

Desloratadine and loratadine use associated with improved melanoma survival

To the Editor,

As cancer, like allergy, can result from chronic inflammation, anti-inflammatory allergy medications are a particularly suitable starting point in the search for novel cancer therapeutics.¹ Some H₂-antihistamines have shown promise in cancer therapy, but modern H₁-antihistamines have not been widely studied in this role, despite being ubiquitous, affordable, and safe, as well as having much lower toxicity than conventional chemotherapeutics.

Previously, we found that desloratadine and loratadine use may improve survival in breast cancer,² and there is ever-increasing evidence of effects of H₁-antihistamines on inhibiting tumor growth and promoting cell death in various tumors, including melanoma.³⁻⁸ Here, we set out to ascertain whether a similar association can be seen for patients with primary invasive cutaneous malignant melanoma (CMM). While treatment of CMM has improved in recent years to include BRAF and MEK inhibitors and immunotherapy, treatment options are still limited.

We analyzed use of the six major H₁-antihistamines desloratadine, cetirizine, loratadine, clemastine, ebastine, and fexofenadine and melanoma-specific and overall survival among all 24 562 individuals diagnosed with primary CMM 2006-2014, using the Swedish Melanoma Register, Prescribed Drug Register, and Cause of Death Register. Cox regression analyses were done stratified for age and gender (as a proxy for sex) and crude as well as adjusted for education level and tumor characteristics. Follow-up was until December 31, 2018.

1253 individuals were antihistamine users. The most commonly used antihistamine was desloratadine with 395 users, followed by cetirizine (324 users), loratadine (251 users), and clemastine (192 users). Ebastine and fexofenadine were used by markedly fewer individuals (Table S1). Few antihistamine users used more than one of the six antihistamines (data not shown).

We found an association with consistently improved survival for use of desloratadine (HR = 0.46; 95% CI 0.29-0.73, *P* = .001) and loratadine (HR = 0.50; 95% CI 0.28-0.88, *P* = .02), relative to non-use, regardless of patient or tumor characteristics, both in the adjusted and crude analyses. Use of other antihistamines was not associated with significantly altered melanoma survival (Table 1 and Figure S1).

When the mortality of desloratadine users of different age groups (65 years of age and below, vs above 65 years of age) was compared to non-users of the same age groups, desloratadine users

had markedly improved survival. In fact, older desloratadine users with CMM appeared to have mortality rates similar to those of younger non-users (Figure 1).

To study any potential as prophylaxis of desloratadine and loratadine, the risk of developing a second CMM was analyzed, and we found that desloratadine and loratadine use appeared to reduce the risk of a new primary CMM, although not to a statistically significant degree, possibly due to insufficient sample size (HR = 0.83; 95% CI 0.60-1.14, *P* = .25) (Figure S2).

As the study was done on the entire Swedish population, external validity is high for this study, and in comparison with clinical trials or other studies where subjects are selected, our study does not suffer from any such selection bias. Prescription-free use precludes us from ascertaining the full exposure for cetirizine, loratadine, and ebastine, that were available prescription-free in Sweden throughout the study period. Desloratadine and clemastine, however, were prescription-only until 2014, as was fexofenadine until 2011, so a full or nearly full exposure can be appreciated.

We are confident that the associations with improved survival that we show here are not due to some underlying diagnosis, such as allergic rhinitis or atopy. Any effects should then have been more uniform in direction for the different types of antihistamines, when, instead, the point estimates here suggest that a similar pattern to what we found for breast cancer could hold for CMM, with clemastine and possibly cetirizine potentially being associated with a worse rather than better survival. Furthermore, a study undertaken by Hemminki et al⁹ on medically diagnosed allergic rhinitis and cancer risk in Sweden found a somewhat increased risk of melanoma for those with allergies, rather than any protective effect, and while atopy has been shown to be inversely associated with melanoma risk, it has not been connected to any difference in prognosis,¹⁰ and other studies have shown both reduced and increased and no difference in melanoma risk for atopic patients.^{11,12}

A major advantage of desloratadine and loratadine when compared to other H₁-antihistamines that have shown effects on melanoma cells, such as terfenadine, is their safety. Terfenadine has been withdrawn worldwide due to its cardiotoxicity, something that precludes its simple implementation into melanoma therapy, as well as posing difficulties with population-based studies and clinical trials. In comparison with terfenadine, or astemizole, another H₁-antihistamine that may have promise in cancer

