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Beta-Blocker Use and Lung Cancer Mortality in a Nationwide Cohort Study of Patients with Primary Non–Small Cell Lung Cancer

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ABSTRACT

Background: β-Adrenergic receptor blockers have been associated with improved survival among patients with different types of malignancies, but available data for patients with non–small cell lung cancer (NSCLC) are contradictory and limited to small hospital-based studies. We therefore aimed to investigate whether β-blocker use at the time of cancer diagnosis is associated with lung cancer mortality in the largest general population-based cohort of patients with NSCLC to date.

Methods: For this retrospectively defined nationwide cohort study, we used prospectively collected data from Swedish population and health registers. Through the Swedish Cancer Register, we identified 18,429 patients diagnosed with a primary NSCLC between 2006 and 2014 with follow-up to 2015. Cox regression was used to estimate the association between β-blocker use at time of cancer diagnosis ascertained from the Prescribed Drug Register and cancer-specific mortality identified from the Cause of Death Register.

Results: Over a median follow-up of 10.2 months, 14,994 patients died (including 13,398 from lung cancer). Compared with nonuse, β-blocker use (predominantly prevalent use, 93%) was not associated with lung cancer mortality [HR (95% confidence interval): 1.01 (0.97–1.06)]. However, the possibility that diverging associations for specific β-blockers and some histopathologic subtypes exist cannot be excluded.

Conclusions: In this nationwide cohort of patients with NSCLC, β-blocker use was not associated with lung cancer mortality when assessed in aggregate in the total cohort, but evidence for some β-blockers is less conclusive.

Impact: Our results do not indicate that β-blocker use at lung cancer diagnosis reduces the cancer-specific mortality rate in patients with NSCLC.

Introduction

Lung cancer has been the most common cancer for several decades and continues to be the leading cause of cancer-related mortality worldwide (1). Non–small cell lung cancer (NSCLC) comprises about 80%–85% of lung cancer diagnoses and includes pulmonary adenocarcinoma, squamous cell carcinoma, and large cell carcinoma in descending order of frequency (2). Given an estimated 5-year survival rate of only 15% (3) and modest benefits of available treatments (1), it is critically important to explore strategies for improved survival.

Accumulating evidence from preclinical studies suggests a role of neuroendocrine regulation of physiologic and pathologic pathways in tumor growth and progression, and indicates that β-adrenergic receptor blockers may inhibit many downstream consequences of sympathetic nervous system activation (4–6), especially in early-stage disease (7). However, there may be variation by tumor site (8, 9) and subtype (10). For lung cancer, *in vitro* and *in vivo* studies suggest that the response to β-adrenergic signaling may differ across histopathologic subtypes due to potentially diverse growth-regulating pathways (6). *In vitro*, studies further suggest that even tumors of the same histologic subtype may respond differently (6, 11). Thus, while Clara cell–derived adenocarcinomas have been shown to be sensitive to cancer-promoting effects of β-adrenergic agonists, human cancer cells derived from alveolar type-II cells have demonstrated resistance to β-adrenergic agonists (11).

Few small, hospital-based observational studies have so far investigated the role of β-blockers in overall survival of patients with NSCLC and reached contradicting results (12–14). We therefore investigated whether the use of any or specific β-blockers at the time of cancer diagnosis is associated with lung cancer mortality in the largest general population-based cohort of patients with NSCLC to date.

Materials and Methods

Study population and data sources

In this retrospectively defined cohort study, we used prospectively collected data available through national Swedish registers with linkage using the unique personal identification numbers assigned to all residents in Sweden.

The Swedish Cancer Register (15) was used to identify all patients aged 18 years or older, diagnosed with a first primary malignant lung

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cancer [International Classification of Diseases (ICD) 7th revision code 162.1] between July 1, 2006, and December 31, 2014, as well as obtain information on tumor histology and stage, year of diagnosis, and age at diagnosis.

Using the Prescribed Drug Register (16), we identified β-blocker prescriptions and indications, as well as other relevant dispensed medications using the Anatomic Therapeutic Chemical (ATC) classification system. The number of distinct medication classes was used to derive a comorbidity score, a measure of overall disease burden (17, 18). Medications collected during one year before lung cancer diagnosis were considered.

