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ORIGINAL ARTICLE



# Desloratadine and loratadine stand out among common $H_1$-antihistamines for association with improved breast cancer survival

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**ABSTRACT**

**Background:** As tumors maintain an inflammatory microenvironment, anti-inflammatory medication can be useful in cancer therapy. We have previously shown an association with improved survival in melanoma for use of the $H_1$-antihistamines desloratadine and loratadine, and here we examine use of $H_1$-antihistamines and breast cancer mortality.

**Material and methods:** We investigated use of the six major $H_1$-antihistamines (cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine) and breast cancer-specific and overall mortality in a nation-wide register-based study of all 61,627 Swedish women diagnosed with breast cancer 2006–2013. Both peri- and post-diagnostic antihistamine use was analyzed using Cox regression models. Analyses were stratified for age and subgroup analyses based on estrogen receptor status and menopausal status were performed.

**Results:** We found a consistently improved survival of desloratadine users (HR = 0.67; 95% CI 0.55–0.81, $p < .001$), as well as of loratadine users (HR = 0.80; 95% CI 0.67–0.95, $p = .012$), relative to nonusers, regardless of patient age, menopause, estrogen receptor status or stage of the tumor, or whether breast cancer-specific or overall survival was analyzed. The survival of users of other antihistamines varied relative to non-users.

**Conclusion:** Based on their safety and current use within the patient population, together with our observations, we suggest the initiation of trials of desloratadine and loratadine as treatment of breast cancer as well as studies of the mechanism behind their possible effect. Further studies on any effects of other $H_1$-antihistamines may also be merited, as well as of $H_1$-antihistamine use and survival in other malignancies.

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## Introduction

Tumors maintain an inflammatory microenvironment and anti-inflammatory medication, including $H_2$-antihistamines [1], has shown potential in cancer therapy. We have previously shown an improved survival in melanoma for users of the $H_1$-antihistamines desloratadine and loratadine [2] as well as in breast cancer in our pilot study [3] and a Danish study demonstrated improved survival associated with use of some cationic amphiphilic antihistamines among patients with non-small cell lung cancer and non-localized cancer [4], as well as in ovarian cancer in another study [5].

Here, we examined use of the six major $H_1$-antihistamines (cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine) and breast cancer-specific as well as overall mortality among Swedish women[1] with breast cancer in a national observational study – the first of its kind – using some of the comprehensive Swedish health care registers. As breast cancer is a highly heterogeneous disease, with factors such as estrogen receptor (ER) status and menopausal status greatly impacting both prognosis and treatment [6–11], we included subgroup analyses based on both factors (using age 50 as a proxy for menopause and prescribed treatment as a proxy for ER status).

## Material and methods

### Data handling and registers

Our study population includes all 61,627 women with newly diagnosed breast cancer 2006–2013 in the Swedish Cancer Register (SCR), a database of all cancer cases in Sweden since 1958 with high coverage. Use of the six major $H_1$-antihistamines (cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine) was established through the Swedish Prescribed Drug Register (PDR), a record of all dispensed prescribed pharmaceuticals in Sweden since July 1st 2005. Prescription-free use, non-dispensed doses, or use of other, uncommon, types of antihistamines is here considered non-

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use. Follow-up was until December 31st 2014. Causes of death were obtained from the Swedish Cause of Death Register, a record of all deaths since 1952. Data was pseudo-anonymized, and the study was approved by the Regional Ethics Board.

