ORIGINAL RESEARCH

DOI: 10.37047/jos.2020-79561

Subclinical Hypothyroidism in Patients with Newly Diagnosed Breast Cancer

Müjdat KARA[a], Öykü BEYAZ[b], Elif Sitre KOÇ[b], Özlem SÖNMEZ[c]

[a]Department of Endocrinology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, TURKEY
[b]Department of Internal Medicine, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, TURKEY
[c]Department of Oncology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, TURKEY

ABSTRACT Objective: The association between thyroid function and breast cancer is controversial and has been studied for more than 50 years in both animals and humans with mixed results. The type of relationship between hypothyroidism and the risk of breast cancer remains to be elucidated. Subclinical hypothyroidism (SCH) may have a role in breast cancer development. In this study, the prevalence of SCH was investigated in patients with newly diagnosed breast cancer at a single center. **Material and Methods:** A total of 910 breast cancer patients were screened, and 403 women (mean age, 55.7±10.7 years) were included for the analysis. The staging of breast cancer patients was based on The Staging Manual of the American Joint Committee on Cancer. SCH was defined as elevated TSH (normal range: 0.25-4.55 µIU/mL) with normal free T4 (normal range: 11.5-22.7 pmol/L) and normal free T3 (normal range: 3.5-6.5 pmol/L) concentrations and these were used to compare SCH-positive (n=46) and SCH-negative (n=357) patients. **Results:** The prevalence of SCH among newly diagnosed breast cancer patients was 11.4%. SCH-positive and SCH-negative patients were comparable in terms of menopausal status and tumor grade. **Conclusion:** The rate of SCH among newly diagnosed breast cancer patients in this study indicates that SCH may be a coincidental condition in breast cancer patients.

Keywords: Subclinical hypothyroidism; breast tumor; neoplasm grading; menopause

According to the cancer statistics, breast cancer has become the most common malignant disease, with two million new cases and more than 600,000 deaths in 2018, making it vital to identify the associated risk factors.[1,2] Many earlier studies have attempted to assess an association between thyroid disease and breast cancer, but it is difficult to distinguish a cause-and-effect relationship between the two conditions despite their high prevalence in women.[3] The relation between hypothyroidism and the risk of breast cancer was first published in 1976 by Kapdi and Wolfe, who observed a higher breast cancer incidence rate among patients undergoing thyroid supplement treatment.[4] Since then, four meta-analyses have studied thyroid dysfunction and the risk of breast cancer.[5-8] Angelousi et al. examined 12 studies and found no association between hypothyroidism and increased risk of breast cancer, five and further suggested that thyroid hormone replacement therapy did not reduce the prevalence of breast cancer. In a later meta-analysis, Fang et al. reported no relationship between thyroid dysfunction and risk of breast cancer, while Wang et al. found a reduced risk of breast cancer due to hypothyroidism in the European population.[7,8]

These meta-analyses also stressed several drawbacks such as heterogeneity of the studies, confounders that might weaken the results, or a limited number of studies. Therefore, further studies are required to prove a causal relationship. A highly prevalent form of thyroid dysfunction, subclinical hypothyroidism (SCH), is characterized by elevated thyroid- stimulating hormone (TSH) together with normal thyroxin (T_4) levels. SCH was recently found to relate to an increased risk of colorectal and thyroid cancer.[9] There is only one study to have investigated the association and found no relationship between SCH and increased risk of breast cancer.[10] In this study, we investigated the prevalence of SCH in patients with newly diagnosed breast cancer at a single center.

Correspondence: Müjdat KARA
Department of Endocrinology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, TURKEY/TÜRKİYE
E-mail: drmujdat@hotmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 14 Oct 2020 ***Received in revised form:*** 17 Feb 2021 ***Accepted:*** 02 Mar 2021 ***Available online:*** 10 Mar 2021

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT POPULATION

This study was performed at the Oncology Outpatient Clinics of Acıbadem University Hospital between 2017-2019. This study was approved by the ethics committee of Acıbadem Mehmet Ali Aydınlar University on 5.11.2020 (study number 2020-23/06). This study was conducted in accordance with the Declaration of Helsinki Principles. Female patients with newly diagnosed breast cancer also took the thyroid hormone test. Thus, inclusion criteria were newly diagnosed breast cancer, female gender, and age above 18 years. The criteria for exclusion were known thyroid disease, using thyroid medication, previous thyroid surgery, radiotherapy, radioactive iodine therapy, and male gender. A total of 910 patients were screened, and 403 women (mean age, 55.7±10.7 years) were finally included for the analysis.