The Patient Register (19) provided data on specific comorbid conditions. The Total Population Register provided information on migration, while LISA (Swedish acronym for Longitudinal Database of Education, Income and Occupation; ref. 20) provided information on level of attained education, marital status, and region of residence. The Cause of Death Register (21) provided information on the date of death and the underlying cause of death.

We excluded from the analysis patients diagnosed with lung cancer other than NSCLC (Supplementary Fig. S1).

β-Blocker exposure assessment

Because prescriptions normally cover a period of 30 to 90 days (maximum 1 year) in Sweden, patients were considered exposed if β-blockers were collected from the pharmacy at any time during the year before diagnosis and were estimated to last at least until the date of cancer diagnosis (considering number of tablets dispensed and number of tablets prescribed for daily use). β-Blocker exposure was further defined by receptor selectivity (cardio-selective, nonselective, nonselective with α1-adrenoreceptor blocking activity), and by solubility (lipophilic, hydrophilic). Low or high dose use was based on the prescribed daily dose below or above median value 0.50, calculated for all β-blockers except metoprolol–felodipine combination tablet [(tablet strength (mg) × number of tablets used per day)/type-specific defined daily dose] (18).

In a sensitivity analysis performed in patients diagnosed on or after October 1, 2006, β-blocker users were classified as incident or prevalent users, wherein users were defined as incident if they collected their β-blockers from the pharmacy within 90 days before cancer diagnosis date, but had no recorded collection in the previous year.

Outcome assessment

Lung cancer–specific mortality (CSM) was identified from the Cause of Death register using ICD-10 codes C33-34. Patients were followed from the date of cancer diagnosis until date of emigration, death, or December 31, 2015, whichever occurred first.

Statistical analysis

Patient characteristics were tabulated by β-blocker use and compared using the χ^2 or t test (two-sided) as appropriate. The actuarial method was used to estimate the observed 6-month, 1-year, and 5-year overall survival proportions. We used Cox regression with time since diagnosis in months as the underlying time scale to estimate HR and 95% confidence intervals (CI) for β-blocker–CSM association comparing β-blocker use with nonuse. Linearity of relationships between continuous variables and the log-hazard of mortality was assessed by the multivariable fractional polynomials method (22). Test and plots of Schoenfeld residuals were used to evaluate the assumption of proportional hazards.

The adjusted model included age at cancer diagnosis and the comorbidity score modeled using restricted cubic splines with five knots; year of diagnosis modeled as a linear measure, sex, tumor histology (categories: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and other NSCLC), tumor–node–metastasis (TNM) stages 1 to 4; education [categories: compulsory (up to 9 years), secondary (10 to 12 years), and postsecondary (more than 12 years)], marital status (categories: unmarried, married/cohabiting, divorced/separated, or widowed), region of residence, medications (other anti-hypertensive agents, NSAIDs, aspirin, and statins), and comorbidity at lung cancer diagnosis (coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, and diabetes) modeled as binary variables. Multiplicative interaction term was added to the adjusted model to test whether β-blocker–CSM association differed for men and women.

The analyses were performed in the entire study cohort as well as stratified by stage [early-stage (TNM: I–II), locoregionally advanced (TNM: III), and distant metastases (TNM: IV)]. Exploratory analyses looked at association with selected β-blockers. Other exploratory analyses examined histology-stratified associations. Further exploratory analysis stratified by adenocarcinoma variants was not pursued due to limited number of patients with alveolar type II cell ($n = 342$) and Clara cell–derived ($n = 73$) adenocarcinomas.

In a sensitivity analysis, we further adjusted for medications for obstructive airway diseases, which include β-agonists. To further address potential sources of confounding, we performed another sensitivity analysis where β-blocker users were compared with a more comparable reference population of nonusers who were prescribed medications used for the same main indications (coronary artery disease, acute myocardial infarction, congestive heart failure, cardiac arrhythmias, hypertension) as β-blockers within 1 year before cancer diagnosis (see ref. 17 for the ATC codes). We also examined the overall β-blocker–CSM association in a sample of patients matched by propensity score. The propensity score, the predicted probability of exposure given covariates, was estimated with logistic model regressing β-blocker use on covariates in the adjusted analysis. We performed nearest-neighbor one-to-one ratio matching without replacement on the logit of the propensity score using caliper of width equal to 0.2 of the SD of the logit of the estimated propensity score (23). Standardized differences, used to check covariate balance between treatment groups in the matched sample, assured that optimal balance was achieved across all covariates (the standardized percentage bias for each covariate was < 5%). HR was estimated using Cox regression stratified on the matched pairs as recommended in some papers (23).

