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# Toluene concentrations in the blood and risk of thyroid cancer among residents living near national industrial complexes in South Korea: A population-based cohort study

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ABSTRACT

*Background:* Toluene is classified as a possible carcinogen, but its role on thyroid cancer is not well established. Vehicle emissions are one of the largest contributed sources of toluene, but no studies evaluating the influence of living near a road on the association between toluene and the incidence of thyroid cancer have been reported. Therefore, we examined potential associations between blood toluene concentrations and incidence risk of thyroid cancer, and an effect modification of living near a road.

*Methods:* We conducted a prospective cohort study using data from South Korean "Monitoring Project for Exposure to Environmental Pollutants and Health Effects among Residents Living near Industrial Complexes" survey. Study participants living near national industrial complexes were recruited from January 2003 to 2011. Incidence and mortality cases of thyroid cancer (C73, ICD-10 code) were identified using the National Cancer Registry and Statistics Korea, respectively. Blood toluene concentrations were measured using gas chromatography mass spectrometry. We used Cox proportional hazards regression models to estimate the hazard ratios (HR) and the 95% confidence interval (CI) between blood toluene concentrations and thyroid cancer risk.

*Results:* During the follow-up (median 8.6 years), 33 cases of thyroid cancer were diagnosed. The geometric mean of the toluene concentration in the blood was 0.56 μg/L for cases and 0.29 μg/L for non-cases. After adjusting for potential confounders, a positive association between blood toluene concentrations and thyroid cancer was found (HR = 2.77, 95% CI = 1.00–7.65 in the highest tertile vs. the lowest tertile, $p$ for trend = 0.044). This positive association was stronger in people living near a road (≤50 m).

*Conclusions:* Blood toluene concentrations may be positively associated with the incidence risk of thyroid cancer. Moreover, this association may be stronger among people living near a road.

## 1. Introduction

Thyroid cancer is the most common endocrine malignancy and the most rapidly increasing cancer in the past half-century, partially because of improvements in detection. Globally, the age-standardized incidence rate of thyroid cancer for both sexes increased 20% between 1990 and 2013 (Fitzmaurice et al., 2015). In 2018, the Global Cancer Observatory (GLOBOCAN) estimated 567,000 new cancer cases and 41,000 cancer deaths worldwide, and the incidence rates for women was three times higher than for men, with geographical differences (Bray et al., 2018).

Although the global effect of thyroid cancer is widespread, its cause remains poorly understood. The most likely risk factor for developing thyroid cancer is exposure to ionizing radiation. However, several epidemiological studies suggest other potential factors, from individual-level (obesity and genetic factors) to environmental-level (imbalance of iodine supply, volcanic ash, and occupation) factors (Kim et al., 2020).

*Abbreviations:* BMI, body mass index; CI, confidence interval; GM, geometric means; GSD, geometric standard deviation; HR, hazard ratios; LOD, limit of detection; NIER, the National Institute of Environmental Research; RERI, relative excess risk due to interaction; SD, standard deviation; T1, first tertile; T2, second tertile; T3, third tertile; VOCs, volatile organic compounds.

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Certain chemical pollutants are also suspected of playing a role in the development of thyroid tumors (Fiore et al., 2019).

Volatile organic compounds (VOCs) are organic chemicals that evaporate easily into the air at room temperature. Some VOCs are classified as definite or possible carcinogens (such as benzene, vinyl chloride, and 1,3-butadiene), but data on the role of other VOCs in human health are limited. Toluene, a VOC, is widely used to produce other chemicals and consumer products in a variety of industries and its toxicity and carcinogenicity in human health have been continuously suggested (WHO (World Health Organization), 2000).

Previous studies report that exposure to toluene increases tumorigenesis at specific organ sites in experimental studies (Dees et al., 1996; Dees and Travis, 1994; Maltoni et al., 1997). Toluene increases hyperphosphorylation of p53 in rat liver cells (Dees et al., 1996; Dees and Travis, 1994), which are involved in tumor promotion, and oral exposure to toluene in male and female rats for 104 weeks increased malignant tumors at a variety of sites (Maltoni et al., 1997). However, only a few epidemiological studies have assessed the association between toluene exposure and the risk of thyroid cancer, and they were mostly conducted in occupational settings exposed to a mixture of solvents, including toluene (Lope et al., 2009; Wingren et al., 1993).

Toluene levels in the blood may be a valid evaluation method for reflecting toluene exposure at a low concentrations in the air (Kawai et al., 1994). The general population is exposed to toluene through inhalation, and the most important source of toluene in ambient air is vehicle emissions (Buczynska et al., 2009). Growing evidence suggests that living near busy roads can threaten residents' health because of exposure to multiple pollutants, but no studies evaluating the influence of living near a road on the association between toluene and the incidence of thyroid cancer have been reported.

