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SYSTEMATIC REVIEW

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Risk Factors of Synchronous Breast and Thyroid Cancer: a Controlled Multicenter Study and Review of the Literature

¹Breast Unit, REA Maternity Hospital, Athens, Greece

²Department of Midwifery, University of West Attica, Athens, Greece

³Democritus University of Thrace, Alexandroupolis, Greece

⁴Department of Obstetrics and Gynecology, St. Vinzenz-Krankenhaus Hanau, Main, Germany

Corresponding author: George Iatrakis. MD, PhD. Department of Midwifery, University of West Attica, Athens, Greece. Phone: (30)6944816582. E-mail: giatrakis@uniwa.gr. ORCID ID: <http://www.orcid.org/0000-0000-0000-0000>.

Stefanos Zervoudis^{1,2}, Georgios Iatrakis², Anisa Markja², Georgios Tsatsaris³, Anastasia Bothou², Georg FG. von Tempelhoff⁴, Mirsini Balafouta², Pana Tsikouras³

ABSTRACT

Background: Breast cancer (BC) is one of the most common cancers diagnosed in women in the United States. Thyroid cancer (TC) is also one of the fastest increasing cancer types in the United States, with most cases being papillary thyroid carcinomas. **Objective:** To identify possible risk factors for the synchronous or metachronous co-occurrence of breast and thyroid cancers. **Methods:** We carried out a study, which consisted of data from four gynecological clinics: two in Greece (Athens, Alexandroupolis, Ioannina) and one in Germany, collected from June 2017 to June 2020. The patients were divided into two groups: the first group consisted of 58 patients with breast cancer and a personal history of thyroid cancer. The second group (control group) included 50 patients with the same characteristics as to age, parity, type of pregnancy, treatment for sterility, polycystic ovaries, regularity of the menstrual cycle, breast density, BMI, family history of cancer, blood group rhesus and histological results of breast cancer. The data we collected were analyzed using version 20 of the SPSS statistical package. The Chi-square test was used for statistical analysis and a p-value < 0.005 was considered statistically significant. **Results:** The only factors that seem to be related with the association of breast and thyroid cancer were: history of abortion and multiparity. **Conclusion:** In our study there is a higher chance of developing breast cancer after diagnosing thyroid cancer and vice versa. More than genetic mutations, a possible hormonal pathway of these two malignancies is

possible. The hormonal change in women who had many children or abortions could be a risk factor to develop both cancers. More studies are necessary to confirm our findings.

Keywords: multiple cancer, thyroid cancer, thyroid and breast cancer.

1. BACKGROUND

Breast cancer (BC) is one of the most common cancers diagnosed in women in the United States (1). Thyroid cancer (TC) is also one of the fastest increasing cancer types in the United States, with most cases being papillary thyroid carcinomas (2).

In general, BC and TC commonly affect women (3). The co-occurrence of these two types of cancer synchronously (with the second malignancy being diagnosed within six months) was first reported by Billroth in 1889 (4).

An increased risk of TC following BC has been observed and vice versa (5). Herein, we have gathered a few case reports of patients that have been diagnosed with both BC and TC and identified possible mechanisms for the synchronous or metachronous co-occurrence of these cancers.

2. OBJECTIVE

The purpose of this controlled study was to determine a possible relationship between thyroid and breast cancer.

3. MATERIAL AND METHODS

Our study included data from four gynecological clinics: three in Greece in Athens, Ioannina and Alexandroupolis, and one in Germany. The data was collected from 6/2017 to 6/2020. In total, there were 58 patients with breast cancer and a personal history of thyroid cancer (group BT). We also enrolled 50 patients with the same characteristics of the patients of group BT, but with only breast cancer (group B). The patients' age ranged between 26 and 79 years with a mean age of 54,3 years.

Characteristics of patients were: age, parity, type of pregnancy, treatment for sterility, polycystic ovaries, regularity of the menstrual cycle, breast density, BMI, family history of cancer, hypo or hyperthyroidism, blood group rhesus. Moreover, we analyzed the histological results of breast cancer: histology, grade SBR and the Hormonal receptors. The factors of hypo and hyperthyroidism had missing data and we weren't able to analyze them.

