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Relationship Between Leukotriene Receptor Antagonists on Cancer Development in Patients With Bronchial Asthma: A Retrospective Analysis

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Abstract. *Background/Aim: An association between leukotriene receptor antagonists (LTRA) and cancer has been previously reported, but the relationship between LTRA use and cancer prevention remains controversial. This study aimed to clarify the cancer-preventive effect of LTRA in Japanese patients with bronchial asthma. Patients and Methods: We obtained information from a large population-based medical information database to analyze data on patients who were newly diagnosed with bronchial asthma between 2006 and 2015. Eligible participants were patients who were prescribed an LTRA for at least 30 days (LTRA users) and those who were not using LTRA (LTRA non-users) during the objective period. LTRA users and LTRA non-users were matched 1:1 using propensity scores. Results: The 1:1 propensity score matching of LTRA users and LTRA non-users facilitated the inclusion of 3,744 participants each, in these two subgroups. The results of the Cox proportional hazards model after adjustment for covariates showed no significant difference in the cancer risk between LTRA users and non-users [adjusted hazard ratio (HR)=0.83, 95% confidence interval (CI)=0.59-1.16]. The subgroup analysis showed no significant difference in the cancer risk between the LTRA low-cumulative dose group and LTRA non-users, or between the LTRA medium-cumulative dose group and LTRA non-users. In contrast, the LTRA high-cumulative dose group had a significantly lower risk of developing cancer compared with LTRA non-users (adjusted HR=0.57, 95% CI=0.33-0.98). Conclusion: LTRA use may prevent cancer in patients with bronchial asthma.*

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Key Words: Cancer, leukotriene receptor antagonists, bronchial asthma patients, chemoprevention, cohort study.

Worldwide, the number of cancer cases as well as the number of cancer-related deaths are increasing (1-4). With population aging, cancer-related mortality will increase and, although it is important to identify a method to prevent cancer, same as to establish a cure for cancer. In recent years, drug repositioning – the discovery of new applications of existing drugs – has occupied an important position in drug development (5-7). In our study, this method was applied to leukotriene receptor antagonists (LTRAs). LTRAs, such as montelukast and pranlukast, act on leukotriene receptors, particularly the cysteinyl leukotriene (CysLT) 1 receptor, and they inhibit leukotriene function, suppress the body's allergic response, and dilate bronchial tubes, thereby preventing bouts of coughing caused by asthma (8). LTRAs are mainly used for bronchial asthma and allergic rhinitis (8).

Previous studies have reported an association between LTRA and cancer (9-12). Various human tumor cell types, both malignant and benign, express the CysLT receptor (9-11). In vitro, LTRA induces tumor cell apoptosis (10, 12, 13). A clinical study, which was based on a Taiwan database, showed that LTRA treatment significantly reduced the incidence of cancer (14). However, the association between LTRA use and cancer prevention remains controversial.

Therefore, using a large medical information database, we aimed to clarify whether LTRA has a preventive effect on cancer development in Japanese patients with bronchial asthma. In order to clarify the above objectives, the primary endpoint was the difference in developing cancer risk depending on whether or not LTRA was taken, and the secondary endpoint was the difference in developing cancer risk depending on the cumulative dose of LTRA.