Therefore, we examined a potential association between blood toluene and the incidence risk of thyroid cancer and identified whether this association was modified by living near a road among residents living close to an industrial complex.

## 2. Methods

### 2.1. Study design and participants

We conducted a prospective cancer-cohort study using data from the "Monitoring Project for Exposure to Environmental Pollutants and Health Effects among Residents Living near Industrial Complexes" survey supervised by the National Institute of Environmental Research (NIER) in South Korea. This project is a prospective multicenter cohort study designed to investigate environmental pollutants and health effects in residents living near National Industrial Complexes. From 2003 to 2011, 25,707 participants were recruited from 12 regions located in Ulsan, Pohang, Gwangyang, Yeosu, Hadong, Namhae, Cheongju,

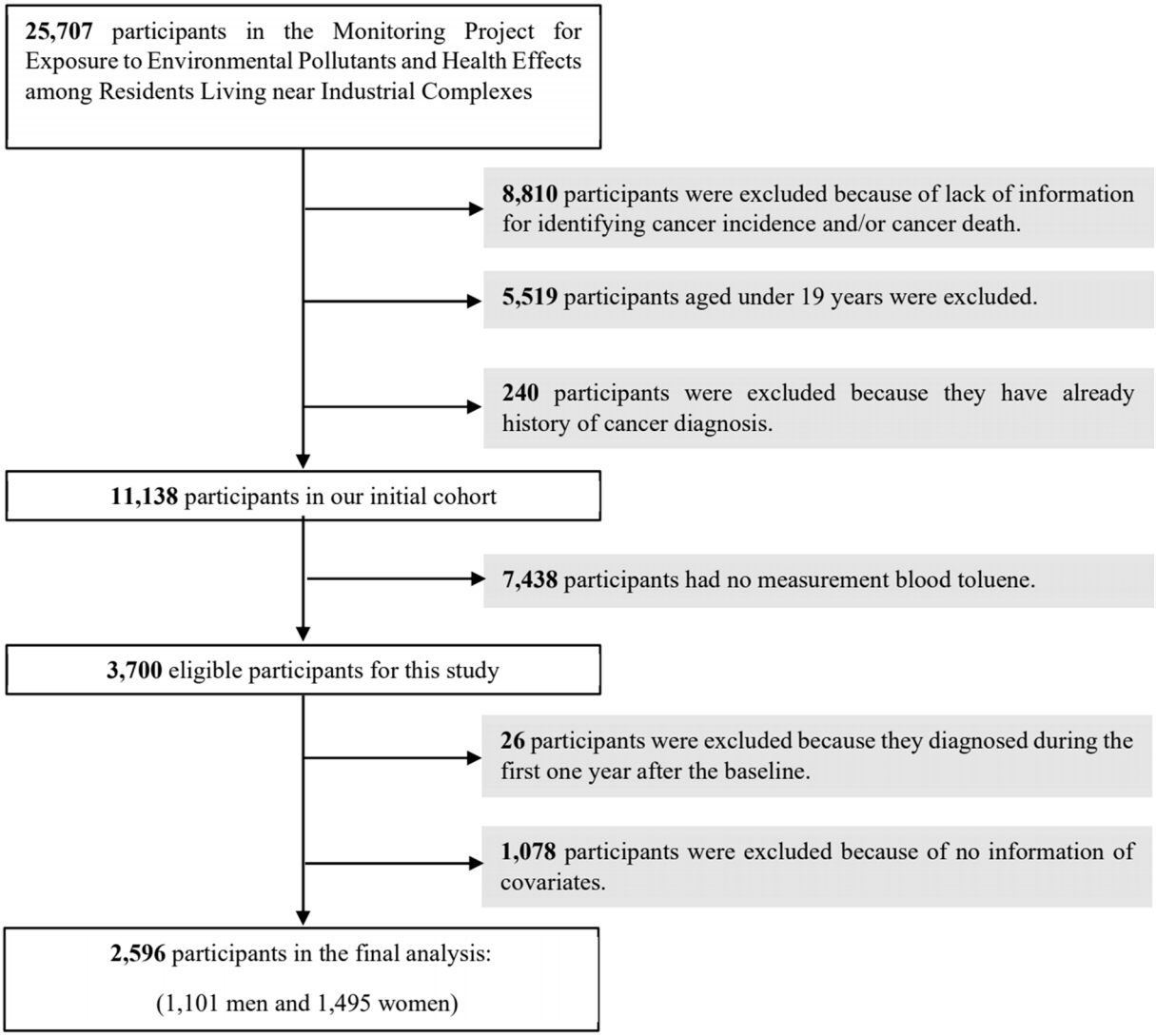


**Fig. 1.** Flowchart of study participants with exclusion criteria.

Daesan, Gangneung, Chungju, Sihwa, and Banwoul. This survey consisted of a self-reported questionnaire that included information about socio-demographics, lifestyle, medical history, residential environment, and health examination. Passive incidence follow-up data from the Korea Central Cancer Registry were used to identify people diagnosed with cancer from 2003 to 2016.

