Self-reported hypothyroidism is increased in women with breast cancer treated with surgery, chemotherapy, and radiotherapy

Reinertsen KV, Cvancarova M, Wist E, Bjoro T, Dahl AA, Danielsen T, Fossa SD. thyroid function in women after multimodal treatment for breast cancer stage II/III: comparison with controls from a population sample. Int J Radiat Oncol Biol Phys 2009. S0360-3016(08)03860-1 [pii];10.1016/j.ijrobp.2008.11.037 [doi]

SUMMARY

BACKGROUND There is a relationship between breast cancer, thyroid dysfunction, and malignant thyroid tumors. However, it is uncertain whether this is due to a genetic link between breast cancer and thyroid tumors or the result of thyroid-tissue injury inflicted by radiotherapy, chemotherapy, or antiestrogens. Although radiation-induced thyroid damage may be the key factor in this situation, it is difficult to be certain, because external-beam radiation techniques have changed considerably in the past few years, during which standardized radiation-field techniques have been gradually altered to offer greater accuracy and individualization of the radiation fields for patients receiving adjuvant radiotherapy. The aim of this study was to assess the prevalence of thyroid disease, particularly hypothyroidism, in women who have received multimodal treatment of stage II/III breast cancer as compared with that in the general population. A secondary aim was to compare the thyroid effects between standardized radiation-field techniques (T-RT) and CT-based treatment fields (CT-RT).

METHODS The study subjects were women with breast cancer treated with radiotherapy after surgery for stage II/III breast cancer at the Norwegian Radium Hospital during the years 1998 through 2002. To assess the late effects of treatment, patients were invited in 2004 to participate in a follow-up questionnaire and thyroid blood testing. The inclusion criteria for the study were age ≤75 years, no evidence of residual breast cancer or other cancers except basal-cell cancer, in situ cancer of the uterine cervix, or prior surgery for contralateral stage I breast cancer. Surgery consisted of modified radical mastectomy or breast-conserving surgery with axillary dissection. Postoperative adjuvant treatment was given according to national guidelines. As a result, during 1999, adjuvant chemotherapy for women <55 years of age changed from nine 3-week cycles of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) to six 3-week cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). From 2001, adjuvant FEC chemotherapy was also given to those between the ages of 55 through 64 years with hormone receptor–negative disease. Patients with inoperable tumors received preoperative chemotherapy before modified radical mastectomy and axillary dissection and were treated with the FEC regimen or were randomly assigned to receive four to eight 3-week cycles of epirubicin 90 mg/m^2 or paclitaxel 200 mg/m^2. Patients with hormone receptor–positive tumors or unknown receptor status were advised to take tamoxifen 20 mg daily for 5 years. Before 2000, radiotherapy (RT) was based on a standardized T-RT field, but since 2000, treatment was based on computed tomography images (CT-R. For each patient with breast cancer, five cancer-free and age-matched women were randomly selected as controls from a national Norwegian Health study.

RESULTS From 2004 through 2005, 318 of 418 eligible patients (77%) participated in the study, but three were subsequently excluded from the survey because of lack of blood samples in 2 and detection of new metastasis in 1. In 2007, 308 living patients were invited to participate in a new follow-up study. In

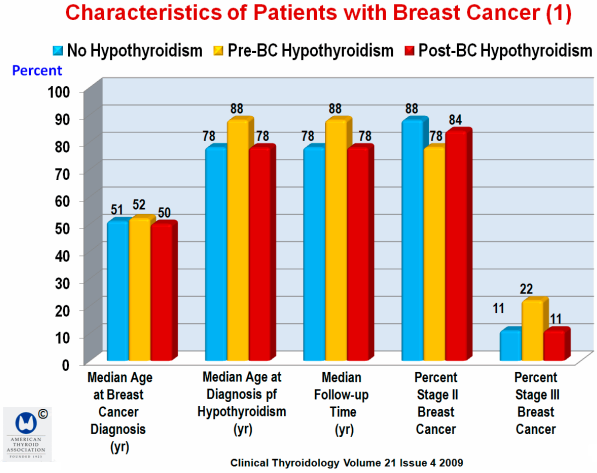

Figure 1. The baseline characteristics of the study population with breast cancer (BC) are derived from Table 1 of the study by Reinertsen et al.

