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Risk of Suicide Attempt after Thyroidectomy: A Nationwide Population Study in South Korea

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Objective To investigate the association between thyroidectomy and suicide attempt.

Methods A nationwide population-based electronic medical records database of South Korea between January 1, 2009 and June 30, 2016 was used to investigate incidence rate ratios (IRRs) of suicide attempts and probable suicide attempts before and after thyroidectomy using a self-controlled case series design.

Results In 2,986 patients who attempted suicide or probable suicide, the IRRs of suicidal behaviors during risk periods one year before and after thyroidectomy were investigated. Generally, after thyroidectomy, there was no increase in IRR compared to the non-risk period. When data were analyzed according to thyroidectomy type, after partial thyroidectomy, IRR increased up to 1.43 (95% CI: 1.03–1.98, p=0.032) in the days 91–181 period. In the subgroup with major depressive disorder (MDD), the IRR increased up to 1.74 (95% CI: 1.21–2.51, p=0.003) before thyroidectomy, and increased up to 1.67 (95% CI: 1.16–2.41, p=0.006) after thyroidectomy.

Conclusion Although the general risk of suicide attempt was not increased after thyroidectomy, patients with MDD showed increased risk of suicide attempt before and after thyroidectomy. These results suggest that suicidality should be evaluated when depressive symptoms are present in patients who have undergone thyroidectomy.
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Key Words Suicide attempt, Thyroidectomy, Incidence rate ratios.

INTRODUCTION

Thyroidectomy is surgical removal of all or part of the thyroid gland and can affect secretion of thyroid hormones, causing hypothyroidism. Hypothyroidism is known to be associated with psychiatric manifestations such as mood[1,2] and cognition;[1,3] rarely, severe hypothyroidism in myxedema can lead to agitation and psychosis.[4,5] In addition, studies about thyroidectomy have shown that thyroidectomy increases psychiatric morbidity. Recently, we studied the incidence of major depressive disorder (MDD) after thyroidectomy using claim data of South Korea and revealed that MDD increased between one and two years after surgery, especially for those over 50 years old.[6] In addition, another study found that patients with thyroid cancer who undergo thyroidectomy have depressive disorder more frequently compared to normal controls.[7] A comparative study found that depressed patient with hypothyroidism had more anxiety symptoms and greater agitation and fewer severe core depressive symptoms and biological signs of MDD, and suggested that MDD associated with hypothyroidism is differentiated from MDD without hypothyroidism.[8] Another study found the increased regional homogeneity reflecting

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disturbed neural modulations in multiple brain areas in patients with hypothyroidism after total thyroidectomy, and this change was associated with poorer mental quality of life and depression.[9] In an animal model, lateral habenula in the brain region is suggested to be associated with depressive symptoms that occur after thyroidectomy.[10]

Many studies have investigated suicide attempts, and various factors have been associated with suicide attempt, including genetic loading,[11,12] brain dysfunction,[13,14] psychopathologies,[15,16] emotional states such as aggression and impulsivity,[12,17] comorbid physical diseases including cancers,[18,19] use of hypnotics or substance,[12,20] and personal experience such as childhood trauma.[11,21] In addition, previous studies have consistently reported that depression is the most common psychiatric disorder in people died by suicide.[22-25]

Thyroidectomy and suicide attempt are suggested to share many features considering that hypothyroidism is associated with psychiatric manifestations, depressive symptoms can occur after thyroidectomy, and thyroid disease such as thyroid cancer lead to thyroidectomy. However, as mentioned above, although hypothyroidism caused by thyroidectomy can lead to depression, the manifestation of it is different from that unrelated to thyroid problem. Therefore, it is an important to identify the effect of psychosocial changes after thyroidectomy on suicide attempts. However, the association between thyroidectomy and suicide attempt is not well established.

This study aimed to investigate the association between thyroidectomy and suicide attempt. In this study, we hypothesized that 1) thyroidectomy would be associated with suicide attempt or probable suicide attempt, 2) the risk of suicide attempts or probable suicide attempts after total thyroidectomy would be higher than after partial thyroidectomy, and 3) the risk of suicide attempts or probable suicide attempts after thyroidectomy would be higher in people with thyroid cancer than in people with benign thyroid disease.