TABLE 1 Peri-diagnostic antihistamine use^a and melanoma mortality. Crude and adjusted^b hazard ratios and 95% confidence intervals for melanoma-specific mortality of antihistamine users with melanoma compared with non-users^{c,d}

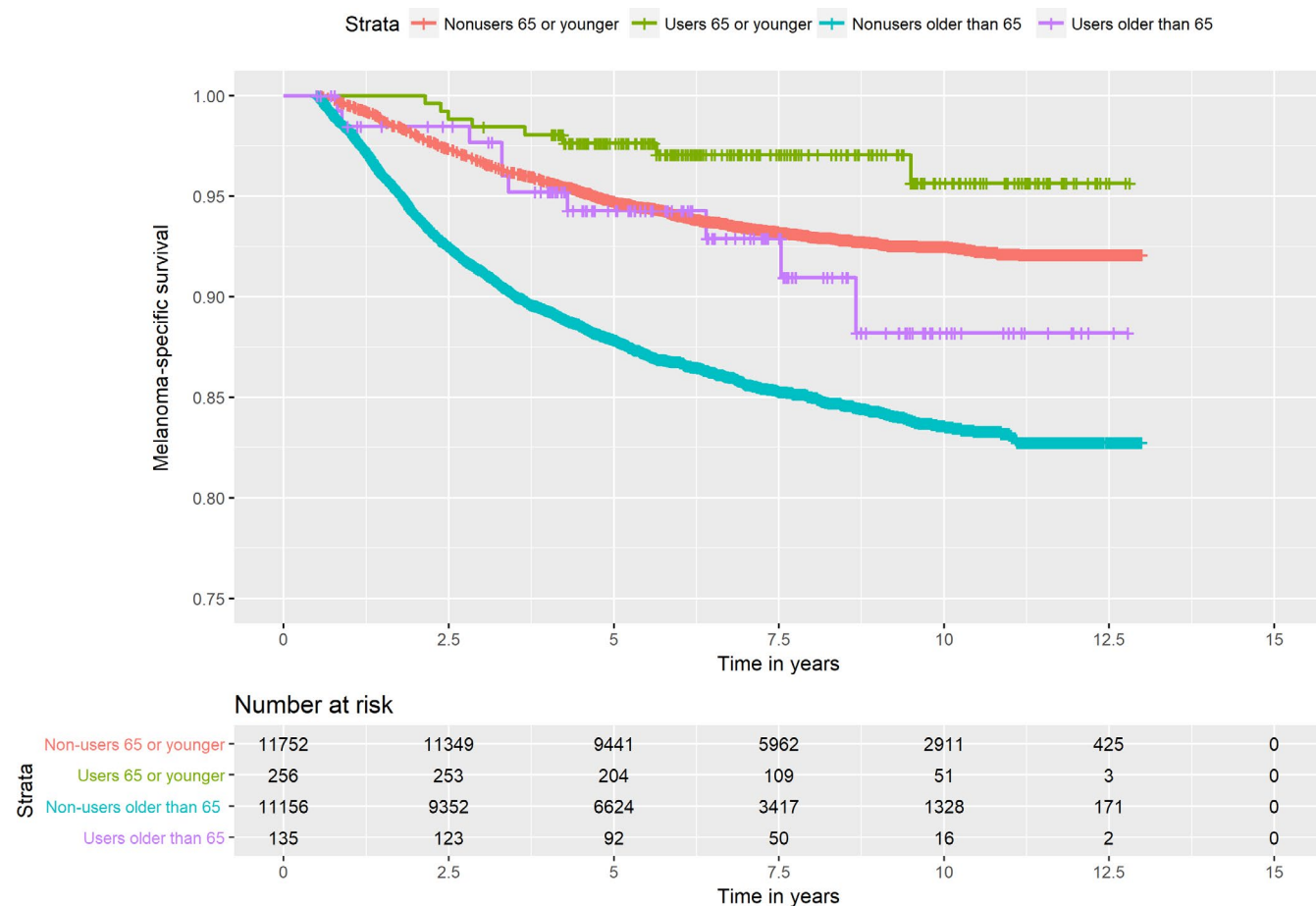
Antihistamine type	Crude			Adjusted ^b		
	HR	95% CI	P	HR	95% CI	P
Desloratadine	0.456	(0.287-0.725)	.001	0.569	(0.329-0.982)	.043
Cetirizine	1.009	(0.708-1.439)	.959	0.962	(0.638-1.453)	.856
Loratadine	0.501	(0.284-0.883)	.017	0.534	(0.277-1.028)	.061
Clemastine	1.237	(0.805-1.901)	.332	1.005	(0.582-1.736)	.984
Ebastine	1.531	(0.729-3.214)	.261	1.032	(0.332-3.204)	.957
Fexofenadine	0.688	(0.222-2.135)	.518	0.901	(0.225-3.609)	.883