All analyses were performed with Stata version 14/SE for Windows (StataCorp) software.

The study was approved by an ethical review board in Uppsala (DNR: 2012-361).

Results

Study population and overall survival estimates

The study cohort comprised 18,429 patients with a primary NSCLC, of whom 45.0% had no known distant metastases at diagnosis. The median age at diagnosis was 69 years (range: 30–99 years). The cancer diagnosis was primarily based on either histopathology (69.5%) or cytology (30.5%). Clinical examination ($n = 2$) or imaging technologies including X-ray, scintigraphy, ultrasound, MRI, CT ($n = 2$) were uncommon.

Over 29,472 person-years of observation time (median follow-up 10.2 months), 14,994 (81.4 %) patients died (13,398 of lung cancer, 458 of other tumors, 542 of cardiovascular disease, and 597 of other causes), 27 emigrated, and 3,408 were followed to the end of the

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Table 1. Baseline characteristics of patients diagnosed with primary NSCLC in Sweden between July 1, 2006 and December 31, 2014 by β-blocker use at cancer diagnosis.

	β-Blocker user (*N* = 5,114)		Nonuser (*N* = 13,315)		
	n	**Col %**	***n***	**Col %**	***P*[a]**
Age at diagnosis, years (mean, SD)	71.9	8.3	67.8	9.8	<0.001[b]
Male	2,756	53.9	6,602	49.6	<0.001
Attained education					<0.001
Compulsory	2,433	47.6	5,554	41.7	
Secondary	2,010	39.3	5,558	41.7	
Post-secondary	671	13.1	2,203	16.5	
Marital status at diagnosis					<0.001
Unmarried	462	9.0	1,770	13.3	
Married/cohabiting	2,582	50.5	6,445	48.4	
Divorced/separated	1,087	21.3	3,227	24.2	
Widowed	983	19.2	1,873	14.1	
TNM stage					0.022
Stage 1	707	13.8	1,644	12.3	
Stage 1 or 2[c]	179	3.5	471	3.5	
Stage 2	348	6.8	813	6.1	
Stage 3A	429	8.4	1,227	9.2	
Stage 3B/C	681	13.3	1,730	13.0	
Stage 4	2,440	47.7	6,602	49.6	
Recorded incompletely[d]	185	3.6	492	3.7	
Missing[e]	145	2.8	336	2.5	
Tumor histology					0.035
Adenocarcinoma	3,106	60.7	8,325	62.5	
Squamous	1,344	26.3	3,274	24.6	
Adenosquamous	65	1.3	156	1.2	
Large cell	178	3.5	533	4.0	
Other NSCLC	421	8.2	1,027	7.7	
Comorbidity score (median, IQR)[f]	10	(7–14)	6	(3–10)	<0.001[b]
Comorbidity diagnosed before lung cancer diagnosis					
Coronary artery disease	2,041	39.9	1,182	8.9	<0.001
Coronary heart failure	934	18.3	479	3.6	<0.001
Cerebrovascular disease	889	17.4	1,175	8.8	<0.001
Chronic obstructive pulmonary disease	854	16.7	1,753	13.2	<0.001
Asthma	199	3.9	563	4.2	0.303
Diabetes	1,085	21.2	1,297	9.7	<0.001
Other medications[g] (ATC code)					
Other antihypertensive medications[h]	3,603	70.5	4,012	30.1	<0.001
Nonsteroidal anti-inflammatory drugs (M01A)	1,228	24.0	3,636	27.3	<0.001
Aspirin (B01AC:06,30; N02BA:01,51)	2,719	53.2	2,537	19.1	<0.001
Statin (C10AA)	2,693	52.7	2,564	19.3	<0.001