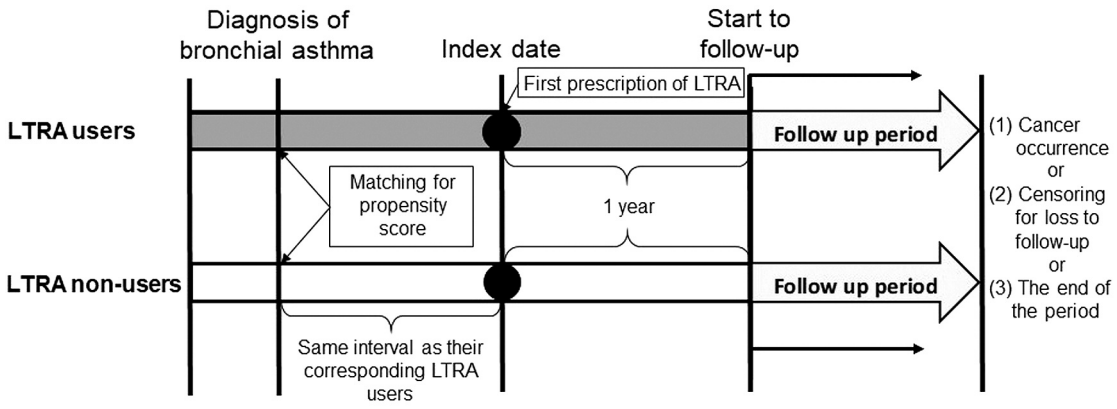

Figure 1. *Study design. The date of the first leukotriene receptor antagonist (LTRA) prescription was defined as the index date and, for LTRA non-users, the index date was defined as the date of bronchial asthma diagnosis plus the period between the date of bronchial asthma diagnosis and the date of first prescription of LTRA for the corresponding LTRA users. The period required for the onset of LTRA effects was specified as 1 year. Start of follow-up was defined as 1 year after the index date. The conditions marking the end of the follow-up period included: 1) cancer onset, 2) censoring for loss of follow-up, and 3) the end of observation period in the database (December 31, 2015), defined as the earliest day of these events.*

Patients and Methods

Database and study population. This study used medical information obtained from a large population-based health insurance claims database held by JMDC Co., Ltd. (Tokyo, Japan) that comprised approximately 3.7 million members and includes data on: 1) medical expense statements for inpatients and outpatients; 2) prescription medications coded according to the Anatomical Therapeutic and Chemical (ATC) categorization system of the World Health Organization for inpatients and outpatients (with the dosage and number of days prescribed); 3) medical checkup data (*e.g.*, smoking and drinking); 4) demographics (*e.g.*, age and sex); 5) disease names coded by the International Classification of Disease 10th Revision (ICD-10); and 6) medical procedures. The data are anonymized but ensure that each patient's data can be tracked over time even if the patient has visited multiple medical institutions. Eligible participants of this study comprised patients who were newly diagnosed with bronchial asthma between January 2006 and December 2015 and were at least 40 years old at the time of the diagnosis. Patients had "definite" and "suspected" diagnosis codes, and those with "suspected" diagnosis codes were excluded. A "newly diagnosed patient" was defined as one who had a medical record for at least 1 year prior to the first diagnosis of bronchial asthma during the study period. Bronchial asthma was defined on the basis of two or more outpatient claims or one or more inpatient claims for bronchial asthma (15). Therefore, patients with 1 outpatient claim and 0 hospitalizations were excluded from this study as were patients who were diagnosed with cancer prior to being diagnosed with bronchial asthma. Furthermore, patients who were using zafirlukast, which has now been discontinued in Japan, were excluded. This research was conducted in compliance with the World Medical Association's Declaration of Helsinki, and the research protocol was approved by the Tokyo University of Science Ethical Review Committee (approval number: 16010).

Study cohort. Patients with bronchial asthma who were prescribed an LTRA (montelukast, ATC code: R03DC03 or pranlukast, ATC code: R03DC02) for at least 30 days were considered "LTRA users". In Japan, the approved doses for the treatment of asthma are 10 and 450 mg/day for montelukast and pranlukast, respectively. Patients who had used an LTRA prior to the diagnosis of bronchial asthma, those who had been diagnosed with cancer before the start of follow-up, and those who had the end of observation period before start of follow-up were excluded. Moreover, patients whose medical checkup data were not complete or missing in the year preceding the diagnosis of bronchial asthma were excluded. Patients with bronchial asthma who were not using LTRA during the study period were considered "LTRA non-users." LTRA users and LTRA non-users were then matched 1:1 using propensity scores.

