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Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study

Research Year Report

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Preface

This study was carried out during my research year at Department of Clinical Epidemiology, Aarhus University Hospital, Denmark (September 2010 – April 2011) and at the Channing Laboratory, Brigham and Woman's Hospital, Harvard Medical School, Boston, USA (May 2011 – September 2011).

First of all, I would like to express my sincere gratitude to my supervisors: Professor Timothy Lash for always providing skillful and constructive feedback and patiently sharing his comprehensive knowledge. I am deeply grateful to him for introducing me to Tom Ahern, helping me set up my stay and new research project in Boston, and for his valuable guidance and everlasting support both in Denmark and while I was abroad. Professor Henrik Toft Sørensen (Chair) for sharing his comprehensive knowledge in clinical epidemiology, for providing excellent research facilities - including research courses on statistical and epidemiological topics taught by highly qualified professors from all over the world – for facilitating the project, and for generously giving me the opportunity to work on other research projects during my research year. Associate professor Deirdre Cronin-Fenton for useful advice, valuable help, positive attitude and support. Tom Ahern, my excellent supervisor at Channing Laboratory, for his highly skilled scientific help, practical help and pleasant personality. I feel very privileged to have worked together with all of you and I look forward to continue our collaborations.

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During my research year, I received financial support from the Danish Medical Research Council, the Danish Agency of Science, Technology and Innovation, the Aarhus University Research Foundation, the Regional Clinical Epidemiological Monitoring Initiative for Central and North Denmark Regions, and the Karen Elise Jensen Foundation. My 4-month stay in Boston was made possible by support from the Helga and Peter Korning's Foundation, the "Einar Willumsens Mindelegat", and the Oticon Foundation.

Finally, my warmest thanks to my boyfriend Mads Filtenborg Mogensen, and my parents, Elsebeth Lilliane Vrelits and Per Christian Sørensen for their unconditional support at all times.

Gitte Vrelits Sørensen, September 2011

Contents

List of abbreviations

OR	Odds ratio
CI	Confidence interval
aOR	Adjusted odds ratio
IBD	Inflammatory bowel disease
COPD	Chronic obstructive pulmonary disease
HRT	Hormone replacement therapy
RA	Rheumatoid arthritis
CPR	Civil personal registration
CRS	Civil Registration System
ATC	Anatomical Therapeutic Chemical
DCR	Danish Cancer Registry
DNPR	Danish National Patient Registry
ICD	International Classification of Diseases
IGF-1	Insulin-like growth factor-1

Abstract

Background: Glucocorticoids are widely prescribed drugs. However, the effect of glucocorticoid use on the risk of breast cancer is not clear.

Methods: We conducted a case-control study using population-based medical databases from Northern Denmark (1.8 million inhabitants) to investigate the association between glucocorticoid prescriptions and breast cancer risk. Cases were diagnosed with a first primary breast cancer between 1994 and 2008. We selected up to 10 population controls matched to cases on birth year and residence using risk-set sampling. Using conditional logistic regression, we estimated the odds ratios (ORs) and 95% confidence intervals (CIs) associating glucocorticoid use with breast cancer occurrence, controlling for prescriptions of postmenopausal hormone replacement therapy, anti-diabetics, immunosuppressive drugs, and hospital diagnosis of obesity, diabetes, chronic pulmonary diseases and autoimmune diseases.

Results: The study included 9,488 cases and 94,876 controls. We found no effect on breast cancer risk in ever users (>2 prescriptions) of any glucocorticoids (adjusted OR (aOR)=1.0; 95% CI: 0.96, 1.1), systemic glucocorticoids (aOR=1.0; 95% CI: 0.96, 1.1), or inhaled glucocorticoids (aOR=1.0; 95% CI: 0.95, 1.1), each compared to never users of any glucocorticoids. Associations for recent use (preceding two years) and former use (more than two years earlier) were near null in all dose categories (low, medium and high number of prescriptions). Intensity of systemic glucocorticoid use (cumulative prednisolone equivalent doses), regardless of duration (<1, 1–5, 5+ years), was also not associated with breast cancer risk.

Conclusions: Overall, our study provides no evidence that glucocorticoid use affects the risk of breast cancer.

Introduction

Glucocorticoid is an adrenocortical hormone, belonging to the same steroid superfamily as estrogen, which is known to play a role in breast cancer risk [1]. Glucocorticoid is the main stress hormone and controls a variety of physiological processes including metabolism and immune response [2]. Thus, it could potentially play a role in the risk of breast cancer by several mechanisms.