METHODS

Data source

This study used data obtained from the Korea National Health Insurance (KNHI) Claims Database of the Health Insurance Review and Assessment Service (HIRA) in South Korea.[26] HIRA is a public institution responsible for evaluation of medical expenses of medical institutions and appropriateness of medical care benefits. Such data are open to the public and cover all health services including admission, emergency room visits, ambulatory care visits, and pharmaceutical services. This data provide medical information for approximately 50 million Koreans, but does not include information related to death. Nearly 97% of the total population is enrolled in this service, while the remaining 3% is covered by the Medical Aid Program. HIRA data are anonymized to protect the privacy of individuals, and the HIRA provides individual numbers for researches that replace the social security numbers. The data are widely used in various fields of medical research.[20,27,28] The study protocol was approved by the Institutional Review Board of Samsung Medical Center (No. 2019-04-022).

Case identification

We used HIRA data from January 1, 2009 to June 30, 2016 and identified 187,176 patients who had undergone partial (P4551, P4553) or total (P4552, P4554, P4561) thyroidectomy only once during the period January 1, 2011 to June 30, 2015.

Patients having received an intentional self-harm code (X60–X84) were categorized into the suicide attempt group based on the International Statistical Classification of Disease and Related Health Problems 10th revision (ICD-10). Those with several ICD-10 codes not explicitly identified as suicide attempt but highly suspected as suicide attempts were included in the group of probable suicide attempts (Supplementary Table 1 in the online-only Data Supplement). According to previous studies, it is estimated that 62–81% of suicide attempts are not detected by physicians.[29-31] We assumed that because of self-concealment, many people would not have suicide attempt code even if they had come to the hospital for physical problems associated with suicidal intention. Previous studies have shown that many people tend to conceal their suicidal intention from physicians,[29,31,32] and even if they come to the hospital after a suicide attempt, physicians may not notice suicidality when they focus on the physical condition that was caused by suicidal behavior.[30,33] A previous study has shown that it is difficult to determine the intention of behavior in cases of death due to hanging or suffocation, poisoning, falling, and drowning.[34] Similarly, when treated for these causes, suicidality is likely to be ignored. Also, even if the physician knows suicidal intention of a patient, there is a possibility that the physician enters codes only related to physical problem resulted from suicide attempt. If the outcome is defined by the codes of suicide attempt, underestimation of suicidality may occur, and this can lead to bias. Because of this, we also established a probable suicide attempt group and included them in the analysis.

Among 187,176 patients who had undergone thyroidectomy during the study period, 16 had codes of suicide attempt and 3,362 had codes of probable suicide attempts. One patient with suicide attempt and 389 patients with probable suicide attempt in 2009 were excluded. In addition, two patients were excluded because of probable suicide attempt on the day of thyroidectomy. Including four patients with both codes of suicide attempt and probable suicide attempt, 2,986 patients were in-

cluded in statistical analysis (Supplementary Figure 1 in the online-only Data Supplement).

We performed subgroup analyses to identify patterns and outcomes according to thyroidectomy type, thyroid disease and diagnosis of MDD. For subgroup analysis according to thyroid disease, people with ICD-10 code of C73 were classified into the thyroid cancer group while those without this code were classified under the benign thyroid disease. For subgroup analysis in people with MDD, people with ICD-10 codes of F32 or F33 were classified into the MDD group.

Self-controlled case series design

We used a self-controlled case series (SCCS) study design[35] to investigate the association of thyroidectomy with suicide attempts and probable suicide attempts. In this study design, individuals act as their own control. Because the comparisons were made within individuals, only those who experienced an event were included, while all time-invariant confounders were eliminated (i.e., genetic factors, individual frailty, and psychosocial factors).[36] SCCS represents an alternative epidemiologic study design to resolve difficulties in selecting an appropriate comparison group in cohort or case-control studies investigating suicide attempt.[35] Considering that various complex factors and their timing affect suicide attempts, case-control design has major limitations in the research on suicide attempt due to inadequate control for key confounders such as psychiatric condition, psychosocial stress, genetic loading, and personal experience. The SCCS was determined as an appropriate model for attenuating significant bias in research on suicide attempt.[20,37] The SCCS method estimates the incidence of events during risk periods compared with the incidence during all other periods.[35]