Patient characteristics. For the analysis including patient background characteristics as a covariate, we used: 1) sex, 2) age at the date of diagnosis of bronchial asthma; 3) number of outpatient visits; 4) number of hospitalizations; 5) medical history; 6) concomitant medications; 7) results of medical checkup conducted within 1 year before the date of diagnosis of bronchial asthma; 8) the Charlson Comorbidity Index score (16) obtained from the information available in the database within 1 year prior to the date of diagnosis of bronchial asthma (14, 17). Medical histories were obtained using the following ICD-10 codes: 1) heart disease [cardiac failure (ICD-10 codes I50 and J81), cardiac infarction (I21-I23), angina pectoris (I20), other ischemic cardiac diseases (I24 and I25)], 2) peripheral vascular disease (I70-I74 and I77); 3) cerebrovascular disease [transient ischemic attack (G45), ischemic cerebral infarction (I60-I64), other cerebrovascular diseases (I65-I69)]; 4) hepatic disease (B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0, B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, and I85); 5) diabetes mellitus (E10-E14); 6) renal disease (I12, I13, N00-N05, N07, N11, N14, N17-N19, and Q61); 7) depression (F32, F33, and F34.1); 8) hypertension (I10 and I11); and 9) dementia (F00-F03, F05.1, and G30). Data on concomitant medications were obtained using the following ATC codes: Aspirin (B01C1, N02B) (18, 19), adrenergic agents (inhalants; R03A), glucocorticoids (R03BA), anticholinergics (R03BB), antiallergic agents (R03BC), xanthines (R03DA; 8, 16, 17). Medical checkup data were obtained for smoking and drinking (20-22).

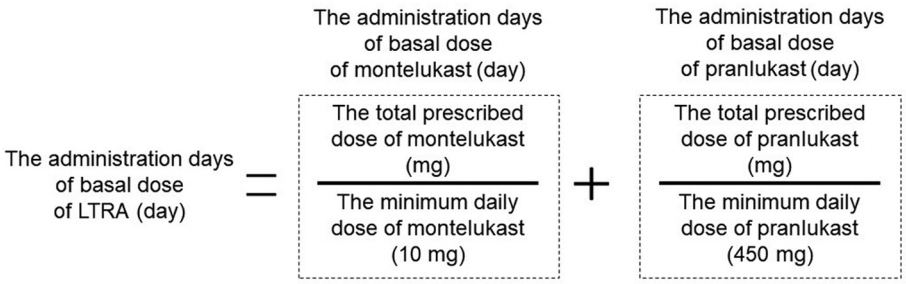

Figure 2. *The formula of administration days of basal dose of leukotriene receptor antagonist (LTRA).*

Study outcomes and follow-up. The primary outcome was the diagnosis of any type of cancer indicated by an ICD-10 code (ICD-10 middle classification codes: C00-C14, C15-C26, C30-C39, C40-C41, C43-C44, C45-C49, C50-, C51-C58, C60-C63, C64-C68, C69-C72, C73-C75, C76-C80, C81-C96, and C97 onwards). The period required for the onset of LTRA effects was specified as 1 year (Figure 1). The date of the first LTRA prescription was defined as the index date and, for LTRA non-users, the index date was defined as the date of bronchial asthma diagnosis plus the period between the date of bronchial asthma diagnosis and the date of first prescription of LTRA for the corresponding LTRA users. The outcome was followed 1 year after the index date. The conditions marking the end of the follow-up period included: 1) cancer onset, 2) censoring for loss of follow-up, and 3) the end of observation period in the database (December 31, 2015), defined as the earliest day of these events.

Statistical analysis. To improve the robustness of our study results, propensity score (PS) matching was performed as this method is useful in observational studies for reducing the influence of confounding factors (23). For calculating the PS, logistic regression analysis was first performed with all background factors. Based on the results, logistic regression analysis was repeated by using only the items that were significant as covariates, and the PS was calculated. Items with significant intergroup differences included age, sex, total number of outpatient visits and hospitalizations, smoking, liver disease, hypertension, use of adrenergic agents/inhalers, glucocorticoids, anticholinergics, systemic corticosteroids, antiallergic agents (excluding corticosteroids), and xanthines, as well as the Charlson Comorbidity Index score. PS values were used to match LTRA users and LTRA non-users 1:1, with a caliper value of 0.02.

For comparison of background factors among LTRA users and LTRA non-users, the Student's *t*-test was performed for analyzing age, whereas the Mann-Whitney *U*-test for the Charlson Comorbidity Index score, number of outpatient visits and number of hospitalizations and the chi-square test were used to analyze other variables. With regard to the association between the use of LTRA and the risk of developing cancer, the Cox proportional hazard model was used to estimate the crude hazard ratio (HR), adjusted HR and 95% confidence interval (CI).