For the present study, we included 11,378 people ≥19 years old at baseline and who had available data for identifying confirmed cases of cancer. We excluded 240 participants because they had a history of cancer diagnosis at baseline. Of the 11,138 participants, 3700 were selected randomly based on their age, sex, and region of residence to measure their blood toluene concentrations. We also excluded people who were diagnosed during the first one year after the baseline survey (n = 26) and who had missing data for important covariates (educational level, smoking status, employment status, body mass index (BMI), and distance from the nearest road to home) (n = 1078). Finally, 2596 participants (1101 men and 1495 women) were included in the analysis (Fig. 1). This study was approved by the Institutional Review Board of the National Cancer Center, Goyang, Korea. Written informed consent was obtained from all participants prior to enrollment into the cohort.

### 2.2. Ascertainment of thyroid cancer cases

Cancer incidence data were collected through two sources, the Korea Central Cancer Registry and death certificate information from Statistics Korea, which contains accurate and virtually complete data on cancer incidence in South Korea. The proportion of cancer cases from death certificates was up to 26.1% until December 2016. The 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was used to identify all cancer cases (C00–C97) and thyroid cancer cases (C73). We identified only primary thyroid cancer cases and excluded thyroid cancer cases caused by metastasis from other cancers. In total, 161 and 33 cases were diagnosed with all cancers and thyroid cancer, respectively.

### 2.3. Assessment of blood toluene concentrations

During the health examination, a blood sample was collected at each local center. To measure blood toluene concentration, 1 mL sample was transferred to a 10-mL vial for headspace, internal standards of 2.0 μg/L and 4 mL of purified water were added. After heating for 30 min in a constant temperature bath at 80 °C, the upper gas phase was extracted with headspace (Pohang, Gangneung, Cheongju, Daesan) or with headspace-solid phase microextraction (Ulsan, Gwangyang, Yeosu, Hadong, Namhae, Chungju) and analyzed using gas chromatography mass spectrometry. Quality assurance and control was performed according to the manual recommended by NIER in South Korea. For quality control, each of seven samples with concentrated standard to 0.05 μg/L was prepared and analyzed in the same procedures mentioned above. Method detection limits were calculated by multiplying the standard deviation (of the seven replicates) by 3.14. Precision and accuracy measurements were calculated by multiplying by the relative standard deviation of more than five replicated measurements. The range of precision should be within 75–125% and the accuracy within 25%. If the results from the analysis of a quality control sample did not meet these criteria, then all results for the analysis were reconducted. The correlation coefficient of the calibration curve was more than 0.990. The limit of detection (LOD) for blood toluene was 0.1–0.3 μg/L in Pohang; 0.01–0.03 μg/L in Cheongju and Daesan; 0.05–0.5 μg/L in Ulsan; 0.1 μg/L in Gwangyang, Yeosu, Hadong, and Namhae; 0.05 μg/L in Gangneung; and 0.025 μg/L in Chungju.

### 2.4. Assessment of potential confounders

We obtained information on the participant characteristics from questionnaires and health examinations. We selected potential confounders that were known risk factors for thyroid cancer from a previous review (Kim et al., 2020), such as age at baseline, sex, educational level, smoking status, obesity, and current occupation. The BMI was calculated as the ratio of the weight (kg) to squared height ($m^2$) and categorized into two groups according to the World Health Organization (WHO) standards for Asians: underweight and normal-weight (<23 kg/$m^2$), overweight (≥23 kg/$m^2$) (WHO, 2000). The education level was classified into two groups by medians as lower education (≤9 years) and higher education (>9 years). Occupational information was collected based on the Korean Standard Classification of Occupation at baseline. We then categorized the two groups by employment status: employee, worker, and self-employed were considered as 'yes', and other non-workers as 'no'.

### 2.5. Statistical analyses

Blood toluene concentrations were natural log-transformed for assumption of normality and equal variance and categorized into three groups by tertile represented as T1 (the reference), T2, and T3. All measured values of blood toluene were used, including the values below the LOD (Schisterman et al., 2006), where that value ranked in the reference group.

We used Student's *t*-test for continuous variables and Fisher's exact test for categorical variables to test the differences in baseline characteristics between cases and non-cases, and the differences in blood toluene concentration according to the characteristics.