Exposure and outcomes

The SCCS design requires establishing the risk period likely affected by the exposure during the observation period. The index date of exposure was defined as the day of thyroidectomy. We defined the pre- and post-exposure periods as one year before and after the index date, respectively. Regarding post-exposure period, because the direct evidence on risk of suicide attempt after thyroidectomy was insufficient, we established risk period considering relevant previous studies. According to a study of suicide in cancer patients, the standardized mortality ratio of suicide among patients with thyroid cancer was highest at 2 to 11 months after diagnosis.[19] And other studies have reported the increased risk of depressive disorder after thyroidectomy up to postoperative year 1.[6,7] Considering that depression constitutes 60−70% of all suicides,[38] the risk of suicide attempt is assumed to increase when the risk of depression increases. In addition, we had established the pre-exposure risk period as one year before thyroidectomy considering the time from diagnosis of thyroid cancer to thyroidectomy. According to a previous study of cancer patients, distress is known to be the greatest in the waiting period for surgery or treatment after diagnosis.[39] In South Korea, the waiting time from diagnosis of thyroid cancer to surgery varies depending on the individuals, but it is known to take up to 10−12 months.[40,41]

We then divided the period into three-month intervals. The pre-exposure period was then divided into -365−-271, -270−-181, -180−-91, and -90−-1 segments with regard to the days before thyroidectomy. The post-exposure period was divided into 1−90, 91−180, 181−270, and 271−365 segments and represents the days after thyroidectomy. In order to set the subdivided risk period, we had examined the incidence rate ratios (IRR) in various time windows, and found there was no difference in trend of risk change in various time windows. Therefore, we divided the risk period into three-month intervals considering the general interval for visit to physicians. The first event in individuals who attempted multiple suicides or probable suicides was analyzed in this study.

Statistical analysis

To investigate the association between thyroidectomy and suicide attempts or probable suicide attempts, we investigated the IRRs of suicide attempts and probable suicide attempts during in sub-risk periods. Data from day 0 (day of thyroidectomy) were not included in the analysis. Adjusted IRRs and corresponding 95% CIs were calculated using conditional Poisson regression after adjusting for age and season. The IRR in each sub-risk period was defined as the relative ratio of incidence of event in sub-risk period compared to that in non-risk period. The same methods were applied to subgroup analyses according to thyroidectomy type and thyroid disease and subgroup analysis in people with MDD.

RESULTS

Sample characteristics

Among 187,176 patients who had undergone thyroidectomy during the study period, excluding those who were coded with suicide attempt or probable suicide attempt in 2009 or on the day of thyroidectomy, 2,986 individuals who had record of at least one suicide attempt or probable suicide attempt per protocol were included in our analyses. Of these, 15 had a record of a suicide attempt, while 2,971 had record of a probable attempt. Four individuals had both codes of suicide attempt and probable suicide attempt. Males constituted 13.33% of those attempting suicides and 22.01% of those attempting probable suicide. The mean age of patients having undergone thyroidectomy was 47.27 (SD=15.17) years in suicide attempt-

Table 1. Demographic and clinical characteristics of subjects in suicide attempt and probable suicide attempt groups

Variables	Suicide attempt[a] (N=15)	Probable suicide attempt[b] (N=2,971)		
		MDD[c]	Non-MDD	Total
Male (N, %)	2 (13.33)	91 (16.25)	563 (23.35)	654 (22.01)
Age at thyroidectomy (SD)	47.27 (15.17)	53.47 (12.56)	49.82 (12.30)	50.51 (12.43)
Age at first suicide or probable suicide attempt (SD)	48.60 (13.81)	53.89 (12.82)	50.35 (12.52)	51.01 (12.65)
Diagnosis of thyroid cancer[d] (N, %)	13 (86.67)	473 (86.81)	2093 (84.46)	2566 (86.37)
Number of events				
Pre-exposed risk period				
Number of events	0	86	327	413
Patient-days	5,475	204,400	880,015	1,084,415
No. of events/patient-days (per 10,000) (95% CI)	0 (0.00−6.74)	4.21 (3.32−5.10)	3.72 (3.31−4.12)	3.81 (3.44−4.18)
Post-exposed risk period				
Number of events	4	103	316	419
Patient-days	5,400	201,600	867,960	1,069,560
No. of events/patient-days (per 10,000) (95% CI)	7.41 (2.02−18.96)	5.11 (4.12−6.10)	3.64 (3.24−4.04)	3.92 (3.54−4.29)
Non-risk period				
Number of event	11	371	1,768	2,139
Patient-days	27,465	1,025,360	4,414,541 MDD	5,439,901
No. of events/patient-days (per 10,000) (95% CI)	4.01 (2.00−7.17)	3.62 (3.25−3.99)	4.00 (3.82−4.19)	3.93 (3.77−4.10)