Note: Patients were considered exposed to β-blocker use if β-blockers collected during 1 year before cancer diagnosis would last until cancer diagnosis date, unexposed otherwise. Tumor staging follows the American Cancer Society classification 6th (until 2010) and 7th (since 2010) editions [stage 1: T1/N0/M0 or T2a/N0/M0; stage 2: T(2b-3)/N0/M0 or T(1-2)/N1/M0; stage 3A: T(1-2)/N2/M0 or T3/N(1-2)/M0 according to the 6th and T(1-3)/N2/M0 or T3/N1/M0 or T4/N(0-1)/M0 according to the 7th editions; stage 3B/C: T(1-4)/N3/M0 or T4/N(0-2)/M0 according to the 6th and T(1-4)/N3/M0 or T4/N2/M0 according to the 7th editions; stage 4: any T, any N, M1]. T stands for the extent (size) of the tumor; N indicates the spread to nearby lymph nodes; M denotes the spread (metastasis) to distant sites. TNM recording in the Cancer Register was introduced in 2004 and has improved over time. Tumor histology was defined using WHO histologic classification of the lung tumors (ICD-O-3 morphologic codes for adenocarcinoma: 8140/3, 8141/3, 8200/3, 8250/3, 8252/3, 8253/3, 8254/3, 8255/3, 8260/3, 8310/3, 8480/3, 8490/3, 8550/3; for squamous cell carcinoma: 8052/3, 8070/3, 8073/3, 8083/3, 8084/3; for adenosquamous carcinoma: 8560/3; for large cell carcinoma: 8012/3; 8013/3, 8014/3, 8082/3, 8123/3; for other or undifferentiated NSCLC: 8022/3, 8031/3, 8032/3, 8033/3, 8046/3, 8972/3,8980/3). Diabetes was defined using ICD codes from the Patient Register and antidiabetic medications (ATC: A10) from the Prescribed Drug Register; other comorbid diagnoses were defined using ICD codes in the Patient Register.

Abbreviations: ATC, Anatomic Therapeutic Chemical classification system; IQR, interquartile range.

[a]*P* values are from a χ^2 test.

[b]Two-sample *t* test for age at diagnosis and median test for comorbidity score.

[c]Stages 1 versus 2 could not be distinguished whenever T2 a/b subtypes were not specified in the Cancer Register.

[d]Either T, N, or M stage was not specified.

[e]T, N, and M stages were missing or recorded as TxNxMx.

[f]Number of distinct medication classes (medications with the same initial five characters of ATC classification) within 1 year before cancer diagnosis was used to derive a comorbidity score.

[g]Medications (yes/no variables) are dispensed within 1 year before cancer diagnosis and are not mutually exclusive.

[h]Include angiotensin-converting enzyme inhibitors (ATC: C09: A, BA, BB), angiotensin receptor blockers (ATC: C09: C, DA, DB), calcium channel blockers (ATC: C08), and thiazide diuretics (ATC: C03A).

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Table 2. β-Blocker use at lung cancer diagnosis compared with nonuse in relation to lung cancer–specific mortality in 18,429 patients diagnosed with primary NSCLC in Sweden between July 1, 2006 and December 31, 2014.

β-Blocker use[a]	No. of events	HR[b] (95% CI)	HR[c] (95% CI)
Any β-blocker	3,695	1.06 (1.02–1.10)	1.01 (0.97–1.06)
By adrenoreceptor selectivity			
β1-Receptor selective[d]	3,402	1.06 (1.02–1.10)	1.01 (0.96–1.05)
Nonselective (β1/β2-blocking)[e]	239	1.05 (0.93–1.20)	1.08 (0.95–1.23)
α1- and β1/β2-Blocking[f]	70	0.93 (0.74–1.18)	0.88 (0.70–1.12)
By solubility			
Lipophilic[g]	2,840	1.05 (1.01–1.09)	1.02 (0.97–1.07)
Hydrophilic[h]	914	1.06 (0.99–1.14)	1.00 (0.93–1.07)
By prescribed daily dose			
Low dose[i]	2,002	1.06 (1.01–1.11)	1.01 (0.95–1.06)
High dose[i]	1,661	1.06 (1.00–1.11)	1.01 (0.96–1.07)