From these 108 patients, 58 patients were diagnosed with breast and thyroid cancer. All the patients in group BT had thyroid cancer first, and were diagnosed with breast cancer after 1 to 12 years, on average. These patients had had a thyroidectomy followed by radioiodine therapy and, later, a mastectomy or breast-conserving surgery followed by radiotherapy. Forty patients in group BT and 32 in group B received adjuvant chemotherapy.

All women who were enrolled in our study gave us written and informed consent. The collected data were analyzed with version 20 of the statistical package. For the statistical analysis, we used Chi-square test (χ^2) and a p-value < 0,005 was considered statistically significant.

4. RESULTS

One hundred and eight women were included in the study, 58 of whom were diagnosed with thyroid and breast cancer and 50 with breast cancer only. The only factors that seem to have a positive correlation between the two groups are abortion and parity.

Of the 50 breast cancer patients who gave information about their abortions, 31(62%) patients had one abortion, 12(24%) had no abortions and only 7(14%) had three abortions. On the other hand, of the 58 women with breast and thyroid cancer, 47(81%) had one abortion, 10(17,2%) had two abortions and 1(1,7%) had six abortions (Table 1). A statistically significant positive correlation was found between the study group and abortions ($\chi^2=16.308$, $p=0,001$) (Table 2). Specifically, 98,3% of these patients had at least one abortion in their life.

Furthermore, parity seems to have an important role as a factor. It was found that in the group of patients with breast and thyroid cancer, 25(50%) had given birth once, 23(46%) had given birth twice and 2(4%) had given birth three times in their lives. In the group with breast cancer only, 10(20%) were nulliparous, 31(62%) had given birth once and 9(18%) had given birth twice (Table 3). It seems that women who had given birth once or twice in their lives have a positive association for both types of cancer ($\chi^2=18.768$, $p<0,001$) (Table 4).

5. DISCUSSION

ROLE OF SEX HORMONES

As it is known sex steroids are really important for the proper development of the breast tissue (6). The majority of BC cases express estrogen (EG) and/or progesterone (PG) receptors (approximately 75%) (7). In a study of 405 women that had been diagnosed with breast cancer, they reported that they had also used contraceptive pills for a long period of time, meaning that there is a possible association between breast cancer and the use of oral contraception (8). This, was confirmed by other studies as well (9). A higher rate of thyroid malignancies in woman that had used oral contraception was observed, with a higher risk of TC when using contraception containing EG and not PG (10, 11). The intake of PG and EG contraceptive pills decreased the risk of TC (12, 13). This may happen mostly because when no pregnancies have occurred, there are no hormonal changes in the thyroid gland (13). Another meta-analysis study found that the use of oral contraception might be helpful for the reduction of thyroid risk, but overall further research needs to be done to come in a more specific conclusion (14).

Also, hormone-replacement therapy seems to increase the chance of developing BC when it is currently and or recently used, and when a significant period of time passes (somewhere in between 5 years) once they stop its consumption, the risk of developing this malignancy seems to be reduced if not eliminated (15).

EG have been confirmed as breast carcinogens by epidemiological studies and one of the possible mechanisms through which they gain such a function is through their receptor mediated hormonal activity (16). It is really important that there is the correct analogy, distribution and transient pattern of expression of each receptor in order for the proper responses to be arbitrated. During the growth of breast cancer, we have a confluence of EG and PG receptors and modified relative expression of PG isoforms and thus pernicious stimulation of proliferation (17). Therefore, if exogenous hormones were to be consumed breast cancer could occur, since there would be disruptions in this analogy.

EG and PG receptors besides being observed in deleterious breast tumours, they have also been observed in deleterious thyroid tumours (18-21). A study about TC, mentioned the ways EG and EG receptors communicate with each other. This could happen via a genomic or non, EG-signaling and EG response element-independent genomic actions and ligand-independent signaling. It seems that estradiol E2 has a sufficient role in the genesis of thyroid cancer with an anti-apoptosis efficacy. After being attached to EG receptors α and β and then moving into the nucleus, it binds to the retrograde estrogen response element and therefore, to a co-activator recruitment that will result in the expression of genes that participate in the proliferation of the thyroid gland (classical estrogen signaling) like PI3K/Akt is (22).

