 30 (5.9 %) developed a subsequent bladder cancer compared to 0.1, 0.2 and 0.3 % of male patients in the universe. Of the 12,590 male patients with renal cell cancer, 10 (0.1 %) developed breast cancer, 50 (0.4 %) subsequently developed thyroid cancer and 530 (4.2 %) developed bladder cancer, compared to 0.01, 0.1 and 0.3 % respectively, of male patients in the universe. Of the 15,460 male patients with bladder cancer, 20 (0.1 %) developed a subsequent thyroid cancer, which was the same for all male patients in the universe; however, 520 (3.4 %) and 30 (0.2 %) subsequently developed renal cell and breast cancer, respectively, compared to only 0.2 and 0.01 % of male patients in the universe.

Trends in the internal control group within the Explorys system over the 3 years of follow-up were similar to our overall findings in the entire universe with the exception of bladder cancer patients having a higher subsequent prevalence of thyroid cancer in both genders (Table 2).

TABLE 2 Subset of cancer prevalence rates over a defined 3-year period of time in Explorys database

	Total # patients	% Baseline prevalence	Male patients only	% Baseline prevalence	Female only	% Baseline prevalence
Total # active patients	6,068,770		2,664,870		3,397,560	
Thyroid cancer	17,510	0.29 %	4,420	0.17 %	13,090	0.39 %
Breast cancer	88,810	1.46 %	1,240	0.05 %	87,570	2.58 %
Renal cell cancer	17,340	0.29 %	10,500	0.39 %	6,840	0.20 %
Bladder cancer	19,810	0.33 %	14,580	0.55 %	5,230	0.15 %
	Total # patients	Total rate male + female	# Male patients only	Male rate	# Female patients only	Female rate
Thyroid cancer with 3+ years follow-up	4,940		1,090		3,850	
Leading to primary kidney	40	0.81 %	20	1.83 %	20	0.52 %
Leading to primary breast	180	3.64 %	10	0.92 %	170	4.42 %
Leading to primary bladder	30	0.61 %	20	1.83 %	10	0.26 %
Breast cancer with 3+ years follow-up	29,940		450		29,490	
Leading to primary thyroid	230	0.77 %	10	2.22 %	220	0.75 %
Kidney cancer with 3+ years follow-up	5,530		3,340		2,190	
Leading to primary thyroid	40	0.72 %	20	0.60 %	20	0.91 %
Bladder cancer with 3+ years follow-up	5,440		3,950		1,490	
Leading to primary thyroid	20	0.37 %	10	0.25 %	10	0.67 %

DISCUSSION

Our study revealed that patients with thyroid, breast, renal cell and bladder cancer were at higher risk for subsequently developing one of the other cancers than the general population. In female patients with a primary cancer, we demonstrated a reciprocal increase in the prevalence of all other cancers. The same was true of our male cancer patients except that male bladder cancer survivors did not have an elevated risk of subsequent thyroid cancer. Our study is unique in that we used data from the novel Explorys data system. Previous studies evaluating subsequent cancer risk after a primary cancer have utilized cancer registries or the National Cancer Institutes' SEER database.

Of the male and female thyroid cancer patients combined, we found a 1.5-fold, twofold and 0.5-fold increase in the subsequent development of breast, renal cell and bladder cancer, respectively. We demonstrated that patients with breast and renal cell cancer have a 4-fold and threefold increase in thyroid cancer, respectively. This may have an important impact on clinical practice. The foresight of knowing what cancers occur more often after a primary cancer allows the clinician the opportunity to ask pertinent questions, search for physical findings and obtain additional screening tests such as mammography, urinalysis and thyroid ultrasound.

Ronckers et al.[12] have also reported that the incidence of a subsequent thyroid cancer is higher in patients with a known malignancy and that the incidence of other malignancies is higher in patients with thyroid cancer. A multinational study of second primary cancers in 39,002 thyroid cancer patients over a 25 year period found a standardized incidence ratio(SIR) of 1.31 for a second primary cancer at all sites with pooled data showing a 30 % increased risk of a second primary cancer after thyroid cancer compared with the general population.[11] SEER Cancer Registry data analysis showed an absolute excess risk of all cancers following thyroid cancer of 7.64.[12] and the overall risk of thyroid cancer after any malignancy was 42 % higher than expected with significant excesses observed for both male and female patients.[12]

Several studies have shown a bidirectional association between thyroid cancer and breast cancer.[4,8,11,12,22,23] The first documented bidirectional association between thyroid and breast cancer was by Chalstrey in 1966 who noted that 8.7 % of thyroid cancer patients also had breast cancer.[18] About half of the patients had thyroid cancer as the initial primary cancer, and half had breast cancer as the initial primary cancer. Ronckers et al.[12] found that breast cancer accounted for 36 % of all second malignancies that developed after thyroid cancer. Garner et al.[7] also showed that breast cancer was the most common second cancer in female thyroid cancer survivors. Other studies have only been able to demonstrate a unidirectional association between thyroid cancer and subsequent breast cancer.[14,15] Our results are concordant with others who have demonstrated a bidirectional association between thyroid cancer

and breast cancer.[4,8,11,12,22,23] The bidirectional associations of various malignancies that were found in our study, using the unique Explorys database, is an important contribution to the literature.

