

# The correlation between breast cancer and urinary iodine excretion levels

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## Abstract

**Objective:** To compare urinary iodine excretion levels in patients with breast cancer and control subjects.

**Methods:** In this prospective pilot study, patients with breast cancer and normal controls were recruited. Age and menopausal status were recorded. Levels of serum thyroid-stimulating hormone, blood urea nitrogen and creatinine and urine iodine concentration (UIC) were measured. UIC levels were divided into three categories: low ( $<100 \mu\text{g/l}$ ), normal ( $100\text{--}200 \mu\text{g/l}$ ) or high ( $>200 \mu\text{g/l}$ ).

**Results:** A total of 24 patients with breast cancer and 48 controls were included in the study. There were no statistically significant differences between the two groups with regard to thyroid-stimulating hormone, blood urea nitrogen or creatinine levels. When considered overall, there was no statistical difference in UIC between patients and controls. However, comparisons within each category (low, normal or high UIC) showed a significantly higher percentage of patients with breast cancer had a high UIC compared with controls.

**Conclusions:** A high UIC was seen in a significantly higher percentage of patients with breast cancer than controls. UIC may have a role as a marker for breast cancer screening. Further studies evaluating UIC and iodine utilization in patients with breast cancer are warranted.

## Keywords

Urinary iodine excretion, breast cancer, screening

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## Introduction

The correlation between breast disease, iodine and thyroid disease has been a subject of scientific debate for more than 100 years. One of the earliest reports on the association between breast cancer and thyroid disease was published in 1896, when Beatson<sup>1</sup>

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described the use of oophorectomy and thyroid extraction to treat inoperable breast cancer. Since that time many studies have shown associations between breast cancer and hyperthyroidism, hypothyroidism, thyroxine replacement therapy and thyroiditis.<sup>2-4</sup>

In 2000, a study by Tazebay et al.<sup>5</sup> showed that the majority of human breast cancer samples tested (80%) expressed the sodium/iodide symporter (NIS), which is involved in the cellular uptake of iodine. In addition, Wapnir et al.<sup>4</sup> reported that 80% of breast fibroadenoma samples also expressed NIS. The similar role for NIS in mediating iodide uptake in the thyroid gland and in lactating breast tissue suggests that radioactive iodine might be used in the treatment of breast cancer. However, whilst the majority of breast cancers express NIS,<sup>6,7</sup> radionuclide uptake was seen in only 16–25% of breast cancer patients.<sup>6,8</sup> It has been demonstrated that only 27% of NIS-positive breast tumours showed NIS at the cell surface, whereas in the remaining samples NIS appeared as cytoplasmic staining,<sup>9</sup> suggesting that the localization of the NIS may be the reason for the low iodine uptake in breast cancer cells.

The incidence of breast cancer is significantly lower in Japan than in the USA, with an age-adjusted breast cancer incidence of 25.3 per 100 000 in Japan compared with 76.7 per 100 000 in the USA in 2008.<sup>10</sup> However, the incidence of breast cancer in Japanese women who emigrate to the USA and adopt a Western diet equals that of non-Japanese women living in the USA.<sup>10</sup> The lower incidence of breast cancer has been attributed to the increased dietary intake of iodine in the traditional Japanese diet.<sup>11</sup>

If a lack of iodine is linked with breast cancer, this association may be reflected in altered urinary iodine excretion levels. The present pilot study compared urinary iodine excretion levels in patients with breast cancer and control subjects.

## Patients and methods

### Patients

Female patients newly diagnosed with invasive or in-situ ductal breast carcinoma at the Department of General Surgery, Bezmialem Vakif University Faculty of Medicine, Istanbul, Turkey, between December 2014 and March 2015 were included in the study. Patients who had received neoadjuvant chemotherapy were excluded in order to eliminate the unknown effects of chemotherapy drugs. Patients with metastatic disease were also excluded.

Controls in a ratio of 1:2 were recruited from consecutive patients examined at the breast outpatient clinic as part of a breast cancer screening programme. After clinical examination, volunteers were also evaluated by bilateral mammography and bilateral breast ultrasonography. Those with fibrocystic breast disease, simple cysts, fibroadenomas or other benign breast disorders were excluded from the study.

Further exclusions for both patients and controls were the presence of thyroid disease (either benign or malignant), a history of lactation in the previous year, the presence of a chronic disease necessitating drug treatment, and abnormal blood urea nitrogen levels (>1.1 mg/100 ml) and/or abnormal creatinine levels (>20 mg/100 ml).