Person-years for each participant were calculated using the interval between the visit date and the first date of any cancer diagnosis or censoring. If a person was not matched to cancer incidence or death, they were considered alive through the follow-up period and censored 31 December 2016. We used random-effects Cox's proportional hazard regression model to assess the hazard ratios (HR) and 95% confidence interval (CI) of all cancers and thyroid cancer across the tertiles of blood toluene concentrations. We checked the proportional hazard assumption using Schoenfeld's residual test, and the assumption was not violated. To evaluate the dose-response relationship between blood toluene concentrations and the incidence of cancer, the median values of each tertile of toluene concentration were considered as a continuous variable in the Cox's proportional hazards model. We ultimately selected covariates among potential confounders using a directed acyclic graph (Supplementary Fig. 1) (Greenland et al., 1999) and included them in the full model as follows: age at baseline, sex, education level (≤9 or >9 years), employment status (yes or no), and BMI (<23 or ≥23 kg/$m^2$). We also adjusted for survey regions by random effect to account for potential heterogeneity from the six national industrial complexes.

To examine the influence of living near a road on the association between toluene and the incidence of thyroid cancer, we conducted stratified analyses for each question using the nearest road from the residence. Self-reported questions were provided at baseline as follows: 1) distance categorized by equal or less than 50 m, 51–100 m, 101–500 m, and more than 500 m; 2) lanes categorized by 2, 4, 6, and 8 lanes; and 3) traffic volume categorized by light, moderate, heavy, and greater than heavy. We divided each question into two groups based on half of the proportion because of the small sample size. We also evaluated the effect modification on an additive scale [relative excess risk due to interaction (RERI)] as recommended by Knol and Vander Weele with the 95% CI for the RERI computed using the delta method (Knol and VanderWeele, 2012). Range of RERI can be from negative infinity to positive infinity. RERI = 0 represents no interaction or exactly additive; RERI < 0 represents negative interaction or less than additive; RERI > 0 represents positive interaction or more than additive, which means the presence of a synergistic effect of two risk factors.

All statistical analyses were performed using commercially available software (SAS version 9.4; SAS Institute Inc., Cary, North Carolina) and the level of statistical significance was set at 0.05 in two-sided tests.

## 3. Results

### 3.1. Characteristics of study population

The total number of participants in this study consisted of 1101 men (42.4%) and 1495 women (57.6%) and their mean age was 51.0 (standard deviation, 14.1) years. Half of the participants had received middle school education (9 years of education), were employed, and lived within 50 m of the nearest road. There were more non-smokers than smokers and more obese people (BMI $\geq$ 23) than non-obese people. When comparing the characteristics of cases and non-cases, the proportion of women was higher in cases with thyroid cancer than in non-cases, whereas other characteristics did not statistically differ between the two groups. For toluene concentration in the blood, the geometric means were approximately two-fold higher in the cases compared to non-cases (Table 1). Characteristics between total cohort and study population were represented in Supplementary Table 2. Although no statistically significant differences were found in the characteristics of the two groups, the participants included in the analyses were composed of 10% fewer women, were 6% less educated, and contained 6% more current workers.

### 3.2. Toluene concentrations according to the characteristics

Table 2 presents the concentrations of toluene in the blood according to the characteristics of the study population. Overall, less educated people had higher concentrations of blood toluene. In thyroid cancer cases, the toluene concentrations were higher in women and overweight people (BMI $\geq$ 23 kg/m$^2$). The toluene concentrations in cases were higher in respondents living near a road with more than two lanes than those living near a road with less than two lanes. On the other hand, the toluene concentrations of the non-cases were higher in respondents living near a road with less than two lanes or less than moderate traffic volume compared with those living near a road with more than two lanes.

**Table 1**
The characteristics of thyroid cancer cases and non-cases in study participants.

| | Total | Cases | Non-cases | *p*-value[a] |
|---|---|---|---|---|
| ***N*** | 2596 | 33 | 2563 | |
| Age (years); Mean (SD) | 51.0 (14.1) | 51.2 (8.5) | 51.0 (14.1) | 0.952 |
| Women (n, %) | 1495 (57.6) | 27 (81.8) | 1468 (57.3) | 0.004 |
| Education level (n, %) | | | | |
| ≤9 years | 1352 (52.1) | 20 (60.6) | 1332 (52.0) | 0.382 |
| >9 years | 1244 (47.9) | 13 (39.4) | 1231 (48.0) | |
| Smoking status (n, %) | | | | |
| Yes | 712 (27.4) | 6 (18.2) | 706 (27.5) | 0.325 |
| No | 1884 (72.6) | 27 (81.8) | 1857 (72.5) | |
| BMI (n, %) | | | | |
| <23 kg/m$^2$ | 998 (38.4) | 8 (24.2) | 990 (38.6) | 0.109 |
| ≥23 kg/m$^2$ | 1598 (61.6) | 25 (75.8) | 1573 (61.4) | |
| Employment status (n, %) | | | | |
| Yes | 1405 (54.1) | 19 (57.6) | 1386 (54.1) | 0.728 |
| No | 1191 (45.9) | 14 (42.4) | 1177 (45.9) | |
| Distance from the nearest road (n, %) | | | | |
| ≤50 m | 1175 (45.3) | 18 (54.5) | 1157 (45.1) | 0.296 |
| >50 m | 1421 (54.7) | 15 (45.5) | 1406 (54.9) | |
| Toluene in blood (ug/L) | | | | |
| GM (GSD) | 0.29 (0.01) | 0.56 (0.15) | 0.29 (0.01) | 0.042 |
| 25th percentile | 0.15 | 0.23 | 0.15 | |
| Median | 0.30 | 0.57 | 0.30 | |
| 75th percentile | 0.93 | 1.15 | 0.93 | |

Note: BMI, body mass index; GM, geometric means; GSD, geometric standard deviation; SD, standard deviation.