### Statistical analysis

Both peri- and post-diagnostic antihistamine use was analyzed using Cox regression. Peri-diagnostic antihistamine use is here defined as dispensed prescriptions of any of the six antihistamines cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine from six months pre-diagnosis to six months post-diagnosis. (Individuals who used more than one of the antihistamines were defined as users of the main antihistamine used peri-diagnostically, in terms of dispensed defined daily doses, or DDDs.) Survival probability was plotted in a graph for cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine users vs non-users, both as a group and separately for each drug. Post-diagnostic antihistamine use is here defined in a cumulative manner, as the total number of dispensed prescriptions of any of the six antihistamines cetirizine, clemastine, desloratadine, ebastine, fexofenadine and loratadine from diagnosis up until a specific time during follow-up. Time-varying covariates were used for the analysis, allowing the cumulative use to change with time as a subject continues to use antihistamines during follow-up. Additionally, this allows a single individual to potentially provide data as both a non-user and user, as well as concomitant use of multiple antihistamines. Cumulative DDDs were analyzed by log transformation. Hazard ratios compare mortality between groups of antihistamine users differing in cumulative use by an approximate factor of three. Study start was set to six months following diagnosis for the peri-diagnostic analysis, and to the time of diagnosis for the post-diagnostic analysis. Cox regression analyses were stratified for patient age at diagnosis in four categories ($\leq$50, $>$50 - $\leq$60, $>$60 - $\leq$70 and $>$70). Statistical analyses were performed using R [12]. Two-sided tests and corresponding P-values were used, and a test based on Schoenfeld residuals was done to assess the proportional hazards assumption. ER status was determined by identifying treatment with aromatase inhibitors, tamoxifen or fulvestrant in the PDR. Correction for stage was done by means of multiple imputation [13], as much of the information required to asses stage was missing, likely due to a coding error in the SCR. The imputation model was based on the proportional odds model, and included variables for alive/dead status, cumulative hazard of death, type of antihistamine, ER status and age at diagnosis, and was performed using the MICE package [14]. Imputations were repeated ten times and burn in and imputed data value distribution for each dataset was examined for analysis integrity. The post-diagnostic analysis was additionally extended to include lag from zero to five years in six month-intervals for all antihistamines except ebastine and fexofenadine. In these analyses, the time-varying covariate showing cumulative post-diagnostic antihistamine use from diagnosis up until a specific time x during follow-up, was altered to cumulative use from diagnosis until x minus the time defined by the lag. (For example, a one-year lag would mean that antihistamine use was accumulated from diagnosis until one year before the time x.) The lag was added in order to evaluate whether any potential effects of antihistamines were delayed in time compared to the initiation of use, and to exclude any potential over- or under-use due to patients using antihistamines more or less because of poor health (or to counter side effects of other treatments) at the end of life. Hazard ratios corresponding to the effect of use with different lag periods for overall mortality respectively of cetirizine, clemastine, desloratadine and loratadine users vs non-users were plotted in a graph.

## Results

18.4% of women died during the study period, with 58.9% of deaths recorded as breast cancer-related. A majority of women (81.6%) were above age 50 at diagnosis, and are thus here considered postmenopausal. 65.8% had dispensed prescribed medications for ER positive tumors. 23.9% of women used antihistamines peri-diagnostically during the study period (six months pre- and post-diagnosis 2006–2013). On average, 50 DDDs were dispensed for an antihistamine user in a year. The most common antihistamine used was cetirizine, followed by clemastine, loratadine and desloratadine. Ebastine and fexofenadine were used by much fewer women (Table 1).

When antihistamine users were grouped together, there was no significant difference in breast cancer survival compared to non-users (data not shown), however, when analyzed according to antihistamine type, those who used clemastine and cetirizine had lower survival rates than non-users, whereas desloratadine, ebastine, fexofenadine and loratadine users had better survival rates than non-users. Desloratadine and ebastine users in particular had markedly better survival rates within two years after diagnosis up until ten years after. Mean follow-up time was 4.5 years (Figure 1).

Peri-diagnostic use of desloratadine, ebastine and loratadine was associated with better breast cancer-specific survival than non-use. Peri-diagnostic cetirizine use was not associated with any significant difference in breast cancer mortality. Clemastine use peri-diagostically was associated with an increased risk of breast cancer-related death, while the result for fexofenadine was non-significant. The same analysis done with regard to overall mortality yielded similar results: compared with non-use, desloratadine and loratadine use peri-diagnostically were associated with a decreased risk, cetirizine, ebastine and fexofenadine use was not associated with any significant difference in risk, while clemastine use was associated with an increased risk of overall death (Table 2).