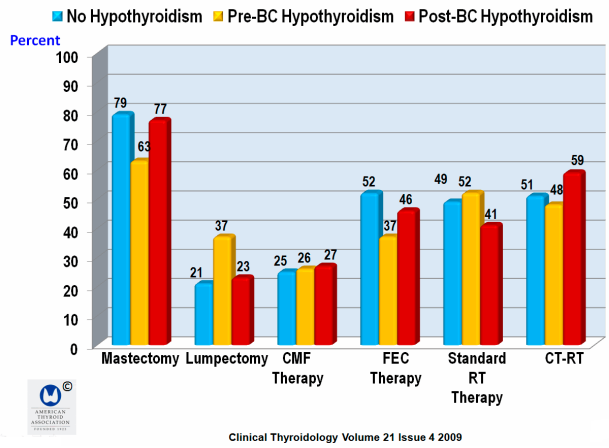

Figure 2. The surgical and medical treatment of patients with breast cancer is shown. BC = breast cancer; CMF = cyclophosphamide, methotrexate, and fluorouracil; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; RT = radiotherapy; Standard RT therapy = radiotherapy with a fixed radiation field; CT-RT = therapy with radiotherapy fields based on computed tomography imaging.

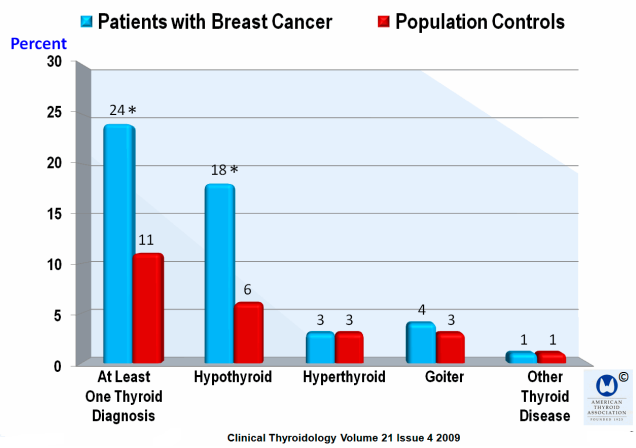

Figure 3. The prevalence of thyroid disease is based on patient self-reporting. *P<0.001 for patients versus controls.

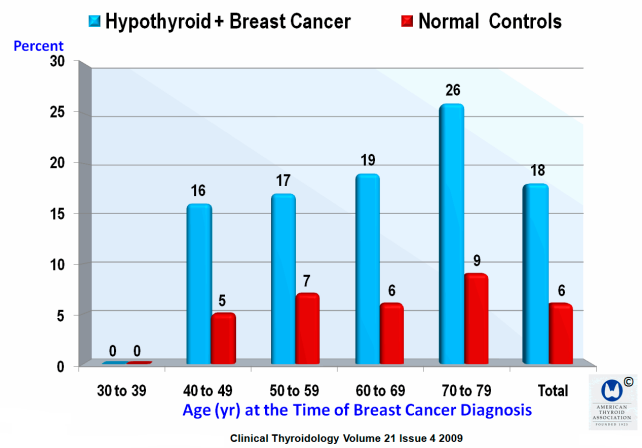

Figure 4. The prevalence of hypothyroidism increased steadily with age in patients with breast cancer.

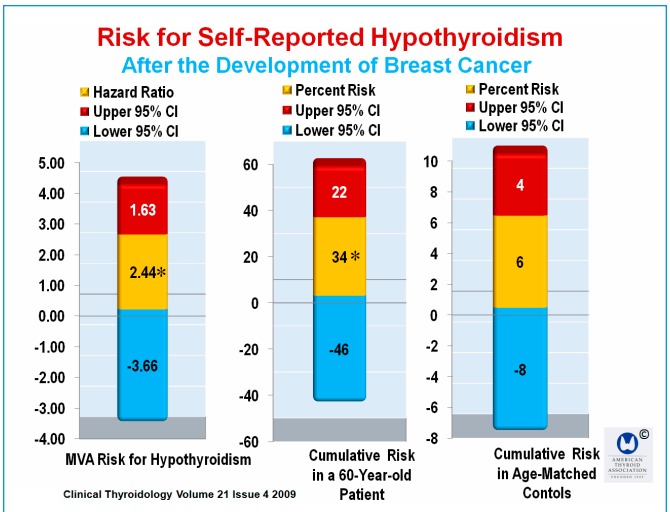

Figure 5. The risk for hypothyroidism is assessed by multivariate analysis (MVA) and as a cumulative risk in a 60-year-old patient with breast cancer as compared with five age-matched cancer-free women for each patient with breast cancer. *P<0.001.

addition, 145 additional patients not identified in 2004 were also invited to participate. In 2007, 336 patients (74%) had returned at least one completed questionnaire and had blood samples taken. Thus, a total of 403 patients participated in the study, but 16 participated only in 2004, 88 participated only in 2007 and 248 participated in both 2004 and 2007.