[a] *P*-values for difference between cases and non-cases were tested by Student's *t*-test for continuous variables and by Fisher's exact test for categorical variables. Significance level: P < 0.05.

### 3.3. Toluene concentrations and risk of thyroid cancer

Table 3 shows associations of continuous and tertiles of toluene concentration on risk of thyroid cancer. In the age- and sex-adjusted model, blood toluene was positively associated with the incidence risk of thyroid cancer. After adjusting for other potential confounders, blood toluene still had a positive association with the incidence risk of thyroid cancer (HR = 1.22, 95% CI: 1.00–1.49 in continuous levels; HR = 2.77, 95% CI: 1.00–7.65 in T3 vs. T1; $p$ for trend = 0.044). However, we did not observe a significant association between blood toluene and the incidence risk of all cancers.

### 3.4. Effect modification of thyroid cancer by living near a road

After stratifying by the distance (≤50 m) from home to the nearest road, we conducted further analyses to examine whether the effect of blood toluene on the incidence risk of thyroid cancer is modified by living near a road (Table 4). High toluene concentration was associated with a significantly increased risk of thyroid cancer, after adjusting for confounders (adjusted model 2: HR = 3.73, 95% CI: 1.02–13.62 in T3 vs. T1), including a strong positive trend across toluene concentrations in the residents living near a road ($p$ for trend = 0.036). We did not observe a significant association with the incidence risk of all cancers. The RERI for the synergistic effect was 3.78 (95% CI: −9.13 to 16.68) between the highest tertile of toluene and living near a road, so there is positive effect modification of blood toluene across strata of the distance (≤50 m) from home to the nearest road on an additive scale (Supplementary Table 2).

## 4. Discussion

In this study, we found that blood toluene concentration was positively associated with the incidence risk of thyroid cancer. This positive association tended to be stronger in residents living near a road. However, we did not observe an association between the toluene concentration in the blood and the incidence risk of all cancers.

Toluene is an important organic compound in a variety of industries and is used to synthesize many chemicals. It is widely used as a solvent to produce many consumer products (paints, adhesives, and rubber) and used as a component of fuels. Because of its volatility, people are frequently exposed to toluene through the air. In nonoccupationally exposed people, toluene was detected in most blood samples with a mean concentration of < 1 part per billion (ppb) (Ashley et al., 1994). In our study, blood toluene concentration in the total number of participants had a geometric mean of 0.29 μg/L. This value was similar to the concentration in NHANES III 1999–2000 (0.28 ppb, median) (Ashley et al., 1994), but lower than the concentration in residents, living near the Gulf of Mexico in the USA, exposed to oil spills (0.51 ng/ml, mean). We studied the residents living near national industrial complexes. This investigation was conducted during the daytime on weekdays, and we found that most of the participants were not employed as industrial plant workers but were family members of the plant workers. Our study population, therefore, likely consisted of the general population living near industrial complexes located in large cities, and their toluene exposure may have arisen from environmental rather than occupational factors.

