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Glucocorticoid prescriptions and breast cancer recurrence: a Danish nationwide prospective cohort study

L. W. Lietzen[1]*, T. Ahern[2], P. Christiansen[4], A. B. Jensen[5], H. T. Sørensen[1], T. L. Lash[1,3] & D. P. Cronin-Fenton[1]

[1]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark;* [2]*Departments of Surgery and Biochemistry, College of Medicine, University of Vermont, Burlington;* [3]*Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, USA; Departments of* [4]*Surgery;* [5]*Oncology, Aarhus University Hospital, Aarhus, Denmark*

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Background: Treatment with synthetic glucocorticoids (GCs) depresses the immune response and may therefore modify cancer outcomes. We investigated the association between GC use and breast cancer recurrence.

Materials and methods: We conducted a population-based cohort study to examine the risk of breast cancer recurrence associated with GC use among incident stage I–III female breast cancer patients aged >18 years diagnosed 1996–2003 in Denmark. Data on patients, clinical and treatment factors, recurrence, and comorbidities as well as data on GC prescriptions and potential confounders were obtained from Danish population-based medical registries. GCs were categorized according to administrative route: systemic, inhaled, or intestinal. Women were followed for up to 10 years or until 31 December 2008. We used Cox proportional hazards regression models to compute hazard ratios (HRs) and associated 95% confidence intervals (95% CIs) to evaluate the association between GC use and recurrence. Time-varying drug exposures were lagged by 1 year.

Results: We included 18 251 breast cancer patients. Median recurrence follow-up was 6.9 years; 3408 women developed recurrence during follow-up. Four thousand six hundred two women filled at least one GC prescription after diagnosis. In unadjusted models, no association was observed among users of systemic, inhaled, and intestinal GCs ($HR_{systemic}$ = 1.1, 95% CI 0.9–1.3; $HR_{inhaled}$ = 0.9, 95% CI 0.7–1.0; and $HR_{intestinal}$ = 1.0, 95% CI 0.9–1.2) versus nonusers. In adjusted models, the results were also near null ($HR_{systemic}$ = 1.1, 95% CI 0.9–1.2; $HR_{inhaled}$ = 0.8, 95% CI 0.7–1.0; and $HR_{intestinal}$ = 1.0, 95% CI 0.8–1.2).

Conclusion: We found no evidence of an effect of GC use on breast cancer recurrence.

Key words: breast neoplasm, glucocorticoids, outcome, epidemiology

*Correspondence to: Dr Lone W. Lietzen, Department of Clinical Epidemiology, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Tel: +45-87168063. E-mail: lwl@clin.au.dk

introduction

Synthetic glucocorticoids (GCs) are frequently prescribed anti-inflammatory drugs [1]. They have a general immunosuppressive effect on a large and diverse set of diseases, but are also associated with many serious side-effects including diabetes, obesity, osteoporosis, fractures, psychosis, and catabolism [1]. In women with breast cancer, GCs are often used to prevent surgery-induced and chemotherapy-induced nausea and emesis [2–4]. Given their immunosuppressive effects, use of GCs may promote tumorigenesis, by facilitating tumor cell evasion of immune surveillance [5, 6].

GCs belong to the same steroid superfamily as estrogens, which are known to play a role in breast cancer development [7], but the potential effect of GCs on breast cancer cell growth has not been fully elucidated [5, 8]. A laboratory-based study of human breast cancer cells found that treatment with GCs induced a better prognostic profile in ER-negative tumor cells (cells became more differentiated and less invasive), but not in ER-positive cells, compared with untreated ER-negative and ER-positive cells, respectively [9]. In contrast, GCs have also been shown to inhibit the cytotoxic effects of chemotherapy in human breast cancer cell culture models [10]. We previously found no evidence of an effect of GCs on breast cancer risk [11, 12]. However, to our knowledge, the impact of GCs on breast cancer prognosis has never been investigated.

