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Antihistamine use and risk of ovarian cancer: A population-based case-control study

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ABSTRACT

Objective: Histamine is suggested to play a role in ovarian carcinogenesis. We examined the association between antihistamine use and ovarian cancer risk in a nationwide case-control study.
Study design: Cases (n = 5 556) comprised all women in Denmark aged 30–84 years with a histologically verified first diagnosis of epithelial ovarian cancer during 2000-2015. Age-matched population controls (n = 83 340) were selected using risk-set sampling. Data on prescription use, patient and demographic characteristics were retrieved from nationwide registries.
Main outcome measures: We used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for epithelial ovarian cancer associated with antihistamine use (≥2 prescriptions). The association was evaluated according to patterns of antihistamine use, menopausal status, and histological subtype of ovarian cancer.
Results: Ever use of antihistamines was not associated with ovarian cancer overall (OR = 0.97, 95% CI = 0.90–1.05). The lack of association remained in subanalyses for patterns of antihistamine use. We observed an inverse association between antihistamine use and ovarian cancer among pre-menopausal women (< 50 year: OR = 0.72, 95% CI = 0.57-0.90), but not post-menopausal women (≥50 year: OR = 1.02, 95%CI = 0.93–1.11). In analyses of histological subtypes, an inverse association emerged for mucinous ovarian cancer (OR = 0.74, 95% CI = 0.57-0.96), but not for other subtypes.
Conclusion: Antihistamine use was not associated with overall ovarian cancer risk. Additional research is needed to confirm inverse associations between antihistamine use and mucinous ovarian cancer, and overall ovarian cancer among pre-menopausal women.

1. Introduction

Histamine, an endogenous amine and immune modulating agent, has been suggested to play a role in cancer development and progression [1–4]. Accumulation of histamine has been reported in various human neoplastic lesions, including ovarian tumours [5–8]. The effects of histamine are mediated by four types of receptors (H1, H2, H3, and H4). Of these, the H1 histamine receptor is expressed in the ovaries, thus constituting a potential target for ovarian cancer prevention [5,9].

Preclinical studies have demonstrated antineoplastic effects of antihistamines with predominantly H1-receptor blocking effect (denoted antihistamines in the following). However, the precise interplay between antihistamines and cancer development or progression remains unresolved, and epidemiological studies of the association are few and have reported equivocal results [3]. In a recent study combining preclinical and epidemiologic results in Denmark, Ellegaard et al. reported antineoplastic effects of antihistamines, mainly those with cationic amphiphilic properties [10]. Another recent Danish registry-based study, screening broadly for potential drug-cancer associations, suggested an inverse association between use of fexofenadine, a potent antihistamine, and serous ovarian cancer [11].

The above considerations prompted us to evaluate whether

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antihistamines may hold promise for ovarian cancer prevention by conducting a nationwide case-control study of the association between antihistamine use and risk of epithelial ovarian cancer.

2. Material and methods

2.1. Setting and data sources

We retrieved and linked data from several nationwide registries [12–20] using the unique personal identification number assigned to all residents of Denmark [19,21].

From the Danish Cancer Registry [12,13], we identified all women (cases) aged 30–84 years with primary epithelial ovarian cancer (ICD-10: C56) diagnosed between 2000 and 2015. We required histological verification of the ovarian cancer cases and restricted cases to the well-defined subtypes, i.e., serous, endometrioid, mucinous, or clear cell carcinomas. Cases were excluded if they were not Danish residents on January 1 st, 1995 (start of prescription registry) and at the date of diagnosis (defined as index date). We also excluded cases with previous cancer (except non-melanoma skin cancer, ICD-10: C44) prior to the index date.

For each case, we selected 15 female population controls matched on date of birth (± one month), using the Civil Registration System [19,21] and risk-set sampling [22], i.e., eligible controls were selected at and had to be alive and at risk of a first diagnosis of ovarian cancer at the index date of the corresponding case. Exclusion criteria for controls were the same as for cases and additionally included bilateral oophorectomy prior to index date. Women were eligible as controls before they became cases; hence, the calculated odds ratios (ORs) provide unbiased estimates of corresponding incidence rate ratios in the source population.