^aWithin 6 mo preceding and 6 mo following diagnosis.

^bAdjusted for Breslow depth, sentinel lymph node status and education level, gender, and age of the patient.

^cHere, antihistamine use is defined as dispensed prescribed doses of any of the six major antihistamines (desloratadine, cetirizine, loratadine, clemastine, 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.

^dThe crude analysis includes 24 144 individuals, and the adjusted analysis includes 20 579 individuals.

**FIGURE 1** Desloratadine use and melanoma survival for different age groups. Survival of CMM patients, 65 years of age and below, and above age 65, who used desloratadine compared with CMM patients who did not use any antihistamines

therapy^{4,6} but which has also been withdrawn in most countries due to cardiotoxicity, desloratadine and loratadine have minimal side effects, making them excellent candidates for repurposing purposes.

BRAF and MEK inhibitors and immunotherapy against CTLA-4 and PD-1 are important in treatment of advanced metastatic melanoma now, but only very few of the 24 562 CMM patients included in our study were given interferon and BRAF and MEK inhibitors, and

no individuals were given immunotherapy with monoclonal antibodies against either CTLA-4 or PD-1. Thus, any survival benefit of treatment of desloratadine or loratadine together with modern melanoma therapy remains to be seen. We hypothesize that it could be even greater than what we can show here, as these antihistamines may in fact work synergistically with and/or potentiate the effects of modern chemotherapy and immunotherapy agents, as some studies have shown.^{5-6,8}

We made multiple analyses and adjustments for education level (as a proxy for socioeconomic status), as well as age, gender (as a proxy for sex), and various tumor characteristics, and see similar results across all analyses, which suggest that the possible effect of desloratadine and loratadine on melanoma mortality is not due to bias, but dependent on true properties of those drugs on major mechanisms crucial to cancer cells.

In our analysis of the risk of a second CMM, we found that in the group using desloratadine and loratadine, there was a larger proportion of patients free from a second CMM than among the nonusers, and although the result of this analysis did not reach the level required for statistical significance, it nonetheless suggests that desloratadine and loratadine may—besides positively influencing melanoma survival—also have a preventive effect which could be utilized for melanoma prophylaxis.

We demonstrate for the first time, in a nation-wide study, that desloratadine and loratadine use is associated with improved survival for patients with CMM independent of age, gender (as a proxy for sex), education level, and tumor characteristics and that these drugs could have potential in CMM treatment. We suggest immediate randomized trials where different dosages and modes of administration tailored to CMM patients can be studied, to determine what could be optimal as melanoma therapy.

KEYWORDS

chemotherapy, epidemiology, histamine antagonists, histamine H1 antagonists, pharmacology and pharmacogenomics

ACKNOWLEDGMENTS

This research was supported in part by grants from the Swedish Cancer Society, Berta Kamprad's Foundation, the Mats Paulsson Trust, the Stefan Paulsson Trust, the Welander Foundation, the S. R. Gorthon Foundation, the LMK Foundation, and local hospital foundations. The funding sources had no role in the design, execution, or manuscript preparation associated with this study.

CONFLICTS OF INTEREST

All authors have approved the submission of this manuscript, and it is not submitted for publication elsewhere, and we have no conflicts of interest or ethical considerations to report; however, a patent for desloratadine therapy in breast cancer has been granted in the US based on our other work, and another patent application has been filed for the findings presented here for melanoma.