We defined SCH as elevated TSH (normal range: 0.25-4.55 μIU/mL) with normal free T4 (normal range: 11.5-22.7 pmol/L), and normal free T3 (normal range: 3.5-6.5 pmol/L) concentrations. After detecting elevated TSH in the first measurement, we defined TSH elevation with two consecutive tests. Data collected included age, body mass index (BMI), free T3, free T4, TSH, anti-thyroglobulin (anti-TG, normal range 0-60 IU/mL), anti-thyroid peroxidase (anti-TPO, normal range 0-60 IU/mL) values, and tumor grades at the time of the diagnosis. BMI was calculated as the patient's weight (kg) divided by the square of height (m). The staging of the breast cancer was determined at the first visit using the tumor, node, metastasis (TNM) staging classification system according to the 7th edition of the staging manual of the American Joint Committee on Cancer.[11] In brief, this system uses the extent of the primary tumor (T), the status of regional lymph nodes (N), and distant metastasis (M).

STATISTICAL ANALYSIS

Statistical analyses were performed using Predictive Analytics Software (PASW version 18) and EXCEL 2016 datasheet. Descriptive statistics included frequency values, means, and standard deviations. Between-group comparisons between SCH-positive versus SCH-negative patient groups were performed using the independent-samples t-test. The mean TSH levels among patients with different cancer stages were compared using one-way analysis of variance (ANOVA). Categorical parameters, such as cancer stage and patients with or without SCH, were evaluated by the Chi-square test. A p-value less than 0.05 was considered statistically significant.

RESULTS

General characteristics of the recruited breast cancer patients with or without SCH are mentioned in (Table 1). Among newly diagnosed breast cancer patients, the prevalence of SCH was 11.4%. There was no significant difference between the two groups in terms of age, weight, height, and BMI. While free T_3 and T_4 levels were within normal limits in both groups, TSH levels were significantly higher in the SCH group than in the control group (4.6±0.6 versus 1.6±1.0 μUI/mL, respectively; p<0.001). The distribution of patients with different stages of cancer in the SCH group was comparable and similar to that in the control group (Table 2). We also compared TSH levels among different cancer stages in the SCH-pos-

TABLE 1: General characteristics of the breast cancer patients with or without subclinical hypothyroidism.

	SCH-positive patients	Control patients
	n (%)=46 (11.4)	n (%)=357 (88.6)
Age, year	53.8±11.2	55.9±10.6
Weight, kg	66.3±7.6	68.9±10.9
Height, m	1.62±0.04	1.62±0.04
BMI, kg/m2	25.0±2.8	26.0±4.1
fT3, pmol/L	4.3±1.1	4.1±1.0
fT4, pmol/L	14.8±2.9	14.6±2.4
TSH, uIU/mL	4.6±0.6	1.6±1.0*

SCH: Subclinical hypothyroidism; BMI: Body mass index; TSH: Thyroid-stimulating hormone.
*p<0.001; Reference values for fT3, 3.5-6.5; fT4, 11.5-22.7; TSH, 0.25-4.00

TABLE 2: A comparison of patients with different stages of SCH-positive breast cancer versus healthy patients.

	Stage 1	Stage 2	Stage 3	Stage 4
SCH group, n (%)	5 (11.4)	30 (68.2)	9 (20.5)	0 (0.0)
Control group, n (%)	25 (7.0)	241 (67.5)	73 (20.4)	18 (5.0)

SCH: Subclinical hypothyroidism.
Chi-square p>0.05

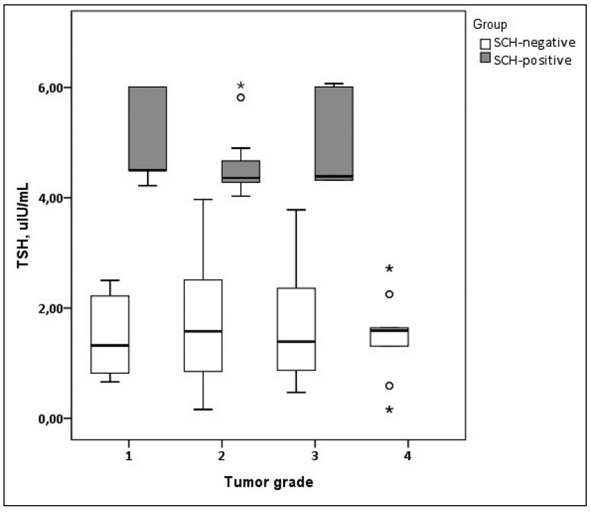

FIGURE 1: A comparison of TSH levels among the patients with different stages of cancer shows that TSH levels were comparable among the patients (One-way ANOVA p>0.05). TSH: Thyroid-stimulating hormone; SCH: Subclinical hypothyroidism.