From the Danish Prescription Registry [14,15], we retrieved all prescriptions for antihistamines (ATC: R06 A) filled by cases and controls from 1995 until one year prior to the index date. We disregarded use within one year of the index date to reduce possible reverse causation and to allow some latency of a potential anti-neoplastic effect [23–25]. Ever use of antihistamines was defined as two or more filled prescriptions on separate dates, and non-use as fewer than two prescriptions. Recent use was defined as two or more prescriptions within 1–3 years prior to the index date, and former use as ≥2 prescriptions since 1995, but ≤1 prescription within 1–3 years prior to the index date. Cumulative amount of antihistamines was calculated as the total number of defined daily doses (DDDs) dispensed [26]. Intensity of use was calculated as the cumulative amount divided by the duration of use in days, with duration defined as days between first and last antihistamine prescription plus 60 days. Cumulative amount and intensity of use were categorized according to approximate tertiles (low, medium, high) in the control population. Finally, we categorized antihistamines by their cationic amphiphilic drug (CAD) properties (Supplementary Table S1), and we also performed subanalyses according to specific commonly used antihistamines, including cetirizine, acrivastine, fexofenadine/terfenadine, and desloratadine/loratadine. Desloratadine and fexofenadine are active metabolites of, respectively, loratadine and terfenadine, of which the latter was withdrawn from the market in 2004 due to cardiac toxicity [27].

2.2. Statistical analysis

We used conditional logistic regression to estimate age- and multivariable-adjusted ORs and 95% confidence intervals (CIs) for the association between antihistamine use and epithelial ovarian cancer. Adjustment for potential confounding factors was based on predefined potential confounders, obtained from the nationwide registries. Multivariable adjusted models included parity (0, 1, 2, ≥3) [16], hysterectomy (yes/no) [17], tubal ligation (yes/no) [17], highest achieved education (short, medium, long, unknown) [18], marital status (divorced, married, unmarried, widow) [19], highest income (quintiles) [20], history of diabetes or endometriosis; infertility (combined measure of diagnosis of infertility and/or ≥1 prescription for infertility drugs) [17], and other drug use (≥2 prescriptions of aspirin, non-aspirin non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol, hormonal replacement therapy [HRT], hormonal contraceptives, proton-pump inhibitors, H2-receptor blockers, metformin, insulin and analogues, and other oral antidiabetics) [14,15]. As for antihistamine use, the year preceding the index date was disregarded in the assessment of covariates.

In the main analysis, we estimated ORs for ovarian cancer associated with ever use of antihistamines compared to non-use, and evaluated the influence of exposure patterns (i.e., timing, cumulative amount, and intensity). In secondary analyses, we evaluated potential effect measure modification for parity (0, 1, 2, ≥3), clinical stage (localized, non-localized), and histological subtype of epithelial ovarian cancer (serous, mucinous, endometrioid, and clear cell). In addition, we evaluated associations according to age (< 50, ≥50 years) as a proxy for menopausal status.

Finally, we performed two pre-defined sensitivity analyses. First, we restricted the study population to women with a drug prescription history of at least ten years (i.e., index date between 2005 and 2015). Second, we restricted the study population to women born after 1953, for whom we had complete information on family history of breast or ovarian cancer, as well as a more comprehensive history of use of hormonal contraceptives and infertility drugs.

All analyses were performed using R statistical software version 3.2.3 [28].

3. Results

The study population comprised 5 556 ovarian cancer cases and 83 340 age-matched population controls. Fifty percent of cases had non-localized disease; and the histological subtypes of serous, endometrioid, mucinous and clear cell tumours constituted 69%, 15%, 11% and 6%, respectively, of the case population. Compared with controls, cases had a higher prevalence of nulliparity (19% vs. 13%, overall parity $p < 0.01$) and use of hormonal replacement therapy (38% vs. 35%, $p < 0.01$), but a lower prevalence of hormonal contraceptive use (8% vs. 11%, $p < 0.01$). Further, cases had a higher educational level than controls ($p < 0.01$) (Table 1).

Ever use of antihistamines was associated with a multivariable adjusted OR of 0.97 (95% CI = 0.90–1.05) for epithelial ovarian cancer. A similar neutral OR occurred for recent or former use, and with increasing cumulative amount or intensity of antihistamine use (Table 2). Neutral associations were also observed for use of CAD antihistamines (Table 3), and for the majority of the specific antihistamines examined (i.e., cetirizine, acrivastine, and desloratadine/loratadine) (Supplementary Table S2). Use of fexofenadine/terfenadine was associated with a slightly reduced OR for epithelial ovarian cancer (0.88; 95% CI = 0.74–1.05) (Table 3).

