**Author’s response to reviews**

**Title:** Association between benign thyroid disease and breast cancer: a single center experience

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**Author’s response to reviews:**

Trieste, July 17, 2019

Dear Ciaran Martin Fitzpatrick,

BMC Endocrine Disorders

We thank the Editorial Board for the review report, which has helped us improve the quality of the manuscript.

Please find the point-by-point response to BEND-D-19-00145R1 review report and the revised version of our manuscript titled “Association between benign thyroid disease and breast cancer: a single center experience”.

All authors have read and approved the submission of this manuscript, which has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

Hoping you will find the manuscript acceptable for publication in the BMC Endocrine Disorders, I look forward to hearing from you at your earliest convenience.

After examination of your mail, we have revised the manuscript: “BEND-D-19-00145R1 Association between benign thyroid disease and breast cancer: a single center experience” so that you consider a revised version of our paper for publication in the BMC Endocrine Disorders Journal.

We are enclosing a new revised version of manuscript with details of how we have attended to each of the Editorial Office’ comments.

CHANGES:

Editor Comments:

We modified all the discussion of the manuscript. The discussion, now, represents an interpretation of our findings, future perspectives, and also limitations are included. The revised discussion is not a repeat of the result's section.

Discussion section, page 11, lines 21-22. The sentence “that BC and thyroid disease are strictly related” are deleted.

• Discussion section, page 11, lines 22-23 and page 12 lines 1-5. The sentences: “on the contrary, other (A)authors [4], did not (found) find any statistically significant correlation regarding the co-presence of thyroid disease and BC. The exact mechanism linking thyroid disease and BC has not been identified yet, but several hypotheses have been advanced, such as the co-presence of sodium-iodine symporter in both thyroid and breast tissue [12]. Other Authors speculated that absorption and oxidation of iodine may play an important role in the development of BC. In fact, some studies [13-15] demonstrated a greater incidence of BC in iodine-deficient geographic areas [16]” were substitute with: “Several hypotheses have been postulated on the mechanism linking TD and BC. Some Authors believe that the absorption and oxidation of iodine may play an important role in the development of BC, which is known to have a greater incidence in iodine-deficient geographic areas [13-16]. Another possible interaction may be based on the presence of a sodium/iodine symporter in both the thyroid and breast tissue [12].”

• Discussion section, page 12, lines 17-20. The sentences: “First of all, we analyzed the correlation between menopausal status and presence of thyroid disease. Our cohort of women
(762 patients) was divided into two subgroups aged ≥60 and <60 years according to the NCCN guidelines definition of menopause [7]. Considering presence/absence of BTD and thyroid functional status” were deleted.

• Discussion section, page 13, lines 17-21. The sentences: “At statistical analysis, no significant correlation was found the correlation with the menopausal status was investigated and showed no differences (p=0.49 Chi Square). Sogaard et al. [26], in a case-control epidemiological study conducted on a large cohort of Danish women, showed an increased risk of BC in women with hyperthyroidism and a slightly increased risk of BC in women with hypothyroidism.” were changed in: “At statistical analysis, no significant correlation was found the correlation with the menopausal status was investigated and showed no differences (p=0.49(Chi Square). Sogaard et al. [26], in a case-control epidemiological study conducted on a large cohort of Danish women, showed an increased risk of BC in women with hyperthyroidism and a slightly increased risk of BC in women with hypothyroidism.

• Discussion section, page 13, lines 22-24. The sentences:”Regarding breast cancer the possible relationship between BC staging related to and the presence of benign TD thyroid disease, we this study found a clear majority of patients (55.2%) with stage I (TNM) among women with normal thyroid function.” were changed with “Regarding breast cancer the possible relationship between BC staging related to and the presence of benign TD thyroid disease, we this study found a clear majority of patients (55.2%) with stage I (TNM) among women with normal thyroid function.”

• Discussion section, page 14, lines 10-12. The sentences:”Regarding the distribution of breast cancer stage according to the presence or absence of autoimmune thyroid disease, only in stage III there was a statistically significant difference, while in other stages it was not present (see Table 4). In detail, breast cancer “ were deleted.

• Discussion section, page 14, lines 20-23. The sentences:“Although this case series is very small, it reflects the greater epidemiological frequency of papillary thyroid carcinoma. Another goal of our study was to correlate breast cancer grading with benign thyroid disease.” were deleted.