Synthetic glucocorticoids affect immune function and are commonly used as anti-inflammatory and immunosuppressive therapy in diseases such as asthma, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD), inflammatory arthritis, and other connective tissue disorders [3]. The immune system has a role in preventing cancer development and progression [4–5], so suppression of the immune system may promote tumor development. However, the role of the immune system in cancer is dual and complex, since it may also promote tumor growth [4]. In addition, decreased glucose tolerance, a well-known side effect of glucocorticoids [3], has been suggested to promote mammary carcinogenesis [6–8].

To our knowledge, only one study has previously been published on the relation between glucocorticoid use and breast cancer risk [9]. Our previous study included nearly 33,000 women, ascertained prescriptions for systemic glucocorticoids between 1989 and 1996, ascertained breast cancers until 1998, and recorded a total of 367 breast cancer cases. We reported no association between glucocorticoid prescriptions and breast cancer risk. Due to a relatively short average follow-up time (mean 5.8 years), we were not able to investigate the effect of long-term use. Also, we were only able to control for age as a potential confounder.

A recent review called for further research investigating the potential association between glucocorticoid use and breast cancer risk [10]. We therefore conducted a large population-based case-control study with prospectively collected prescription data to examine the association between glucocorticoid use and breast cancer risk. In addition to following a larger population over a longer period, we have extended our previous study [9] by incorporating more information on potential confounders, such as parity, age at first birth, use of postmenopausal hormone replacement therapy (HRT), anti-diabetic medicine, immunosuppressive drugs, any history of hospital diagnosed obesity, diabetes, COPD, asthma, rheumatoid arthritis (RA), IBD and other autoimmune diseases (see Appendix A).

Methods

Source population

We conducted this population-based case-control study among female residents of the Central and North Denmark Regions between 1 February 1994 and 31 December 2008. Together, these regions represent about one-third of the Danish population (≈1.8 million inhabitants). The Danish National Health Service provides tax-supported health-care to all residents of the country and refunds part of the patients' expenditures on most physician-prescribed drugs, including glucocorticoids [11].

All health-related services are registered to individual patients by use of their civil personal registration (CPR) number, assigned to all Danish citizens since 1968 by the Danish Civil Registration System (CRS). This number encodes gender and date of birth [12] and facilitates accurate individual-level linkage between population-based registries.

The Danish regions are served by pharmacies equipped with computerized accounting systems through which data are sent to a regional prescription database hosted by Aarhus University [11], with key information about prescriptions for refundable drugs. Thus, the prescription database includes information on each patient's CPR number; the type and quantity of drug prescribed according to the Anatomical Therapeutic Chemical classification system (ATC), and the date the prescription was filled [11, 13]. The Danish regions were until 1 January 2007 divided into counties. Because the different counties started contributing data to the prescription database at different times, they differ with respect to the earliest availability of prescription data, with the earliest being 1989 [11]. To ensure that we had at least minimal prescription data history for each case and their corresponding controls, we only included women who had more than 5 years of prescription history before their index date (as defined below). Women who were resident in the study area for less than five years before index date were excluded from the source population, as were women with any malignant cancer diagnosis before their index dates (except non-melanoma skin cancers).

Cases

We used the Danish Cancer Registry (DCR) to identify all women with an incident diagnosis of breast cancer (see Appendix A). The DCR has recorded all incident cancers through December 31, 2008 [14] and has near 100% completeness for breast cancer diagnosis [15].

Population controls

Controls were identified using the CRS [12, 16]. A pool of eligible individuals with the same birth year and county/region of residence as each breast cancer patient was sampled from the general-population among all women alive and free of breast cancer on the date of the matched case's breast cancer diagnosis. This date of diagnosis therefore served as the index date for the case and all of the controls matched to the case. Ten individuals from this pool were randomly selected for each case. All eligible controls were included when the risk-set of matched controls included fewer than 10 individuals.

Data collection

The prescription database [11] was used to identify all prescriptions before index date for systemic (oral and injected), inhaled and local-acting glucocorticoids with intestinal anti-inflammatory effect (“local glucocorticoids” hereafter). The following preparations were available and prescribed during the study period (see Appendix A for ATC codes): betamethasone, dexamethasone, methylprednisolone, prednisolone, prednisone, triamcinolone, cortisone, hydrocortisone, beclomethason, budesonide, flunisolid, fluticasone, and mometason.