TABLE 3: A comparison of the menopausal status of patients between SCH-positive versus SCH-negative breast cancer patient groups.

	Pre-menopause	Menopause
SCH group, n (%)	6 (13.0)	40 (87.0)
Control group, n (%)	68 (19.0)	289 (81.0)

SCH: Subclinical hypothyroidism.
Chi-square p>0.05

itive and negative groups and observed similar TSH levels in all different tumor groups (Figure 1) (p>0.05). The menopausal status of the patients is mentioned in (Table 3). More than 80% of the patients in both groups were in a menopausal state. The groups did not differ significantly in terms of menopausal state (p>0.05).

DISCUSSION

In this study, the prevalence of SCH among newly diagnosed breast cancer patients was 11.4%. The prevalence of SCH in the adult population without known thyroid disease varies between 4% to 8.5% and increases with age and female gender.[12] SCH is prevalent in nearly 20% of women older than 60 years.[12] As the data are inconsistent, it is difficult to predict whether the prevalence of SCH in this study was higher or lower in breast cancer patients in comparison to the general population.

The hallmark of SCH is elevated serum TSH concentration. Nearly 90% of all SCH patients have serum TSH levels between 4 and 10 μIU/mL.[13] SCH is categorized as grade 1 when TSH level is between the upper limit of the reference range and 9.9 μIU/mL, and as grade 2 if TSH level is higher than 9.9 μIU/mL.[14] All the patients with SCH in our study group had Stage 1. It is important to stage SCH patients because there is no consensus whether the patients with a TSH level <10 μIU/mL should be treated. Thyroid dysfunction has been shown to play some pathophysiological role in certain cancer types; it is necessary to examine the possible link between untreated SCH and the risk of breast cancer. The rate of SCH among newly diagnosed breast cancer patients in this study indicates that SCH may be a coincidental condition in breast cancer patients. Likewise, a meta-analysis of case-control studies found no association between thyroid dysfunction and the risk of breast cancer.[7]

In adults, the thyroid hormone is necessary for the regulation of important physiological processes, including cell growth, differentiation, metabolism, and proliferation. These genomic and non-genomic effects of thyroid hormones are regulated via thyroid hormone receptors, which also control tumor cell proliferation and regulate defense pathways in cancer cells.[15] Both thyroid hormone receptors (TRα and TRβ) are expressed in nuclei of breast cancer cells. Thyroid hormone receptor beta (TRβ) shows tumor suppressor activity in breast cancer through T3-mediated repression of RUNX2 signaling.[16] TRβ was also shown to mediate depletion and inhibit the self-renewal capacity of luminal breast cancer stem cells.[17] However, the links between subcellular localization of TRβ isoforms and their association with the patient outcome are complex, with contrasting roles in breast tumorigenesis.[18] Nonetheless, these findings collectively suggest that hypothyroidism may inhibit tumor development and proliferation in breast cancer.

Menstrual and reproductive factors have been investigated as determinants of women's risk of breast cancer since the 1970s.[19,20] The high-risk factors include early menarche, late menopause, and nulliparity, whereas the risk-mitigating factors include

lactation and higher parity.[21] A late menarche and early menopause lead to shorter lifetime exposure to sex hormones, which means lower breast cancer risk. To our knowledge, no previous report investigated the occurrence of menopause at the time of breast cancer diagnosis in patients with or without SCH. We found no significant difference between SCH-positive versus SCH-negative patients in terms of menopausal status (Table 3). In a prospective cohort study, postmenopausal women with hypothyroidism were found to have a 9% lower risk of breast cancer than women who had normal thyroid function.[22] The risk reduction was most significant among those who had never used menopausal hormone therapy, although the study was compromised by the lack of a premenopausal control group.