The study protocol was approved by the ethical committee of the Bezmialem Vakif University Faculty of Medicine, Istanbul, Turkey, and all study participants gave written informed consent.

### Patient assessment

Age and menopausal status were recorded for all study participants.

Blood samples (5 ml) were collected in tubes treated with sodium polyanethol sulphonate. The blood was allowed to clot for 30 min at 25°C and then centrifuged at 2000 g for 15 min at 4°C. The serum layer

was then removed by pipette and stored at  $-80^{\circ}\text{C}$  if not analyzed immediately. Serum levels of thyroid-stimulating hormone, blood urea nitrogen and creatinine were measured using standard procedures.

Urine samples (5 ml) were collected from each study participant in the morning. Urine iodine concentration (UIC) was measured using the ammonium persulfate method, as described previously.<sup>12</sup> UIC was divided into three categories according to the classification used by the World Health Organisation:<sup>12</sup> low ( $< 100\ \mu\text{g/l}$ ), normal ( $100\text{--}200\ \mu\text{g/l}$ ) or high ( $> 200\ \mu\text{g/l}$ ).

In addition, tumour size, lymph node status and hormone receptor status were recorded for each patient.

### Statistical analyses

The number of patients and controls needed was confirmed by a power analysis. Continuous variables were expressed as the mean  $\pm$  SD. Categorical variables were expressed as frequencies and evaluated using the  $\chi^2$  test. Correlations between variables were analysed using the Pearson's correlation test. One-way analysis of variance was used to compare differences in age

and UIC between patients and controls, and multiple linear regression analysis was used to determine the effect of age on UIC. A  $P$ -value  $\leq 0.05$  was considered to be statistically significant. All statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

### Results

A total of 24 patients with breast cancer and 48 controls were included in the study. The mean ages of the patients and controls were  $51.4 \pm 12.4$  years and  $43.5 \pm 11.06$  years, respectively ( $P = 0.005$ ). The menopausal status of the two groups was similar. There were no statistically significant differences between the patients and controls with regard to thyroid-stimulating hormone, blood urea nitrogen or creatinine levels (Table 1).

When considered overall, there was no statistical difference in the UIC between patients and controls. However, comparisons within each category (low, normal or high UIC) showed that a significantly higher percentage of patients had a high UIC compared with controls ( $P = 0.001$ ). The range of UIC in the low, normal and high

**Table 1.** Laboratory findings in patients with breast cancer and controls.

	Patients with breast cancer $n = 24$	Controls $n = 48$	Statistical significance
Thyroid-stimulating hormone, mIU/l	$2.27 \pm 2.14$	$2.86 \pm 1.97$	NS
Blood urea nitrogen, mg/100 ml	$11.4 \pm 4.1$	$10.9 \pm 4.0$	NS
Creatinine, mg/100 ml	$1.0 \pm 0.4$	$1.1 \pm 0.6$	NS
UIC, $\mu\text{g/l}$	$104.60 \pm 1609.38$ (18.03–6021.40)	$75.99 \pm 40.6$ (21.6–201.31)	NS
Low UIC ( $< 100\ \mu\text{g/l}$ )	11 (45.8)	34 (70.8)	$P = 0.001$
Normal UIC ( $100\text{--}200\ \mu\text{g/l}$ )	5 (20.8)	13 (27.1)	NS
High UIC ( $> 200\ \mu\text{g/l}$ )	8 (33.3)	1 (2.1)	$P = 0.001$

Data presented as mean  $\pm$  SD, mean  $\pm$  SD (range) or number (%).

UIC, urine iodine concentration.

NS, no statistically significant difference ( $P > 0.05$ ) using the  $\chi^2$  test or Pearson's correlation test.

**Table 2.** Tumour characteristics in patients with breast cancer ( $n = 24$ ).

Tumour size, cm	2.2 ± 0.8
Lymph nodes involved, $n$	1.9 ± 2.3 (0–11)
Oestrogen receptor status	
Positive	18 (75.0)
Negative	6 (25.0)
Progesterone receptor status	
Positive	20 (83.3)
Negative	4 (16.7)
cErbB2 status	
Positive	4 (16.7)
Negative	20 (83.3)

Data presented as mean ± SD, mean ± SD (range) or number (%).

categories was 24.3–83.6 µg/l, 101.24–151.1 µg/l and 227.0–6021.4 µg/l, respectively. Due to the age discordance between the groups, Pearson's correlation test was performed between UIC and age, but the results were not statistically significant.