We therefore investigated the potential association between GC use and breast cancer recurrence in a large population-based cohort of breast cancer patients, using high-quality clinical data with complete follow-up. We hypothesized that GC use would increase the risk of breast cancer recurrence in humans due to impaired immune response.

materials and methods

setting

We conducted a nationwide cohort study using Danish population-based medical registries, covering a population of ~5.6 million persons. Denmark's National Health Service provides tax-supported health care to the Danish population, including access to hospital care and partial reimbursement for prescribed medications. The unique civil personal registration (CPR) number, assigned to all Danish residents at birth or emigration [13], permitted individual-level data linkage across the following Danish registries: the Danish Breast Cancer Cooperative Group (DBCG) registry [14, 15], the Danish National Registry of Patients (DNRP) [16], the Danish National Prescription Registry (DNPR) maintained by Statistics Denmark [17], and the Danish Civil Registration System (DCRS) [18].

study population and data collection

Since 1977, the DBCG has registered nearly all invasive breast cancers diagnosed in Denmark [14, 15, 19]. Completeness of breast cancer registration by the DBCG has improved over time, from 87% in 1986 [19] to ~95% in 2010 [20]. During the first 5 years following diagnosis, women in the DBCG registry undergo physical examination every 3–6 months to detect recurrences and an annual exam in years 6 to 10 following diagnosis, also to detect recurrences. A mammography is carried out every second year [21]. Recurrences diagnosed between examinations are reported to the Registry. Our study included all cases of incident primary female breast cancer stages I, II, or III diagnosed between 1 January 1996 and 31 December 2003 in Denmark and registered in the DBCG. Information on age and menopausal status at diagnosis, date of diagnosis, type of surgery, stage, histological grade, estrogen receptor (ER) status, receipt of adjuvant chemotherapy, endocrine therapy (ET) and/or radiation therapy, and eventual date of recurrence were obtained from the DBCG registry. From the DCRS, we retrieved information on date of birth, death, and emigration.

data on prescriptions

All members of the study cohort were linked to the DBCG and the DNPR. The DNPR has automatically recorded detailed information on all prescriptions redeemed at Danish pharmacies since 1995. We retrieved prescription information on full Anatomical Therapeutic Chemical (ATC) codes, and the date and quantity dispensed for all systemic GCs, inhaled GCs, and intestinal-acting GCs. We also retrieved data on potential confounder drugs, including postmenopausal hormone replacement therapy, NSAIDs, aspirin, statins, anticoagulants, β-blockers, ACE inhibitors, COPD medications (without GC), angiotensin receptor blockers, α-blockers, acetyl salicylic acids, antidiabetic medications, and immune-modulating drugs (methotrexate and azathioprine) (see Appendix I for ATC codes).

data on comorbid diseases

Members of the study cohort were also linked to the DNPR, which has collected information on all diagnoses from nonpsychiatric inpatient hospital admissions since 1977 and from outpatient contacts since 1995. The diagnoses are recorded according to WHO's 'International Classification of Diseases' (ICD). To ascertain information about potential confounding comorbidities, we obtained data on selected ICD diagnoses, including both diseases included in the Charlson Comorbidity Index and additional diseases for which GCs are indicated, and summarized the data for each woman between 1977 and the date of her breast cancer surgery (see Appendix II for ICD-8 and ICD-10 codes).

definition of analytic variables

Age at diagnosis was categorized into decades for stratified analyses, but was used as a continuous variable in regression models. Histologic grade was defined as low, moderate, or high. Receipt of adjuvant chemotherapy and administration of radiation therapy were categorized dichotomously. ER status and ET were summarized using a design variable: ER+/ET+, ER−/ET−, ER+/ET−, and ER−/ET+.

We categorized GC exposure in several ways. First, we classified GC use as a time-varying dichotomous variable updated yearly after breast cancer surgery. In each yearly interval, women were classified as exposed to GCs if they had at least one prescription registered in the DNPR with an ATC code corresponding to a systemic, inhaled, or intestinal-acting GC. Women who were prescribed a GC were assumed to be exposed, and women who did not redeem GC prescription were classified as nonusers. GCs were further categorized according to route of administration: systemic (pills and injections), inhaled (inhalants), and intestinal-acting (foam and suppositories).