Potential confounding prescription drugs

The prescription database also provided information on use of the following potential confounding drugs before index date (see Appendix A for ATC codes): postmenopausal HRT [17], anti-diabetics [18], and use of immunosuppressive drugs as a marker of immune-related disease.

Potential confounding diseases

The Danish National Patient Registry (DNPR) contains information about all non-psychiatric hospital admissions since 1977, and since 1995 also outpatient visits [19]. From the DNPR we retrieved data on hospital diagnoses of the following diseases before index date: obesity, diabetes, COPD, asthma, RA, IBD (ulcerative colitis or Crohn's disease), and a list of “other autoimmune diseases” (see Appendix A for the list of diseases and associated International Classification of Diseases (ICD) codes).

Other potential confounders

To obtain information about parity and age at first birth we used the CRS [12]. In the CRS, the CPR numbers of parents are linked to their child, as long as the child lived with the parents in 1968 or later. We limited the analysis adjusted for parity and age at first birth to women born later than 1949, for whom the CRS allows reconstruction of childbearing history with better than 95% completeness [20].

Analytic variables

We categorized glucocorticoid use as never versus ever use. Ever users were further subdivided into two dose categories; one or two prescriptions or more than two prescriptions. We examined the association of overall glucocorticoid use with breast cancer, and then examined the association of systemic and inhaled glucocorticoid use separately. To examine the temporality of glucocorticoid use and the risk of breast cancer, we divided ever use into recent use (only prescriptions within two years of index date) and former use (prescriptions earlier than two years of index date). In the group of any glucocorticoid users we further divided the number of prescriptions into low (1 or 2 prescriptions), medium (3–9) and high (>9). We based these cut-offs on the distribution of prescription counts among the controls with more than 2 prescriptions.

To examine whether breast cancer risk was associated with the intensity and duration of glucocorticoid use, we restricted the analyses to systemic glucocorticoid users and calculated prednisolone equivalent cumulative doses based on the equivalency table in Kelly's Textbook of Rheumatology [21] and grouped into the four categories <200 mg, 200−399 mg, 400–999 mg and ≥1000 mg (for calculations see Appendix B). The duration was defined as the number of days from the date of the first prescription to the date of the last prescription, plus the duration of the last prescription (estimated to be on average 30 days). We divided the duration of glucocorticoid use into short-term (<1 year), medium-term (1–5 years), and long-term (>5 years).

The covariates ever use of immunosuppressive drugs, ever use of postmenopausal HRT, COPD, asthma, IBD, obesity, and RA were coded individually as dichotomous variables. Other autoimmune diseases (see Appendix A) were merged into a dichotomous variable. Since diabetes and metformin use may have counteracting effects on breast cancer risk [18], we coded diabetes and anti-diabetic medicine use as a categorical variable with three possible levels: no diabetes or use of anti-diabetic medicine, diabetes or use of anti-diabetic medicine with ever use of metformin, and diabetes or use of anti-diabetic medicine without ever use of metformin.

Statistical analysis

We computed the frequency and proportion of cases and controls within categories of demographic variables and covariates.

In all analyses, we used never use of any glucocorticoids as the reference group. For the use of any glucocorticoids, systemic glucocorticoids, and inhaled glucocorticoids, we stratified by all covariates, and calculated crude and stratum-specific odds ratios (ORs) to evaluate potential confounding and effect measure modification. We used conditional logistic regression analysis to compute crude and adjusted ORs (aORs) and their associated confidence intervals (95% CI), with simultaneous adjustment for use of postmenopausal HRT, immunosuppressive drugs, hospital diagnosed obesity, diabetes (plus/minus a history of metformin use), COPD, asthma, IBD, RA and "other autoimmune disease." Since we used risk set sampling of controls, the ORs are unbiased estimates of the corresponding incidence rate ratio in the underlying population [22]. We report estimates of association stratified by age categories (<45, 45–55 and >55, as estimated ranges for pre-, peri- and postmenopausal status). In the group of women <45, we were able to make additional adjustment for parity and age at first birth, using the combined variable (see **Table 1**).

We used Stata 11.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA) for the data analyses. Approval number from the Danish Data Protection Agency is 2004-41-4693.