• Limitation of the study are included in the “Conclusion section”. Page 15, lines 9-15. “The present study has a number of limitation. Being a single-center experience based on retrospective non-randomized analysis, the possibility of generalizing the results is potentially limited. Additionally, the sample size is not very large and the observation period might not be long enough. However, the study managed to confirm that there is a relationship between BC and TD, although further studies with prospective analyses and extended follow-up are required in order to elucidate the nature of this relationship.”
Reviewer reports:

Michael O'Reilly (Reviewer 1):

1. Ethical approval – Page 16, lines 10-11: We confirmed that “The immunohistochemical profiling of breast cancer samples was performed as part of routine clinical care and not as a research test.”

2. Introduction - needs to be significantly expanded to 1 page - 2 paragraphs is entirely insufficient.

Page 5, lines 3-13: The Introduction section was significantly expanded because insufficient.

The entire paragraphs “Breast cancer and thyroid disease are both common among female population. In Italy, about 50,000 new cases of breast cancer were diagnosed in 2016. The relationship between breast cancer (BC) and benign thyroid disease (BTD) has been widely investigated and reported in Literature. Despite extensive population studies, the results have been inconsistent and the relationship remains today controversial [1-2]. Recent studies show a strong association between the two diseases [3] while others do not identify any statistically significant relationship between them [4-5]. A meta-analysis of 26 studies [6] found an association between autoimmune thyroid pathologies and breast cancer even if, to date, the causal link between the two diseases is not clear.

Aim of our the study is to analyze a series of consecutive patients treated for BC at the Breast Unit of Trieste in order to evaluate the association between BTD and BC and to assess any differences in clinical presentation, management, and outcome.” are deleted and substitute with “Breast cancer (BC) is the most common cancer in women and the second most common cancer overall. Over 2 million new cases were diagnosed in 2018, accounting for almost 25% of cancer cases among women [1-2]. Although hereditary and genetic factors account for 5-10% of BCs [1-5], in this context, the relationship of BC with thyroid disease (TD) has been widely investigated. However, data are still controversial and, although almost every form of TD, including autoimmunity disorders and thyroid cancer, has been identified in association with BC, no convincing evidence exists of a causal role for TD in BC [1-5].

A recent meta-analysis performed by Hardefeldt et al. [6] found that patients with autoimmune thyroiditis presented an increased risk of BC (OR 2.92) and subgroup analysis identified a significant association with both anti-TPO and anti-TG thyroid antibodies. Although the exact mechanism linking BC and TD has not been found yet, several hypotheses have been postulated. The possible interactions between thyroid gland and breast tissue may be based on the common property of both epithelial tissues to concentrate iodine by means of a sodium/iodine symporter (NIS), as well as on the presence of TSH receptors in fatty tissue, which is abundant in mammary glands [6]. Alternatively, since estrogen receptors have been identified in abnormal thyroid tissue cells, a reversal in the relationship with BC acting as a trigger for thyroid
dysfunction cannot be excluded [3-6]. Additionally, some endocrine stimuli may exert a simultaneous action on both the breast and thyroid gland, determining the coincidence of mammary and thyroid disorders [1-6].

Aim of this study was to evaluate the prevalence of TD in a consecutive series of patients treated for primary BC in order to assess any possible association in terms of clinical presentation, management, and oncologic outcome.”

3. Discussion are shortened. (View Response to Editor’s comments.)

We modified all the discussion of the manuscript. The discussion, now, represents an interpretation of our findings, future perspectives, and also limitations are included. The revised discussion is not a repeat of the result's section.

Discussion section, page 11, lines 21-22. The sentence “that BC and thyroid disease are strictly related” are deleted.

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Editor’s and Reviewers comments:

Because, in the text, there were language and spacing issues we revised the entire manuscript’s format. We corrected language and grammar errors.

The manuscript has now been revised with the help of a professional Medical Doctor who is fluent in English. We added Marina Troian as Authors of this manuscript. (see Author’s contribution section).

Author’s contribution section, page 17 linws 11-12.

M.T.: Participated in conception, design, and execution of the study and in the analysis and interpretation of data and in the revision of English language of the entire manuscript.

We thank the Editorial Board for the review report, which has helped us improve the quality of the manuscript.

Thank you for your suggestions. I’m looking forward to hearing from you soon. With best regards,

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