In addition, subgroup analyses were performed according to the cumulative dose of LTRA treatment to investigate whether the cumulative dose affected the results. For LTRA users, we calculated administration days of basal dose of LTRA for each patient to clarify the condition of cumulative dose (Figure 2). First, we calculated administration days of basal dose of montelukast and pranlukast and then added these administration days of basal dose of both drugs as administration days of basal dose of LTRA. The administration days of basal dose of montelukast was calculated divided the total prescribed dose of montelukast by the minimum daily dose of montelukast 10 mg (24). The administration days of basal dose of pranlukast was calculated by dividing the total prescribed dose of pranlukast by the minimum daily dose of pranlukast 450 mg in the same way. The administration days of basal dose of LTRA was calculated using the following formula: ("Total dose for montelukast"/"minimum daily dose of montelukast") + ("Total dose for pranlukast"/"minimum daily dose of pranlukast"). Based on the results, the study cohort was divided into the low-cumulative dose, medium-cumulative dose, and high-cumulative dose subgroups at the 33rd and 66th percentile points relative to the number of participants, and subgroup analyses were performed in the same manner as were the main analyses.

Statistical analysis was performed using SAS 9.4 (SAS institute, Cary, NC) and R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). To develop the Cox proportional hazards model, we used the Cmprsk package (25). A p-value <0.05 was considered statistically significant.

Results

Participant characteristics. In total, 166,710 patients were diagnosed with bronchial asthma during the study period, and, among them, 33,042 and 20,588 patients were included as LTRA users and LTRA non-users, respectively. The 1:1 PS matching of LTRA users and LTRA non-users facilitated the inclusion of 3,744 participants each in these two subgroups (Figure 3). The participant's background characteristics are shown in Table I. Only the proportion of prescription of glucocorticoids differed between LTRA users and LTRA non-users, with significantly more LTRA non-users than LTRA users in the entire cohort.

Cancer risk. Table II shows the results of a multivariable Cox regression analysis on LTRA use and the risk of developing cancer. The incidence rate of cancer was 8.34 and 9.84 per 1000 person-years for LTRA users and LTRA non-users, respectively. The results of the Cox proportional hazards model after adjustment for covariates showed no significant