Results

We identified 9,488 breast cancer cases and 94,876 population controls. Median age at index date was 62.1 years. Characteristics of cases and controls are shown in **Table 1**. As expected, a higher proportion of cases than controls had ever used postmenopausal HRT by their index date (24% versus 19%). In the subgroup of women born later than 1949 (n=31,130), a lower proportion of cases than controls had a first birth before age 25 (45% versus 49%) and had three or more children (25% versus 27%). In all other characteristics, there were no important differences between cases and controls.

We found no effect on breast cancer risk in ever users (>2 prescriptions) of any glucocorticoids compared to never users (aOR=1.0; 95% CI: 0.96, 1.1). The association among former users with high number of prescriptions (>9) was null (aOR 1.0; 95% CI: 0.93, 1.1). In addition, among recent users who only had prescriptions within the two years before index date, we found null associations. Restricting the analysis to systemic or inhaled glucocorticoid use also showed no associations. Ever use (>2 prescriptions) of systemic (aOR=1.0; 95% CI: 0.96, 1.1), or inhaled glucocorticoids (aOR=1.0; 95% CI: 0.95, 1.1), each compared to never use of any glucocorticoids, were both null **(Table 2).** Intensity of systemic glucocorticoid use (cumulative prednisolone equivalent doses), regardless of duration (<1, 1–5, 5+ years), showed no pattern of association **(Table 3)**. Stratifying into estimates of pre-, peri-, and postmenopausal status by age group also did not show any association. In the subgroups of women <45 years old (**Table 4**) and all women born later than 1949 (n=31,130), additional adjustment for parity and age at first birth did not change our overall estimates of null association. In the latter group, the aOR for >2 glucocorticoid prescriptions ever, compared to never, was 1.0 (95% CI 0.88, 1.2).

Discussion

Overall, this population-based case-control study of over 100,000 women provided no evidence of an association between glucocorticoid use and breast cancer risk. The null association was consistent when dividing the use of glucocorticoids into recent and former use, intensity and duration of use, and also consistent with our previous study [9]. Our results answer the need for research on the role of glucocorticoids in breast cancer risk, which has not been well studied [10].

Our study has several strengths. The uniformly organized Danish healthcare system with complete hospital history and access to appropriate population controls allows a population-based case-control design. The use of population-based prescription registries, with a completeness approaching 100% [11, 13] ensured unbiased assessment of exposure data preceding breast cancer diagnosis and the registry source eliminated recall bias. In all our analyses, we included only persons with at least 5 years of prescription history, thus potential bias due to left censoring of exposure information was reduced compared with the earlier study [9].

Our study also had limitations. We had no data regarding adherence with prescriptions, potentially leading to non-differential misclassification of some non-users as users. However, our drug exposure assessment was based on redeemed prescriptions, and because patients had to pay a proportion of the drug cost, our estimates are likely to reflect actual use, especially in women with more than two prescriptions. In support of this expectation, a validation study on postmenopausal HRT by Danish women showed good agreement between self-reported use and prescription data in the registry [23]. We also had no information on body mass index, alcohol consumption or family history of breast cancer, and other factors that may impact the risk of breast cancer [24]. To confound our results substantially they would also have to be related to glucocorticoid use conditional on adjustment for the measured covariates, which we have no reason to expect.

A more important limitation might be our inability to examine the impact of glucocorticoid use on breast cancer risk by specific breast cancer characteristics such as hormone receptor status. Studies have addressed the possibility of cross-talk between estrogen receptor and glucocorticoid receptor in mammary epithelial cells [25] and recently *in vivo* studies have suggested that glucocorticoids may stimulate the expression of the sulfotransferase SULT1E1, which plays a role in deactivating estrogen [26]. Thus, estrogen levels and estrogen receptor expression might well impact the action of glucocorticoids. Glucocorticoid response may also vary due to glucocorticoid receptor gene polymorphisms. The increased risk of squamous cell carcinoma in glucocorticoid users is more pronounced in the presence of the allele with the common genetic variant in the glucocorticoid receptor gene, compared with the homozygote wild types [27], but we were unable to evaluate this gene-drug interaction. Finally, glucocorticoids increase the expression of insulin-like growth factor-1 (IGF-1) receptors [28] and the levels of circulating IGF-1 [29]. IGF-1 receptor expression patterns in epithelial cells of normal breast tissue biopsies were associated with an increased risk of subsequent breast cancer [30], and a meta-analysis from 2010 concluded that circulating IGF-1 levels are positively related to estrogen-receptor-positive breast tumors, regardless of menopausal status [31]. Our study did not, however, have measurements of IGF-1 receptor or circulating IGF-1 available for analyses.