Prednisolone-equivalent cumulative doses were used to perform dose–response calculations for systemic GCs, based on the methods of Sørensen et al. [11]. The cumulative dose was calculated as the product of the number of pills (or injections) dispensed, the dose per pill (or injection), and the prednisolone-equivalent conversion factor associated with each prescription's ATC code [11]. These values were aggregated and updated in each follow-up cycle according to the following categories of use: nonuse, 1–999, 1000–4999, or ≥5000 mg. Duration of GC use was estimated by the cumulative number of years exposed to GC, ranging from 0 to 10 years.

Table 1. Baseline characteristics and relevant drug exposures among stage I–III breast cancer patients diagnosed in Denmark from 1996 to 2003, by glucocorticoid (GC) use ($N = 18\,251$)

Characteristics	Women, No. (%)		Recurrence, No. (%)		Total person-years, No. (%)	
	GC users ($N = 4602$)	Nonusers ($N = 13\,649$)	GC users ($N = 621$)	Nonusers ($N = 2787$)	GC users ($N = 23\,004$)	Nonusers ($N = 71\,341$)
Age at diagnosis (years)						
≤29	19 (0.4)	51 (0.4)	8 (1.3)	22 (0.8)	100 (0.4)	189 (0.3)
30–39	242 (5.3)	667 (4.9)	48 (7.7)	210 (7.5)	1234 (5.4)	3384 (4.7)
40–49	861 (19)	2593 (19)	102 (16)	528 (19)	4697 (20)	14 741 (21)
50–59	1498 (33)	4576 (34)	187 (30)	960 (35)	7796 (34)	25 173 (35)
60–69	1439 (31)	3969 (29)	200 (32)	780 (28)	6846 (30)	20 172 (28)
70–79	531 (12)	1681 (12)	75 (12)	278 (10)	2297 (10)	7397 (10)
≥80	12 (0.3)	112 (0.8)	1 (0.2)	9 (0.3)	34 (0.2)	285 (0.4)
Menopausal status at diagnosis						
Premenopausal	1417 (31)	4103 (30)	177 (28)	875 (31)	7827 (34)	23 157 (32)
Postmenopausal	3184 (69)	9544 (70)	444 (72)	1911 (69)	15 174 (66)	48 181 (68)
Missing	1	2	NA	NA	NA	NA
Medical history at diagnosis[a]						
Myocardial infarction	45 (1.0)	164 (1.2)	6 (1.0)	22 (0.8)	211 (0.9)	678 (1.0)
Congestive heart failure	58 (1.3)	108 (0.8)	6 (1.0)	9 (0.3)	220 (1.0)	379 (0.5)
Peripheral vascular disease	73 (1.6)	186 (1.4)	8 (1.3)	28 (1.0)	319 (1.4)	746 (0.9)
Cerebrovascular disease	124 (2.7)	333 (2.4)	21 (3.4)	58 (2.1)	520 (2.3)	1427 (1.0)
Chronic pulmonary disease	448 (9.7)	235 (1.7)	66 (11)	44 (1.6)	2122 (9.2)	1034 (1.4)
Diabetes without complications	86 (1.9)	291 (2.1)	15 (2.4)	56 (2.0)	327 (1.4)	1314 (1.8)
Diabetes w/organ damage	28 (0.6)	108 (0.8)	2 (0.3)	20 (0.7)	99 (0.4)	490 (0.7)
Renal disease	32 (0.7)	59 (0.4)	4 (0.6)	6 (0.2)	152 (0.7)	298 (0.4)
Liver disease (mod./severe)	3 (0.1)	20 (0.2)	0 (0)	0 (0)	4 (0)	91 (0.1)
RA	39 (0.9)	137 (1.0)	8 (1.3)	28 (1.0)	205 (0.1)	620 (0.9)
COPD	285 (6.2)	169 (1.2)	40 (6.4)	28 (1.0)	1330 (5.8)	743 (1.0)
Asthma	242 (5.3)	71 (0.5)	35 (5.6)	17 (0.6)	1191 (5.2)	339 (0.5)
IBD	55 (1.2)	52 (0.4)	4 (0.6)	8 (0.3)	272 (1.2)	263 (0.4)
UICC stage						
I	1889 (41)	4999 (37)	171 (28)	643 (23)	10 006 (44)	26 688 (37)
II	1957 (43)	5991 (44)	247 (40)	1098 (39)	10 105 (44)	32 668 (46)
III	732 (16)	2593 (19)	199 (32)	1033 (37)	2773 (12)	9788 (14)
Missing	2	5	NA	NA	NA	NA
Histological grade						
Low	1290 (28)	3622 (27)	114 (18)	515 (19)	6850 (30)	20 864 (29)
Moderate	1617 (35)	4854 (36)	230 (37)	1042 (37)	7943 (35)	24 756 (35)
High	850 (19)	2705 (20)	160 (26)	779 (28)	3959 (17)	12 440 (17)
Missing	845 (18)	2468 (18)	NA	NA	NA	NA
ER/adjuvant ET status						
ER−/ET−	900 (20)	2784 (20)	157 (25)	718 (26)	4384 (19)	13 260 (19)
ER+/ET−	1415 (31)	4143 (30)	160 (26)	713 (26)	7282 (32)	22 569 (32)
ER+/ET+	2097 (46)	6197 (45)	271 (44)	1222 (44)	10 392 (45)	32 798 (46)
Missing	190 (4.1)	525 (3.9)	33 (5.3)	134 (4.8)	NA	NA
Type of primary therapy						
Mastectomy	2000 (43)	5857 (43)	289 (47)	1209 (43)	9859 (43)	29 437 (41)
Mastectomy + RT	998 (22)	3341 (24)	170 (27)	922 (33)	4764 (21)	16 252 (23)
BCS + RT	1603 (35)	4451 (33)	161 (26)	656 (24)	8375 (36)	25 652 (36)
Missing	1	0	NA	NA	NA	NA
Adjuvant chemotherapy						
Yes	1369 (30)	4071 (30)	211 (34)	976 (35)	7208 (31)	21 675 (30)
No	3233 (70)	9578 (70)	410 (66)	1811 (65)	15 795 (69)	49 666 (70)
Drug exposure[a]						
Statins, pre and post[b]	946 (21)	2290 (17)	62 (10)	194 (7)	5360 (23)	15 472 (22)
Simvastatin, pre and post[b]	857 (19)	2111 (16)	42 (6.8)	156 (5.6)	4932 (21)	14 539 (20)

