Original Research Article

Breast Cancer In Thyroid Cancer Patients, can one lead to another?

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ABSTRACT

Aims: To demonstrate the increased risk of developing a second primary thyroid or breast cancer in patients with prior breast or thyroid cancer and to study the clinicopathological characteristic of breast cancer (B2) as a secondary malignancy following a diagnosis of thyroid cancer (T1) or thyroid cancer (T2) following a diagnosis of breast cancer (B1) to find a common aetiology.

Study design: Retrospective cohort study

Place and Duration of Study: Breast & Endocrine Surgery Unit, Surgery Department Hospital Putrajaya between January 2008 and December 2018.

Methodology: Data of patients with breast cancer as first primary malignancy and thyroid cancers as second primary malignancy, and vice versa, between January 2008 to December 2018 was extracted using electronic search through the hospital information system database and compared for their tumor's histological type, size, hormonal status (ER/PR), presence of locoregional lymph node and distant metastasis. We also examine any history of radiotherapy for first primary breast cancer patients and history of radioactive iodine ablation for first primary thyroid cancer.

Results: 1.1% (n:4) of T1 develops B2 while 0.5% (n:8) of B1 develops T2 but we are unable to demonstrate a significant correlation between hormonal status of the tumour, radioiodine ablation or radiation therapy and the risk of developing second primary malignancy.

Conclusion: There is an increased risk of thyroid cancer as a secondary malignancy following breast cancer and an increased risk of breast cancer as a secondary malignancy following thyroid cancer. No common aetiology can be demonstrated from this study.

Keywords: Breast cancer, Thyroid cancer, Second Primary Cancer, Breast and Thyroid Cancer Correlation

1. INTRODUCTION

Breast cancer remains the most common cancer diagnosed in women in Malaysia with 8418 newly diagnosed cases which represents 17.3% of all new cancer cases diagnosed in 2020[1] while thyroid cancers which also predominantly affects women, represent the most

common endocrine malignancy in Malaysia with 795 new cases reported in 2020 making up 1.6% of all cancers [1]. Survivors of breast cancer are at increased risk of a second cancer, frequently thyroid cancer [14,15]. The first case of a synchronous breast and thyroid malignancy was reported by Billroth in 1889[3] and it has been fairly rare ever since. An association between thyroid and breast cancer in women was first reviewed in 1966 [14]. Since then, more studies have suggested that breast cancer is diagnosed more frequently than in thyroid cancer patients and vice versa [3–5].

Factors such as genetic, environmental, young age [14], nulliparity [4], and radioactive iodine (RAI) therapy [9] have been suggested as potential risk factors for the secondary primary cancer. As a center for Breast and Endocrine Surgery in Malaysia, Hospital Putrajaya has seen a number of patients developing both malignancies. This retrospective cohort study is conducted to compare the clinicopathological characteristic between the B1 (Breast cancer as first primary) and the B2 (Breast cancer as second primary) as well as the T1 (Thyroid cancer as first primary) and the T2 (Thyroid cancer as second primary) groups. In addition, we are aiming to identify common etiological factors for Breast and Thyroid Cancers.

2. METHODOLOGY

We conducted a retrospective cohort study on the breast cancer and thyroid cancer patients that were treated in Hospital Putrajaya in the period of 10 years between January 2008 until December 2018. A list of thyroid and breast cancer patients was compiled with the help of hospital's Department of Information Technology by using electronic search through the Hospital Information System database. Female patients with either Papillary or Follicular Thyroid Carcinoma as the first primary cancer (T1) who underwent a Total Thyroidectomy and female patients with Breast Cancer as first primary cancer (B1) who underwent a curative surgery were included in this study. A total of 2059 patients were then selected, among which 362 are T1 and the remaining 1697 are B1.