Conclusions

Thus, there are several mechanisms by which glucocorticoid prescriptions might affect breast cancer risk in subpopulations defined by molecular subcharacteristics. Evaluations of these associations would require a study with detailed biologic data. Overall, however, our results provide no evidence of an increased risk of breast cancer in glucocorticoid users compared with never users.

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Table 1 Frequency distribution of cases and matched population controls in North Jutland County between 1994−2008, Aarhus County between 2001−2008, and Viborg- and Ringkjøbing Counties between 2003−2008

Characteristic	Cases (N= 9,488)		Controls[a] (N= 94,876)	
	N	%	N	%
Age at index date[a]				
<45	899	9.5	9,072	9.6
45−55	1,932	20	19,108	20
>55	6,657	70	66,696	70
County at index date[a,b]				
North Jutland	4,424	47	44,236	47
Aarhus	3,168	33	31,680	33
Viborg	931	10	9,310	10
Ringkjøbing	965	10	9,650	10
Calendar year at index date[a]				
1994−1998	1,253	13	12,530	13
1999−2003	2,910	31	29,100	31
2004−2008	5,325	56	53,246	56
Use of any glucocorticoids				
Never	6,692	71	68,064	72
≤2 prescriptions ever	1,452	15	13,891	15
>2 prescriptions ever	1,344	14	12,921	14
Use of other immunosuppressive drugs				
Never	9,395	99	93,880	99
Ever	93	1.0	996	1.0
Use of postmenopausal hormone replacement therapy				
Never	7,252	76	76,919	81
Ever	2,236	24	17,957	19
Hospital diagnosed diabetes or ever use of anti-diabetic medicine				
Never	8,961	94	90,180	95
Yes & never metformin	215	2.3	2,041	2.2
Yes & ever metformin	312	3.3	2,655	2.8
Hospital diagnosed chronic obstructive pulmonary disease				
No	9,093	96	91,161	96
Yes	395	4.2	3,715	3.9
Hospital diagnosed asthma				
No	9,266	98	92,583	98
Yes	222	2.3	2,293	2.4

Characteristic	Cases (N= 9,488)		Controls[a] (N= 94,876)	
	N	%	N	%
Hospital diagnosed inflammatory bowel disease				
No	9,407	99	94,117	99
Yes	81	0.9	759	0.8
Hospital diagnosed rheumatoid arthritis				
No	9,392	99	93,733	99
Yes	96	1.0	1,143	1.2
Other autoimmune diseases[c]				
No	9,086	96	91,201	96
Yes	402	4.2	3675	3.9
Hospital diagnosed obesity				
No	9,240	97	92,512	98
Yes	248	2.6	2,364	2.5
Age at first birth in women born later than 1949 (n=31,130)[d]				
Nulliparous	344	12	3,373	12
<25	1,284	45	13,845	49
25−30	885	31	8,345	30
>30	317	11	2,737	10
Parity in women born later than 1949 (n=31,130)[d]				
Nulliparous	344	12	3,373	12
1 child	445	16	4,170	15
2 children	1,341	47	13,005	46
≥3 children	700	25	7,752	27
Combined parity & age (y) at first birth in women born later than 1949 (n=31,130)[d]				
Nulliparous	344	12	3,373	12
1 child & <25y	154	5.4	1,444	5.1
2 children & <25y	658	23	6,956	25
≥3 children & <25y	472	17	5,445	19
1 child & ≥25y	291	10	2,726	9.6
2 children & ≥25y	683	24	6,049	21
≥3 children & ≥25y	228	8.1	2,307	8.2

[a] Controls were matched to cases on county/region of residence and birth year.

[b] The counties were merged into the two regions in 2007. Thus, from 2007−2008 the women were instead matched on former county. The higher proportion of people in North Jutland County was a result of longer prescription history.

[c] See Appendix A for the list of hospital diagnosed other autoimmune diseases.

[d] To assure complete data on every birth of the woman we made a subgroup of women born later than 1949 (n=31,130).

