Discussion | Between 2009 and 2016, after 3 decades of rapid increase,[1] the incidence of thyroid cancer incidence in the United States reached a plateau and possibly started to decline. Increasing trends in the incidence of subcentimeter thyroid cancers, most prone to increasing detection, began to reverse direction between 2013 and 2016. Limitations of this study include the nature of observational analyses, which cannot prove causality, and that the trends may not generalize to other areas of the United States beyond the SEER 13 geographic regions.

Although a true decline in the occurrence of thyroid cancer is a possible explanation for these changing trends, less intensive workup of thyroid nodules is more likely. These changes have occurred during a time of evolving understanding of overdiagnosis and the indolent nature of many small thyroid cancers, reflected in changing clinical practice guidelines, including recommendations against screening for thyroid cancer by the US Preventive Services Task Force in 2017.[5] Recently, several US professional societies have developed radiographic classification systems for thyroid nodules and introduced risk-stratified recommendations against routine biopsy of nodules more likely to be benign or represent indolent cancers. For example, in 2009 and 2015, American Thyroid Association guidelines introduced size and appearance-based criteria, recommending observation rather than immediate biopsy for many smaller, lower-risk nodules.[6]

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Incidence of Hypoparathyroidism After Thyroid Cancer Surgery in South Korea, 2007-2016

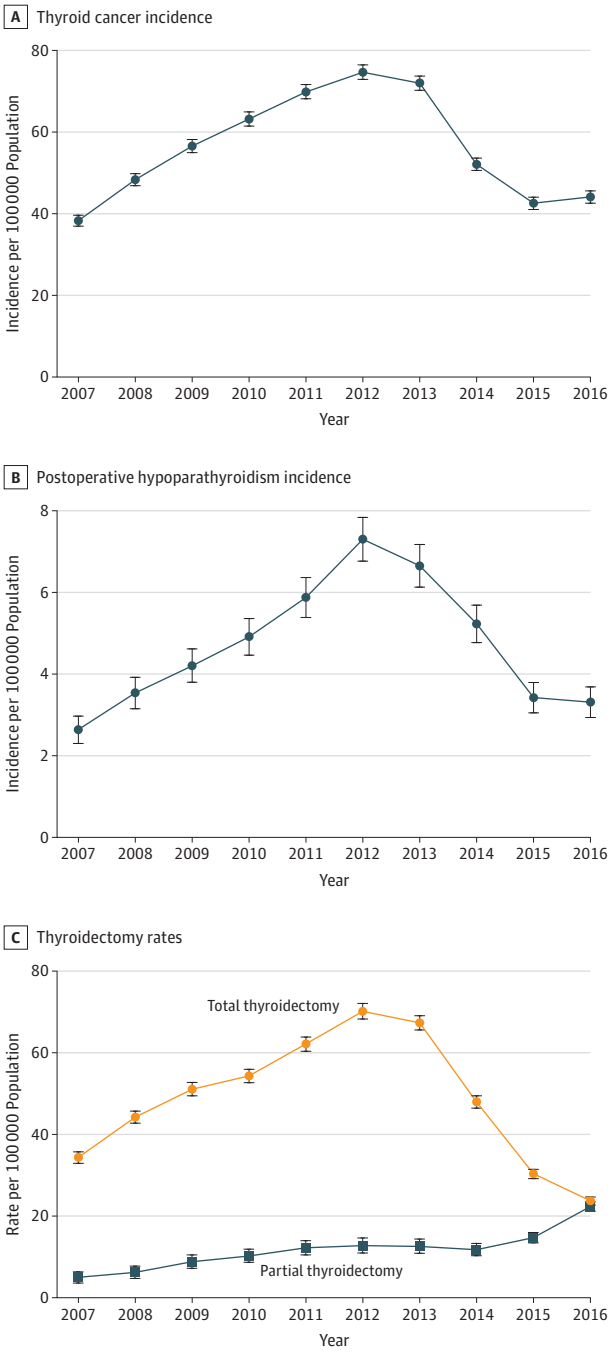
In 1999, the South Korean government initiated a national cancer screening program, which led to increased high-resolution ultrasonography screening for thyroid cancer. Consequently, thyroid cancer incidence increased from 7.2 per 100 000 population in 1999 to 68.7 per 100 000 population in 2011,[1,2] and most patients received surgery. However, many screen-detected cancers were small and likely indolent. Concerns about overdiagnosis were raised beginning in 2012, and ultrasonographic screening was discouraged in 2014, leading to decreased incidence of thyroid cancer and thyroidectomies.[3,4] We assessed the changes in incidence rates of postoperative hypoparathyroidism, a complication of thyroidectomy, between 2007 and 2016.