Note: "No. of events" column shows number of outcome events among β-blocker users. Dose was calculated for 99% of β-blocker users.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Exposed if β-blockers collected during 1 year before cancer diagnosis would last until cancer diagnosis date, unexposed otherwise.
[b]Unadjusted for covariates.
[c]Adjusted for age, sex, stage, histology, year of diagnosis, region of residence, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 1 year prior to diagnosis), comorbidity (coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, diabetes), other antihypertensive medications, nonsteroidal anti-inflammatory drugs, aspirin, statins.
[d]Includes metoprolol, atenolol, bisoprolol.
[e]Includes pindolol, propranolol, sotalol.
[f]Includes labetalol, carvedilol.
[g]Includes bisoprolol, carvedilol, labetalol, metoprolol, pindolol, propranolol, metoprolol + felodipine.
[h]Includes sotalol, atenolol.
[i]Calculated as [tablet strength (mg) multiplied by number of tablets prescribed for daily use] divided with the β-blocker–specific defined daily dose (mg).

study. The median survival was 11.4 months, and the estimated 6-month, 1-year, and 5-year overall survival proportions were 64%, 46%, and 16%, respectively.

β-Blocker use

Characteristics of all patients are presented in **Table 1** by β-blocker use. Overall, 5,114 (28%) patients met the exposure definition. The majority were prevalent users, and only a few were classified as incident users ($n = 334$ in the entire cohort). β-Blocker use was somewhat more common in men than in women, and users tended to be older, have fewer years of education, be married, cohabiting, or widowed. Users were also more likely to have comorbid conditions and prescriptions for other antihypertensive medications, statins, and aspirin, but less likely to have NSAID prescriptions. Distant metastases were slightly less common among β-blocker users.

The most commonly prescribed β-blocker was β1-cardio-selective metoprolol (Supplementary Table S1). Only 6% of users received nonselective β-blockers. Few (<2%) users received β-blockers of several classes (for example, selective and nonselective). Prescribed daily dose was calculated for 99% of β-blocker users, of whom 45% were classified as receiving a high dose. The most common indications specified in the Drug Register were hypertension (61%) and heart disease (59%). Indications could not be identified from the prescription records for 13% of the users.

β-Blocker use and lung cancer mortality

The CSM rates (per 100 person-months) were slightly higher among β-blocker users compared with nonusers [4.06 (95% CI, 3.93–4.19) and 3.70 (95% CI, 3.62–3.77), respectively], resulting in a statistically significant but low-magnitude crude HR of 1.06 (1.02–1.10). Further multivariable adjusted analyses suggested no statistically significant association either overall (**Table 2**) or across tumor stage strata (**Table 3**). The overall β-blocker–CSM association did not differ by sex ($P_{\text{interaction}}$ term = 0.313). Histology-stratified exploratory analyses suggested some variation in the direction and the magnitude of the estimates (**Table 4**; Supplementary Table S2).

The results were largely statistically nonsignificant in relation to any β-blocker use as well as β-blockers with different pharmacologic properties, although the possibility that diverging associations for some combinations of histopathology, stage and β-blocker types may exist cannot be excluded (**Tables 2–5**; Supplementary Table S2). For example, a higher mortality rate is suggested for nonselective propranolol (**Table 5**).

In the sensitivity analysis using the incident and prevalent user definitions of exposure, survival curves for incident and prevalent β-blocker use and nonuse did not demonstrate substantial differences (Supplementary Fig. S2).

Sensitivity analysis additionally adjusted for medications indicated for obstructive airway diseases (including β-agonists), as well as analysis comparing β-blocker users with a more comparable reference population of patients who dispensed medications used for the same main indications as β-blockers (Supplementary Table S3), produced similar results. Propensity score matched sensitivity analysis in a sample of 8,030 patients (4,015 users and 4,015 nonusers) produced consistent results [1.02 (0.96–1.10)].

Discussion

In this large population-based cohort of patients with NSCLC, association between β-blocker use at cancer diagnosis and lung cancer mortality was overall statistically nonsignificant, regardless of tumor stage at diagnosis, β-adrenoreceptor selectivity, solubility, or dose of β-blocker. Although the data provided evidence for near-null β-blocker–CSM association when β-blockers were assessed in

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Table 3. β-Blocker use at lung cancer diagnosis compared with nonuse in relation to lung cancer–specific mortality by tumor stage in patients diagnosed with primary non–small cell lung cancer in Sweden between July 1, 2006 and December 31, 2014.