Continued

Table 1. *Continued*

Characteristics	Women, No. (%)		Recurrence, No. (%)		Total person-years, No. (%)	
	GC users ($N = 4602$)	Nonusers ($N = 13\,649$)	GC users ($N = 621$)	Nonusers ($N = 2787$)	GC users ($N = 23\,004$)	Nonusers ($N = 71\,341$)
HRT, pre	1236 (27)	2855 (21)	142 (33)	477 (17)	6337 (28)	15 517 (22)
NSAIDs, pre and post	3414 (53)	8635 (63)	406 (65)	1612 (58)	17 920 (78)	48 812 (68)
ASAs, pre and post	1030 (22)	2510 (18)	92 (15)	342 (12)	5410 (24)	14 559 (20)
α-Blockers, pre and post	73 (1.6)	171 (1.3)	4 (0.6)	26 (0.9)	394 (1.7)	995 (1.2)
Anticoagulants, pre and post	1103 (24)	2788 (20)	98 (16)	390 (14)	5734 (25)	15 980 (22)
Antidiabetics, pre and post	86 (1.9)	297 (2.3)	13 (2.1)	40 (1.4)	412 (1.8)	1590 (2.2)
ACE inhibitors, pre and post	845 (18)	2203 (16)	84 (14)	245 (8.8)	4552 (20)	13 565 (19)
Angiotensin receptor blocker, pre and post	621 (14)	1357 (9.9)	58 (9.3)	160 (5.7)	3407 (15)	8200 (12)
β-Blockers, pre and post	995 (22)	2613 (19)	85 (14)	380 (14)	5262 (23)	15119 (21)
COPD drugs, pre and post	1685 (37)	1107 (8.1)	244 (39)	155 (5.6)	8352 (36)	6035 (8.5)
Immune drugs[c]	48 (1)	48 (0.04)	3 (0.4)	6 (0.2)	298 (1.3)	258 (0.4)