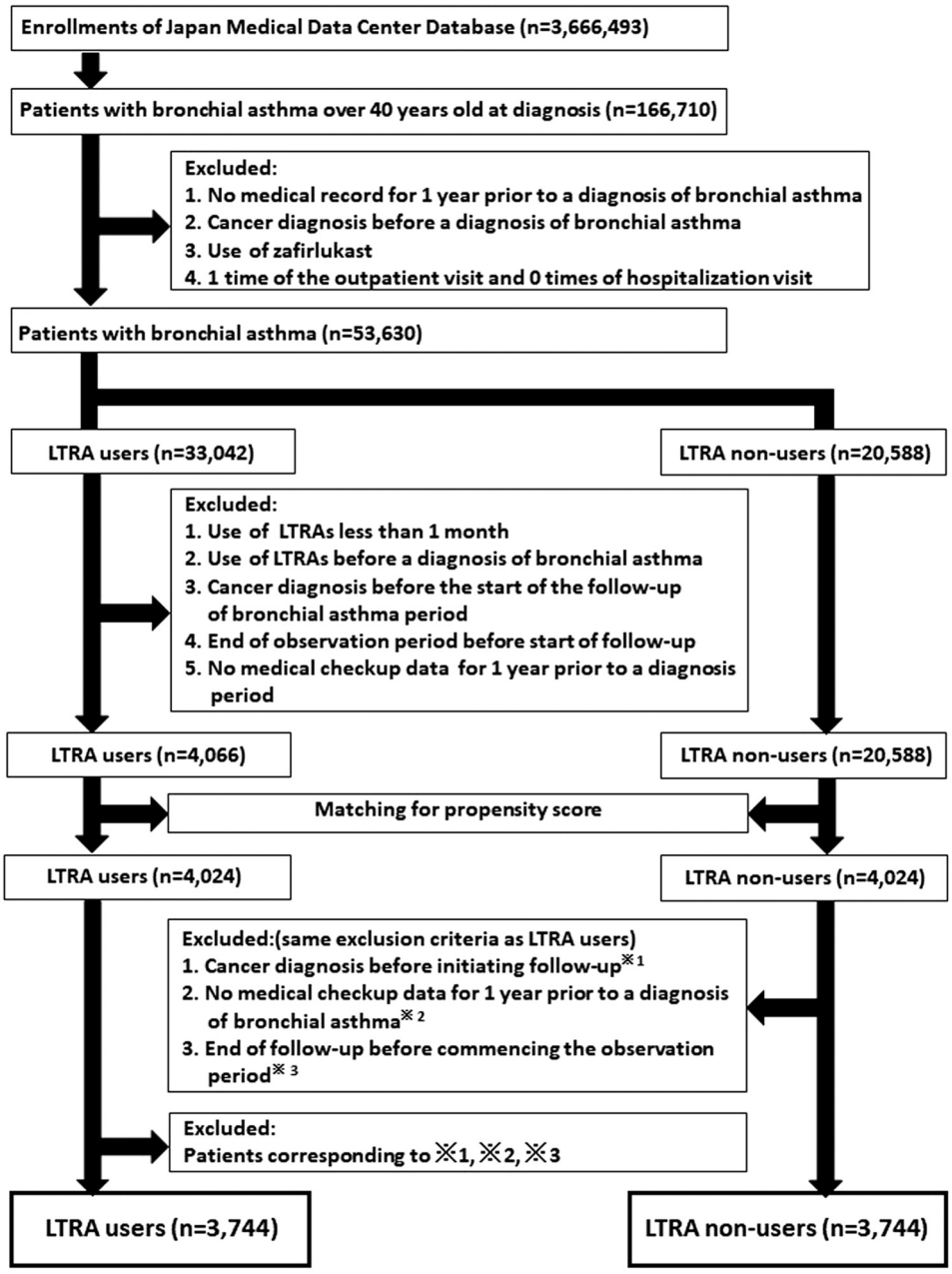

Figure 3. *Study flowchart. Patients with bronchial asthma over 40 years old at diagnosis were extracted from large population-based medical information databases. Excluded patients had exclusion criteria 1-4. Patients were then divided into leukotriene receptor antagonist (LTRA) users and LTRA non-users. Patients with exclusion criteria 1-5 were removed from LTRA users. The propensity score (PS) was calculated by logistic regression using covariates significant in two groups. LTRA users and non-users were matched 1:1 using PS values. If LTRA non-users had exclusion criteria 1-3, they were removed and their corresponding LTRA users were matched to other LTRA non-users again. This was done until there were no matching partners for LTRA users.*

difference in the cancer risk between LTRA users and LTRA non-users (adjusted HR=0.83, 95% CI=0.59-1.16).

Subgroup analyses. Table III shows the results of the subgroup analysis for the risk of developing cancer by the cumulative LTRA dose. The median cumulative dose of LTRA treatment was 36.5, 66.0, and 201.0 days for the low-cumulative dose, medium-cumulative dose, and high-cumulative dose groups, respectively. The incidence rate of cancer was 10.7, 8.59, and 5.78 per 1,000 person-years in the LTRA low-cumulative