	Early disease (stages I–II) *N* = 4,162		Locoregionally advanced (stage III) *N* = 4,067		Distant metastases (stage IV) *N* = 9,042	
β-Blockers[a]	**No. of events**	**HR[b] (95% CI)**	**No. of events**	**HR[b] (95% CI)**	**No. of events**	**HR[b] (95% CI)**
Any β-blocker	432	1.01 (0.89–1.16)	866	0.96 (0.88–1.06)	2,163	1.01 (0.95–1.07)
By adrenoreceptor selectivity						
β1-Receptor selective[c]	398	1.03 (0.90–1.18)	788	0.94 (0.85–1.03)	2,005	1.01 (0.95–1.07)
Nonselective (β1/β2-blocking)[d]	26	0.90 (0.61–1.33)	60	1.26 (0.97–1.63)	133	0.99 (0.83–1.18)
α1- and β1/β2-blocking[e]	10	1.06 (0.56–2.00)	17	0.76 (0.47–1.24)	39	0.88 (0.64–1.21)
By solubility						
Lipophilic[f]	336	0.98 (0.85–1.13)	668	1.00 (0.90–1.10)	1,654	1.02 (0.96–1.09)
Hydrophilic[g]	102	1.04 (0.84–1.29)	214	0.90 (0.78–1.04)	540	0.99 (0.90–1.09)

Note: "No. of events" column shows number of outcome events among β-blocker users.
[a]Exposed if β-blockers collected during 1 year before cancer diagnosis would last until cancer diagnosis date, unexposed otherwise.
[b]Adjusted for age, sex, stage, histology, year of diagnosis, region of residence, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 1 year prior to diagnosis), comorbidity (coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, diabetes), other antihypertensive medications, nonsteroidal anti-inflammatory drugs, aspirin, statins.
[c]Includes metoprolol, atenolol, bisoprolol.
[d]Includes pindolol, propranolol, sotalol.
[e]Includes labetalol, carvedilol.
[f]Includes bisoprolol, carvedilol, labetalol, metoprolol, pindolol, propranolol, metoprolol + felodipine.
[g]Includes sotalol, atenolol.

aggregate in the total NSCLC cohort, evidence for some beta-blockers is less conclusive, especially in stratified analyses, and deserves further investigation.

Preclinical evidence for a regulatory role of β-adrenergic signaling in lung cancer growth dates back to 1989 (24), and suggests an effect on apoptosis, angiogenesis, cell proliferation, and migration (2, 6, 24). However, most of these effects have been observed in pulmonary adenocarcinoma cell lines (6). Because lung cancer comprises a heterogeneous disease, and the effects of catecholamines may differ in different lung cancer cells, failure to discriminate lung cancer by histologic subtype may mask the effects of β-adrenoreceptor inhibitors (6). This could partly explain our overall findings as well as the near-null associations observed in previous population-based cohort studies that did not discriminate lung cancer by histology (17, 25–28) and previous conflicting results among patients with NSCLC (12–14). Except a hospital-based study in patients with stages I–III NSCLC treated with definitive radiotherapy (13), the other studies (12, 14) have not provided evidence of a survival benefit in patients with NSCLC on β-blockers. Furthermore, at least one (14) of these studies has been found to be prone to immortal time bias (17).

In preclinical studies, not only NSCLC family subtypes have been shown to respond differently to β-adrenergic signaling, but also adenocarcinoma cell variants (alveolar type-II cell and Clara cell derived, both of which have been reported as the predominating type of human pulmonary adenocarcinoma subject to the investigated patient population and/or the applied diagnostic methods; ref. 11). However, we could not examine β-blocker–CSM association across these adenocarcinoma subtypes (which are not used clinically; ref. 29), because the most commonly recorded (95%) adenocarcinoma morphology code in the Cancer Register (ICD-O-3 code 8140/3) does not distinguish cell origin.