[a]Proportions of patients, recurrences, and person-years calculated with denominators equal to sums within GC exposure groups because categories are not mutually exclusive.
[b]One year before diagnosis and up to 10 years after diagnosis.
[c]Methotrexate and azathioprine.
RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; ER, estrogen receptor status; ET, adjuvant endocrine therapy; BCS, breast-conserving surgery; RT, radiation therapy; ACE, angiotensin-converting enzyme; HRT, combination hormone replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; ASAs, acetyl salicylic acids (high and low dose).

outcome data

Breast cancer recurrence was defined according to the DBCG convention as any local, regional, or distant recurrence, or cancer of the contralateral breast [15]. Follow-up of each woman began on the date of primary breast cancer surgery and continued until breast cancer recurrence, death, emigration, accrual of 10 years of follow-up, the last date of follow-up registered in the DBCG, or 31 December 2008 (end of the study period), whichever came first. Patients who died without a breast cancer recurrence or who emigrated from Denmark were censored on their date of death or emigration.

statistical analysis

Frequencies and proportions of patients, recurrences, person-time according to patient, tumor, and treatment characteristics, and exposure to GCs and other medications are presented in Tables 1 and 2. We computed 10-year recurrence hazard ratios (HRs) and 95% confidence intervals (95% CI) for the three GC groups (systemic, inhaled, and intestinal-acting) in unadjusted and multivariable Cox regression models, with medication exposures characterized as time-varying covariates lagged by 1 year. Exposure of GC and recurrence was handled as a dichotomous variable in each exposure year. We lagged GC exposure by 1 year to allow the effect of the drug to accrue. Accordingly, GC exposure in the year before surgery was modeled for its association with recurrence in the first year after surgery; GC exposure in the first year after surgery was modeled for its association with recurrence in the second year after surgery. This procedure was followed for the whole follow-up period. The lagged exposure time allowed for a reasonable induction period for an effect of GC and co-prescriptions on recurrence, and guarded against the possibility that imminent recurrence affected prescription patterns. Since women who receive chemotherapy are at higher risk of recurrence and receive substantial unmeasured doses of GC as inpatients, we stratified analyses by receipt of adjuvant chemotherapy to evaluate modification of the association by this variable. We also stratified our analyses by ER status to investigate the potential relation between ER-negative breast cancer and prognostic profile [9].

We used unadjusted and multivariable Cox regression models to estimate the 10-year HR of recurrence and 95% CI for equivalent cumulative dose categories, using nonusers as the reference group. We also used Cox models to estimate the association between duration of GC use, as a time-varying exposure lagged by 1 year and measuring the cumulative number of years exposed to GC, and the rate of breast cancer recurrence. All multivariable Cox regressions were restricted to women with no missing information about any potential confounders. All statistical analyses were carried out with SAS 9.3.

ethics

The study was approved by the Board of the DBCG Registry and the Danish Data Protection Agency [journal number: 2006-41-6387].

results

The study included 18 773 women with a first incident breast cancer diagnosis. After excluding 486 women with only 0 or 1 day of follow-up and 36 women with ER-negative tumors who received ET (contrary to indication), 18 251 women remained in the cohort. The median age was 57 years (range: 21–95 years). There were 3408 recurrences of breast cancer during 94 345 person-years of follow-up (median = 6.9 years), equaling an incidence rate of 36 recurrences per 1000 person-years. Table 1 presents characteristics of the cohort and the distribution of subjects according to GC exposure and key demographic, tumor, and treatment variables. During follow-up, 4602 women redeemed at least one GC prescription. Users of any GC were more likely to be older, to be postmenopausal at breast cancer diagnosis, and to have more comorbid conditions compared with nonusers (Table 1).