Second primary cancer is defined as Thyroid Cancer (T2) or Breast Cancer (B2) that were diagnosed at least 2 years after the first primary cancer. Among the 362 patients in T1 group, 8 patients were identified to develop B2 (T1B2) while 4 from the 1697 patients in B1 group were known to have developed T2 (B1T2). Each patient who fit both T1B2 and B1T2 criteria were examined through their Electronic Medical Record (EMR), where the age at which they were diagnosed, the histological type, the tumor size, presence of locoregional lymph node and distant metastasis for each cancer were compared. Additionally, the hormonal status (ER/PR) and Human Epidermal Growth Factor Receptor 2 (HER2) status of the breast tumor and the presence of multifocality as well as extrathyroidal extension of the thyroid tumor were examined for each patient. In terms of treatment modalities, history of radiotherapy for breast tumor and history of Radioactive Iodine (RAI) ablation for thyroid tumor were included for comparison.

For statistical analysis, SPSS software (SPSS, Inc., Chicago, IL, USA) was utilised. Chi square and Fisher's exact tests were carried out to compare the clinicopathological characteristics between the T1B2 and B1T2 groups. A value of $P<0.05$ was considered as a statistically significant difference.

3. RESULTS AND DISCUSSION

Table 1. Clinicopathological characteristics between the T1B2 and B1T2 groups

	T1B2 (n: 4) mean *median	(SD) / (%) (*IQR)	B1T2 (n:8) mean *median	(SD) / (%) (*IQR)	p value
Breast Cancer					
Age at dx	65.5	(6.61)	50.4	(8.93)	0.014
Family history	0	-	0	-	-
Histological type					
DCIS	4	100%	8	100%	-
IDC	0	-	5	62.5%	-
Tumor size (cm)	1.63	(0.479)	3.13	(1.356)	0.020
Lymph Node Metastasis	1	25%	3	37.5%	-
Distant Metastasis	0	-	0	-	-
ER	4	100%	8	100%	-
PR	4	100%	8	100%	-
HER2	0	-	0	-	-
Recurrence	0	-	0	-	-
Radiation therapy	1	25%	4	50%	-

Thyroid Cancer					
Age at dx	61.3	(7.76)	54.5	(8.12)	0.199
Family history	0	-	0	-	-
Histological type PTC	4	100%	8	100%	-
Tumor size (cm)	*3.5	*(3.00)	*2	*(3.00)	0.43
Lymph Node Metastasis	1	25%	1	12.5%	-
Distant Metastasis	0	-	0	-	-
Multifocality	1	25%	1	12.5%	-
Extra-thyroidal extension	1	25%	1	12.5%	-
Recurrence	0	-	0	-	-
RAI	3	75%	6	75%	-
Age at primary cancer Duration to 2^{o} cancer	61.3 *2	(7.76) *(6.00)	50.4 *4	(8.93) *(2.00)	0.07 0.17

All of our cancer patients are followed up and monitored closely and most of the second primary cancer were detected during the interval surveillance. A careful monitoring after diagnosis of a primary tumor has led to a detection bias as frequent examination of the cancer patients eventually leads to the discovery of a new tumor. Furthermore, this has been contributed by the good compliance to surveillance mammography in the thyroid cancer patient group while a routine CT imaging for staging purposes in breast cancer patient leads to the detection of non-palpable thyroid lesion every now and then. A retrospective cohort study on 486 Chinese patients with thyroid cancer, of which 8 patients develop concomitant breast cancer, the author had suggested that surveillance bias as the main reason for the increased detection of a second primary cancer [6]. Our study focused on a period of only 10 years, thus we believe that the incidence of a concomitant thyroid and breast cancer either synchronous or metachronous, would increase even more for an extended period of follow-up considering the fact that median interval between first and second primary cancer in B1T2 group is 4 years (IQR 2), though the interval is shorter for T1B2 group with a median of 2 years (IQR 6). Therefore, diligent follow-up and examination of these patients proved to be beneficial in early detection of a second primary cancer, thus ensuring excellent prognosis.

As it is well known, breast tumors express estrogen and progesterone receptors which act as an important indicator for the 5-year survival rate in breast cancer patients [7]. Thyroid tumors have also been shown to express these receptors [8] which suggests that exposure to

Estrogen hormones may not only increase the risk of development of primary cancer but appears to play a role in the development of either breast or thyroid cancer as a secondary malignancy. However, in our study we could not demonstrate any comparison as all the breast tumors are ER and PR positive in both T1B2 and B1T2 groups. Data analysis has been further limited due to immunohistochemistry staining for ER/PR status in thyroid lesions are not widely practiced.