Preclinical data has linked β-adrenergic agonists with inhibition of squamous cell growth (6), while our data suggested little or no influence of β-blockers on the survival of patients with squamous cell carcinoma when they were considered together. However, diverging associations were suggested in relation to some β-blockers.

The distribution of receptors may determine the clinical effect of the medication (30). Expression of β-adrenoreceptors, including β2-adrenoreceptors, has been shown to be downregulated in human lung tumor tissue compared with normal control tissues (31–33), possibly due to the neoplastic process itself as neoplastic cells are genetically

Table 4. β-Blocker use compared with nonuse in relation to lung cancer–specific mortality by histology among patients diagnosed with non–small cell lung cancer in Sweden between July 1, 2006 and December 31, 2014.

	All patients		Early stage (I–II) disease	
	No. of events	**HR[a] (95% CI)**	**No. of events**	**HR[a] (95% CI)**
In adenocarcinoma	2,210	1.02 (0.97–1.08)	225	0.93 (0.77–1.12)
In squamous cell carcinoma	945	1.00 (0.92–1.09)	145	0.93 (0.74–1.15)
In large cell carcinoma	139	0.99 (0.78–1.27)	22	2.76 (1.20–6.32)
In adenosquamous carcinoma	48	1.58 (0.94–2.65)	8	Not estimated

Note: 'No. of events' column shows number of outcome events among β-blocker users.
[a]Adjusted for age, sex, stage, year of diagnosis, region of residence, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 1 year prior to diagnosis), comorbidity (coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, diabetes), other antihypertensive medications, nonsteroidal anti-inflammatory drugs, aspirin, statins.

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Table 5. Selected β-blocker use compared with nonuse in relation to lung cancer–specific mortality overall and by stage among patients diagnosed with NSCLC in Sweden between July 1, 2006 and December 31, 2014.

			All patients $N = 18,429$		Early disease (stages I–II) $N = 4,162$		Locoregionally advanced (stage III) $N = 4,067$		Distant metastases (stage IV) $N = 9,042$	
β-Blockers[a]	Selectivity ratio	Solubility	No. of events	HR[b] (95% CI)	No. of events	HR[b] (95% CI)	No. of events	HR[b] (95% CI)	No. of events	HR[b] (95% CI)
Nonselective[c]	β2 vs. β1									
Propranolol	8.3	HL	140	1.22 (1.03–1.45)	18	1.01 (0.63–1.61)	32	1.25 (0.88–1.78)	77	1.14 (0.91–1.43)
Sotalol	12.0	HD	78	1.00 (0.80–1.25)	6	0.70 (0.31–1.56)	23	1.17 (0.77–1.77)	44	0.95 (0.71–1.28)
Carvedilol[d]	4.5	ML	67	0.86 (0.67–1.10)	8	0.91 (0.45–1.86)	17	0.77 (0.47–1.24)	38	0.87 (0.63–1.20)
β1-Receptor selective	β1 vs. β2									
Metoprolol	2.3	HL	2,064	1.00 (0.95–1.06)	233	0.92 (0.79–1.08)	473	0.94 (0.84–1.05)	1,225	1.03 (0.97–1.11)
Atenolol	4.7	HD	836	0.99 (0.92–1.07)	96	1.06 (0.86–1.32)	191	0.87 (0.75–1.02)	496	0.99 (0.90–1.09)
Bisoprolol	13.5	ML	582	1.05 (0.96–1.14)	78	1.21 (0.94–1.55)	143	1.04 (0.87–1.24)	325	0.98 (0.87–1.10)

Note: "No. of events" column shows number of outcome events among β-blocker users.
Abbreviations: HD, hydrophilic; HL, highly lipophilic; ML, moderately lipophilic.
[a]Exposed if β-blockers collected during 1 year before diagnosis would last until cancer diagnosis date, unexposed otherwise.
[b]Adjusted for age, sex, stage, histology, year of diagnosis, region of residence, attained education, marital status, comorbidity score (number of distinct ATC classes prescribed during 1 year prior to diagnosis), comorbidity (coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, diabetes), other antihypertensive medications, nonsteroidal anti-inflammatory drugs, aspirin, statins.
[c]Block β1 and β2 adrenergic receptors.
[d]Carvedilol is a nonselective β-blocker that blocks β1 and β2 adrenergic receptors as well as the α1 adrenergic receptors.