The main findings remain the same across subgroups based on ER status or menopause: cetirizine use was associated with worse or not significantly altered survival, clemastine users had a consistently worse survival and the results for ebastine and fexofenadine were usually non-significant (although the point estimates for ebastine were positive, and

**Table 1.** Survival, menopausal status, stage, estrogen receptor status and peri-diagnostic antihistamine use of all Swedish women diagnosed with breast cancer 2006–2013 ($n = 61,627$).

| | Non-users[a] ($n = 46,916$) | Cetirizine users ($n = 4196$) | Clemastine users ($n = 3408$) | Desloratadine users ($n = 3080$) | Ebastine users ($n = 519$) | Fexofenadine users ($n = 244$) | Loratadine users ($n = 3264$) | All ($n = 61,627$) |
|---|---|---|---|---|---|---|---|---|
| Survived, all causes | 37,983 (81.0) | 3412 (81.3) | 2699 (79.2) | 2754 (89.4) | 460 (88.6) | 219 (89.8) | 2777 (85.1) | 50,304 (81.6) |
| Died, all causes | 8933 (19.0) | 784 (18.7) | 709 (20.8) | 326 (10.6) | 59 (11.4) | 25 (10.2) | 487 (14.9) | 11,323 (18.4) |
| Survived, breast cancer | 41,738 (89) | 3653 (87.1) | 3009 (88.3) | 2884 (93.6) | 492 (94.8) | 226 (92.6) | 2957 (90.6) | 54,959 (89.2) |
| Died, breast cancer[b] | 5178 (11) | 543 (12.9) | 399 (11.7) | 196 (6.4) | 27 (5.2) | 18 (7.4) | 307 (9.4) | 6668 (10.8) |
| Premenopausal (Age <50) | 8115 (17.3) | 949 (22.6) | 722 (21.2) | 678 (22) | 131 (25.2) | 58 (23.8) | 716 (21.9) | 11,369 (18.4) |
| Postmenopausal (Age >50) | 38,801 (82.7) | 3247 (77.4) | 2686 (78.8) | 2402 (78) | 388 (74.8) | 186 (76.2) | 2548 (78.1) | 50,258 (81.6) |
| Stage[c] unknown | 16,003 (34.1) | 1401 (33.4) | 1126 (33.0) | 1047 (34.0) | 170 (32.8) | 86 (35.2) | 1036 (31.7) | 20,869 (33.9) |
| Stage 0 | 4302 (9.2) | 360 (8.6) | 293 (8.6) | 316 (10.3) | 60 (11.6) | 28 (11.5) | 290 (8.9) | 5649 (9.2) |
| Stage 1 | 13,912 (29.7) | 1206 (28.7) | 994 (29.2) | 984 (31.9) | 155 (29.9) | 66 (27) | 983 (30.1) | 18,300 (29.7) |
| Stage 2 | 9268 (19.8) | 883 (21) | 739 (21.7) | 558 (18.1) | 110 (21.2) | 51 (20.9) | 733 (22.5) | 12,342 (20) |
| Stage 3 | 2245 (4.8) | 250 (6.0) | 190 (5.6) | 138 (4.5) | 21 (4.0) | 11 (4.5) | 175 (5.4) | 3030 (4.9) |
| Stage 4 | 1186 (2.5) | 96 (2.3) | 66 (1.9) | 37 (1.2) | 3 (0.6) | 2 (0.8) | 47 (1.4) | 1437 (2.3) |
| ER-[d] | 16,068 (34.2) | 1499 (35.7) | 1126 (33) | 996 (32.3) | 183 (35.3) | 92 (37.7) | 1099 (33.7) | 21,063 (34.2) |
| ER+[d] | 30,848 (65.8) | 2697 (64.3) | 2282 (67) | 2084 (67.7) | 336 (64.7) | 152 (62.3) | 2165 (66.3) | 40,564 (65.8) |

Values are *n* (%).