Table 2 Number of prescriptions (pres.) and temporality of any glucocorticoid (GC) use, systemic GC use and inhaled GC use and odds ratio of breast cancer

Characteristics	Cases (N=9,488)		Controls[a] (N=94,876)		Odds Ratio[b]	95% Confidence Interval
	N	%	N	%		
Any GC use						
Never use	6,692	71	68,064	72	reference	reference
Ever use						
≤ 2 pres.	1,452	15	13,891	15	1.0	0.98, 1.1
> 2 pres.	1,344	14	12,921	14	1.0	0.96, 1.1
Recent use[c]						
≤ 2 pres.	284	3.0	2,949	3.1	0.96	0.84, 1.1
3–9 pres.	72	0.8	781	0.8	0.93	0.73, 1.2
> 9 pres.	13	0.1	156	0.2	0.82	0.46, 1.4
Former use[d]						
≤ 2 pres.	1,168	12.3	10,942	11.5	1.1	0.99, 1.1
3–9 pres.	655	6.9	6,142	6.5	1.0	0.96, 1.1
> 9 pres.	604	6.4	5,842	6.2	1.0	0.93, 1.1
Systemic GC use						
Never use of any GC	6,692	71	68,064	72	reference	reference
Only inhaled/local GC use	451	4.8	4,401	4.6	1.0	0.93, 1.1
Ever use of systemic GC						
≤ 2 pres.	1,437	15	13,719	15	1.0	0.98, 1.1
> 2 pres.	908	10	8,692	9.1	1.0	0.96, 1.1
Recent systemic use[c]						
≤ 2 pres.	278	2.9	2,903	3.1	0.95	0.84, 1.1
> 2 pres.	64	0.7	705	0.7	0.91	0.71, 1.2
Former systemic use[d]						
≤ 2 pres.	1,159	12.2	10,816	11.4	1.1	0.99, 1.1
> 2 pres.	844	8.9	7,987	8.4	1.0	0.96, 1.1
Inhaled GC use						
Never use of any GC	6,692	71	68,064	72	reference	reference
Only systemic/local GC use	1,886	20	17,951	19	1.0	0.98, 1.1
Ever users of inhaled GC						
≤ 2 pres.	317	3.4	3,223	3.4	1.0	0.87, 1.1
> 2 pres.	593	6.2	5,638	6.0	1.0	0.95, 1.1
Recent inhaled use[c]						
≤ 2 pres.	84	0.9	770	0.8	1.1	0.86, 1.4
> 2 pres.	38	0.4	453	0.5	0.83	0.59, 1.2
Former inhaled use[d]						
≤ 2 pres.	233	2.5	2,453	2.6	0.94	0.82, 1.1
> 2 pres.	555	5.8	5,185	5.5	1.1	0.97, 1.2

[a] Controls were matched to cases on county of residence and birth year.

[b] Analysis adjusted for any use of postmenopausal hormone replacement therapy or “other immunosuppressive drugs” before index date, and any hospital diagnosis of obesity, diabetes (+/-

metformin use), chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, rheumatoid arthritis or “other autoimmune disease” before index date.

[c] Recent use: Glucocorticoid use only within two years of diagnosis, and never former user.

[d] Former use: Glucocorticoid use earlier than within two years of diagnosis.

Table 3 Duration and intensity of systemic glucocorticoid (GC) cumulative doses in milligram (mg) prednisolone equivalent doses[a] and odds ratio of breast cancer

Characteristics	Cases (N=9,488) N	Cases (N=9,488) %	Controls[b] (N=94,876) N	Controls[b] (N=94,876) %	Odds Ratio[c]	95% Confidence Interval
Never any GC use	6,692	71	68,064	72	reference	reference
Only inhaled/local use	451	4.8	4,401	4.6	1.0	0.93, 1.1
Short-term (<1 year of use)[d]						
<200 mg	1237	13	11,830	12	1.0	0.97, 1.1
200–399 mg	94	0.99	990	1.0	0.93	0.75, 1.2
400–999 mg	21	0.22	242	0.26	0.88	0.57, 1.4
≥1000 mg	15	0.16	93	0.10	1.6	0.90, 2.8
Medium-term (1–5 years of use)[d]						
<200 mg	289	3.1	2,805	3.0	1.0	0.89, 1.2
200–399 mg	138	1.5	1,166	1.2	1.2	0.97, 1.4
400–999 mg	67	0.71	545	0.57	1.2	0.93, 1.6
≥1000 mg	20	0.21	273	0.29	0.73	0.46, 1.2
Long-term (>5 years of use)[d]						
<200 mg	170	1.8	1,683	1.8	1.0	0.85, 1.2
200–399 mg	123	1.3	1,141	1.2	1.1	0.87 1.3
400–999 mg	96	1.0	1,053	1.1	0.89	0.72, 1.1
≥1000 mg	75	0.79	590	0.62	1.2	0.96, 1.6

[a] For calculations see Appendix B.