**Table 2**
The blood toluene concentration according to the characteristics of study population.

| Characteristics | Total (n = 2596) | | | Cases (n = 33) | | | Non-cases (n = 2563) | | |
|---|---|---|---|---|---|---|---|---|---|
| | GM | (95% CI) | *p*-value[a] | GM | (95% CI) | *p*-value[a] | GM | (95% CI) | *p*-value[a] |
| Sex | | | | | | | | | |
| Men | 0.29 | (0.26–0.32) | 0.568 | 0.29 | (0.19–0.44) | 0.023 | 0.29 | (0.26–0.32) | 0.708 |
| Women | 0.30 | (0.27–0.33) | | 0.65 | (0.36–1.20) | | 0.30 | (0.27–0.33) | |
| Education level | | | | | | | | | |
| ≤9 years | 0.35 | (0.32–0.39) | <**0**.0001 | 0.77 | (0.41–1.44) | 0.122 | 0.35 | (0.31–0.38) | <**0**.0001 |
| >9 years | 0.24 | (0.22–0.27) | | 0.35 | (0.14–0.84) | | 0.24 | (0.22–0.27) | |
| Smoking status | | | | | | | | | |
| Yes | 0.29 | (0.25–0.33) | 0.655 | 0.31 | (0.16–0.58) | 0.069 | 0.29 | (0.25–0.33) | 0.754 |
| No | 0.30 | (0.27–0.32) | | 0.64 | (0.35–1.18) | | 0.29 | (0.27–0.32) | |
| BMI (kg/m$^2$) | | | | | | | | | |
| <23 | 0.30 | (0.27–0.34) | 0.727 | 0.23 | (0.07–0.72) | 0.039 | 0.30 | (0.27–0.34) | 0.565 |
| ≥23 | 0.29 | (0.27–0.32) | | 0.75 | (0.43–1.31) | | 0.29 | (0.26–0.32) | |
| Employment status | | | | | | | | | |
| Yes | 0.29 | (0.26–0.31) | 0.340 | 0.72 | (0.39–1.34) | 0.254 | 0.28 | (0.26–0.31) | 0.283 |
| No | 0.31 | (0.28–0.34) | | 0.40 | (0.16–1.00) | | 0.30 | (0.27–0.34) | |
| Distance from the nearest road | | | | | | | | | |
| ≤50 m | 0.28 | (0.26–0.31) | 0.352 | 0.54 | (0.28–1.05) | 0.887 | 0.28 | (0.25–0.31) | 0.331 |
| >50 m | 0.30 | (0.28–0.34) | | 0.59 | (0.24–1.41) | | 0.30 | (0.27–0.33) | |
| Lane [b] | | | | | | | | | |
| ≤2 | 0.33 | (0.30–0.35) | 0.001 | 0.48 | (0.29–0.79) | 0.187 | 0.33 | (0.30–0.36) | 0.001 |
| >2 | 0.24 | (0.22–0.28) | | 1.04 | (0.20–5.51) | | 0.24 | (0.21–0.27) | |
| Traffic volume [b] | | | | | | | | | |
| Moderate or less | 0.34 | (0.31–0.38) | 0.001 | 0.63 | (0.25–1.58) | 0.740 | 0.34 | (0.31–0.37) | 0.001 |
| Heavy | 0.26 | (0.23–0.28) | | 0.52 | (0.27–1.00) | | 0.25 | (0.23–0.28) | |

Note: BMI, body mass index; 95% CI, 95% confidence intervals; GM, geometric means.
[a] *P*-values according to the subgroups were tested by Student's *t*-test. Significance level: P < 0.05.
[b] Numbers of subgroups varies slightly because of missing value for each variable.

**Table 3**
Association between blood toluene concentrations and the risk of thyroid cancer.

| Toluene (ug/L) | No. of case/non-cases | Model1[a] | | | Model2[b] | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | *p* for trend[c] | HR | 95% CI | *p* for trend[c] |
| *All cancer* | | | | | | | |
| Continuous (log$_e$) | | 1.05 | 0.97–1.15 | | 1.05 | 0.96–1.15 | |
| T1 (<0.20) | 37/770 | 1.00 | Reference | | 1.00 | Reference | |
| T2 (0.20–0.63) | 66/852 | 1.31 | 0.88–1.96 | | 1.29 | 0.86–1.94 | |
| T3 (≥0.63) | 58/813 | 1.25 | 0.83–1.90 | 0.283 | 1.25 | 0.83–1.89 | 0.305 |
| *Thyroid* | | | | | | | |
| Continuous (log$_e$) | | 1.22 | 1.00–1.48 | | 1.22 | 1.00–1.49 | |
| T1 (<0.20) | 5/802 | 1.00 | Reference | | 1.00 | Reference | |
| T2 (0.20–0.63) | 13/905 | 2.30 | 0.82–6.47 | | 2.33 | 0.83–6.56 | |
| T3 (≥0.63) | 15/856 | 2.78 | 1.01–7.68 | 0.046 | 2.77 | 1.00–7.65 | 0.044 |

Note: HR, hazard ratios; 95% CI, 95% confidence intervals.
[a] Model1 was adjusted for age (years), sex (men/women).
[b] Model2 was adjusted for age (years), sex (men/women), BMI (<23/≥23 kg/m$^2$), education level (≤9/> 9 years), employment (yes or no), and region (random effect).
[c] *p* for linear trend was calculated in the Cox model by treating the median values of each tertile as continuous variables. Significance level: P < 0.05.