The characteristics of the tumours in the patients with breast cancer are shown in Table 2.

## Discussion

Iodine is found in nature in various forms: inorganic sodium and potassium salts (iodides and iodates), inorganic diatomic iodine (molecular iodine or  $I_2$ ) and organic monoatomic iodine. The salted spices widely consumed in Asian countries, though not in Turkey, contain molecular iodine and iodine bound to proteins. These forms of iodine are absorbed through the intestinal tract via two different mechanisms. Molecular iodine is transported by facilitated diffusion, whereas iodides are absorbed via NIS, a molecule found in a variety of tissues in the body that utilize and concentrate iodine, including thyroid, breast, salivary gland and cervical tissue.<sup>13</sup>

In individuals, urinary iodine excretion can vary from day to day and even within a

given day. Studies have demonstrated that a profile of iodine concentrations in morning or other casual urine specimens (child or adult) provides an adequate assessment of a population's iodine nutrition, provided a sufficient number of specimens are collected.<sup>12</sup> Urinary iodine is a well-accepted, cost-efficient and easily obtainable indicator for iodine status. Since the majority of iodine absorbed by the body is excreted in the urine, it is considered a sensitive marker of current iodine intake and can reflect recent changes in iodine status.

Studies on iodine and breast cancer in both human and animal models point to a closer association between iodine and malignant cell growth. Iodine deficiency has been shown to alter the structure and function of rat mammary glands, especially the alveolar cells.<sup>14</sup> Molecular iodine is more effective than iodides at diminishing ductal hyperplasia and perilobular fibrosis in mammary glands using the same total iodine doses.<sup>15</sup> A clinical study of breast cancer patients found levels of iodine were significantly lower in the breast tissue of women with diagnosed breast cancer than in women with either normal breasts or benign fibroadenoma.<sup>5</sup>

The findings of Tazebay et al.<sup>5</sup> suggested that radioactive iodine may act as a therapeutic agent in breast cancer as in papillary thyroid cancer. However, its efficacy is limited due to low functional NIS expression.<sup>4,8</sup> This led to the use of drugs that induce endogenous NIS, the most potent and investigated single agent of which is retinoic acid,<sup>16</sup> but its usage cannot achieve more than 20–40% ID/g of iodide uptake in tumour cells.<sup>17</sup>

The findings of Beyer et al.<sup>6</sup> that only 27% of NIS-positive tumours show NIS localized at the cell surface, whereas in the remaining samples NIS appeared as cytoplasmic staining, may explain the conflicting reports in the literature where, in spite of a very high percentage of NIS positivity reported, only

17–25% of radionuclide uptake in breast cancer patients is observed.<sup>8</sup>

The aim of the present study was to evaluate the UIC in patients with breast cancer. It was thought that high expression of NIS in breast cancer tissue may lead to a low UIC, although the low functional activity of NIS in breast cancer cells may offset this, leading to a normal UIC. However, surprisingly, the UIC in patients with breast cancer was higher than in controls. In view of the significant age difference between the patients and the controls, further analysis of the association between age and UIC was performed, but no significant correlation was found.

As the patients and controls in the present study were from the same rural area, it can be assumed that their eating habits and therefore iodine intake were similar. The higher UIC in breast cancer patients compared with controls suggests that the overexpression of NIS in breast cancer tumour cells is associated with faulty uptake of iodine. This is consistent with the findings of Smyth<sup>18</sup> that the thyroid volume of patients with breast cancer was significantly higher than that of the controls.

The present study showed a higher percentage of patients with breast cancer with a high UIC compared with controls. This finding may be the result of low functional NIS expression, but further studies are required.

Despite studies using NIS induction in the treatment of breast cancer,<sup>19</sup> there is no widely accepted clinical usage of this approach. It may be more effective to investigate the effects of NIS overexpression on iodine utilization. In addition, the high UIC seen in patients with breast cancer may have a role as a marker for breast cancer screening. Further studies on a larger population would be necessary to evaluate this potential use of UIC.

The limitations of the present study include the low number of patients with

breast cancer (although the number of patients was determined by statistical power analysis) and the significant age difference between the patients and the controls.

In conclusion, in the present pilot study the percentage of patients with a high UIC was significantly higher in patients with breast cancer compared with controls. Further studies evaluating UIC in patients with breast cancer and the effect of an overexpression of NIS on iodine utilization are warranted.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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