Methods | We used the South Korean National Health Insurance Sharing Service Database, an administrative database based on health insurance claims from the entire population of South Korea, to calculate the change in incidence of thyroid cancer, total and partial thyroidectomies, and postoperative hypoparathyroidism per 100 000 between 2007 and 2016. Definitions of partial and total thyroidectomies were adopted from a previous report[5]; partial thyroidectomies are less likely to result in hypoparathyroidism. Data on incidence of postoperative hypoparathyroidism and thyroid cancer were age-standardized to the South Korean standard population of 2000. The operational definition of postoperative hypoparathyroidism was modified from a previous report.[6] The following conditions had to be satisfied, in the corresponding year but not in the previous 3 years, to meet the definition of permanent postoperative hypoparathyroidism: (1) thyroidectomy prior to first active vitamin D prescription; (2) thyroid cancer before first active vitamin D prescription or diagnostic code for hypoparathyroidism after thyroidectomy; and (3) at least three 90-day prescriptions for active vitamin D. The incident date of hypoparathyroidism was defined as the first date of active vitamin D prescription. The operational definition was validated through a separate retrospective chart review at a single medical center, in which we queried electronic medical records to identify cases of postsurgical hypoparathyroidism between 2010 and 2018 and verified the results by manual chart review. Sixty-five of 81 cases (81.5%) identified by electronic medical record were confirmed to have hypoparathyroidism, suggesting an acceptable positive predictive value for the operational definition.

We calculated 95% confidence intervals for incidences using SAS software, version 9.4 (SAS Institute Inc). The Gachon University Gil Medical Center institutional review board approved this study with a waiver of informed consent.

Results | Between 2007 and 2016, 29 063 cases of postoperative hypoparathyroidism were identified, including 1466 cases

Figure. Incidence of Thyroid Cancer and Postoperative Hypoparathyroidism and Rates of Thyroid Cancer Surgeries in South Korea



Error bars indicate 95% confidence intervals. A, The incidence of thyroid cancer per 100 000 population in 2007 was 38.3 (95% CI, 37.7-38.8) and in 2016 was 44.1 (95% CI, 43.5-44.7). B, The incidence of postoperative hypoparathyroidism per 100 000 population in 2007 was 2.6 (95% CI, 2.5-2.7) and in 2016 was 3.3 (95% CI, 3.2-3.5). C, The rate of total thyroidectomy per 100 000 population in 2007 was 34.8 (95% CI, 33.7-34.8) and in 2016 was 23.6 (95% CI, 23.2-24.0); the rate of partial thyroidectomy per 100 000 population in 2007 was 4.8 (95% CI, 4.3-5.4) and in 2016 was 22.2 (95% CI, 21.8-22.7).

in 2007 and 2135 cases in 2016. Between 2007 and 2012, the incidence of thyroid cancer, total thyroidectomies, and postoperative hypoparathyroidism increased. Postoperative hypoparathyroidism increased from 2.6 (95% CI, 2.5-2.8) per 100 000 population in 2007 to 7.3 (95% CI, 7.1-7.5) per 100 000 population in 2012, an increase of 177% (**Figure**), and total thyroidectomies increased from 34.3 (95% CI, 33.7-34.8) per 100 000 population in 2007 to 70.1 (95% CI, 69.4-70.9) per 100 000 population in 2012, an increase of 104%. After 2012, the rate of thyroid cancer and total thyroidectomies decreased, the latter reaching 23.6 (95% CI, 23.2-24.0) per 100 000 population in 2016, and the incidence of postoperative hypoparathyroidism decreased to 3.3 (95% CI, 3.2-3.5) per 100 000 population. In contrast, the rate of partial thyroidectomies increased gradually between 2007 and 2016, comprising 18% of total thyroidectomies in 2012 (6369/35 307) and 94% in 2016 (11 365/12 066).