[a]subjects who had undergone thyroidectomy only once and had at least one suicide attempt, [b]subjects who had undergone thyroidectomy only once and had at least one probable suicide attempt, [c]diagnosis by F32, F33 per ICD-10 before and after thyroidectomy, [d]diagnosis by C73 per ICD-10. MDD: major depressive disorder, SD: standard deviation, CI: confidence interval

ers and 50.51 (SD=12.43) years in probable suicide attempters. The mean age of patients at first suicide attempt was 48.60 years (SD=13.81), and the mean age of patients at first probable suicide attempt was 51.01 years (SD=12.65). About 87% of all patients were diagnosed with thyroid cancer. Numbers of events/person-days (per 10,000) or suicide attempts or probable suicide attempts during the non-risk, pre-exposed risk, and post-exposed risk periods were 4.01 (95% CI: 2.00−7.17), 0 (no suicide attempt was occur during pre-exposed risk period), and 7.41 (95% CI: 2.02−18.96), respectively, in the suicide attempt group and 3.93 (95% CI: 3.77−4.10), 3.81 (95% CI: 3.44−4.18), and 3.92 (95% CI: 3.54−4.29) in the probable suicide attempt group. Further, we divided the probable suicide attempt group into MDD and non-MDD subgroups. In the MDD subgroup, there were fewer men, and the number of events/patient-days was higher in the risk period than in the non-risk period compared to the non-MDD group (Table 1).

Incidence rate ratios of suicide attempts and probable suicide attempts before and after thyroidectomy

Table 2 shows the IRRs of total of suicide attempt and probable suicide attempt before and after thyroidectomy in different risk windows. After adjusting for age and season, there was no statistical difference of IRRs in divided risk periods.

Table 3 shows the IRRs of suicide attempt or probable suicide attempt before and after thyroidectomy in different risk windows according to types of thyroidectomy and thyroid disease. In the patients who had undergone partial thyroidectomy, IRR increased 91−180 days after thyroidectomy (IRR: 1.43, 95% CI: 1.03−1.98, p=0.032). In other risk periods, there was no significant difference in IRR. In patients who had undergone total thyroidectomy, there was no significant difference in IRRs in divided risk periods. In the results according to thy-

Table 2. Adjusted Incidence Rate Ratios of total of suicide attempts[a] and probable suicide attempts[b] before and after the thyroidectomy in different risk windows

Risk period[c] (days)	IRR (95% CI)	p-value
-365−-271	1.05 (0.87−1.26)	0.624
-270−-181	1.09 (0.90−1.31)	0.388
-180−-91	0.82 (0.66−1.01)	0.068
-90−-1	0.92 (0.75−1.13)	0.419
1−90	0.88 (0.72−1.09)	0.242
91−180	1.06 (0.88−1.29)	0.524
181−270	0.95 (0.77−1.16)	0.593
271−365	1.10 (0.91−1.32)	0.337

Adjusted for age and season. [a]subjects who had undergone thyroidectomy and had at least one suicide attempt (N=15), [b]subjects who had undergone thyroidectomy and had at least one probable suicide attempt (N=2,971), [c]interval from the day of thyroidectomy. IRR: incidence rate ratio, CI: confidence interval

Table 3. Adjusted Incidence Rate Ratios of total of suicide attempts[a] and probable suicide attempts[b] before and after the thyroidectomy in different risk windows according to thyroidectomy type and thyroid disease

Risk period[c] (days)	Thyroidectomy type		Thyroid disease	
	Partial thyroidectomy (N=748)	Total thyroidectomy (N=2,234)	Thyroid cancer[d] (N=2,576)	Benign thyroid disease (N=406)
	IRR (95% CI)			
-365−-271	0.85 (0.56−1.28)	1.12 (0.91−1.38)	1.02 (0.83−1.25)	1.22 (0.76−1.97)
-270−-181	0.84 (0.55−1.28)	1.17 (0.95−1.45)	1.13 (0.92−1.37)	0.84 (0.47−1.50)
-180−-91	0.84 (0.56−1.28)	0.81 (0.63−1.04)	0.80 (0.64−1.01)	0.92 (0.52−1.60)
-90−-1	0.67 (0.42−1.07)	1.00 (0.80−1.26)	0.91 (0.73−1.13)	1.01 (0.59−1.72)
1−90	1.01 (0.69−1.49)	0.84 (0.66−1.08)	0.87 (0.69−1.09)	1.00 (0.59−1.72)
91−180	1.43 (1.03−1.98)*	0.94 (0.74−1.18)	1.08 (0.88−1.32)	0.97 (0.57−1.67)
181−270	0.92 (0.62−1.37)	0.96 (0.76−1.20)	0.93 (0.75−1.16)	1.05 (0.62−1.76)
271−365	0.78 (0.51−1.21)	1.20 (0.98−1.48)	1.11 (0.91−1.36)	0.99 (0.58−1.70)