[a]Here, antihistamine use is defined as dispensed prescribed doses of any of the six listed major antihistamines (cetirizine, clemastine, desloratadine, ebastine and fexofenadine) recorded in the Swedish Prescribed Drug Register. Prescription-free use, non-dispensed doses, or use of other types of antihistamines, is here considered non-use.

[b]Breast cancer-related death (as recorded in the Swedish Cause of Death Register).

[c]Stage was calculated based on the TNM information recorded in the Swedish Cancer Register, which in turn is mostly based on pathological grading, and the large proportion of tumors with unknown stage is due in part to a likely coding error in the register for several years included in this study.

[d]Estrogen receptor status was determined through dispensed prescribed doses of treatments for ER + tumors recorded in the Swedish Prescribed Drug Register.

in postmenopausal women, ebastine use was associated with a markedly improved – and statistically significant – survival with HR = 0.32). Desloratadine and loratadine use was consistently associated with a better survival for women with both ER positive and negative tumors, though the results for loratadine were not always statistically significant. Among postmenopausal women, both desloratadine and loratadine users had a pronouncedly improved survival, however, for premenopausal women, the results were not statistically significant (Tables 3 and 4; Supplemental Table 1 and Supplemental Table 2).

The majority of peri-diagnostic antihistamine users (92.5%) used only one of the six antihistamine types, and excluding those who used multiple types yielded nearly identical results as above (Supplemental Table 3).

The imputation analysis, done as a correction for stage, also yielded near identical results as the main analysis (Supplemental Table 4).

Compared with non-use, post-diagnostic desloratadine use and ebastine use was associated with a lowered risk of breast cancer-related death. Loratadine and fexofenadine use was associated with a similar survival rate to non-use, though the result was non-significant. Post-diagnostic cetirizine and clemastine use was associated with a somewhat increased risk of breast cancer-related death. The same analysis done with regard to overall mortality yielded similar results (Table 5).

The lag-time analysis of desloratadine and loratadine use revealed no plateau within the duration of this study: an increased cumulative dose was associated with better survival for up to five years. (Supplemental Figure 1 and Supplemental Figure 2). The lag-time analysis of clemastine as well as cetirizine use suggests that the increased mortality is reduced when the time adjacent to death was excluded. (Supplemental Figure 3 and Supplemental Figure 4).

## Discussion

Survival in breast cancer was improved for women taking desloratadine, ebastine and loratadine. Findings were most pronounced and consistent for desloratadine, and it is possible that the observed association of loratadine use with improved survival is due to desloratadine being the active metabolite of loratadine. Hemminki *et al* found no protective effect of hay fever or allergic rhinitis on breast cancer, rather, a somewhat increased breast cancer risk [15], and other conditions for which antihistamines may be prescribed are similarly not associated with reduced breast cancer risks. Furthermore, the increasing number of studies showing effects of various antihistamines on inhibiting tumor growth and promoting apoptotic cell death of tumor cells [16–20] also support our findings. However, these studies often focus on older antihistamines, such as the discontinued drug terfenadine, that have serious side effects hampering their usefulness as human therapy, whereas our focus is on the safe antihistamines currently in use in Sweden.