As for PG higher levels of it, seem to have a protective effect against thyroid cancer but PG-to-EG ration could be too, consequential. Use of EG alone therapy would decrease this specific ratio and therefore the possibility of thyroid cancer will increase (11).

In TC, lower levels of androgen receptors (AR) could rouse the epithelial-mesenchymal transition when tumor

metastasis happens or its progression, and also tumors with AR(+) seemed to be more aggressive than those that are AR (-). Besides this diminished AR mRNA is linked with a higher cancer risk (23, 24). Androgens are also frequently expressed in breast cancer and in normal breast tissue (25).

In post-menopausal women, higher levels of androgens, in particular free testosterone, DHEAS and androstenedione and steroid hormones binding globulin, are associated with an increased BC risk but not all studies have found this connection. AR in BC that also expresses EG receptors, have the ability to bind to the same areas of DNA that EG receptor binds, or it could make it easier for EG receptors to bind to the DNA. Furthermore, AR has a more powerful effect on the EG receptor a transactivation, and might also adjust the non-genomic actions controlled by EG receptors. Independently of the underlying mechanism AR could promote or suppress cellular proliferation and these opposing processes could be determined by multiple proteins that interact with AR. In tumors with EG receptors being negative, it is clear that AR stimulates cell proliferation and promotes expanding by acting at different levels (26). Also, there was no relation between AR expression in physiological breast terminal duct lobular units and following breast cancer risk (27) and in post-menopausal women AR expression was not related with prognosis in early stage ER(+) breast cancer (28).

In a case report, a woman that exhibited concomitant breast and thyroid cancer had also used for more than 5 years IM injections of androgen, EG and PG due to malfunction uterine bleeding and adenomyosis. So, taking for such a long period of time hormonal therapy, might have caused simultaneous breast and thyroid cancer (29). It is possible that through the mechanism that were mentioned using a replacement hormonal therapy with estrogens, breast and thyroid gland might develop synchronously cancer.

ROLE OF THYROID HORMONES

Thyroid hormones (TH) play a significant role in the digestion, growth, function and development of a lot of tissues, including mammary and thyroid gland (30). Several studies have shown a connection between TH and mammal cancer development (31, 32). Thyroid dysfunctions like hyperthyroidism are associated with an increased chance of BC (33, 34) while the risk of this malignancy seems to be diminished in women with hypothyroidism (35). Also, hypothyroidism doesn't seem to play a role in the iteration of breast cancer (36). In general, the exact role of hypothyroidism on breast cancer, is a pretty controversial matter, because some believe it is related with a higher chance of breast cancer, others with a decreased chance and others believe that there is no connection (37). As for TC, patients that have hyperthyroidism have a higher chance of developing it, especially those with Grave's disease (38, 39). On the other hand, patients with hypothyroidism and more specifically with Hashimoto disease, had also a higher chance of developing thyroid cancer. This could happen mostly because by having Hashimoto's disease for a big period of time, thyroid stimulating hormone (TSH) serum levels could be accreted and thus thyroid cancer could occur (40).

High levels of TSH seem to be linked with differentiated

TC in people whose TSH levels were within the normal range and also high TSH levels, according to a study that contained 2.775 women, seem to be increasing the risk for BC (41, 42). Another big research examined 17,035 women didn't report an association between TSH levels and BC (43). On the contrary, patients with nodular ailments had a greater chance of developing a thyroid malignancy when TSH levels rose (44). Thyroid stimulating hormone receptor (TSHR) is a receptor for TSH, that has the ability to affect gene expression (45). The signaling sequences that are stimulated by TSHR, has been observed that they could be used as oncogenic pathways in thyroid malignancies. This happens predominantly in malignancies with alterations at V600E in B-Raf proto-oncogene. Besides TSH that activates TSHR there are a lot of other mutations happening in the TSHR gene, that could be germline or tumor specific mutations and could trigger automatically cascades and therefore encourage cell proliferation, like V509A, C672Y and M453T. Meaning that TSHR has a somehow oncogenic role in TC but to develop into a proper malignancy there should be also other existing mutations (46, 47). In a study it was showed that there were TSHR in normal breast tissue and its expression was increased in breast tumors but further studies need to be done to confirm the exact role of TSHR in breast malignancies (48).

