Letters to the Editor

Risk of Breast Cancer in Patients with Thyroid Cancer Receiving ^{131}I Treatment: Is There an Immortal Time Bias?

TO THE EDITOR: We perused with interest the article titled, "Risk of Breast Cancer in Patients with Thyroid Cancer Receiving or Not Receiving ^{131}I Treatment: A Nationwide Population-Based Cohort Study" (*1*). The article reported a nationwide population-based cohort study showing an increased risk of breast cancer among thyroid cancer patients who have received ^{131}I therapy, with an adjusted hazard ratio of 1.34 (95% confidence interval [CI], 1.06–1.69). The association was stronger after a follow-up of more than 5 y, with an adjusted hazard ratio of 1.81 (95% CI, 1.27–2.57). For patients with thyroid cancer but without ^{131}I therapy, the increment in risk was not statistically significant, with adjusted hazard ratios of 1.26 (95% CI, 0.90–1.76) and 1.28 (95% CI, 0.72–2.26) for the overall group and the subgroup having more than 5 y of follow-up, respectively. The result was compatible with the existing knowledge of radiation-induced carcinogenesis, a process that takes several years to decades (*2*).

However, this study also showed that cumulative ^{131}I dose (>4.44 GBq vs. ≤4.44 GBq) is not associated with an increased risk. The authors hypothesized that the main reason for carcinogenesis is not radiation exposure but an increase in sodium iodide symporter expression before ^{131}I treatment. Nevertheless, it seems that "immortal time bias" (*3–6*) could explain the lack of correlation between radiation dose and breast cancer risk. Because the occurrence of breast cancer is the primary endpoint and also the end of the observation period, as stated by the authors, the effect of further ^{131}I treatment for residual or recurrent thyroid cancer after breast cancer diagnosis would be ignored. Consequently, the patients who "survive" longer have a greater chance of receiving more courses of ^{131}I treatment and, thus, a higher cumulative dose. This will bias the estimated hazard ratio of treatment effect toward zero, that is, a false protective effect. Indeed, if the bias is corrected, a high cumulative ^{131}I dose might actually be associated with an increased breast cancer incidence.

Another problem is that the differences in baseline characteristics and survival between patients with and without ^{131}I may also be correlated to risk of breast cancer. In addition to multivariable regression analysis, as already done in this study, propensity score analysis and competing-risk analysis may further clarify this issue.

Immortal time bias is common in observational cohort studies. A review of the literature by van Walraven et al. demonstrated that, in leading medical journals, more than 40% of clinical studies using survival analyses with a time-dependent factor were susceptible to immortal time bias (*7*). Fortunately, the bias could be removed by time-dependent analysis, such as Cox regression with cumulative ^{131}I dose as a time-dependent covariate (*3,5*). We hope that a reanalysis of the original data can be performed to clarify this issue.

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REPLY: We appreciate your concerns about our study (*1*). The Taiwan National Health Insurance Database (NHIRD) provides no detailed information on factors such as a patient's lifestyle, behavioral habits, body mass index, physical activity, socioeconomic status, and family history, all of which were possible and important confounding factors in our study. The fact that complete confounding factors are not available in NHIRD for propensity score matching was one of the limitations of the study and was described as such in our article. Furthermore, the study adjusted for differences in the incidence of comorbidities. As we stated in the article, the 5-y survival rate of all people with thyroid cancer is approximately 98%. Because of the very low mortality in well-differentiated thyroid cancer, there was no need to consider it a competing risk.

In view of your concerns, we have performed Cox regression with cumulative ^{131}I dose as a time-dependent covariate, adjusted for age, all comorbidities, hormone therapy, mammography, and ultrasonography. During the study period, the ^{131}I-treated group exhibited a 1.26- and 1.15-fold higher risk of breast cancer than the nontreated group, according to the crude and adjusted time-dependent Cox proportional hazards models, respectively (95% confidence intervals, 0.76–2.09 and 0.69–1.92). This difference was not statistically significant. Similar results were found in the