No overall survival benefit was seen when antihistamine users were grouped together, likely due to the fact that clemastine and cetirizine, two of the most commonly used $H_1$-antihistamines, may negatively influence survival, counteracting the any potentially positive effects of desloratadine, ebastine and loratadine. We recommend that studies assessing risks and prognoses associated with antihistamine use should analyze the different drugs separately, as any combined effect may very well be negligible. This is supported by our study on survival in melanoma [2] and the Danish

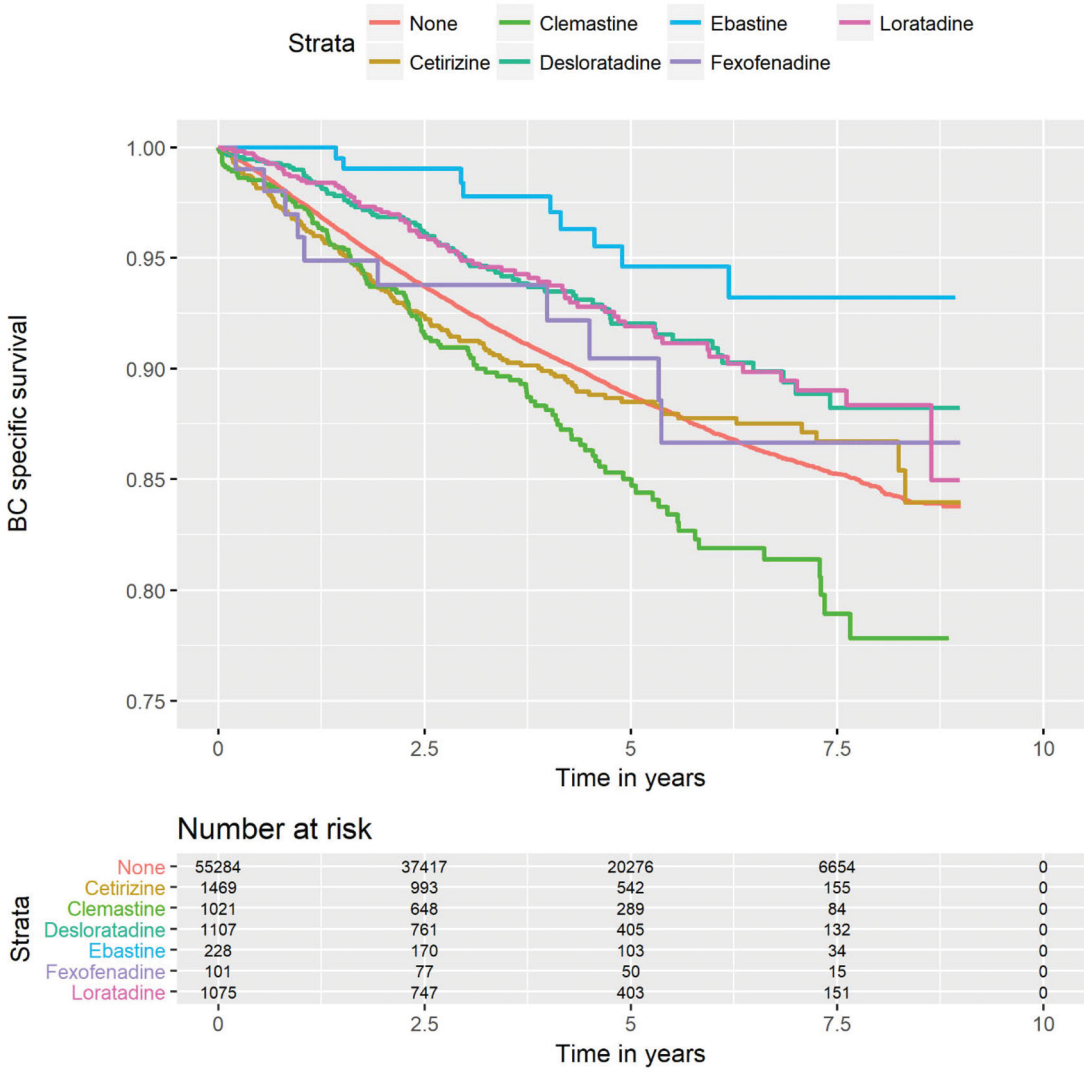


**Figure 1.** Peri-diagnostic antihistamine use and breast cancer survival. Survival probability of women diagnosed with breast cancer 2006–2013 who used the $H_1$-antihistamines cetirizine, clemastine, desloratadine, ebastine, fexofenadine or loratadine within six months pre-diagnosis and six months post-diagnosis, compared with women with breast cancer who did not use those antihistamines.