The unadjusted Cox regression model indicated no notable association between use of systemic, inhaled, or intestinal-acting

Table 2. HR and 95% CI for GC exposures (according to route of administration), stratified by presence/absence of chemotherapy and positive/negative estrogen receptor (ER) status, and for categories of prednisolone-equivalent doses (only systemic GC) and cumulative increase in GC exposure over 10 years

	Unadjusted[a] HR (95% CI)		Adjusted[ab] HR (95% CI)	
Systemic GC	1.1 (0.9–1.3)		1.1 (0.9–1.3)	
Inhaled GC	0.9 (0.7–1.0)		0.9 (0.7–1.0)	
Intestinal GC	1.0 (0.9–1.2)		1.0 (0.8–1.2)	
	Chemotherapy	No chemotherapy	Chemotherapy	No chemotherapy
Systemic GC	1.1 (0.9–1.4)	1.0 (0.9–1.2)	1.1 (0.9–1.4)	1.0 (0.8–1.2)
Inhaled GC	0.9 (0.6–1.2)	0.9 (0.7–1.1)	0.9 (0.6–1.3)	0.8 (0.7–1.0)
Intestinal GC	0.9 (0.7–1.2)	1.1 (0.9–1.3)	0.9 (0.6–1.2)	1.0 (0.8–1.3)
	ER positive	ER negative	ER positive	ER negative
Systemic GC	1.1 (0.9–1.3)	1.1 (0.8–1.4)	1.1 (0.9–1.3)	1.0 (0.8–1.4)
Inhaled GC	0.9 (0.7–1.1)	0.8 (0.6–1.2)	0.8 (0.7–1.0)	1.0 (0.7–1.4)
Intestinal GC	1.0 (0.8–1.2)	1.0 (0.7–1.4)	1.0 (0.8–1.2)	1.0 (0.7–1.4)
Prednisolone-equivalent dose (mg)[c]				
1–999	0.9 (0.8–1.0)		0.9 (0.8–1.1)	
1000–4999	0.9 (0.8–1.1)		0.8 (0.7–1.0)	
≥5000	1.0 (0.7–1.5)		0.9 (0.6–1.4)	
Cumulative increase in duration of GC exposure over a 10-year period[c]	1.0 (0.9–1.0)		1.1 (0.9–1.3)	

Reference group is nonusers. Stage I–III breast cancer patients diagnosed in Denmark, 1996–2003 ($N = 18\,251$).

[a]Models incorporating yearly updated drug exposure, lagged by 1 year.

[a]Models adjusted for age at diagnosis (continuous), menopausal status at diagnosis, UICC stage (design variables), histological grade (design variables), ER status and receipt of adjuvant endocrine therapy (conjugated, design variables), receipt of adjuvant chemotherapy, type of primary surgery received, Charlson Comorbidity Index score (design variables), pre-diagnosis combination HRT, and co-prescriptions (time-varying, updated yearly, and lagged by 1 year) of any β-blockers, ACE inhibitors, ARBs, ASAs, and simvastatin.

[b]Applies only to systemic GCs.

[c]The cumulative increase in the duration of GC exposure over a 10-year period was updated yearly. GC exposure was lagged by 1 year.

GCs and risk of 10-year breast cancer recurrence, compared with nonuse (unadjusted $HR_{systemic\ GC} = 1.1$, 95% CI 0.9–1.3; unadjusted $HR_{inhaled\ GC} = 0.9$, 95% CI 0.7–1.0; unadjusted $HR_{intestinal\ GC} = 1.0$, 95% CI 0.9–1.2) (Table 2). In adjusted models, the association remained near null for GC use and 10-year risk of breast cancer recurrence (adjusted $HR_{systemic\ GC} = 1.1$, 95% CI 0.9–1.2; adjusted $HR_{inhaled\ GC} = 0.8$, 95% CI 0.7–1.0; and adjusted $HR_{intestinal\ GC} = 1.0$, 95% CI 0.8–1.2) (Table 2).