Among pre-menopausal (< 50 years) women, ever use of antihistamines was associated with a reduced risk of ovarian cancer, notably serous ovarian cancer with (OR = 0.63, 95% CI = 0.46-0.87), whereas post-menopausal (> 50 years) women exhibited a neutral association (OR = 1.02, 95% CI = 0.93–1.13)(Table 3). Ever use of antihistamines was also associated with a reduced risk of mucinous ovarian cancer (OR = 0.74, 95% CI = 0.57-0.96), and the inverse association was independent of menopausal status (< 50 years: OR = 0.72; ≥50 years: OR = 0.75) (Table 3). We observed no apparent variations in OR estimates according to clinical stage or parity (data not shown).

In the sensitivity analyses restricted to women with 10+ years exposure history, or among women born after 1953, we found no overall association between antihistamine use and ovarian cancer risk and no apparent influence of cumulative amount and intensity of antihistamine use (Supplementary Table S3-S4).

Table 1
Characteristics of women with epithelial ovarian cancer and age-matched population controls.

	Cases n	(%)	Controls n	(%)	p-value[a]
Age at index date					
< 50	737	(13.3)	11 055	(13.3)	–[b]
50-59	1 305	(23.5)	19 575	(23.5)	
60-69	1 719	(30.9)	25 785	(30.9)	
> 69	1 795	(32.3)	26 925	(32.3)	
Parity					
0	1 033	(18.6)	10 936	(13.1)	< 0.01
1	1 073	(19.3)	14 311	(17.2)	
2	2 174	(39.1)	34 742	(41.7)	
≥3	1 276	(23.0)	23 351	(28.0)	
Comorbidity					
Infertility[c]	240	(4.3)	2 521	(3.0)	< 0.01
Endometriosis	114	(2.1)	1 298	(1.6)	0.01
Diabetes mellitus	206	(3.7)	2 918	(3.5)	0.42
Previous surgical procedures					
Hysterectomy	539	(9.7)	7 216	(8.7)	0.01
Tubal ligation	300	(5.4)	5 346	(6.4)	< 0.01
Drug use					
Low-dose aspirin	781	(14.1)	11 572	(13.9)	0.71
Non-aspirin NSAIDs	2 827	(50.9)	42 512	(51.0)	0.85
Hormonal contraceptives	427	(7.7)	9 347	(11.2)	< 0.01
Hormonal replacement therapy	2 099	(37.8)	28 833	(34.6)	< 0.01
Paracetamol	881	(15.9)	14 164	(17.0)	0.02
Metformin	144	(2.6)	2 686	(3.2)	0.01
Insulin and analogues	82	(1.5)	1 189	(1.4)	0.77
Oral antidiabetics other	135	(2.4)	2 248	(2.7)	0.22
Proton pump inhibitors	883	(15.9)	13 478	(16.2)	0.57
H2-receptor antagonists	387	(7.0)	5 884	(7.1)	0.79
Highest achieved education					
Short	1 604	(28.9)	25 741	(30.9)	< 0.01
Medium	2 471	(44.5)	36 937	(44.3)	
Long	1 259	(22.7)	17 931	(21.5)	
Unknown	222	(4.0)	2 731	(3.3)	
Highest income (quintiles)					
1 lowest	1 117	(20.1)	16 471	(19.8)	0.07
2	1 081	(19.5)	16 940	(20.3)	
3	1 153	(20.8)	16 881	(20.3)	
4	1 106	(19.9)	16 784	(20.1)	
5 highest	1 099	(19.8)	16 264	(19.5)	
Marital status					
Divorced	729	(13.1)	11 839	(14.2)	< 0.01
Married	3 195	(57.5)	49 103	(58.9)	
Unmarried/unknown	651	(11.7)	7 291	(8.7)	
Widow	981	(17.7)	15 107	(18.1)	

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs.
[a] calculated using conditional logistic regression.
[b] matched on age.
[c] diagnosis and/or ≥1 prescription for infertility drugs.

Table 2
Risk of epithelial ovarian cancer by use of antihistamines.

Antihistamine use	Cases (n =)	Controls (n =)	OR (95% CI)		Adjusted[a] OR (95% CI)	
Non-use[b]	4 731	70 610	1	reference	1	reference
Ever use[c]	825	12 730	0.97	(0.89 - 1.04)	0.97	(0.90 - 1.05)
Recent use[d]	247	3 869	0.95	(0.83 - 1.09)	0.95	(0.83 - 1.09)
Former use[e]	578	8 861	0.97	(0.89 - 1.06)	0.98	(0.89 - 1.07)
Cumulative amount used						
Low	297	4 671	0.95	(0.84 - 1.07)	0.96	(0.85 - 1.08)
Medium	268	3 848	1.04	(0.91 - 1.18)	1.04	(0.92 - 1.19)
High	260	4 211	0.92	(0.81 - 1.05)	0.92	(0.81 - 1.05)