Ildikó Fritz¹ 
 Philippe Wagner¹
 Matteo Bottai²

Hanna Eriksson^{3,4,5}

Christian Ingvar⁶

Isabelle Krakowski^{3,7}

Kari Nielsen⁸

Håkan Olsson^{1,9}

¹Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden

²Division of Biostatistics, Institute of Environmental Medicine, Karolinska Institute, Solna, Sweden

³Department of Oncology and Pathology, Karolinska Institute, Solna, Sweden

⁴Skin Cancer Center/Theme Cancer, Karolinska University Hospital, Solna, Sweden

⁵Department of Oncology/Theme Cancer, Karolinska University Hospital, Solna, Sweden

⁶Department of Surgery, Clinical Sciences, Lund University, Lund, Sweden

⁷Department of Dermatology/Theme Inflammation, Karolinska University Hospital, Solna, Sweden

⁸Department of Dermatology, Clinical Sciences, Lund University, Lund, Sweden

⁹Department of Oncology, Clinical Sciences, Lund University, Lund, Sweden

Correspondence

Ildikó Fritz, Lund University, Department of Cancer Epidemiology, Skåne University Hospital, Remissgatan 4, 221 85 Lund, Sweden.
 Email: ildiko.fritz@med.lu.se

ORCID

Ildikó Fritz  <https://orcid.org/0000-0001-8661-5433>

REFERENCES

1. Faustino-Rocha AI, Ferreira R, Gama A, Oliveira PA, Ginja M. Antihistamines as promising drugs in cancer therapy. *Life Sci*. 2017;172:27-41.
2. Olsson HL, Einefors R, Broberg P. Second generation antihistamines after breast cancer diagnosis to improve prognosis both in patients with ER+ and ER- breast cancer. *J Clin Oncol*. 2015;33(15_suppl):3062.
3. Nicolau-Galmes F, Asumendi A, Alonso-Tejerina E, et al. Terfenadine induces apoptosis and autophagy in melanoma cells through ROS-dependent and -independent mechanisms. *Apoptosis*. 2011;16(12):1253-1267.
4. Garcia-Quiroz J, Garcia-Becerra R, Santos-Martinez N, et al. In vivo dual targeting of the oncogenic Ether-a-go-go-1 potassium channel by calcitriol and astemizole results in enhanced antineoplastic effects in breast tumors. *BMC Cancer*. 2014;14:745.
5. Varbanov HP, Kuttler F, Banfi D, Turcatti G, Dyson PJ. Screening-based approach to discover effective platinum-based chemotherapies for cancers with poor prognosis. *PLoS ONE*. 2019;14(1):e0211268.
6. Ellegaard AM, Dehlendorff C, Vind AC, et al. Repurposing cationic amphiphilic antihistamines for cancer treatment. *EBioMedicine*. 2016;9:130-139.

7. Fagone P, Caltabiano R, Russo A, et al. Identification of novel chemotherapeutic strategies for metastatic uveal melanoma. *Sci Rep*. 2017;7:44564.
8. Laverdiere I, Boileau M, Neumann AL, et al. Leukemic stem cell signatures identify novel therapeutics targeting acute myeloid leukemia. *Blood Cancer J*. 2018;8(6):52.
9. Hemminki K, Forsti A, Fallah M, Sundquist J, Sundquist K, Ji J. Risk of cancer in patients with medically diagnosed hay fever or allergic rhinitis. *Int J Cancer*. 2014;135(10):2397-2403.
10. Marasigan V, Morren MA, Lambert J, et al. Inverse association between atopy and melanoma: a case-control study. *Acta dermato-venereologica*. 2017;97(1):54-57.
11. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy*. 2005;60(9):1098-1111.
12. Eriksson NE, Holmen A, Hogstedt B, Mikoczy Z, Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy*. 1995;50(9):718-722.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

SUPPLEMENTARY METHODS

Registers and data handling

The Swedish Melanoma Register is a national quality register of CMM in Sweden since 1990 comprising 99% of all cases of melanoma in the country. Melanoma in any other site and melanoma in situ is not included in this register. Variables include age of the patient and information on the histopathology of the tumors (e. g. Breslow thickness and Clark measures), as well as sentinel lymph node status. The Swedish Prescribed Drug Register is a database where all dispensed prescribed pharmaceuticals in Sweden have been recorded since July 1st, 2005. The Swedish Cause of Death Register is a register where all deaths have been recorded since 1952. Socioeconomic data on education level was obtained from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies, or LISA, which includes data on all adult and adolescent Swedes since 1990. Data was pseudo-anonymized and the study was approved by the Regional Ethics Board.