Table I. *Baseline characteristics of the study population.*

Characteristic[a]	LTRA users (n=3,744) N (%)	LTRA non-users (n=3,744) N (%)
Sex		
Male	2,111 (56.4%)	2,161 (57.7%)
Female	1,633 (43.6%)	1,583 (42.3%)
Age	48.7±7.0	48.4±6.9
Number of outpatient visits	8 (0-61)	7 (0-61)
Number of hospitalizations	0 (0-8)	0 (0-7)
Smoking (habitually)		
Yes	702 (18.8%)	740 (19.8%)
No	3,042 (81.2%)	3,004 (80.2%)
Drinking		
Every day	1,665 (44.5%)	1,640 (43.8%)
Sometimes	1,198 (32.0%)	1,232 (32.9%)
Rarely	881 (23.5%)	872 (23.3%)
Medical history		
Cardiovascular disease	200 (5.3%)	200 (5.3%)
Cardiac failure	84 (2.2%)	82 (2.2%)
Cardiac infarction	10 (0.3%)	10 (0.3%)
Angina pectoris	129 (3.4%)	130 (3.5%)
Other ischemic cardiac disease	23 (0.6%)	31 (0.8%)
Peripheral vascular disease	113 (3.0%)	97 (2.6%)
Cerebrovascular disease	98 (2.6%)	121 (3.2%)
Transient ischemic attack	12 (0.3%)	16 (0.4%)
Ischemic cerebral infarction	32 (0.9%)	36 (2.2%)
Other cerebrovascular disease	68 (1.8%)	87 (1.0%)
Hepatic disease	246 (6.6%)	253 (6.8%)
Diabetes mellitus	93 (2.5%)	85 (2.3%)
Renal disease	55 (1.5%)	36 (1.0%)
Depression	223 (6.0%)	219 (5.8%)
Hypertension	675 (18.0%)	672 (18.0%)
Dementia	0 (0.0%)	3 (2.3%)
Charlson Comorbidity Index[b]	1 (1-7)	1 (1-8)
Concomitant medication		
Aspirin	70 (1.9%)	66 (1.8%)
Adrenergic drug (inhaled drug)	1,618 (43.2%)	1,642 (43.9%)
Glucocorticoids	347 (9.3%)	424 (11.3%)**
Anticholinergic drugs	12 (0.3%)	7 (0.2%)
Anti-allergy medications	143 (3.8%)	146 (2.2%)
Xanthine	746 (19.9%)	752 (20.1%)
Systemic corticosteroids	1,537 (41.1%)	1,537 (41.1%)

[a]n=3,744 for each group; Values are expressed as number (%), mean±standard deviation (SD) or median (range). [b]Charlson Comorbidity Index is a score for evaluating comorbidities and complications, and a high value indicates high severity. Student's *t*-test was performed for Age, Mann–Whitney *U*-test for the Charlson Comorbidity Index score, number of outpatient visits and number of hospitalizations and the chi-square test were used to analyze other variables. **$p<0.01$. LTRA, Leukotriene receptor antagonist.

dose, LTRA medium-cumulative dose, and LTRA high-cumulative dose groups, respectively. The results of the Cox proportional hazards model, after adjustment for covariates, showed no significant difference in the cancer risk among the LTRA low-cumulative dose group and LTRA non-users, or between the LTRA medium- cumulative dose group and LTRA non-users (LTRA low-cumulative dose group: adjusted HR=1.07, 95% CI=0.69-1.66; LTRA medium-cumulative dose group: adjusted HR=0.87, 95% CI=0.53-1.42). In contrast, compared with the LTRA non-users, the LTRA high-cumulative dose group had a significantly lower cancer risk (adjusted HR=0.57, 95% CI=0.33-0.98).

Discussion

The results of the retrospective cohort study that analyzed data from a large medical information database suggested that higher cumulative doses of LTRAs may reduce the risk of developing cancer in Japanese patients with bronchial asthma and this may contribute to cancer chemoprevention.

Table II. *Multivariable Cox model analysis of the association between leukotriene receptor antagonist (LTRA) use and the risk of cancer among patients with bronchial asthma.*

Participants (n=3,744)	Total of follow-up period (person-years)	No. of incident cancer cases	Incidence rate of cancer (case/1,000 person-years)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
LTRA non-users	6,908	68	9.84	1	1
LTRA users	7,918	66	8.34	0.85 (0.60-1.20)	0.83 (0.59-1.16)

[a]Adjusted for sex, age, and glucocorticoid users. CI, Confidence interval; LTRA, leukotriene receptor antagonist; HR, hazard ratio.