When we repeated analyses within strata of adjuvant chemotherapy use, we observed the same pattern of associations as in the unstratified models (Table 2). We also repeated our analyses stratifying by ER status, with little change in the effect estimates (Table 2). Furthermore, associations remained near null across categories of cumulative prednisolone-equivalent dose of GC and for the duration of GC exposure (Table 2). We tested the proportionality of hazards by evaluating the significance of the interaction between GC use and the logarithm of person-time, and saw no evidence of a departure from proportionality.

discussion

In this large cohort of breast cancer patients, we observed no evidence of an association between prescriptions for systemic, inhaled, or intestinal-acting GC and risk of breast cancer recurrence. There was also no evidence of a dose–response relationship. These results remained unchanged after stratification by chemotherapy. To the best of our knowledge, this is the first study to evaluate the association between GC use and breast cancer recurrence.

The validity of our estimates depends on several factors. The large size of the study population, in a country with free and equal access to high-quality health care, reduced the potential for selection bias. CPR numbers facilitated individual-level data linkage across registries, ensuring accurate and complete follow-up of the entire cohort. Use of registry-based prescription records eliminated the potential for differential exposure misclassification due to recall bias. The validity of the DBCG registry data is exceptionally high—the positive predictive value for classification of breast cancer recurrence by the DBCG registry was found to be 99.4%, using medical records as a gold standard [22]. Together with the prospective mandatory registration of prescription data, our study is unlikely to be prone to information bias. The study also benefitted from comprehensive information on potential confounders, including comorbid diseases and prescribed drugs. Except for aspirin, all the potentially confounding drugs are only available by prescription in Denmark. Residual confounding due to over-the-counter aspirin use is a potential concern. However, patients are reimbursed a proportion of the cost of prescribed medicine, so long-term, continuous use of aspirin is likely to be via prescription.

Our use of lagged exposures reduced the likelihood of reverse causation [23, 24]. The 1-year lag time allowed for a reasonable interval for the drug to affect the process of recurrence, but was

not too long to weaken any potential association between the exposure drug and the outcome measure.

Locally administered GCs acting on the ear, nose, eye, or skin were not included in the exposure, as they are not thought to act systemically [25]. Low-dose locally administered GCs are available in limited supply over the counter in Denmark, while systemically acting GCs are only available by prescription. Any use of over-the-counter GCs in our patient cohort was likely to have a minimal effect on our recurrence estimates. We also lacked information on in-hospital GC use, which may have biased our estimates. Our previous medical record review of 200 breast cancer patients showed that all women who received chemotherapy were treated with systemic GC to alleviate treatment-related cytotoxic reactions [26]. When we stratified our estimates by receipt of chemotherapy to address this potential exposure misclassification, we found no change in the effect estimate.

Another concern is our reliance on redeemed prescriptions as a measure of drug use. We thus lacked information on compliance with treatment. However, because patients have to pay a portion of the cost of their prescription medication, it is likely that redeemed prescriptions reflect actual use [27]. GC dosing varies depending on the administrative route and indication for treatment. A set dose can be taken on a regular basis, or the dose may fluctuate according to variation in the severity of symptoms. Among women who took inhaled or intestinal-acting drugs, the exact bioavailability is thus not known. We therefore restricted our dose–response analysis to systemically administered GCs.

We lacked information on HER-2 status and therapies with anti-HER-2 antibodies such as trastuzumab, since this treatment was not introduced into routine care in Denmark until 2006, 3 years after the last woman in our cohort had been diagnosed. The potential interaction between GCs and trastuzumab would be interesting to evaluate in future studies.

Our study is the first to examine directly the use of GCs and breast cancer recurrence, rather than diseases potentially treated with GCs [28]. GCs are widely used co-medications in breast cancer treatment so our findings are reassuring to clinicians and women with breast cancer when assessing the risks of these drugs.