**Table 2.** Peri-diagnostic antihistamine use[a] and breast cancer-specific and overall mortality of women with breast cancer.

| Breast cancer mortality | | | | | Overall mortality | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Antihistamine type | **HR**[b] | 2.5 % | 97.5 % | *p* | Antihistamine type | **HR**[b] | 2.5 % | 97.5 % | *p* |
| Cetirizine | 1.16 | 0.99 | 1.35 | .067 | Cetirizine | 1.07 | 0.93 | 1.22 | .363 |
| Clemastine | 1.34 | 1.14 | 1.59 | <.001 | Clemastine | 1.45 | 1.27 | 1.67 | <.001 |
| Desloratadine | 0.69 | 0.55 | 0.86 | .001 | Desloratadine | 0.67 | 0.55 | 0.81 | <.001 |
| Ebastine | 0.49 | 0.27 | 0.88 | .018 | Ebastine | 0.79 | 0.54 | 1.16 | .231 |
| Fexofenadine | 1.06 | 0.57 | 1.97 | .856 | Fexofenadine | 0.89 | 0.51 | 1.58 | .700 |
| Loratadine | 0.78 | 0.63 | 0.96 | .021 | Loratadine | 0.80 | 0.67 | 0.95 | .012 |

Adjusted hazard ratios[b] and 95% confidence intervals for breast cancer-related and overall mortality of peri-diagnostic antihistamine users with breast cancer compared with non-users.
[a]Within six months preceding and six months following diagnosis.
[b]Adjusted for patient age at diagnosis.

studies on survival in lung and ovarian cancer where these cationic amphiphilic antihistamines (a group to which clemastine, desloratadine, ebastine and loratadine belong) are associated with improved survival, but cetirizine and fexofenadine are not [4,5]. As clemastine is sometimes prescribed to counteract side effects of chemotherapy [4], our findings regarding its potentially detrimental effect on survival may be artefactual. To address this possible bias, we analyzed both peri-diagnostic and post-diagnostic use, as well as introduced lag time into the cumulative post-diagnostic analysis, excluding the time period adjacent to death, which would be most affected by any prescription bias for clemastine for terminal patients. Based on the lag-time analyses, we believe that the association with improved survival of desloratadine and loratadine is not artefactual, however, we cannot here draw the same conclusions regarding the possibly negative

**Table 3.** Peri-diagnostic antihistamine use[a] and breast cancer-specific and overall mortality of women with estrogen receptor positive breast cancer.

| Breast cancer mortality | | | | | Overall mortality | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Antihistamine type | HR[b] | 2.5 % | 97.5 % | *p* | Antihistamine type | HR[b] | 2.5 % | 97.5 % | *p* |
| Cetirizine | 0.97 | 0.78 | 1.21 | .792 | Cetirizine | 0.93 | 0.78 | 1.11 | .417 |
| Clemastine | 1.34 | 1.09 | 1.65 | .005 | Clemastine | 1.36 | 1.16 | 1.60 | <.001 |
| Desloratadine | 0.71 | 0.54 | 0.93 | .012 | Desloratadine | 0.69 | 0.55 | 0.85 | .001 |
| Ebastine | 0.53 | 0.26 | 1.06 | .073 | Ebastine | 0.75 | 0.48 | 1.20 | .233 |
| Fexofenadine | 1.37 | 0.69 | 2.75 | .369 | Fexofenadine | 1.01 | 0.52 | 1.93 | .986 |
| Loratadine | 0.84 | 0.65 | 1.08 | .184 | Loratadine | 0.78 | 0.63 | 0.96 | .018 |

Adjusted hazard ratios[b] and 95% confidence intervals for breast cancer-related and overall mortality of peri-diagnostic antihistamine users with estrogen receptor positive breast cancer compared with non-users.
[a]Within six months preceding and six months following diagnosis.
[b]Adjusted for patient age at diagnosis.