Statistical analyses

We analyzed both the peri-diagnostic use and cumulative post-diagnostic use of antihistamines among CMM patients using Cox regression analyses. Peri-diagnostic use was defined as the main antihistamine (in terms of dispensed defined daily doses, or DDDs) used within six months pre-diagnosis and six months post-diagnosis (in these analyses, users of multiple antihistamines were treated as single-type users). Cox regression analyses were stratified for gender (as a proxy for sex)^a and age at diagnosis in four categories (≤ 50 , $>50 - \leq 60$, $>60 - \leq 70$ and >70) and adjusted for tumor thickness according to the Breslow scale and sentinel lymph node status. Analyses were also adjusted for education level (highest attained at the time of diagnosis). Study start was set to six months following diagnosis. For the analysis of cumulative post-diagnostic antihistamine use, time varying covariates were used. This allowed for a single individual to provide data as both a non-user and user of different antihistamines, as well as concomitant use of multiple antihistamines, so in these analyses, users of multiple antihistamines were treated as such. Cumulative DDDs were analyzed using a log transformation¹. Statistical analyses were performed using R². Two-sided tests and corresponding P-values were used, and a test based on Schoenfeld residuals was done to assess the proportional hazards assumption.

SUPPLEMENTARY RESULTS

The distribution between women and men was equal in the population, however, among the antihistamine users, women were in a majority (approximately 60% for most antihistamines). Among the 24 562 individuals, 6 692 deaths occurred. 2 471 deaths were noted as melanoma-specific in the Swedish Cause of Death Register. Mean age was 63 years, and mean follow-up time was 6.73 years. One person (not among the antihistamine users) had been treated with dacarbazine. 594 individuals (including 24 antihistamine users) were treated with protein kinase inhibitors against BRAF or MEK (mainly dabrafenib and trametinib), and 50 individuals were given interferon alpha-2b, although none of them used antihistamines. (Supplementary Table 1.) The analysis of peri-diagnostic antihistamine use and overall mortality yielded similar point estimates, but only the crude analysis of desloratadine use had a P-value sufficient for statistical significance. (Supplementary Table 2.) The analyses of the cumulative post-diagnostic antihistamine use among melanoma patients yielded similar results as the analyses of peri-diagnostic use, albeit only two that were statistically significant. The point estimates again suggested a positive association with survival for desloratadine use. (Supplementary Tables 3 and 4.)

^a The variable "kön" (meaning both sex and gender in Swedish) denotes the legal gender of a person, and it is here used as a proxy variable for sex to adjust for sex-specific differences in survival.

1. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. *Statistics in medicine* 2014;33:881-99.
2. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.

SUPPLEMENTARY TABLES

Supplementary Table 1. Study population characteristics.

	All	Non-users†	Desloratadine	Cetirizine	Loratadine	Clemastine	Ebastine	Fexofenadine
N	24562	23309	395	324	251	192	49	42
Women, n (%)	12314 (50.1)	11578 (49.7)	231 (58.5)	199 (61.4)	148 (59.0)	112 (58.3)	22 (44.9)	24 (57.1)
Men, n (%)	12248 (49.9)	11731 (50.3)	164 (41.5)	125 (38.6)	103 (41.0)	80 (41.7)	27 (55.1)	18 (42.9)
Mean age, years (sd)	62.92 (16.45)	63.04 (16.44)	57.74 (15.32)	64.16 (16.17)	61.84 (16.39)	62.51 (18.12)	54.93 (18.31)	54.72 (13.11)
Follow-up time, years (sd)	6.73 (3.16)	6.73 (3.17)	6.98 (2.79)	6.75 (3.26)	6.76 (3.15)	6.11 (3.2)	6.59 (3.22)	7.86 (3.17)
Melanoma-specific deaths, n (%)	2471 (10.06)	2369 (10.16)	20 (5.06)	34 (10.49)	15 (5.98)	22 (11.46)	8 (16.33)	3 (7.14)
Overall deaths, n (%)	6692 (27.25)	6398 (27.45)	58 (14.68)	93 (28.7)	54 (21.51)	67 (34.9)	16 (32.65)	6 (14.29)
Breslow depth, mm (sd)	1.91 (3.06)	1.93 (3.1)	1.22 (1.48)	1.87 (2.73)	1.59 (1.84)	2.46 (3.28)	1.55 (2.2)	1.12 (1.09)
Sentinel lymph node positive, n (%)	17307 (78.61)	16419 (78.59)	278 (80.58)	240 (80)	178 (77.39)	133 (77.33)	31 (75.61)	28 (77.78)
Education level variable, mean value (sd)	11550 (48.29)	10922 (48.11)	235 (60.72)	140 (44.73)	126 (51.22)	77 (41.85)	25 (52.08)	25 (59.52)
Dacarbazine treatment, n	1	1	0	0	0	0	0	0
Protein kinase inhibitor treatment (against BRAF and MEK), n	594	570	8	4	6	3	3	0
Interferone (alpha 2-b) treatment, n	50	50	0	0	0	0	0	0