To our knowledge, this is the first study to investigate the association of blood toluene with thyroid cancer. Previous epidemiologic studies between toluene and cancer (not including thyroid) have been conducted in occupational settings but their findings were inconsistent (Blanc-Lapierre et al., 2018; El-Zaemey et al., 2018; Gerin et al., 1998; Warden et al., 2018). Recent research using a job-exposure matrix, designed to assess exposure to specific hazards based on job title, reported the associations of occupational exposure to toluene with certain cancers such as colorectal (El-Zaemeyet al. 2018), prostate (Blanc-Lapierreet al. 2018), and lung (Wardenet al. 2018). A few studies have investigated the association of toluene with the increased risk of thyroid cancer (Baet al. 2016; Divine and Barron 1987; Lopeet al. 2009; Sathiakumaret al. 2001). A large retrospective cohort study of Swedish workers was conducted using national registries, including almost three million participants and over 2500 incident cases of thyroid cancer. An almost two-fold increased risk of thyroid cancer occurred in women with probable exposure to solvents, including toluene, mostly working in the shoe-making industry, compared to women without solvent exposure (Lopeet al. 2009). Another population-based case-control study in Connecticut, USA, reported that the risk of thyroid cancer was associated with people engaging in retail and sales and this association was stronger in workers with more than 10 years of experience (Baet al. 2016). The authors suggest that the increased risk of thyroid cancer in this group may be partly explained by exposure to solvents such as VOCs, including toluene, emitted from furniture or gasoline from motor vehicles (Baet al. 2016). Two studies in the petrochemical industry show a statistically significant association with the risk of thyroid cancer, but only report a small number of cases (Divine and Barron 1987; Sathiakumaret al. 2001). Although these studies measured toluene exposure indirectly, the results of workers exposed predominantly to toluene support our findings that toluene in the blood is positively associated with the risk of thyroid cancer.

Large amounts of toluene are released into the environment each year and the main outdoor sources of toluene are automobile exhaust

**Table 4**
Association between blood toluene and the risk of thyroid cancer stratified by distance from the nearest road.

| Toluene (ug/L) | No. of case/non-case | HR | 95% CI | *p* for trend[a] |
|---|---|---|---|---|
| *All cancer* | | | | |
| ≤50 m (n = 1175) | | | | |
| Continuous ($log_e$) | | 1.04 | 0.92–1.17 | |
| T1 (<0.20) | 19/337 | 1.00 | Reference | |
| T2 (0.20–0.63) | 43/417 | 1.45 | 0.85–2.50 | |
| T3 (≥0.63) | 30/329 | 1.47 | 0.83–2.62 | 0.185 |
| > 50 m (n = 1421) | | | | |
| Continuous ($log_e$) | | 1.10 | 0.96–1.26 | |
| T1 (<0.20) | 18/433 | 1.00 | Reference | |
| T2 (0.20–0.63) | 23/435 | 1.05 | 0.56–2.01 | |
| T3 (≥0.63) | 28/484 | 1.17 | 0.64–2.16 | 0.599 |
| *Thyroid cancer* | | | | |
| ≤50 m (n = 1175) | | | | |
| Continuous ($log_e$) | | 1.26 | 0.96–1.66 | |
| T1 (<0.20) | 3/353 | 1.00 | Reference | |
| T2 (0.20–0.63) | 5/455 | 1.37 | 0.33–5.77 | |
| T3 (≥0.63) | 10/349 | 3.73 | 1.02–13.62 | 0.036 |
| > 50 m (n = 1421) | | | | |
| Continuous ($log_e$) | | 1.23 | 0.91–1.67 | |
| T1 (<0.20) | 2/449 | 1.00 | Reference | |
| T2 (0.20–0.63) | 8/450 | 3.96 | 0.84–18.81 | |
| T3 (≥0.63) | 5/507 | 2.23 | 0.43–11.67 | 0.373 |

Note: Statistical models above were adjusted for age (years), sex (men/women), BMI (<23/≥23 kg/$m^2$), education level (≤9/> 9 years), employment (yes or no), and region (random effect).

[a] *p* for linear trend was calculated in the Cox model by treating the median values as continuous.

and fuel evaporative loss, industrial emissions, petroleum refining and storage, surface coatings, and solvent usage (Registry, 2017). However, in developed and industrialized countries, traffic emissions are the most important source of toluene in ambient air, with levels fluctuating in proportion to automobile traffic (Buczynskaet al. 2009). Recent research shows that living near roads is associated with adverse health effects (Chen et al., 2017; Yorifuji et al., 2013) through multifaceted exposures including VOCs. In our results, the association of blood toluene with the increased risk of thyroid cancer was influenced by the distance from the nearest road. Although we cannot define the primary source contributing to individual toluene levels, we did not see a high level of occupational exposure history to toluene in our participants (data not shown). Therefore, we think that, in our study, blood toluene concentrations more likely reflected toluene exposure from indoor products or outside pollutants rather than occupational exposure. Vehicular road traffic highly contributes to individual toluene levels (Alexopoulos et al., 2006). In addition, evaporated toluene is heavier than air and may accumulate in low-lying areas so that the residents living near roads are more susceptible to automobile emission than others are. This may explain the increased risk of thyroid cancer in people who lived within 50 m of a road.