(*continued on next page*)

Table 2 (*continued*)

Antihistamine use	Cases (n =)	Controls (n =)	OR (95% CI)		Adjusted[a] OR (95% CI)	
Intensity of use						
Low	267	4 205	0.95	(0.83 - 1.08)	0.96	(0.84 - 1.09)
Medium	286	4 324	0.99	(0.87 - 1.12)	0.99	(0.87 - 1.12)
High	272	4 201	0.97	(0.85 - 1.10)	0.96	(0.85 - 1.09)

Abbraviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for: age (by design), parity, hysterectomy, tubal ligation, highest achieved education, marital status, highest income, comorbid conditions (diabetes, endometriosis, infertility), and drug use (aspirin, non-aspirin NSAIDs, paracetamol, HRT, hormonal contraceptives, proton-pump inhibitors, H2-receptor blockers, metformin, insulin and analogues, and other oral antidiabetics).

[b] < 2 filled prescriptions between 1995 and 1 year prior to index date.

[c] ≥ 2 filled prescriptions between 1995 and 1 year prior to index date.

[d] ≥ 2 filled prescriptions within 1–3 years prior to index date.

[e] ≥ 2 prescriptions between 1995 and 1 year prior to index date with ≤ 1 prescription within 1–3 years prior to index date.

Table 3
Risk of epithelial ovarian cancer by use of antihistamines, according to histological subtypes.

Age	Antihistamine use	Epithelial (total)		Mucinous		Serous		Endometrioid		Clear cell	
		Cases	Adjusted OR[a] (95% CI)	Cases	Adjusted OR[a] (95% CI)	Cases	Adjusted OR[a] (95% CI)	Cases	Adjusted OR[a] (95% CI)	Cases	Adjusted OR[a] (95% CI)
	Non-use	4 731	1	529	1	3 245	1	673	1	284	1
	Ever use	825	0.97 (0.90-1.05)	68	0.74 (0.57-0.96)	574	0.97 (0.89-1.07)	130	1.13 (0.93-1.38)	53	0.98 (0.72-1.33)
	CAD[b]	161	0.95 (0.81-1.12)	17	0.92 (0.56-1.51)	106	0.92 (0.76-1.13)	26	1.09 (0.73-1.64)	12	0.97 (0.53-1.76)
	Fexofenadine/ terfenadine[c]	140	0.88 (0.74-1.05)	11	0.60 (0.33-1.11)	96	0.89 (0.72-1.10)	21	0.97 (0.62-1.53)	12	1.08 (0.59-1.98)
< 50y	Non-use	645	1	126	1	367	1	93	1	59	1
	Ever use	92	0.72 (0.57-0.90)	18	0.72 (0.44-1.20)	47	0.63 (0.46-0.87)	22	1.20 (0.74-1.96)	5	0.46 (0.18-1.16)
≥ 50y	Non-use	4 086	1	403	1	2878	1	580	1	225	1
	Ever use	733	1.02 (0.93-1.11)	50	0.75 (0.55-1.02)	527	1.02 (0.93-1.13)	108	1.12 (0.90-1.39)	48	1.12 (0.80-1.55)

Abbreviations: CI, confidence interval; OR, odds ratio; y, year.

[a] Adjusted for: age (by design), parity, hysterectomy, tubal ligation, highest achieved education, marital status, highest income, comorbid conditions (diabetes, endometriosis, infertility), and drug use (aspirin, non-aspirin NSAIDs, paracetamol, HRT, hormonal contraceptives, proton-pump inhibitors, H2-receptor blockers, metformin, insulin and analogues, and other oral antidiabetics).

[b] Ever use of a CAD antihistamine (i.e. ≥ 2 prescription) compared to non-use (i.e., < 2 prescriptions for any antihistamine).

[c] Ever use of fexofenadine or terfenadine (i.e. ≥ 2 prescription) compared to non-use (i.e., < 2 prescriptions for any antihistamine).

4. Discussion

In our large nationwide study, we did not find an overall association between antihistamine use and risk of epithelial ovarian cancer, and this was independent of patterns of use (i.e., timing, cumulative amount and intensity of use). Antihistamine use was, however, inversely associated with ovarian cancer among pre-menopausal women, and with mucinous ovarian cancer, independent of menopausal status. To our knowledge this is the first epidemiologic study of antihistamine use and risk of ovarian cancer. Our case-control study was nested within the entire female Danish population, thereby minimising selection bias. We furthermore used continuously updated, high-quality data on filled prescriptions [15], allowing detailed assessment of timing and quantity of antihistamine and other drug use as well as separate analyses for specific types of antihistamines.