†Here, antihistamine use is defined as dispensed prescribed doses of any of the six major antihistamines (desloratadine, cetirizine, loratadine, clemastine, 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.

Supplementary Table 2. Peri-diagnostic antihistamine use[†] and overall mortality. Crude and adjusted[‡] hazard ratios and 95% confidence intervals for overall mortality of antihistamine users with melanoma compared with non-users^{§,¶}

Antihistamine type	Crude			Adjusted [‡]		
	HR	95% CI	P	HR	95% CI	P
Desloratadine	0.510	(0.39 - 0.667)	<0.0001	0.731	(0.529 - 1.011)	0.058
Cetirizine	1.064	(0.863 - 1.312)	0.559	0.989	(0.782 - 1.251)	0.929
Loratadine	0.771	(0.583 - 1.018)	0.066	0.903	(0.661 - 1.233)	0.520
Clemastine	1.421	(1.111 - 1.818)	0.005	1.384	(1.044 - 1.835)	0.024
Ebastine	1.137	(0.673 - 1.92)	0.632	1.344	(0.699 - 2.587)	0.375
Fexofenadine	0.480	(0.216 - 1.069)	0.073	1.285	(0.534 - 3.091)	0.576

[†]Within six months preceding and six months following diagnosis.

[‡]Adjusted for Breslow depth, sentinel lymph node status and education level, gender and age of the patient.

[§]Here, antihistamine use is defined as dispensed prescribed doses of any of the six major antihistamines (desloratadine, cetirizine, loratadine, clemastine, 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.

[¶]The crude analysis includes 24 144 individuals, and the adjusted analysis includes 20 579 individuals.

Supplementary Table 3. Cumulative post-diagnostic antihistamine use and melanoma-specific mortality.[‡] Hazard ratios and 95% confidence intervals for melanoma-specific mortality of post-diagnostic antihistamine users.

Antihistamine type [†]	HR	95% CI	P
Desloratadine	0.893	(0.794 - 1.003)	0.057
Cetirizine	1.012	(0.932 - 1.099)	0.782
Loratadine	0.861	(0.742 - 0.999)	0.048
Clemastine	1.005	(0.86 - 1.173)	0.954
Ebastine	1.041	(0.842 - 1.286)	0.713
Fexofenadine	0.935	(0.688 - 1.271)	0.667

[†]As log (n DDD + 1)

[‡]Analysis is adjusted for age, gender, education level, Breslow depth and sentinel lymph node status.