Thyroid receptors are found to be located in physiological breast cells and in malignant breast cells. The effects of T3 have been studied in vitro, on MCF-7 and T47-D human BC cell lines and its function is very alike of E2, since they can stimulate the growth of BC cells, or they enhance E2 actions regarding BC proliferation (49). Also T3 might stimulate the expression of hypoxia inducing factor 1 and transforming growth factor alpha in MCF7 BC cell line, which are known for their favorable role in the procedure of carcinogenesis. Furthermore, this stimulation could happen by the PI3K pathway which has been put into function by T3 (50). PI3K/Akt pathway could cause tumor genesis in breast and thyroid cancer since THR binding can start the PI3K pathway of BC (48). T3 and E2 in T47D BC cell lines control cell cycle progression and proliferation increasing the p53 level and inducing hyperphosphorylation of pRb (51). Also, thyroid hormone receptor b1 mutations were found to be associated with breast cancer since this specific receptor is expressed both in thyroid and breast tumors (52).

Active iodide transport, is mediated via the Na⁺/I⁻ symporter in the thyroid gland. Iodide is really important for the synthesis of TH. Through the NIS, radioiodine can also be transported. This is used to diagnose, treat and monitor thyroid pathologies. TSH and I⁻ are predominantly the regulators of NIS in the thyroid. High levels of I⁻ may cause TC by increasing the production of reactive oxygen species. NIS function has also been noticed in lactating breast, and has been expressed in human BC samples as well (53). This suggests new forms of therapy in BC using the NIS. NIS proteins seem to be mainly expressed in cytoplasm in breast tumors especially when we have a ER (-) BC, while in the thyroid tissue it is mainly expressed in the cell membrane (54). Beside this, the use of radioactive iodine in the treatment of TC, according to a study does not seem to indicate a risk for BC (55). Another study that examined the possible

association between thyroid and breast cancer, came to the conclusion that dietary iodide inadequacy and intracellular iodide insufficiency resulted by mislocalization of NIS in breast and thyroid tissue might be a risk factor for the initiation of both breast and thyroid cancer, and also that by using radioactive iodine therapy for a thyroid malignancy, the breast tissue might also absorb radioactive iodine when expressing NIS. As we can see the role of radioactive iodine in the initiation of BC is a pretty controversial matter (56).

ROLE OF GENE MUTATIONS

Lynch syndrome characterized by germline mutations of human mismatch repair genes, MSH2, MSH6, MLH1 and PMS2. It is associated with many of types of cancer such as colorectal and endometrial cancer (57). BC is also one of the malignancies that is linked with Lynch syndrome, and the mutation that tends to be shown more frequently in these women is the one of PMS2 and MSH6 (58). This syndrome is also associated with TC and the most common mutations concern MLH1 MSH2 mismatch repair genes, Nevertheless further investigation needs to be done regarding thyroid cancer and Lynch syndrome (59, 60). Cowden syndrome which is characterized by a mutation in the PTEN gene and is associated seems to be linked with both thyroid and breast malignancies (61-65).

ROLE OF OTHER FACTORS

In patients with BC it seems that the only predictor of them developing TC, is family history and as for the age, an age above 50 was associated with a bigger thyroid tumor size (66). According to another study in patients with BC the use of chemotherapy with docetaxel and cyclophosphamide might stimulate the genesis of TC but further studies are needed to be done in order to confirm this (67). Also in HER-2 negative patients, after the second and third cycle of chemotherapy, TSH levels increased and maybe this could cause the development of a thyroid malignancy as well (68).. An increased risk of BC has been also detected in parous females with a history of TC (69, 70). Furthermore an increased BMI seems to be associated with thyroid and BC risk as well (71, 72). As for radiation therapy in patients with BC, it seems that it is linked with hypothyroidism in patients with small thyroid (73) and therefore it might increase the chance of developing TC simultaneously with BC.

6. CONCLUSION

It is well known that a number of risk factors regarding breast cancer have been identified. However, the association of both thyroid and breast cancer still remains unclear except some genetic mutations that link with these neoplasms. This study analyzes the connection of both malignancies with some specific risk factors. The history of abortion and the high parity are in our series factors linked significantly to the association of breast and thyroid cancer. The pathophysiological mechanism is still indefinite and needs more research to make it clear. Further studies could confirm these findings.

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