Table III. *Subgroup analyses of the multivariable Cox model for the association between the cumulative leukotriene receptor antagonist (LTRA) dose and the risk of cancer among patients with bronchial asthma.*

Treatment groups	Total duration of the follow-up period (person-years)	No. of incident cancer cases (cases)	Incidence rate of cancer (case/1,000 person-years)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
LTRA non-users (n=3,744)	6,908	68	9.84	1	1
Low-cumulative dose LTRA users (n=1,320)	2,703	29	10.7	1.09 (0.71-1.69)	1.07 (0.69-1.66)
Medium-cumulative dose LTRA users (n=1,174)	2,445	21	8.59	0.88 (0.54-1.43)	0.87 (0.53-1.42)
High-cumulative dose LTRA users (n=1,250)	2,770	16	5.78	0.59 (0.34-1.01)	0.57 (0.33-0.98)*

[a]Adjusted for sex, age, and glucocorticoid use. *$p<0.05$. The 33rd and 66th percentile points for the number of the cumulative dose days of LTRA were 49 days and 95.5 days, respectively. We divided into 3 groups according to these points. The cumulative dose days of the low-cumulative dose group was 49 days or less, the medium-cumulative dose group was 49 to 99.5 days, and the high-cumulative dose group was 99.5 days or more. CI, Confidence interval; LTRA, leukotriene receptor antagonist; HR, hazard ratio.

Eicosanoids are produced by various cancer cell types as well as their surrounding cells (12, 13). Various human tumor cell types highly express the CysLT receptor (9-11). The binding of leukotriene D4 (LTD4) to the CysLT1 receptor induces the activation of cyclooxygenase (COX)-2, which inhibits tumor cell apoptosis and promotes proliferation (26). The binding of LTRA to the CysLT1 receptor induces tumor cell G1-phase cell cycle arrest and apoptosis (9, 10, 13). In an in vivo study, we previously showed that LT receptors were expressed in human tumors (26 types) and in spontaneously occurring rat tumors, regardless of malignant or benign tumor (9, 10), and that the induction of tumor cell apoptosis was confirmed when LTRA was administered to rats who had spontaneous tumors (9). In another *in vitro* study, LTRA inhibited the migration of tumor cells through the brain and peripheral capillaries, preventing tumor metastasis and prolonging survival (27). The results of the present study are consistent with those of the previous *in vitro* and in vivo studies on LTRA and cancer. The results of the subgroup analysis suggest that higher-cumulative doses of LTRA reduce the cancer risk and the chemopreventive effect of LTRA was higher with larger cumulative doses, which is consistent with the results of previous clinical studies showing a dose-dependent effect (14).

There are several limitations in this study that should be addressed in future research. First, the average age of the participants was relatively low (~50 years). The database used in this study had only a small number of older adults, who are more likely to develop cancer as cancer incidence increases with age (22). Future research should include studies on older adults. Second, database studies cannot confirm the treatment compliance of patients and ascertain whether they are actually taking their medications. The degree of compliance may be randomly distributed, and this aspect may have influenced the results in this cohort. Third, this study did not allow for stratified analysis by cancer type or the LTRA drug because the number of patients decreased by using PS matching. However, our study was analyzed using PS and, therefore, the patient backgrounds were more closely matched than in the study by Tsai *et al.* and the results are accordingly likely to be more robust (14). In addition, factors that influence the development of cancer, such as alcohol consumption and smoking, as well as the participant background, including the number of hospitalizations and outpatient visits, (20-22) could be matched between LTRA users and non-users. Further studies by cancer type and LTRA drugs should be conducted using a large medical database to overcome the aforementioned problems.

Conclusion

In conclusion, our study clarified the use of LTRA may prevent the development of cancer in patients with bronchial asthma using a large medical information database. Subgroup analysis revealed that the higher the cumulative dose of LTRA, the lower the risk of developing cancer. Our results are likely to be more robust than previous studies because of PS matching. Currently, there are many medications to treat cancer; however, no drug has been approved for prevention. LTRAs are potentially useful clinically as novel medications to prevent cancer.

Conflicts of Interest

The Authors declare no potential conflicts of interest.

Authors' Contributions

MH, AO, KT, YM conceived the study. AMM, MH, YI analyzed the data and performed the statistical analysis. AMM, MH drafted the manuscript. AO, YK, KN, SS, TI, MS, KT, and YM contributed to discussions and reviewed the final manuscript. All the Authors approved the final manuscript.

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