Adjusted for age and season. [a]subjects who had undergone thyroidectomy and had at least one suicide attempt (N=15), [b]subjects who had undergone thyroidectomy and had at least one probable suicide attempt (N=2,973), [c]interval from the day of thyroidectomy, [d]diagnosis by C73 per ICD-10, *p<0.05. IRR: incidence rate ratio, CI: confidence interval

roid disease, there was no increased risk of suicide attempt or probable suicide attempt compared to the non-risk period in both groups of thyroid cancer and benign thyroid disease.

When stratified by sex and age of 50, there was no increase in IRR after thyroidectomy in any strata, but IRR increased 270−181 days before thyroidectomy in female of 50 years or older (Supplementary Table 2 in the online-only Data Supplement).

Incidence rate ratios of suicide attempts and probable suicide attempts before and after thyroidectomy in patients with major depressive disorder

According to previous studies, the risk of suicide increased for about one year after diagnosis of thyroid cancer, and the risk of depression increased for one year after thyroidectomy.[6,7,19] In addition, depression is known to be a major cause of suicide.[38] To investigate the effect of thyroidectomy on suicide attempt in people with depression, we conducted subgroup analysis including patients with diagnosis of MDD. As a result, in the pre-exposed risk period, the IRR increased in the -270−-181 period (IRR 1.74, 95% CI: 1.21−2.51, p=0.003) but decreased in the -181−-91 period (IRR 0.50, 95% CI: 0.25−0.97, p=0.039). After thyroidectomy, IRR increased to 1.67 (95% CI: 1.16−2.41, p=0.006) in the 91−180 period (Table 4).

Incidence rate ratios of suicide attempts and probable suicide attempts before and after thyroidectomy in patients with major depressive disorder according to types of thyroidectomy and thyroid disease

Among patients with MDD, after partial thyroidectomy, the IRR increased in 1−90 (IRR 2.05, 95% CI: 1.03−4.08, p=0.042) and 91−180 periods (IRR 2.13, 95% CI: 1.10−4.11, p=0.025). In total thyroidectomy patients with MDD, the pre-exposed risk period, -270−-181, showed an increased IRR to 1.97 (95% CI:1.32−2.93, p=0.001); in the post-exposed risk period, 181−270, the IRR increased to 1.59 (95% CI: 1.03−2.46, p=0.35). In the patients with MDD and thyroid cancer, during the pre-exposed risk period, the IRR increased to 1.78 (95% CI: 1.21−2.63, p=0.004) at -270−-181 but decreased at -180−-91 (IRR 0.46, 95% CI: 0.22−0.96, p=0.040). The IRR increased to 1.75 (95% CI: 1.19−2.58, p=0.005) at the 91−180 period. In patients with MDD and benign thyroid disease, the IRR increased into 2.80 (95% CI: 1.27−6.21, p=0.011) in the post-exposed risk period, 1−90 (Table 5).

Table 4. Adjusted Incidence Rate Ratios of total of suicide attempts[a] and probable suicide attempts[b] before and after the thyroidectomy in different risk windows in patients with MDD[c] (N=565)

Risk period[c] (days)	IRR (95% CI)	p-value
-365−-271	1.09 (0.70−1.70)	0.687
-270−-181	1.74 (1.21−2.51)	0.003
-180−-91	0.50 (0.26−0.97)	0.039
-90−-1	1.33 (0.88−2.01)	0.179
1−90	1.48 (1.00−2.18)	0.051
91−180	1.67 (1.16−2.41)	0.006
181−270	1.42 (0.95−2.12)	0.083
271−365	1.15 (0.74−1.79)	0.530

[a]subjects who had undergone thyroidectomy only once and had at least one suicide attempt, [b]subjects who had undergone thyroidectomy only once and had at least one probable suicide attempt, [c]diagnosis by F32, F33 per ICD-10 before and after thyroidectomy. MDD: major depressive disorder, SD: standard deviation, CI: confidence interval

Table 5. Adjusted Incidence Rate Ratios of total of suicide attempts[a] and probable suicide attempts[b] before and after the thyroidectomy in different risk windows in patients with MDD[c]

