Malignancies in Giant Cell Arteritis: A Population-based Cohort Study

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ABSTRACT. ***Objective.*** To investigate the risk of cancer in patients with biopsy-proven giant cell arteritis (GCA) from a defined population in southern Sweden.

Methods. The study cohort consisted of 830 patients (mean age at GCA diagnosis was 75.3 yrs, 74% women) diagnosed with biopsy-proven GCA between 1997 and 2010. Temporal artery biopsy results were retrieved from a regional database and reviewed to ascertain GCA diagnosis. The cohort was linked to the Swedish Cancer Registry. The patients were followed from GCA diagnosis until death or December 31, 2013. Incident malignancies registered after GCA diagnosis were studied. Based on data on the first malignancy in each organ system, age- and sex-standardized incidence ratios (SIR) with 95% CI were calculated compared to the background population.

Results. One hundred seven patients (13%) were diagnosed with a total of 118 new malignancies after the onset of GCA. The overall risk for cancer after the GCA diagnosis was not increased (SIR 0.98, 95% CI 0.81–1.17). However, there was an increased risk for myeloid leukemia (2.31, 95% CI 1.06–4.39) and a reduced risk for breast cancer (0.33, 95% CI 0.12–0.72) and upper gastrointestinal tract cancer (0.16, 95% 0.004–0.91). Rates of other site-specific cancers were not different from expected.

Conclusion. In this Swedish population-based cohort of GCA, the overall risk for cancer was not increased compared to the background population. However, there was an increased risk for leukemia and a decreased risk for breast and upper gastrointestinal tract cancer. (First Release October 15 2019; J Rheumatol 2020;47:400–6; doi:10.3899/jrheum.190236)

Key Indexing Terms:
GIANT CELL ARTERITIS VASCULITIS NEOPLASIA
HISTOPATHOLOGY EPIDEMIOLOGY

Giant cell arteritis (GCA) is a large-vessel vasculitis that usually affects persons 50 years of age and older and is more common among women. GCA is the most common primary systemic vasculitis especially in Northern Europe and North America, with annual incidence estimates between 14 and 22 per 100,000 persons in the age group 50 years and older[1,2,3]. The mean age at the time of GCA diagnosis is around 75 years. Previous studies have demonstrated that the longterm survival among patients with GCA overall is comparable to that of the general population[3,4,5]. However, excess mortality has been found among those diagnosed before the age of 70 years[3,4]. Patients with GCA have higher rates of some comorbidities, including cardiovascular events, diabetes, severe infections, and visual complications compared to the background population[6,7,8,9]. Increased rates of malignancies have been described among patients with other systemic rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and antineutrophil cytoplasmic antibody–associated vasculitis (AAV)[10,11,12,13].

Systemic vasculitides other than GCA have also been associated with concurrent or subsequent malignancies, and some types of vasculitides may mimic a malignant disease. There are some types of vasculitides with relatively strong association to malignancies (e.g., elderly-onset Henoch-Schönlein purpura and AAV)[14,15,16]. On the other hand, there are malignancies related to specific vasculitic syndromes such as hairy cell leukemia with polyarteritis nodosa and leucocytoclastic vasculitis[17].

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Conflicting results have been reported on the relationship between GCA and malignancies. A study of patients with biopsy-proven GCA from Australia and a population-based cohort study from Olmsted County, Minnesota, USA, did not demonstrate an increased risk for cancer in patients with GCA[18,19]. On the other hand, a previous metaanalysis, which included the 2 aforementioned studies from the USA and Australia, demonstrated a slight but statistically significant increased risk for malignancy in patients with GCA and/or polymyalgia rheumatica (PMR), especially during the first 6–12 months after the onset of GCA/PMR[20].

In this population-based study from southern Sweden, the main objective was to investigate the overall cancer risk in patients with biopsy-proven GCA. As secondary objectives, we described the differences in the incidence of site-specific malignancies and the temporal relationship between GCA and cancer.

MATERIALS AND METHODS

Study area and population. The study area is the Skåne region, the southernmost region in Sweden, with a total population of 1,274,069 on December 2013 (13.2% of the total Swedish population in 2.7% of the total area of Sweden)[21]. More than 95% of the population is white.

Case ascertainment and identification: the GCA cohort. The case identification and retrieval of patients with biopsy-proven GCA in this study was described in detail previously[3]. In short, all patients who underwent temporal artery biopsy (TAB) during the period 1997–2010 were identified from the database at the Department of Pathology in Skåne, which operates at the major hospitals in the area: Skåne University Hospital in Lund and Malmö, Helsingborg Hospital, and the Central Hospital in Kristianstad. A total of 4216 unique persons who underwent a TAB during the study period were identified. After reviewing all the histopathology reports, 840 patients (626 women) were found to have positive TAB diagnostic for GCA.