defective and poorly differentiated (32). This could also potentially explain the absence of an effect in these patients. However, some other studies have reported overexpression of β-adrenoreceptors in lung cancer relative to normal noncancer tissue (34). With respect to specific β-adrenoreceptor expression, a high density of β2-adrenoreceptors has been detected not only in normal lung cells and tissue but also in NSCLC tumor cells (30, 34, 35). Human adenocarcinoma cell lines have been shown to have high expression of both β1- and β2-adrenoreceptors (34). Positive β2-adrenoreceptor expression has further been shown to predict poor progression-free survival in patients with stage I adenocarcinoma (36), while propranolol, a nonselective β-blocker, was shown to reverse the proliferation of NSCLC cells *in vitro* (2). Higher magnitude inverse associations could therefore have been expected in relation to nonselective β-blockers. In our analysis, limited by a low prevalence of nonselective β-blockers (likely due to concerns regarding potential bronchoconstriction; ref. 37), a higher mortality rate was suggested for propranolol and possibly a lower mortality rate for carvedilol.

Strengths of this study include its large size and use of high-quality prospectively collected data from national registers in the setting of a tax-supported universal health care system. This substantially reduces the risk of selection bias, loss to follow-up, and the probability of findings being confounded by socioeconomic characteristics. Given the sample size and failure probability, the study had adequate statistical power (80%) to detect a minimum positive HR of at least 1.08 and a negative HR of at least 0.93 at a significance level of 0.01, accounting for the dependence between β-blocker use and other model covariates. The narrow confidence interval provides further evidence of an adequate statistical power for the evaluation of the overall β-blocker–CSM association. However, the study was underpowered to study the role of less commonly used β-blockers, especially in stratified analyses.

The use of dispensed prescriptions from the Prescribed Drug Register to define exposure to medication(s) prevents problems like recall bias or failure to fill a prescribed medication, while the requirement for patients to pay a component of the dispensed price should increase the probability of actual use. However, drug exposure misclassification is still possible. Our exposure definition does not account for possible changes during follow up, but resembles the intention-to-treat analysis in randomized studies and eliminates the possibility of immortal time bias (17). Analyses to examine adrenoreceptor selectivity and solubility were performed, and further exploratory analysis focused on some individual β-blockers, although these analyses were limited by low prevalence of nonselective β-blockers. Because comparison of prevalent users with nonusers could be subject to selection bias (38), we examined in a sensitivity analysis survival curves for incident, prevalent β-blocker use and nonuse. Our analysis, although limited by a small number of incident users, did not reveal substantial differences between survival curves, further supporting the conclusion that β-blocker use at the time of NSCLC diagnosis is not associated with improved lung cancer survival.

Although the national register data enabled the possibility to account for important potential confounding and prognostic factors, the possibility of residual confounding cannot be excluded in an observational study potentially limiting causal inference. To further mitigate the potential impact of uncontrolled confounding and adherence bias (39), we compared β-blocker users with a more comparable population of non-users who dispensed medications used for the same main indications as β-blockers, and found similar results. Analysis using propensity score matched sample also produced consistent results.

Our study is limited by lack of information on smoking, the strongest known risk factor for all lung cancers (6), which has been linked not only with poor prognosis in patients with lung cancer (40) but also with reduced efficacy of β-blockers (possibly because in smokers β-blockers must compete with nicotine derived nitrosamine for β-adrenergic binding sites; ref. 41). However, our finding for squamous cell carcinoma is less likely to be affected by our inability to stratify by smoking status, because this cancer develops almost exclusively in smokers (6).

In this large population-based study, we did not find an evidence for an association between β-blocker use and lung cancer mortality among

patients with NSCLC, but the possibility that diverging associations for some combinations of histopathology and β-blocker types exist cannot be excluded.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Udumyan, S. Montgomery, A. Ekbom, K. Fall
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.E. Smedby
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Udumyan, F. Fang, A. Ekbom, K. Fall
Writing, review, and/or revision of the manuscript: R. Udumyan, S. Montgomery, F. Fang, H. Hardardottir, A. Ekbom, K.E. Smedby, K. Fall
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Udumyan
Study supervision: K. Fall

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