[b] Controls were matched to cases on county of residence and birth year.

[c] Analysis adjusted for any use of postmenopausal hormone replacement therapy or "other immunosuppressive drugs" before index date, and any hospital diagnosis of obesity, diabetes (+/- metformin use), chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, rheumatoid arthritis or "other autoimmune disease" before index date.

[d] Duration was calculated as time between the first and the last systemic glucocorticoid prescription (plus 30 days from the last prescription), and then divided into short-, medium and long-term use.

Table 4 Any glucocorticoid use and odds ratio of breast cancer stratified by age group as a conservative estimate of menopausal status

Characteristics	Cases (N=9,488)		Controls[a] (N=94,876)		Odds Ratio[b]	95% Confidence Interval
	N	%	N	%		
Age < 45 (pre-menopausal)						
Never use	744	83	7,353	81	reference	reference
Ever use						
≤ 2 prescriptions	98	11	100	11	0.97[c]	0.78, 1.2[c]
> 2 prescriptions	57	6.4	719	7.9	0.83[c]	0.61, 1.1[c]
Age 45–55 (peri-menopausal)						
Never use	1,488	77	14,450	72	reference	reference
Ever use						
≤ 2 prescriptions	248	13	2,757	14	0.87	0.76, 1.0
> 2 prescriptions	196	10	1,901	10	1.0	0.86, 1.2
Age > 55 (post-menopausal)						
Never use	4,460	67	46,261	72	reference	reference
Ever use						
≤ 2 prescriptions	1,106	17	10,134	15	1.1	1.0, 1.1
> 2 prescriptions	1,091	16	10,301	15	1.1	0.99, 1.1

[a] Controls were matched to cases on county of residence and birth year.

[b] Analysis adjusted for any use of postmenopausal hormone replacement therapy or "other immunosuppressive drugs" before index date, and any hospital diagnosis of obesity, diabetes (+/- metformin use), chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, rheumatoid arthritis or "other autoimmune disease" before index date.

[c] Analyses were additionally adjusted for parity and age at first birth. Without the additional adjustment the adjusted odds ratios for ≤2 or >2 prescriptions were 0.97 (95% CI: 0.77, 1.2) and 0.83 (95% CI: 0.61,1.1), respectively.

Appendix A: List of primary exposure drugs, cancer diagnosis, potentially confounder drugs and diseases, and associated ICD and ATC codes

Primary exposure drugs available and prescribed during study period (ATC codes)

Systemic glucocorticoids
- Betamethasone (H02AB01)
- Dexamethasone (H02AB02)
- Methylprednisolone (H02AB04)
- Prednisolone (H02AB06)
- Prednisone (H02AB07)
- Triamcinolone (H02AB08)
- Hydrocortisone (H02AB09)
- Cortisone (H02AB10)

Inhaled glucocorticoids
- Beclomethason (R03BA01)
- Budesonide (R03BA02)
- Flunisolid (R03BA03)
- Fluticasone (R03BA05)
- Mometason (R03BA07)

Local-acting glucocorticoids with intestinal anti-inflammatory effect
- Prednisolone (A07EA01)
- Hydrocortisone (A07EA02)
- Budesonide (A07EA06)

Potentially confounder drugs (ATC codes)

Postmenopausal hormone replacement therapy:
- Estrogens (G03C)
- Estrogens and progesterone combined (G03F)

Anti-diabetic medicine:
- Insulin and insulin analogs (A10A)
- Oral anti-diabetic medications (A10B–A10X) (minus metformin)
- Metformin (A10BA02)

Immunosuppressive medications (L04)

Cancer codes obtained from the Danish Cancer Registry

Breast cancer:
ICD-10: C50.0-50.6, C50.8 & C50.9

Other malignant cancers:
ICD-10: C00–C97 (minus non-melanoma skin cancer: ICD-10: C440–C449)

Hospital diagnose codes on potentially confounder diseases obtained from the Danish National Patient Registry