We found an inverse association between antihistamine use and ovarian cancer risk among pre-menopausal, but not post-menopausal women, suggesting effect modification by hormonal factors. Indeed, ample evidence supports a link between female sex steroid hormones, and maturation and activation of mast cells, the main source of histamines [29,30]. In particular, estradiol and progesterone have been shown to induce migration of mast cells to the female genital tract *in vivo*, and to stimulate release of histamine from mast cells in the ovary and uterus [31,32]. Additional data has shown proliferation of ovarian cancer cell lines in response to exogenous histamine [1,33]. While the complex interplay between steroid hormones, histamine and ovarian cancer is not fully elucidated, it can be hypothesised that the effect of female steroid hormones on ovarian carcinogenesis is at least partly mediated through histamine, and our findings support further evaluation of this hypothesis.

We also found an inverse association between antihistamine use and risk of mucinous ovarian cancer, which appeared independent of menopausal status. As epithelial ovarian cancer is a heterogeneous disease [34], a true antineoplastic effect of antihistamines would conceivably vary according to histological subtype [25]. Mucinous ovarian cancer differs from non-mucinous types in terms of tissue of origin and etiologic factors and mucinous ovarian cancer has been suggested to be influenced more by exogenous factors, than by the traditional endogene reproductive, hormonal or genetic factors [35]. This might explain the inverse association observed between antihistamine use and notably mucinous ovarian cancer, however, due to the preponderance of exogene risk factors for this particular histological subtype, residual confounding from unmeasured lifestyle factors, such as smoking or obesity, cannot be excluded.

The observed variation in risk estimates according to menopausal status (age) and histological subtypes of ovarian cancer warrants additional research in comprehensive epidemiologic studies and potential underlying mechanisms should be tested further in pre-clinical studies.

Our study had some limitations. During the study period, about 40% of all sales of antihistamines were purchased over-the-counter [36], and some exposure misclassification by over-the-counter purchase of antihistamines may have attenuated the associations. We also lacked

information on allergic conditions, a primary indication for antihistamine use. The role of allergy in cancer remains elusive [3], therefore, determining the impact of confounding by indication on our results is difficult. Our finding of inverse associations among women under 50 years of age and for mucinous ovarian cancer may be chance findings. Finally, residual confounding due to unmeasured or unknown factors may be present.

The strengths of the study included the large case-control population, nationwide registry-based approach with virtually complete cancer ascertainment and histological verification [13], and detailed prescription data. The use of continuously updated prescription data with precise information on type and quantity of the drug [15] allowed a thorough evaluation of exposure patterns and avoided recall bias. Further advantages of our study included the availability of accurate data on reproductive factors [16], medical conditions [17], socioeconomic status [18–20], and family history of ovarian and breast cancer [19], enabling broad adjustment for potential confounding.

In conclusion, we found no apparent evidence of an overall influence of antihistamine use on ovarian cancer risk, and this was independent of patterns of use. Our finding of an inverse association between antihistamine use and mucinous ovarian cancers specifically and among pre-menopausal women merit further evaluation in preclinical and epidemiologic studies.

Contributors

Freija Verdoodt was responsible for conceptualization, funding acquisition, investigation, methodology, original draft of the paper, and review and editing.

Anton Pottegård was responsible for methodology, investigation, and review and editing of the paper.

Christian Dehlendorff was responsible for conceptualization, data curation, formal analysis, methodology, investigation, and review and editing of the paper.

Marja Jäättelä was responsible for methodology, investigation, and review and editing of the paper.

Jesper Hallas was responsible for methodology, investigation, and review and editing of the paper.

Søren Friis was responsible for supervision, conceptualization, funding acquisition, investigation, methodology, original draft of the paper, and review and editing.

Susanne K. Kjaer was responsible for supervision, conceptualization, funding acquisition, investigation, methodology, and review and editing of the paper.

Conflict of interest

Freija Verdoodt, Christian Dehlendorff, Marja Jäättelä, Søren Friis, and Susanne K. Kjaer declare that they have no conflicts of interest. Anton Pottegård and Jesper Hallas have received grants from Almirall.

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Ethical statement

The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to Danish law, formal consent is not required for registry-based studies.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The authors do not have permission to share the raw data used in the study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2018.11.014.

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