External beam radiation therapy is a common treatment for breast cancers especially to those who underwent a breast-conserving surgery. Exposure to ionizing radiation early in life has been shown to have increase the risk of developing thyroid, breast and skin cancers [9]. In our study, we have found that only 50% (n: 4) of B1T2 receive radiation therapy post curative surgery, and in addition, the characteristics in terms tumor size, regional and distant metastasis, multifocality, extrathyroidal extension and recurrence rate of T2 is similar to T1 regardless of radiation exposure. This is in line with multiple other studies that concluded there is no significant increase of Thyroid cancer risk following external beam radiation therapy to breast [10, 11, 12].

Most differentiated thyroid cancers like Papillary or Follicular Thyroid Cancer responds well to Radio-iodine Ablation (RAI), and thus commonly given to Thyroid Cancer patients following a Total Thyroidectomy. This has raised the discussion of whether any radiation exposure from RAI therapy in Thyroid Cancer patient increases the risk of developing a secondary Breast Cancer. However, in our study, there is no clear correlation between RAI therapy and Breast Cancer development. 25% (n: 1) of T1B2 group did not receive RAI but still develop Breast Cancer as a secondary malignancy, and 99% (n:358) of all of our T1 patients who receive RAI ablation did not develop a breast cancer as a secondary malignancy. We also found that all B2 (n:3) in T1B2 group has an early breast cancer (DCIS) when in fact the only B2 (n:1) in T1B2 group that did not receive RAI therapy did develop a relatively more advanced breast cancer with lymph node metastasis. There are few other studies in favor of our findings where they concluded there is no significant association between risk of breast cancer development with RAI treatment [13].

Table 2. Incidence of developing secondary cancer in T1 and B1

		Secondary Cancer		Total
		Yes	No	
Primary Cancer	T1	8	354	362
	B1	4	1693	1697
	Total	12	2047	2059

In this study, we could compare incidence rate of developing secondary cancer in both T1 and B1 groups.

Incidence rate of developing secondary cancer in T1 = 8/362 = 0.022099448
Incidence rate of developing secondary cancer in B1 = 4/1697 = 0.002357101
Relative risk = 022099448/002357101 = 9.375691

In conclusion, we have found that T1 patients are 9.4 times more likely to develop secondary cancer than B1. It is important to note that in our study, the T1 age group (60s) is 10 years older than the B1 age group (50s), and considering that breast cancers more often than not occur in older individuals, thus T1 individuals have a higher risk of developing secondary cancer as they grow older. Whereas possibility of B1 developing a secondary cancer is

minimal as the incidence of thyroid cancers, especially the differentiated ones, is higher in younger individuals. Therefore, age may have an influence on the relative risk.

4. CONCLUSION

Patients with Thyroid or Breast Cancer have a higher risk of developing second primary Breast or Thyroid Cancer. In our study, we have found that, 1.1% (n:4) of T1 develops B2 while 0.5% (n:8) of B1 develops T2. This is relatively a higher risk as compared to the general population. The relative risk is also 9.4 times higher in T1, though age may have a contributory factor in it. Estrogen and Progesterone Receptors are present in both groups which raise the possibility of a common etiological factor in the development of both Thyroid and Breast Cancer. Surveillance bias appear to be the contributing factor, while radiation therapy or RAI do not have any significant association on the risk of developing a secondary malignancy. All tumor characteristics of B2 are favorable and has a good prognosis and these histopathological findings may have been the result of early detection by diligent follow up monitoring of T1 patients. Thus, we recommend a close monitoring with interval surveillance mammogram for all patient with Thyroid Cancer to ensure early detection of the development of Breast Cancer as a secondary malignancy. However, screening Thyroid cancer in Breast Cancer patient does not appear to give any additional benefit.

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6. Ethical Approval:

Ethical approval from Clinical Research Centre of Hospital Putrajaya were obtained.

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