In summary, we found no evidence of any impact of systemic, inhaled, or intestinal GCs on breast cancer recurrence in a nationwide prospective cohort of Danish breast cancer survivors.

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disclosure

The authors have declared no conflicts of interest.

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Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials

A. Le Cesne[1*], M. Ouali[2], M. G. Leahy[3], A. Santoro[4], H. J. Hoekstra[5], P. Hohenberger[6], F. Van Coevorden[7], P. Rutkowski[8], R. Van Hoesel[9], J. Verweij[10], S. Bonvalot[1], W. P. Steward[3], A. Gronchi[4], P. C. W. Hogendoorn[11], S. Litiere[2], S. Marreaud[2], J. Y. Blay[12] & W. T. A. Van Der Graaf[9]

[1]Department of Medical Oncology and Surgery, Institut Gustave Roussy, Villejuif, France; [2]EORTC Headquarters, Brussels, Belgium; [3]Department of Medical Oncology, Christie Hospital, Manchester, UK; [4]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [5]Department of Surgical Oncology, University Medical Centre Groningen, Groningen, The Netherlands; [6]Department of Surgical Oncology, Charité Universitaetsmedizin BerlinCampus, Berlin, Germany; [7]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]Department of Soft Tissue and Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [9]Department of Medical Oncology, Radboud University Medical Center, Nijmegen; [10]Department of Oncology, Erasmus University Medical Center–Cancer Institute, Rotterdam; [11]Department of Pathology, University Medical Center, Leiden, The Netherlands; [12]Department of Radio-Oncology, University Claude Bernard Lyon I and Centre Léon Bérard, Lyon, France

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Background: The EORTC-STBSG coordinated two large trials of adjuvant chemotherapy (CT) in localized high-grade soft tissue sarcoma (STS). Both studies failed to demonstrate any benefit on overall survival (OS). The aim of the analysis of these two trials was to identify subgroups of patients who may benefit from adjuvant CT.

Patients and methods: Individual patient data from two EORTC trials comparing doxorubicin-based CT to observation only in completely resected STS (large resection, R0/marginal resection, R1) were pooled. Prognostic factors were assessed by univariate and multivariate analyses. Patient outcomes were subsequently compared between the two groups of patients according to each analyzed factor.

Results: A total of 819 patients had been enrolled with a median follow-up of 8.2 years. Tumor size, high histological grade and R1 resection emerged as independent adverse prognostic factors for relapse-free survival (RFS) and OS. Adjuvant CT is an independent favorable prognostic factor for RFS but not for OS. A significant interaction between benefit of adjuvant CT and age, gender and R1 resection was observed for RFS and OS. Males and patients >40 years had a significantly better RFS in the treatment arms, while adjuvant CT was associated with a marginally worse OS in females and patients <40years. Patients with R1 resection had a significantly better RFS and OS favoring adjuvant CT arms.

Conclusion: Adjuvant CT is not associated with a better OS in young patients or in any pathology subgroup. Poor quality of initial surgery is the most important prognostic and predictive factor for utility of adjuvant CT in STS. Based on these data, we conclude that adjuvant CT for STS remains an investigational procedure and is not a routine standard of care.

Key words: soft tissue sarcoma, adjuvant chemotherapy, predictive factors, treatment outcome

introduction

Surgery remains the cornerstone of treatment and the only curative locoregional approach for localized resectable soft tissue sarcoma (STS). The worldwide most commonly accepted first-line treatment is a wide local excision followed by postoperative radiation therapy (RT), especially in case of narrow margins or a microscopically non-radical resection [1]. An optimal initial resection is one of the most reproducible and reliable prognostic factors of absence of relapse in resectable STS [2–4]. Nevertheless, despite improved local control rates over time, around half of the

*Correspondence to: Dr Axel Le Cesne, Department of Cancer Medicine, Gustave Roussy Cancer Istitute, 114 rue Edouard Vaillant, Villejuif Cedex 94805, France.
Tel: +33-1-42-11-50-40; Fax: +33-1-42-11-52-31; E-mail: axel.lecesne@gustaveroussy.fr