Risk period[c] (days)	Thyroidectomy type		Thyroid disease	
	Partial thyroidectomy (N=132)	Total thyroidectomy (N=433)	Thyroid cancer[d] (N=478)	Benign thyroid disease (N=87)
	IRR (95% CI)			
-365–-271	0.83 (0.30–2.26)	1.18 (0.72–1.93)	0.98 (0.59–1.62)	1.79 (0.71–4.52)
-270–-181	1.05 (0.43–2.61)	1.97 (1.32–2.93)***	1.78 (1.21–2.63)**	1.51 (0.54–4.22)
-180–-91	0.45 (0.11–1.84)	0.52 (0.24–1.09)	0.46 (0.22–0.96)*	0.77 (0.19–3.19)
-90–-1	1.12 (0.45–2.77)	1.40 (0.88–2.23)	1.24 (0.78–1.97)	1.94 (0.77–4.90)
1–90	2.05 (1.03–4.08)*	1.30 (0.81–2.09)	1.27 (0.81–2.00)	2.80 (1.27–6.21)*
91–180	2.13 (1.10–4.11)*	1.50 (0.97–2.35)	1.75 (1.19–2.58)**	1.18 (0.37–3.80)
181–270	0.91 (0.33–2.48)	1.59 (1.03–2.46)*	1.46 (0.96–2.24)	1.20 (0.37–3.86)
271–365	0.45 (0.11–1.82)	1.38 (0.87–2.19)	1.09 (0.67–1.78)	1.60 (0.58–4.44)

Adjusted for age and season. [a]subjects who had undergone thyroidectomy and had at least one suicide attempt (N=15), [b]subjects who had undergone thyroidectomy and had at least one probable suicide attempt (N=2,973), [c]diagnosis by F32, F33 per ICD-10 before and after thyroidectomy, [d]interval from the day of thyroidectomy, *p≤0.05, **p≤0.01, ***p≤0.001. MDD: major depressive disorder, IRR: incidence rate ratio, CI: confidence interval

DISCUSSION

In this study, the risk of suicide attempt one year before and after thyroidectomy was not significantly different compared to the non-risk period. In the subgroup receiving partial thyroidectomy, the risk of suicide attempt increased three to six months after thyroidectomy. When the analysis was limited to those diagnosed with or treated for MDD during the risk period, an increase in risk was observed six to nine months before the operation, and a decrease in risk was noted three to six months before the operation. Risk was increased again three to six months after thyroidectomy, which was similar in subgroup analysis according to thyroidectomy and thyroid disease types, although statistical significance was variable. These findings suggest that risk of suicide attempts after thyroidectomy generally does not increase. However, in patients with MDD, increased risk of suicide attempt was consistently observed regardless of thyroidectomy and thyroid disease types.

In addition to biological factors, individual psychosocial factors are thought to be a major factor in suicide attempt. In the case of thyroidectomy, in addition to the biological changes caused by surgery, the psychological burden due to surgery and distress regarding accompanying diseases were expected.[39] Nevertheless, it is noteworthy that no substantial risk of suicide attempt has been observed. In fact, more than 80% of the people in this study were diagnosed with thyroid cancer, but suicide attempts did not increase during the risk period before and after thyroidectomy. Previous studies have shown an increase in suicide deaths after cancer diagnosis.[42] Further, in the case of thyroid cancer, the standardized mortality ratio after thyroidectomy was increased up to about 14.[19] However, our results did not prove the temporal relationship between thyroidectomy and suicide attempt. In other words, it is difficult to say that the risk of suicide attempt increases after thyroidectomy. As an explanation for the differences in these findings, methodological differences may play a large role. This study does not compare the study individuals with the general population or the control group but rather used the SCCS method, where comparison is performed within individuals. Therefore, the confounding effect of time-invariant factors is thought to be minimal. In addition, we should consider the status of diagnosis of thyroid cancer in South Korea. In the period of case identification, there was rapid increase in the diagnosis of thyroid cancer in South Korea. As of 2012, South Korea had the highest incidence of thyroid cancer worldwide, and the age-standardized incidence of thyroid cancer in South Korea was more than 4 times of that in United States and more than 10 times of that in China and Japan.[43-45] Although the increase of risk factors such as exposure to medical radiation may affect to this,[46,47] experts have raised the rapid increase of medical check-ups and overdiagnosis of thyroid cancer as major causes of the high incidence of thyroid cancer in South Korea.[48,49] Compared to the rapid increase of incidence, the mortality of thyroid cancer in South Korea is very low and unchanged.[45] Therefore, due to the relative good prognosis of thyroid cancer in South Korea, distress after diagnosis may not be large as that of other cancers, and this also may affect to psychopathology related to suicidality.