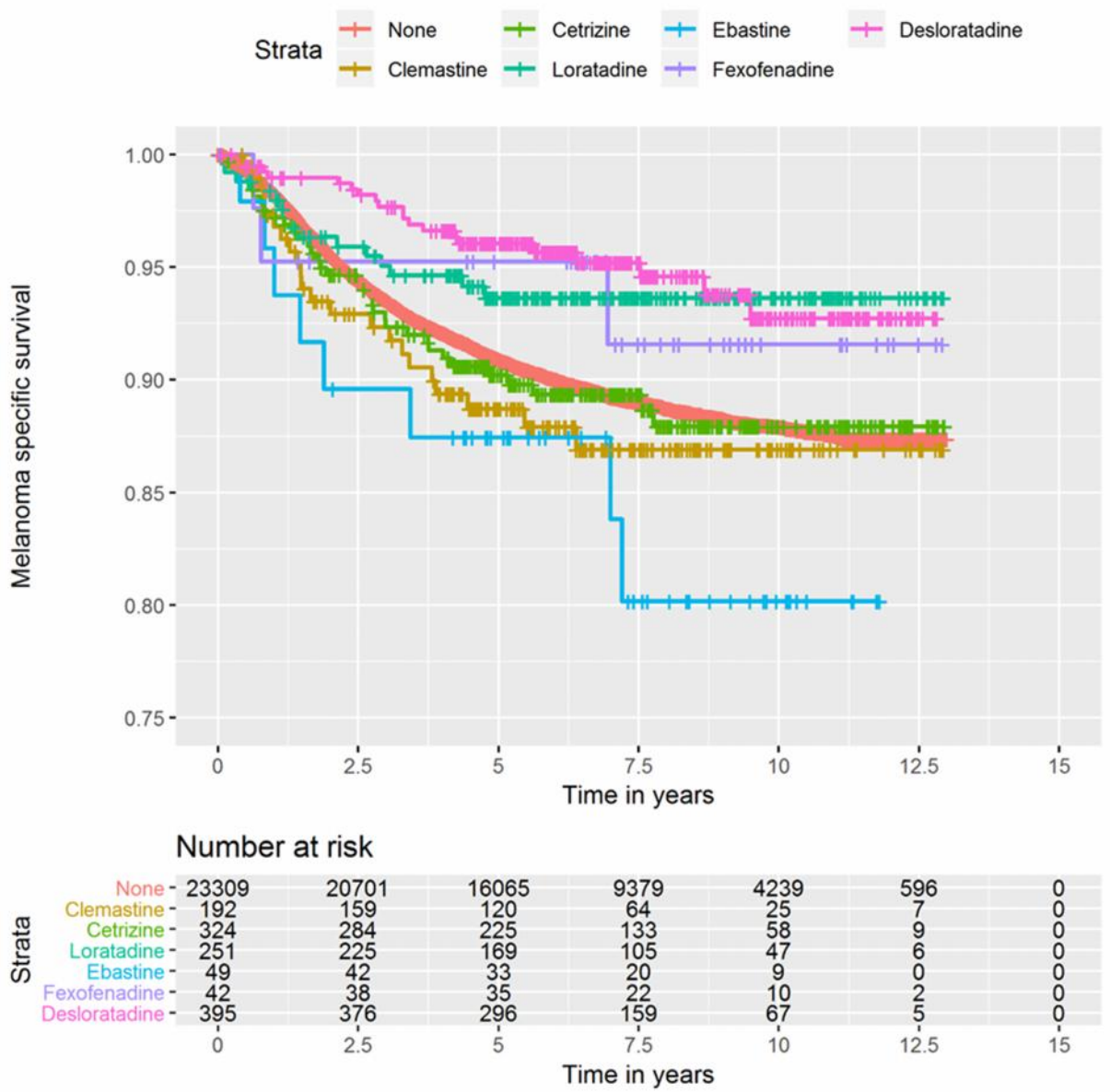
Supplementary Table 4. Cumulative post-diagnostic antihistamine use and overall mortality.[‡] Hazard ratios and 95% confidence intervals for overall mortality of post-diagnostic antihistamine users.

Antihistamine type [†]	HR	95% CI	P
Desloratadine	0.956	(0.894 - 1.022)	0.188
Cetirizine	0.997	(0.949 - 1.047)	0.898
Loratadine	0.961	(0.896 - 1.031)	0.267
Clemastine	1.106	(1.023 - 1.197)	0.012
Ebastine	1.081	(0.949 - 1.231)	0.242
Fexofenadine	1.023	(0.851 - 1.23)	0.806

[†]As log (n DDD + 1)

[‡]Analysis is adjusted for age, gender, education level, Breslow depth and sentinel lymph node status.

Supplementary Figure 1. Peri-diagnostic antihistamine use and melanoma survival. Survival of CMM patients who used the six major antihistamines compared with CMM patients who did not use antihistamines during six months before and after diagnosis.



Supplementary Figure 2. Proportion without a second primary cutaneous malignant melanoma (CMM) for desloratadine and loratadine users with CMM versus non-users with CMM.