The mechanism by which toluene causes thyroid cancer is unknown, but several studies have shown the carcinogenicity potential of toluene. A study showed that hyperphosphorylation of p53 by toluene may be involved in tumor promotion (Dees et al., 1996). Mutation or deletion in the tumor suppressor gene *p53* was recognized in thyroid carcinomas (Manzella et al., 2017). *In vitro*, toluene increased phosphorylation of p53, thus disrupting p53's normal function in controlling the cell cycle and leading to uncontrolled cell proliferation. Accumulation of these genetic errors eventually results in tumor formation (Dees and Travis, 1994). Another study showed that VOCs, especially toluene, produce oxidative stress and change the expression of various genes related to oxidative stress in workers exposed to VOCs (Kim et al., 2011). Oxidative stress, a risk factor for other cancers, may induce DNA damage and result in mutagenic alterations causing the development of cancer (Sosa et al., 2013). Reactive oxygen species can activate MAP kinase and PI3K/Akt pathways, which is a key mechanism in the carcinogenic process of thyroid cancer (Xing, 2010; 2012). Thus, oxidative stress may be involved in the development of thyroid cancer via alterations in the MAP kinase and PI3K/Akt pathways in genes related to thyroid carcinomas such as *BRAF*, *RAS*, *PIK3CA*, and *PTEN* (Xing, 2012).

We found that the blood toluene levels were higher for women than for men with thyroid cancer (Table 2). Our results cannot fully explain the sex differences in the toluene levels among thyroid cancer cases, but one study reported a difference in the metabolism of toluene between male and female rats (Nakajima et al., 1992). Toluene is metabolized to benzoic acid (major) and ortho- and para-cresol (minor) in humans and animals through oxidation by cytochrome P-450. In rat livers, the rate of benzyl alcohol formation and o- and p-cresol formation at high and low concentrations of toluene differed between the sexes, which indicated that toluene was broken down more slowly in female than in male rats (Nakajima et al., 1992). These results may supplement our findings that the blood toluene levels were higher for women than for men.

Our study has several strengths: it is prospective and uses a multicenter cohort near national industrial complexes. We used a biomarker in the blood for directly assessing individual exposure to toluene. However, our findings should be interpreted cautiously, accounting for some limitations. First, our study population included residents living near industrial complexes, so the exposure of toluene may be affected by the type of nearby industry. However, we statistically adjusted for regions in the full model by random effect to attenuate the regional differences. Second, we did not test for exposure to other hazardous substances, such as VOCs, which have been shown to be associated with risk of cancers. The levels of benzene and xylenes may be a leading potential confounder. However, we found no association between other hazardous substances and thyroid cancer in our data. Third, because of the lack of available data, individual covariates such as diet and lifestyle factors were not included in our analyses, although these factors are likely to be associated with cancer incidence. We used data from the Industrial Complexes Monitoring Project launched in 2003 that is one of the Ministry's major monitoring measures. The focus of this project is on population exposure to specific substances to determine whether exposure has occurred rather than to determine whether the substances measured have adverse health effects. Despite the above limitations, this study is meaningful because it verifies the health effects from industrial complexes with high statistical power using pooled data from large-scale environmental epidemiology monitoring studies. Fourth, a substantial number of cohort participants were excluded because of the lack of information on the cancer status such as that for two regions (Sihwa and Banwoul). Because the project was focused on monitoring exposure to environmental pollutants, two cohorts in those industrial regions did not collect personal identification information to link with the cancer registration data. Therefore, the information on these two regions was not reflected in our results. Finally, a small number of incident cases of thyroid cancer may have attenuated the associations for subgroup analyses. In particular, the toluene exposure levels from traffic emissions will likely be affected by incorporated dimensions including road lanes, traffic heaviness, and distance to the nearest road. We attempted to consider them in our analyses, but the sample size of thyroid cancer cases was insufficient to obtain statistical power for these subgroup analyses. As such, we could only present further stratified analyses for traffic heaviness, and the results showed the non-significant positive associations between toluene and thyroid cancer by traffic heaviness (Supplementary Table 3). Therefore, our findings should be verified using large, long-term epidemiological studies with vehicular emission sources.

## 5. Conclusions

In conclusion, toluene was positively associated with the incidence of thyroid cancer and this positive association tended to be stronger in residents living near a road. Given the potentially significant implications of toluene exposure on the increased risk of thyroid cancer, our

findings provide the perspectives in more depth that play the role of environmental and chemical pollutants in the development of thyroid.

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## CRediT authorship contribution statement

**Seyoung Kim:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft. **Eunjung Park:** Data curation, Validation, Writing - review & editing. **Sang-Hwan Song:** Project administration. **Chul-Woo Lee:** Project administration, Writing - review & editing. **Jung-Taek Kwon:** Writing - review & editing. **Eun Young Park:** Writing - review & editing. **Byungmi Kim:** Writing - review & editing, Supervision, Funding acquisition.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106304.

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