On the other hand, in the patients with MDD, the risk of suicide attempt or probable suicide attempt increased and then decreased in pre-exposure risk period, and increased again in post-exposure risk period. As an explanation for the fluctu-

ations in risk of suicide attempts or probable suicide attempts before thyroidectomy, it is possible that distress due to diagnosis of thyroid disease and psychopathology related to manifestation of depression were mixed during this period. In this study, we defined the MDD subgroup as people with codes of MDD at least once during study period including both of risk period and non-risk period. Therefore, the severity of depression might be inconsistent with the risk period established in this study and there might be increase of suicidality irrelevant to thyroidectomy. Nevertheless, the presence of periods where the risk of suicide attempt or probable suicide attempt increases before and after thyroidectomy suggests that suicidality should be assessed if a patient has comorbid MDD. These results were consistent regardless of types of thyroidectomy and thyroid disease. To conclude that biologic changes lead to suicide attempt, the risk of suicide attempts in total thyroidectomy should be higher than in partial thyroidectomy, but the results did not support this relationship.

This study has several limitations. First, to complement the small sample size of suicide attempt codes and the poor use of suicide attempt code in the emergency room or clinic, probable suicide attempt was defined and included in the analysis. Since probable suicide attempt was defined based on ICD-10 codes, unintentional accidents might have been included. However, in our previous study, when we defined probable suicide attempts with the same codes as this study and investigated the association between prescription of hypnotic medication and suicide attempts, the pattern of risk change before and after prescription was similar to the risk change in the suicide attempt group. Second, although age and season were adjusted and subgroup analysis was conducted in the MDD subgroup, other time-varying variables such as comorbid physical disorder and psychiatric disorder might have affected our results. However, because we used the SCCS method, the bias due to time-invariant factors such as intrinsic characteristics of individuals would be small. Third, because we used claim data, clinical information associated with thyroidectomy or suicide attempt might be lacking. For example, information about level of thyroid hormone after surgery, thyroid hormone replacement, or adequacy of postoperative treatment was not included in the analysis. Since thyroid hormone is not naturally produced after total thyroidectomy, synthetic levothyroxine ($_{L}$-T_4) is frequently administered. However, this study did not include such information. Fourth, because the data source does not include information related to death, it was not able to identify the death resulted from the suicide attempt or probable suicide attempt. However, because we included only the first suicide attempt or probable suicide attempt of individuals in the analyses, the lack of information related to death would not affect the results.

To our knowledge, this is the first study investigated the association between thyroidectomy and suicide attempt. This study has strength by employing real world data to identify the risk of suicide attempt in risk period before and after thyroidectomy. In addition, by including not only suicide attempt codes, but also several codes not explicitly identified as suicide attempt but highly suspected as suicide attempt, we tried to overcome the underdetection of suicide attempts at emergency rooms or clinics and provide an evidence for clinical practice.

In conclusion, while the general risk of suicide attempt was not increased after thyroidectomy, patients with MDD showed increased risk of suicide attempt after thyroidectomy. Although this study has the limitation of lacking clinical information, as real world data, this study suggests that suicidality should be evaluated when depressive symptom are present in patients who have undergone thyroidectomy.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2020.0174.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Hyewon Kim, Man Ki Chung, Hong Jin Jeon. Data curation: Hyewon Kim. Formal analysis: Yuwon Kim, Myung-Hee Shin. Funding acquisition: Hong Jin Jeon. Investigation: Hyewon Kim. Methodology: Hyewon Kim, Yuwon Kim. Project administration: Hong Jin Jeon. Supervision: Hong Jin Jeon. Writing—original draft: Hyewon Kim. Writing—review & editing: Hyewon Kim, Kwan Woo Choi, Man Ki Chun, Hong Jin Jeon.

