

Early Life Events and Breast Cancer: Past Surgical History of Appendectomy and Tonsillectomy as an Example

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Received: February 06, 2018; **Published:** February 10, 2018

Volume 1 Issue 1 February 2018

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Introduction

36 years old female diagnosed as having right breast cancer T3N2M0, her disease was both hormone & HER-2 neu positive. The patient had no family history of breast or ovarian cancer. Her past medical history revealed having tonsillectomy at the age of 10 years and appendectomy at 12 yrs. Her menarche started at 13 years of age and now has regular menses. Her first child died at the age of 3 yrs with acute hepatic failure complicating cryptogenic biliary cirrhosis. Currently, she is taking care of another 3 children, all of them are a life and well. She is a smoker, has no other comorbidities and not on any chronic medications.

The main function of immune system is to maintain tissue homeostasis. In addition to the elimination of damaged cells, it protects against infectious pathogens [1].

Evading immune destruction was described as one of the emerging hallmarks of cancer by Hanahan and Weinberg. As enabling characteristic to this mechanism, the innate immune system may promote tumor inflammatory responses that result in enhancing tumorigenesis and facilitate angiogenesis and metastasis [2].

Experimental research has shown that immune system can hold the occult malignant process for some time while immune suppression can allow it to progress [3].

The role of lymphoid tissue including adenoid, tonsils and spleen as a part of immune system, has been described long time ago [4,5]. Although it is controversial, there is an accumulating evidence that appendix can be considered as a part of immune system. In several species, the appendix is a site of immune tissue (gut-associated lymphoid tissue; GALT) concentration [6-8].

The role of tonsillectomy, appendectomy, and splenectomy was evaluated mainly in regard to susceptibility and exposure to infection. Whether these surgical interventions, which are done routinely sometimes, have relation to future development of cancer is a field of clinical research that can be focused on. This could be important since we are in the era where the cancer therapeutic strategies started to target body immunity rather than the cancer cell itself.

Citation: Zuhair Alzibair and Wael Mohammed. "Early Life Events and Breast Cancer: Past Surgical History of Appendectomy and Tonsillectomy as an Example". *Holistic Approaches in Oncotherapy* 1.1 (2018): 23-26.

Objectives

This article is a literature minireview trying to explore the relationship between breast cancer and past medical history of these surgical interventions in clinical practice. For its importance and the strong relationship, we included the history of splenectomy in our review although it was not there in the clinical presentation given above.

Results

The of Investigation of the relationship between tonsillectomy, appendectomy, and carcinogenesis is not a recent issue. This was based on the assumption that the human immunity is weakened by the additional reduction of the lymphoid tissue in patients who have other genetic predisposition to develop cancer [9]. In one study a significant positive association of breast cancer with the history of tonsillectomy, which persisted after multivariate adjustment, among premenopausal (OR 1.50, 95% CI: 1.08–2.08) but not among postmenopausal women (OR 1.05, 95% CI: 0.79–1.38) was observed [10]. Another study from Taiwan related higher incidence of breast cancer after tonsillectomy the difference was noticed 3 yrs or more after the operation [11].

A Danish study included around 82.000 patients, a follow up of 17 years interval showed a slightly higher incidence of cancer 1.05 CI 0.99-1.11 among appendicectomies patients compared to general population. There was no specific excess to any type of cancer [12]. The authors concluded a negative association between the procedure and development of cancer.

An observational study from Israel collected data on appendectomy, cancer type and age at the time form diagnosis in BRCA1 and BRCA2 female Jewish carriers. Overall 38.7% of the mutation carriers had breast cancer (367/947). The P value was 0.001 in breast/ovarian cancer when compared to asymptomatic carriers. The study found that prior appendectomy was more in BRC1& BRCA2 carriers having breast and ovarian cancer than in asymptomatic carriers [13].

Another observational study from China included around 1500 patients studied the incidence of gastric, colorectal and breast cancer in relation to the previous appendectomy. The incidence of appendectomy was higher in the cancer group (P less than 0.001). Again, this was significant for breast cancer (P less than 0.01) when it was related to cancer location. When the results were analyzed by age the difference was only significant to the age group of 50-59 years. The authors support the concept that appendectomy may influence cancer risk [14].

A Scottish retrospective observation done in the 1960s included approximately 1000 patients did not suggest any correlation between appendectomy, breast, colon and cervical cancer [15]. In a study included 136 females, the incidence of breast cancer with investigated in patients diagnosed with Hodgkin's disease and treated with mantle field or mediastinal radiation. Splenectomy was an independent risk factor [16].

In a Swedish study, a large cohort of children performed appendectomy were followed until the age of 40. There was a significant excess of stomach cancer and a borderline increase in NHL but nothing was specific about breast cancer. The difference was noticed 15 yrs after the appendectomy. The authors recommended further monitoring for this cohort [17]

In a Danish retrospective study, 6315 splenectomized patients were included. No increased risk for cancer was observed among patients who underwent splenectomy due to trauma. In contrast, there were excesses of a number of specific cancers among patients who underwent splenectomy for non-traumatic reasons, the authors stated that this could be attributed to the factors related to the underlying disease and/or treatment of the disease [18]. Similar results have been obtained from a Taiwanese nationwide population-based study. The incidence was higher for some site-specific cancers, however, breast cancer was not among one of those [19].

A 40% higher risk of cancer was found among Swedish patients undergoing splenectomy for nonmalignant causes in a study included around 1300 patients. There was a significant increase in lung and ovarian cancer in this population. The elevated cancer risk was experienced by patients splenectomized at the age of 30 years or younger [20].

Discussion

The relationship between appendectomy, tonsillectomy, splenectomy and development of breast cancer is still not confirmed. Further clinical and translational research is required. A larger population is needed in each study to influence future results. The studies which are discussed above are coming from few certain countries. Cohorts from different ethnicities may help to detect any association between these procedures and cancer incidence. Since that carcinogenesis process is multifactorial, introducing genetic epidemiology in future studies may help the exact at-risk population performing these surgeries in breast cancer patients as well as in other types of cancer. Taking into consideration the subset of cancer patients with past surgical history of these procedures included in large randomized studies, whenever possible may help to understand whether their disease course/behavior is different from other patients. This as well as their tolerance and response to cancer treatment including immunotherapy.

Conclusions

Future research may elaborate more correlation between these procedures and carcinogenesis of breast cancer, in addition to the possible impact on tolerance and response to novel cancer therapies.

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