In a prospective cohort study of 115,746 Taiwanese patients, Tseng et al. observed that SCH was independently associated with increased risk of mortality in breast cancer patients.[23] Mortality may be related to tumor grade at diagnosis. A smaller tumor size with fewer metastases would lower mortality. Hence, we analyzed the two groups for the distribution of patients with different tumor stages. Comparison of SCH-positive versus SCH-negative breast cancer patient groups revealed that the two groups were similar in terms of different tumor stages (Table 2). In both groups, most of the patients were stage 2 followed by stage three patients. In the SCH-negative group, 5% of patients were stage 4, whereas, in the SCH-positive group, none of the patients were stage 4. However, this difference failed to achieve statistical significance. A recent study compared found no difference between tumor grade of breast cancer patients and patients without a history of thyroid disorder.[23]

The occurrence of SCH in patients with breast cancer may have some clinical significance during the follow-up period. Acute hypothyroidism and hyponatremia are accepted as concomitant conditions. Furthermore, hypothyroidism is widely accepted as the cause of hyponatremia.[24,25] The most important mechanism of hyponatremia in acute hypothyroidism setting is decreased glomerular filtration rate, which reduces the delivery of water to the diluting segments and decreases free water excretion.[26] In the setting of chronic hypothyroidism, the other important mechanism of hyponatremia includes decreased capacity of free water excretion due to elevated ADH levels.[26] In breast cancer patients with SCH, chemotherapy-induced nausea and vomiting may worsen hyponatremia because of abnormal ADH secretion.

This study has several limitations that warrant mentioning. First, the sample size was small. Second, we had no chance to analyze the receptor profile of breast cancer patients in our study group. A recent study showed that estrogen receptors are mostly positive in patients with autoimmune thyroiditis, adding an estrogen receptor positivity test may be beneficial to examine a possible link between the presence of SCH and estrogen receptor positivity.[27] Finally, the cross-sectional nature of the study prevented us from performing a prospective mortality analysis.

In conclusion, the prevalence of SCH among newly diagnosed breast cancer patients was 11.4% among the participants. The rate of SCH among newly diagnosed breast cancer patients in this study is indicative of it being a coincidental condition in breast cancer patients. Furthermore, menopausal status and cancer stage were comparable in SCH-positive and SCH-negative patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Müjdat Kara, Özlem Sönmez;* ***Design:*** *Müjdat Kara, Öykü Beyaz;* ***Control/Supervision:*** *Müjdat Kara, Elif Sitre Koç;* ***Data Collection and/or Processing:*** *Müjdat Kara, Özlem Sönmez;* ***Analysis and/or Interpretation:*** *Öykü Beyaz, Elif Sitre Koç, Müjdat Kara;* ***Literature Review:*** *Öykü Beyaz, Elif Sitre Koç, Özlem Sönmez;* ***Writing the Article:*** *Müjdat Kara, Elif Sitre Koç;* ***Critical Review:*** *Müjdat Kara, Öykü Beyaz;* ***References and Fundings:*** *Elif Sitre Koç, Öykü Beyaz.*