Lee et al.[5] examined second malignancies in 53,783 breast cancer patients in the Taiwan Cancer Registry over 25 years and found an elevated risk of both thyroid cancer (SIR 1.42) and renal cell cancer (SIR 2.11). Using SEER data, middle-aged women with breast cancer were found to have a higher incidence of renal cell cancer with an observed to expected ratio of 2.79 within 1 year of diagnosis of breast cancer.[24] We also demonstrated a reciprocal relationship between renal cell cancer and breast cancer, most notably between female patients with breast cancer, who had a threefold increase in the prevalence of subsequent renal cell cancer, and male patients with breast cancer who had a 19-fold increase in prevalence of renal cell cancer. This differs from a previous report which showed no elevation in the risk of a subsequent thyroid or renal cancer in male patients with breast cancer.[24]

An increased risk of renal cell cancer following a primary thyroid cancer has been well documented.[2,4,6,11–13,20,23,25] The reciprocal increase in thyroid cancer after renal cell cancer has also been described.[4,11,12,25] A twofold or greater increase in the development of renal cell cancer has consistently been reported in patients with thyroid cancer.[2,4,11–13,25] Some studies indicate no gender differences.[6,11,12] However, others document an increase only in female thyroid cancer survivors.[13] Berthe et al.[13] showed a substantial increased risk of genitourinary cancer ($p < 0.001$), with a SIR of 7.02 for renal cell cancer in women with a history of thyroid cancer. Similarly, our study confirms a reciprocal relationship between thyroid and renal cell cancer. Both male and female patients with a history of thyroid cancer in our study had an elevated prevalence of subsequent renal cell cancer, a 4.5-fold increase in men and a twofold increase in women. In renal cell cancer survivors, there was a threefold and a 1.5-fold increase in the prevalence of subsequent thyroid cancer in men and women, respectively.

A unique finding in our study was the association of thyroid cancer with bladder cancer. We initially chose to use bladder cancer as a negative control in our study based on two prior studies that found no association between thyroid and bladder cancer.[12,25] Surprisingly, in our study, male and female patients with a history of thyroid cancer had a higher incidence of bladder cancer, but the reciprocal was only true for female patients. Furthermore, an association between bladder cancer and renal cell cancer has been documented previously, whereas an association between bladder cancer and breast cancer has not.[26] Of note, the association of bladder cancer to subsequent thyroid malignancy is much less than any of our other study groups as seen in Fig. 3b. The findings in our study may reflect a possible referral or detection bias in the dataset; hospitals specializing in surgical oncology may have a higher incidence of various malignancies, or may detect more malignancies as a result of increased surveillance of known cancer patients. This surveillance bias for known cancer patients is also acknowledged as a potential factor for the increased detection of second malignancies in the SEER cancer registries.[12] Alternatively, our results may reflect a true association of these malignancies, but it is important to interpret these results with caution until a validation study utilizing actual chart review is conducted. Sandeep et al.[11] also noted that despite a large study population, thyroid cancer and some associated cancers are relatively rare, which could reduce the precision of some risk estimates.

Unidirectional associations are more likely to be due to cancer treatment effects.[14,20] However, bidirectional associations such as thyroid cancer and breast cancer and thyroid cancer and renal cell cancer are more likely explained by shared genetic and/or shared environmental risk factors.[7,20,23] Underlying genetic factors such as Cowden or Cowden-like syndromes predispose women to both thyroid and breast cancer. We are in agreement with Lal et al.[25] that there are likely undefined risk factors and/or treatment effect associations between thyroid, breast and renal cancers.

The amount of data generated by electronic medical records has exploded in recent years and will continue to do so. New technologies in data storage and processing of patient electronic records has created a new population database. Advantages of such a large database like Explorys include more frequent occurrences of relatively rare disease events and a more complete longitudinal record of a patient's care as Explorys captures patients that may use different health care institutions with one medical record.[27] Explorys can be queried without institutional review board approval before a study begins, and thus nonpractical studies can be redesigned or even abandoned which improves research efficiency.[27] A disadvantage of Explorys includes restricted data access to only participating institutions or a partnership with a participating institution.

Specific limitations of this study include the small number of male patients with breast cancer and thyroid cancer. In order to maintain HIPAA compliance and deidentification of patients, numbers are rounded to the nearest tenth. This may not be important when large numbers of patients have a disease, but could be important for small sample sizes. Actual latency times to second malignancy cannot be determined on the basis of this analysis alone. Misclassification or incorrect coding may have contributed to errors in diagnosis. This study is based on data originating from electronic medical records. These

systems may not capture all medical care for a given individual. Patients may enter and leave a given health care system over time and therefore be lost to follow-up.

Patients with a history of thyroid, breast, renal cell or bladder cancer have an increased risk of developing a subsequent second primary malignancy. In patients with thyroid cancer, the most common second malignancies are breast and renal cell cancer, although subsequent bladder cancer also appears to be increased. The association of thyroid, breast, renal cell and bladder cancer appears to be a bidirectional with the exception of men with bladder cancer who do not have an increased prevalence of thyroid cancer. An awareness of these associations may help lead to earlier diagnostic evaluation, recognition and treatment.

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