**Table 4.** Peri-diagnostic antihistamine use[a] and breast cancer-specific and overall mortality of women with estrogen receptor negative breast cancer.

| Breast cancer mortality | | | | | Overall mortality | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Antihistamine type | HR[b] | 2.5 % | 97.5 % | *p* | Antihistamine type | HR[b] | 2.5 % | 97.5 % | *p* |
| Cetirizine | 1.42 | 1.13 | 1.78 | .003 | Cetirizine | 1.35 | 1.09 | 1.67 | .007 |
| Clemastine | 1.36 | 1.01 | 1.82 | .041 | Clemastine | 1.69 | 1.33 | 2.15 | <.001 |
| Desloratadine | 0.65 | 0.43 | 0.99 | .046 | Desloratadine | 0.60 | 0.41 | 0.89 | .011 |
| Ebastine | 0.41 | 0.13 | 1.28 | .125 | Ebastine | 0.88 | 0.44 | 1.76 | .718 |
| Fexofenadine | 0.54 | 0.14 | 2.17 | .388 | Fexofenadine | 0.68 | 0.22 | 2.11 | .503 |
| Loratadine | 0.66 | 0.44 | 0.99 | .044 | Loratadine | 0.86 | 0.62 | 1.18 | .353 |

Adjusted hazard ratios[b] and 95% confidence intervals for breast cancer-related and overall mortality of peri-diagnostic antihistamine users with estrogen receptor negative breast cancer compared with non-users.
[a]Within six months preceding and six months following diagnosis.
[b]Adjusted for patient age at diagnosis.

**Table 5.** Cumulative post-diagnostic antihistamine use[a] and breast cancer-specific and overall mortality of women with breast cancer.

| Breast cancer mortality | | | | | Overall mortality | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Antihistamine type[a] | HR[b] | 2.5 % | 97.5 % | *p* | Antihistamine type[a] | HR[b] | 2.5 % | 97.5 % | *p* |
| Cetirizine | 1.13 | 1.11 | 1.16 | <.001 | Cetirizine | 1.08 | 1.07 | 1.10 | <.001 |
| Clemastine | 1.18 | 1.15 | 1.22 | <.001 | Clemastine | 1.16 | 1.14 | 1.19 | <.001 |
| Desloratadine | 0.94 | 0.91 | 0.97 | <.001 | Desloratadine | 0.93 | 0.91 | 0.96 | <.001 |
| Ebastine | 0.88 | 0.81 | 0.97 | .006 | Ebastine | 0.98 | 0.93 | 1.03 | .395 |
| Fexofenadine | 0.99 | 0.90 | 1.09 | .877 | Fexofenadine | 0.95 | 0.87 | 1.03 | .225 |
| Loratadine | 1.03 | 1.00 | 1.05 | .077 | Loratadine | 1.01 | 0.99 | 1.03 | .385 |

Adjusted hazard ratios[b] and 95% confidence intervals for breast cancer-related and overall mortality of post-diagnostic antihistamine users with breast cancer compared with non-users.
[a]Adjusted for patient age at diagnosis.
[b]As log(n DDD + 1).

effects of clemastine and cetirizine, and the cationic amphiphilic properties of desloratadine, loratadine and ebastine may explain some of their potential effect.

While there is no reason to doubt that a death that has been noted as such in the Swedish Cause of Death Register is indeed breast cancer-related, autopsies are not routinely performed in Sweden, thus the true number of breast cancer deaths may be higher than what is recorded. We have therefore included both breast cancer-specific and overall mortality in our analyses, in order to evaluate the potential effect of outcome misclassification.