Rheumatoid arthritis
ICD-8: 712.19, 712.29, 712.39, 712.59
ICD-10: M05−M06, G73.7D, I32.8A, I39.8E, I41.8A, I52.8A

Chronic obstructive pulmonary disease
ICD-8: 490−492
ICD-10: J40−J44, J47

Asthma
ICD-8: 493
ICD-10: J45−J46

Obesity
ICD-8: 277.99
ICD-10: E66

Inflammatory bowel disease (ulcerative colitis or Crohn's disease)
ICD-8: 563.01, 563.19, 569.04
ICD-10: K50.0, K50.1, K50.8, K50.9, K51.0−K51.9

Diabetes
ICD-8: 249−250
ICD-10 codes E10−E11

Other autoimmune diseases:

Hematological system
Autoimmune hemolytic anemia
ICD-8: 283.90
ICD-10: D59.0, D59.1
Idiopathic thrombocytopenic purpura
ICD-8: 287.10
ICD-10: D69.3
Endocrine system
Autoimmune thyroiditis
ICD-8: 244.01, 245.03

ICD-10: E06.3

Addison´s disease

ICD-8: 255.10

ICD-10: E27.1

Grave's disease

ICD-8: 242.00, 242.01, 242.08, 242.09

ICD-10: E05.0

Central nervous / neuromuscular system

Multiple sclerosis

ICD-8: 340

ICD-10: G35

Myasthenia gravis

ICD-8: 733.09

ICD-10: G70.0

Gastrointestinal/hepatobilliary system

Pernicious anemia

ICD-8: 281.00, 281.01, 281.08, 281.09

ICD-10: D51.0

Coelic disease

ICD-8: 269.00

ICD-10: K90.0

Primary biliary cirrhosis

ICD-8: 571.90

ICD-10: K74.3

Skin

Atopic dermatitis

ICD-8: 691.00

ICD-10: L20

Pemphigus/pemphigoid

ICD-8: 694.00-694.03, 694.05

ICD-10: L10.0, L10.1, L10.2, L10.4, L12.0

Dermatitis herpetiformis

ICD-8: 693.08, 693.09

ICD-10: L13.0

Psoriasis

ICD-8: 696.09, 696.10, 696.19

ICD-10: L40, M07.0–M07.3

Connective tissue diseases

Ankylosing spondylitis

ICD-8: 712.49

ICD-10: M45, H221B

Polymyositis/dermatomyositis

ICD-8: 716.09, 716.19

ICD-10: M33

Systemic- and subacute cutaneous lupus erythematosus

ICD-8: 734.19

ICD-10: M32, G05.8A, G73.7C, I32.8B, I39.8C, L93.1, L93.2, N08.5A, N16.4B

Systemic scleroderma

ICD-8: 734.00–734.09

ICD-10: M34.0–34.9

Mixed connective tissue disease

ICD-10: M35.1

Sjögren´s syndrome

ICD-8: 734.90

ICD-10: M35.0, G73.7A, N16.4A

Sarcoidosis

ICD-8: 135.99

ICD-10: D86, G53.2, H22.1A, I41.8B, K77.8B, M63.3

Vasculitis syndromes including polymyalgia rheumatic

ICD-8: 287.09, 446.09–446.99

ICD:10: D69.0B, I77.6, L95, M30–M31, M35.3, M35.6, M79.3, N08.5B–N08.5E

Abbreviations

ATC: Anatomical Therapeutic Chemical; ICD-8: International Classification of Diseases, Eighth Revision; ICD-10: International Classification of Diseases, Tenth Revision.

Appendix B: Cumulative prednisone equivalent dose calculation and list of prescribed systemic glucocorticoids with associated prednisone conversion factor

Systemic glucocorticoid	Equivalent glucocorticoid dose (mg)[a]	Prednisone conversion factor (PCF)
Cortisone	25	0.20
Hydrocortisone	20	0.25
Methylprednisolone	4	1.25
Prednisolone	5	1
Prednisone	5	1
Triamcinolone	4	1.25
Dexamethasone	0.75	6.67
Betamethasone	0.60	8.33

[a] Based on the equivalency table in *Kelly's Textbook of Rheumatology* by Jacobs et al [21].

Cumulative dose calculation:

The cumulative dose was obtained by multiplying number of pills/injections x dose per pill/injection x PCF for each prescription and then summing across all prescriptions.

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