The major patient and treatment characteristics of all patients with breast cancer are shown in Figures 1 and 2. In all, 24% of the patients with breast cancer reported a diagnosis of at least one thyroid disorder, as compared with 11% in the general population. Hypothyroidism was the most common thyroid disorder in both the patients and controls (18% vs. 6%, P<0.001), whereas the prevalence of other thyroid diseases in the two groups were comparable (Figure 3). Hypothyroidism was progressively more prevalent in older patients (Figure 4). Prior to the diagnosis of breast cancer, 24 patients (7%) had a diagnosis of hypothyroidism, as compared with 6% of the controls; However, a median of 35 months (range, 5 to 88) after breast surgery, the diagnosis of hypothyroidism was twice as likely in patients as compared with controls (hazard ratio [HR], 2.44; 95% confidence interval [CI], 1.63 to 3.66) (Figure 5). Although univariate analysis found that the diagnosis of hypothyroidism was associated with a physician visit within the past year and a higher level of education, the hazard ratio was not affected when adjusted to these two variables. The cumulative risk for postoperative hypothyroidism in a 60-year-old patient was 34% (95% CI, 22 to 46), as compared with 6% in the control group (95% CI, 4 to 8). (Figure 5) There was a trend for increased occurrence of postsurgical hypothyroidism in patients treated with CT-RT as compared with 18 patients treated with T-RT (P = 0.08), which remained unchanged after adjustment for age.

Among the patients who reported no thyroid disease, 10% of the patients with breast cancer had elevated serum thyrotropin (TSH) levels, as compared with 7% in the control group (P = not significant) but biochemical hypothyroidism was present in none of the former and only 1% of the latter. Paradoxically, positive serum thyroid peroxidase antibody (TPOAb) tests were more common among patients with breast cancer than among patients with hypothyroidism (P<0.01); however, TPOAb was positive more often in patients in whom hypothyroidism developed before breast cancer than after (26% vs. 41%, P = not significant)

CONCLUSION Self-reported hypothyroidism is increased in women with breast cancer treated with surgery, chemotherapy, and radiotherapy.

COMMENTARY

Hypothyroidism is a potential complication of radiotherapy when the thyroid is included in the treatment fields. The main finding in the study by Reinertsen is that the rate of self-reported hypothyroidism was significantly increased in patients with breast cancer as compared with the general population, whereas prior to the diagnosis of breast cancer the prevalence of hypothyroidism was similar to that of age-matched cancer-free controls. Although there was a trend for ($P = 0.08$) for an increase in hypothyroidism in patients treated with a standardized radiation as compared with CT-guided field, the difference was not statistically significant.

A systematic review by Jereczek-Fossa et al. (1) suggested that radiotherapy-induced thyroid abnormalities remain underestimated and underreported. The sequelae of radiation therapy may include primary or central hypothyroidism, thyroiditis, Graves' disease, euthyroid Graves' ophthalmopathy, benign adenomas, multinodular goiter and radiation-induced thyroid carcinoma. However, primary hypothyroidism is the most common radiation-induced thyroid dysfunction, affecting 20% to 30% of patients following radiotherapy to the neck region, with approximately half of the events occurring within the first 5 years after therapy. The authors of this study acknowledged that the contribution of other treatment methods such as chemotherapy and endocrine therapy, as well as patient- and tumor-related factors is less clear. Their recommendation was to obtain a history for symptoms of thyroid dysfunction, clinical examination, and measurement of thyroid hormones and serum TSH. Several other studies have made similar observations and have recommended similarly appropriate surveillance for this group of patients (2). A study of 10 patients by Hancock et al. (3) found a marked dose-dependent effect of radiation therapy on the development of hypothyroidism.

Smith et al., in the most recent and largest study (4) of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER)-Medicare registry, identified 38,255 women 65 years of age or older with stage 0 to III breast cancer from 1992 to 2002 that was treated with radiotherapy to a supraclavicular field, which typically includes a portion of the thyroid. When the incidence of hypothyroidism in this irradiated cohort was compared with that in 111,944 cancer-free controls, the study found, after adjusting for sociodemographic and clinical characteristics, that the risk for hypothyroidism was not increased in irradiated patients. However, all patients, regardless of radiotherapy status, were more likely to have hypothyroidism as compared with cancer-free controls (HR, 1.21; 95% CI, 1.17 to 1.25). The authors concluded that development of hypothyroidism is fairly common in older breast cancer survivors, and supraclavicular irradiation does not appear to amplify risks, but suggested that further studies of the role of routine thyroid-function monitoring in all patients with breast cancer regardless of treatment may be warranted, given the excess risks as compared with the general population.

It is difficult to make a recommendation on the basis of the study by Reinertsen, mainly because the incidence of hypothyroidism was self-reported, and there may have been ascertainment bias among patients with breast cancer who might have had their thyroid function checked more often than is usual for the general population. Whether this group of irradiated patients with breast cancer should receive more surveillance for hypothyroidism than that in the general population remains uncertain. Still, routine testing for thyroid dysfunction, especially hypothyroidism, is well within the standard of care for postmenopausal women.

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