Prescription-free use precludes us from ascertaining the full exposure for some of the antihistamines, particularly cetirizine, ebastine and loratadine, as these were all available without a prescription in Sweden throughout the study period. Desloratadine and clemastine were not available without a prescription until 2014, and fexofenadine was first made available for prescription-free purchase in 2011, so a full or nearly full exposure can be appreciated for these drugs based on the data from the Swedish Prescribed Drug Register. Since desloratadine and loratadine are now both available without a prescription in Sweden, we suggest that the next logical step, alongside studies that focus on the possible mechanisms involved and on other malignancies, is clinical trials, as our study cannot readily be reproduced.

Desloratadine in particular stands out as a candidate for cancer therapy based on our findings, and its known properties: it has the highest $H_1$-receptor affinity among these antihistamines, outperforming fexofenadine and other compounds in pharmacokinetic studies [21]. Worth noting is that our findings are based on the use of antihistamines to treat allergies, and it remains to be seen what a therapeutic dose of desloratadine as a drug for the treatment of breast cancer may be, though we suspect that it could be higher, as risk appears to decrease with an increasing cumulative dose. Despite the low dosage and the suspected dilution by prescription-free loratadine use, the possible effects of desloratadine and loratadine that we report here are already comparable to those of chemotherapeutic

and endocrine agents currently used in breast cancer therapy [6,8].

As this was a national register-based study, some prognostic and treatment factors, such as histological grade or Ki67 status, were not available. However, Swedish breast cancer treatment is equalized and evidence-based, so while we cannot here adjust for some of the variation within our study population, it is homogenous with regard to treatment regardless of geographical region or treating hospital. While we do not have data on the socioeconomic status of patients, which influences both survival in breast cancer and allergy prevalence, we do, however, see a dose-response and possibly differing effects of different antihistamines, which suggests that there need not be any confounding socioeconomic gradient, and in our previous study on melanoma patients where we could adjust for socioeconomic factors as well as a number of tumor characteristics, an improved survival was seen for desloratadine and loratadine users in both the crude and adjusted analyses [2].

One of the main strengths in a nation-wide study such as this is that there is no selection bias of the sort that often occurs in clinical trials or other studies were subjects are selected. Here, generalizability is very high, and we can be sure that the study population is representative of the target population for possible treatment with $H_1$-antihistamines for breast cancer, as they are one and the same.

That an improved survival is seen regardless of hormone receptor status, menopausal status, age, and probably tumor stage as well, may allow for desloratadine and loratadine to be given in a broad range of breast cancer cases. It is especially promising that there is an association with markedly improved survival of desloratadine and loratadine users with ER negative breast cancer, as some of the most challenging cases, with the most limited treatment options, are found in this subgroup [9,10].

A lysosomal effect is suggested by the authors of the study on antihistamine use and lung cancer mortality [4], however, we postulate that an immunological effect is also likely, as the potential effect is present in all our subgroup analyses. Histamine has been shown to affect the Th1/Th2 balance by turning dendritic cells into Th2 cell-promoters [22], up-regulating Th2-attractors, down-regulating Th1-effectors [23] and disrupting the cytolytic response. Our findings may therefore partly result from the disruption of these histamine-mediated effects on the Th1-dependent cytolotic response. Another mechanism could be the inhibition of myeloid-derived suppressor cells, as histamine promotes the activity of these cells. Studies on tumors and normal tissue in breast cancer patients with and without antihistamine use need to be undertaken to better understand mechanisms involved.

## Conclusions

We believe our results warrant randomized clinical trials of $H_1$-antihistamines, especially desloratadine, as breast cancer therapy, and we suggest further studies of $H_1$-antihistamine use and survival in yet other malignancies.

## Disclosure statement

The authors report no conflicts of interest, however, a patent for desloratadine therapy in breast cancer has been granted in the US based on our findings.

1. Throughout this report, 'woman' denotes an individual whose legal gender is female, as only this variable is available in registers, as a proxy for sex. Breast cancer in men is not included in this study.

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