Discussion | The incidence of postoperative hypoparathyroidism in South Korea increased and then decreased between 2007 and 2016 in parallel with trends in thyroid cancer diagnosis and treatment. The initial increase in the incidence of thyroid cancer might be linked to the initiation of a national cancer screening program, while the subsequent decrease may be related to concerns about overdiagnosis.[3] The limitation of this study was that postoperative hypoparathyroidism might be underestimated because of use of administrative claims. Postoperative hypoparathyroidism is a rare but serious complication of thyroid surgery and an example of harm related to overdiagnosis and overtreatment.

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COMMENT & RESPONSE

Continuing Antipsychotic Medication for Patients With Psychotic Depression in Remission

To the Editor Based on their randomized clinical trial, Dr Flint and colleagues concluded that continuing sertraline and olanzapine compared with sertraline and placebo reduced the risk of relapse of depression in patients with psychotic depression in remission.[1] We are concerned about limitations in their study design.

First, the criteria for remission allowed patients to enter the randomized phase if they had a 17-item Hamilton Depression Rating Scale (HDRS) score of up to 15 points.[1] Even among patients fulfilling the common remission criterion of an HDRS score of 7 or lower, many do not consider themselves to be in remission from their depression.[2] Remission implies that the signs and symptoms of the depression must be absent or nearly absent[3]; the concept of remission lacks validity when many included patients may have substantial morbidity.

Second, patients could be considered in relapse if they had an HDRS score of 18 or higher.[1] Considering that patients may effectively have had syndromal depression when randomized, only a relatively slight increase in symptoms, eg, 3 points on the HDRS, could have led to patients being considered in relapse. The concept of relapse lacks validity in the absence of preexisting remission.[3] Relapse could, in the study by Flint and colleagues,[1] constitute a relatively minor worsening of preexisting depression rather than the reemergence of depression or, given the small symptom difference as the threshold, arise because of unblinding due to adverse events.

Third, the withdrawal design placed participants in the placebo group at risk of developing withdrawal symptoms as part of serotonergic, adrenergic, muscarinic, or histaminergic withdrawal syndromes and/or supersensitivity psychosis.[4] The 4-week switch to placebo did not mitigate such risk, as patients in the placebo group were tapered to 5 mg of olanzapine daily before stopping, a dose at which there is a considerable biological effect of the drug.[5] Distinguishing reemergence of depression or psychosis from withdrawal symptoms can be difficult, and the withdrawal design used by Flint and colleagues may therefore conflate withdrawal reactions with relapse. Their results suggest this was the case: most of the outcomes in the placebo group occurred within the first 8 weeks, whereas from week 8 to 36, only 1 more patient in the placebo group compared with the active group left the trial.[1]

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In Reply Dr Munkholm and colleagues have concerns about the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) II clinical trial,[1] which they argue could affect the validity of the study, including enrolling participants in "near remission" and conflating antipsychotic withdrawal symptoms with relapse.

Only 14 of the 126 randomized participants (11.1%) in the clinical trial had 17-item HDRS total scores in the 11- to 15-point range at the time of randomization. The sertraline plus olanzapine and sertraline plus placebo groups did not significantly differ in the proportion of participants in near remission (9 of 64 [14.1%] and 5 of 62 [8.1%], respectively) nor in the mean HDRS total score at the time of randomization (5.3 [SD, 3.6] and 5.6 [SD, 3.6], respectively). Recognizing that incomplete remission of depressive symptoms may increase the risk of relapse,[2] the Cox proportional hazards model was adjusted for remission-near remission status: as reported in the article, remission status was not significantly