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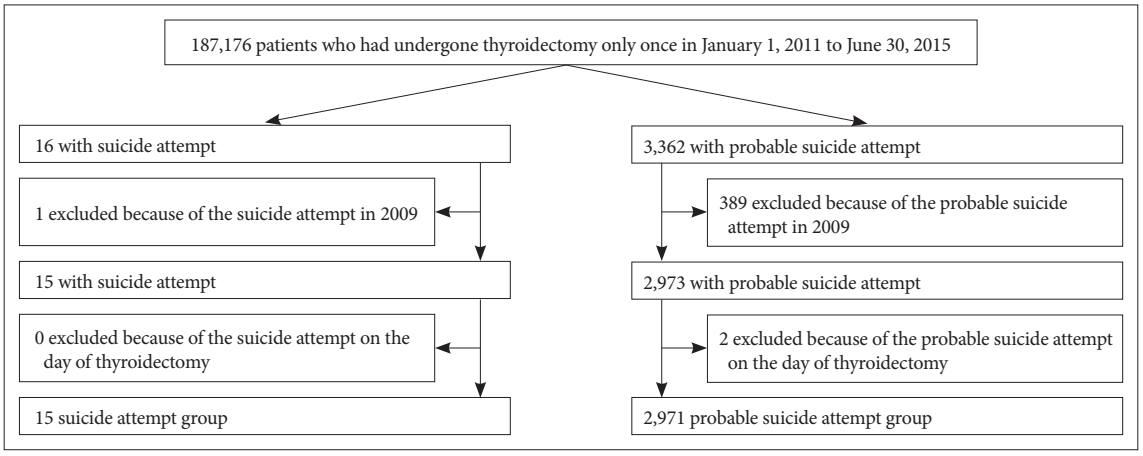
Supplementary Table 1. Definition of suicide attempts and probable suicide attempts by International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10)

Code	Definition
Suicide attempts	
X60–X84	Intentional self-harm
Probable suicide attempts	
S61.9	Wrist laceration
T43	Poisoning by psychotropic drugs, NEC
T50.9	Acute drug intoxication
T52	Toxic effect of organic solvents
T54	Toxic effect of corrosive substance
T58	Toxic effect of carbon monoxide
T60	Toxic effect of pesticides
T65.8	Toxic effect of other specified substances
T65.9	Toxic effect of unspecified substances
W32	Handgun discharge
W33	Rifle, shotgun and larger firearm discharge
W34	Discharge from other and unspecified firearms
W75	Accidental suffocation and strangulation in bed
W76	Other accidental hanging and strangulation
Y10–Y34	Event of undetermined intent
R09.0	Asphyxia
W13–W19	Falls



Supplementary Figure 1. Flowchart showing the identification of subjects.

Supplementary Table 2. Adjusted Incidence Rate Ratios of total of suicide attempts[a] and probable suicide attempts[b] before and after the thyroidectomy in different risk windows stratified by sex and age

Risk period[c] (days)	Male subjects				Female subjects			
	Age <50 years (N=286)		Age ≥50 years (N=369)		Age <50 years (N=1,063)		Age ≥50 years (N=1,264)	
	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value	IRR (95% CI)	p-value
-365–-271	1.05 (0.57–1.93)	0.886	1.09 (0.66–1.80)	0.748	1.28 (0.96–1.71)	0.092	0.84 (0.61–1.16)	0.281
-270–-181	0.76 (0.37–1.54)	0.446	0.72 (0.38–1.35)	0.301	1.02 (0.74–1.42)	0.898	1.32 (1.01–1.72)	0.039
-180–-91	0.88 (0.45–1.72)	0.708	0.71 (0.38–1.34)	0.294	0.97 (0.69–1.36)	0.862	0.70 (0.49–1.01)	0.055
-90–-1	0.88 (0.45–1.72)	0.710	0.49 (0.23–1.05)	0.066	0.89 (0.63–1.27)	0.530	1.08 (0.80–1.44)	0.624
1–90	0.69 (0.32–1.46)	0.328	0.78 (0.43–1.43)	0.419	0.89 (0.63–1.27)	0.522	0.95 (0.70–1.29)	0.735
91–180	1.21 (0.69–2.13)	0.499	1.14 (0.69–1.89)	0.609	0.99 (0.71–1.38)	0.970	1.05 (0.78–1.41)	0.754
181–270	0.77 (0.38–1.56)	0.470	0.57 (0.28–1.15)	0.118	1.08 (0.78–1.48)	0.649	0.99 (0.73–1.35)	0.965
271–365	1.06 (0.58–1.94)	0.855	0.92 (0.53–1.61)	0.770	1.11 (0.81–1.52)	0.516	1.14 (0.86–1.52)	0.370

Adjusted for age and season. [a]subjects who had undergone thyroidectomy and had at least one suicide attempt, [b]subjects who had undergone thyroidectomy and had at least one probable suicide attempt, [c]interval from the day of thyroidectomy. MDD: major depressive disorder, IRR: incidence rate ratio, CI: confidence interval