REFERENCES

1. American Cancer Society. Selected cancers. Global Cancer Facts & Figures. 4th ed. Atlanta: American Cancer Society. 2018, p.12. [Link]
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. Erratum in: CA Cancer J Clin. 2020;70(4):313. [Crossref] [PubMed]
3. Smyth PP. The thyroid and breast cancer. Curr Opin Endocrinol Diabetes Obes. 2016;23(5):389-393. [Crossref] [PubMed]
4. Kapdi CC, Wolfe JN. Breast cancer. Relationship to thyroid supplements for hypothyroidism. JAMA. 1976;236(10):1124-1127. [Crossref] [PubMed]
5. Angelousi AG, Anagnostou VK, Stamatakos MK, Georgiopoulos GA, Kontzoglou KC. Mechanisms in endocrinology: primary HT and risk for breast cancer: a systematic review and meta-analysis. Eur J Endocrinol. 2012;166(3):373-381. [Crossref] [PubMed]
6. Hardefeldt PJ, Eslick GD, Edirimanne S. Benign thyroid disease is associated with breast cancer: a meta-analysis. Breast Cancer Res Treat. 2012;133(3):1169-1177. [Crossref] [PubMed]
7. Fang Y, Yao L, Sun J, et al. Does thyroid dysfunction increase the risk of breast cancer? A systematic review and meta-analysis. J Endocrinol Invest. 2017;40(10):1035-1047. [Crossref] [PubMed]
8. Wang B, Lu Z, Huang Y, Li R, Lin T. Does hypothyroidism increase the risk of breast cancer: evidence from a meta-analysis. BMC Cancer. 2020;20(1):733. [Crossref] [PubMed] [PMC]
9. Gómez-Izquierdo J, Filion KB, Boivin JF, Azoulay L, Pollak M, Yu OHY. Subclinical hypothyroidism and the risk of cancer incidence and cancer mortality: a systematic review. BMC Endocr Disord. 2020;20(1):83. [Crossref] [PubMed] [PMC]
10. Kuijpens JL, Nyklíctek I, Louwman MW, Weetman TA, Pop VJ, Coebergh JW. Hypothyroidism might be related to breast cancer in post-menopausal women. Thyroid. 2005;15(11):1253-1259. [Crossref] [PubMed]
11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual. 7th. New York, NY: Springer; 2010. [Link]
12. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228-238. [Crossref] [PubMed]
13. Pérez-Campos Mayoral L, Hernández-Huerta MT, Mayoral-Andrade G, et al. TSH Levels in Subclinical Hypothyroidism in the 97.5th Percentile of the Population. Int J Endocrinol. Jun 2020;2020:2698627. [Crossref] [PubMed] [PMC]
14. Biondi B, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. JAMA. 2019;322(2):153-160. [Crossref] [PubMed]
15. Liu YC, Yeh CT, Lin KH. Molecular Functions of Thyroid Hormone Signaling in Regulation of Cancer Progression and Anti-Apoptosis. Int J Mol Sci. 2019;20(20):4986. Erratum in: Int J Mol Sci. 2020;21(9): [Crossref] [PubMed] [PMC]
16. Bolf EL, Gillis NE, Barnum MS, et al. The Thyroid Hormone Receptor-RUNX2 Axis: A Novel Tumor Suppressive Pathway in Breast Cancer. Horm Cancer. 2020;11(1):34-41. [Crossref] [PubMed]
17. López-Mateo I, Alonso-Merino E, Suarez-Cabrera C, et al. Thyroid Hormone Receptor β Inhibits Self-Renewal Capacity of Breast Cancer Stem Cells. Thyroid. 2020;30(1):116-132. [Crossref] [PubMed] [PMC]
18. Shao W, Kuhn C, Mayr D, et al. Cytoplasmic and Nuclear Forms of Thyroid Hormone Receptor β1 Are Inversely Associated with Survival in Primary Breast Cancer. Int J Mol Sci. 2020;21(1):330. [Crossref] [PubMed] [PMC]
19. MacMahon B, Cole P, Lin TM, et al. Age at first birth and breast cancer risk. Bull World Health Organ. 1970;43(2):209-221. [PubMed] [PMC]
20. Wu AH, Ziegler RG, Pike MC, et al. Menstrual and reproductive factors and risk of breast cancer in Asian-Americans. Br J Cancer. 1996;73(5):680-686. [Crossref] [PubMed] [PMC]
21. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat. 2014;144(1):1-10. [Crossref] [PubMed] [PMC]
22. Weng CH, Okawa ER, Roberts MB, et al. Breast Cancer Risk in Postmenopausal Women with Medical History of Thyroid Disorder in the Women's Health Initiative. Thyroid. 2020;30(4):519-530. [Crossref] [PubMed] [PMC]
23. Tseng FY, Lin WY, Li CI, Li TC, Lin CC, Huang KC. Subclinical hypothyroidism is associated with increased risk for cancer mortality in adult Taiwanese-a 10 years population-based cohort. PLoS One. 2015;10(4):e0122955. [Crossref] [PubMed] [PMC]
24. Ergin AB, Bena J, Nasr CE. Hypothyroidism and hyponatremia: simple association or true causation. Open J Thyroid Res 2017;1(1):012-016. [Crossref]
25. Ogu I, Surindan S, Shapiro JI. Hyponatremia in hypothyroid disorders: current understanding. JSM Thyroid Disord Manag 2017;2(2):1014. [Link]
26. Liamis G, Filippatos TD, Liontos A, Elisaf MS. Management of endocrine disease: Hypothyroidism-associated hyponatremia: mechanisms, implications and treatment. Eur J Endocrinol. 2017;176(1):R15-R20. [Crossref] [PubMed]
27. Chiappa C, Rovera F, Rausei S, et al. Breast cancer and thyroid diseases: analysis of 867 consecutive cases. J Endocrinol Invest. 2017;40(2):179-184. [Crossref] [PubMed]