Letter to the Editor

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

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Dear Editor:

We peruse with interest “Risk of Breast Cancer in Patients With Thyroid Cancer Receiving or Not Receiving I-131 Treatment: A Nationwide Population-based Cohort Study”(1). The study reported a nationwide population-based cohort study showing an increased risk of breast cancer among thyroid cancer patients who have received I-131 therapy, with an adjusted hazard ratio (HR) of 1.34 (95%CI, 1.06-1.69). The association is stronger after follow up time >5 year, with an adjusted HR of 1.81 (95%CI, 1.27-2.57). For patients with thyroid cancer but without I-131 therapy, the increment in risk is not statistically significant, with adjusted HRs of 1.26 (95%CI, 0.90-1.76) and 1.28 (95%CI, 0.72-2.26) for overall and for subgroup with follow-up > 5 years, respectively. The result is 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 I-131 dose (>4.44 GBq vs. ≤4.44 GBq) is not associated with an increased risk. The authors proposed a hypothesis that increasing sodium-iodide symporter (NIS) expression before I-131 treatment is the main reason of carcinogenesis, rather than radiation exposure. 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 end point
and also the end of observation period, as stated by the authors, further I-131 treatment for residual or recurrent thyroid cancer after breast cancer diagnosis would be ignored. Consequently, the patients who “survive” longer have a greater chance to receive more courses of I-131 treatment, and thus high cumulative dose. It will bias the estimated HR of treatment effect toward zero, that is, a false protective effect. Indeed, if the bias is corrected, high cumulative I-131 dose might actually be associated with an increased breast cancer incidence.

Another problem is that the differences in baseline characteristics and survivals between patients with or without I-131 may also be correlated to risk of breast cancer. In addition to multivariable regression, 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 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 I-131 dose as a time-dependent covariate (3,5). We look forward that reanalysis of the original data can be performed to clarify this issue.
Yours sincerely,

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References


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