Temporal relationship of occurrence of cancer and GCA. To assess any temporal relationship between the time of GCA diagnosis and cancer occurrence, 4 controls per case were randomly selected from the background population. The matching criteria were age, sex, and area of residence. The index date for cases and their controls was the date of GCA diagnosis. The time of cancer diagnosis for patients with GCA and their controls was studied in relation to the corresponding index date. Four time periods were studied: up to 2 years before index date; within 2 years before index date; within 2 years after index date, and 2 years or more after index date.

Swedish Cancer Registry (SCR). The SCR was founded in 1958 and covers the whole population of Sweden. It is obligatory for every healthcare provider to report newly detected cancer cases to the registry. A report has to be sent for every cancer case diagnosed at clinical, morphological, and other laboratory examinations, as well as cases diagnosed at autopsy. Information available in the SCR includes sex, age, place of residence, date of diagnosis, reporting clinical and pathology unit, and the identification number for the tissue specimen[22]. Outcome data in the SCR are also available and include date of death or migration, and cause of death. In addition, clinical data (i.e., the site and the histological type of tumor classified according to the International Classification of Diseases, 7th ed.) are also available.

Data linking. The linking of the 2 cohorts, the GCA cohort and the control cohort, to the SCR was performed using the unique personal identification number (PIN). For people born in Sweden, the number is specified at birth. Immigrants are given a number if they stay longer than 3 months. Medical organizations use these numbers to store information about the individual's health status. Using the PIN, the patients in the GCA cohort and the controls were linked to the SCR to identify all cases diagnosed with cancer during their lifetime.

Statistical analysis. Using the statistical database for cancer from the Swedish National Board of Health and Welfare, we calculated the age-specific, sex-specific, and calendar year–specific incidence rate of cancer for every cancer category and for cancer at all sites in males and females in Skåne who were older than 50 years for the period 1997–2013. Each age stratum covered a 5-year period and the data were divided for every calendar year. The study start was defined as the date of positive TAB, and study endpoints were the first cancer diagnosis, death, or the end of the study on December 31, 2013. Based on these dates, we calculated the time (person-years) during which the patients in the cohort were at risk of developing cancer. As a measure of relative risk, we used the standardized incidence ratio (SIR), which is the ratio of observed cancer cases among patients with GCA to that of the expected number of cases among background population. The expected numbers of cancer cases were calculated by multiplying the 5-year age-, sex-, and 1-year calendar period–specific number of person-years by sex-, period-, and age-specific incidence rates of cancer in Skåne for every cancer category and for cancer in general. The Fisher's exact test was used to calculate the 95% CI. In patients who have developed multiple malignancies after the onset of GCA, we took into account only the first malignancy in each organ system. The time of cancer occurrence in relation to the date of GCA diagnosis (and the corresponding index date for controls) was studied and compared by cross tabulation using the Pearson chi-square test to compare the 4 time periods.

Ethics. The study was done in accordance with the principles of the Declaration of Helsinki. The Regional Ethical Review Board in Lund (Sweden) approved the study (Dnr 2010-517). No informed consent was obtained, because it was not required by the Ethical Review Board.

RESULTS

Patients. A total of 840 patients had a positive TAB during the period 1997–2010 in the Skåne region. We were not able to localize records of 10 patients; hence a total of 830 patients (616 women, 74%) were included in the analysis. Table 1 presents the demographic characteristics of the patients.

Observed malignancies. Among the patients in the GCA cohort, 238 (164 female, 69%) developed altogether 321 malignancies during the observation time (58 patients had > 1 cancer diagnosis). The mean age at cancer diagnosis was 67.1 years (SD 14.9). One hundred thirty-one patients were

Table 1. Demographic characteristics of 830 patients with biopsy-proven giant cell arteritis (GCA) by presence of malignant disease, ever.

Variables	All	No Malignancy	Malignancy (Any Time)
No. patients	830	592	238
Female sex, n (%)	616 (74.2)	452 (76.4)	164 (68.9)
Mean age at diagnosis of GCA, yrs (SD)	75.3 (8.1)	75.1 (8.1)	75.8 (8.1)
Mean age at first diagnosis of cancer ever, yrs (SD)	NA	NA	67.1 (14.9)
Mean age at first diagnosis of cancer after GCA, yrs (SD)	NA	NA	79.1 (7.8)
Mean age at last followup, yrs (SD)	82.6 (7.8)	82.5 (7.8)	82.8 (8)
Death, n	399	262	137

NA: not applicable.

diagnosed with malignancy prior to GCA diagnosis, 25 patients with malignancy both prior and subsequent to GCA diagnosis, and 82 patients with malignancy subsequent to GCA diagnosis only (Supplementary Tables 1 and 2, available with the online version of this article). Accordingly, 107 patients (13%) developed a total of 118 malignancies after the onset of GCA (Figure 1). The most common malignancy diagnosed after the onset of GCA was skin cancer (excluding basic cell carcinoma; 34%), followed by cancer in the lower gastrointestinal (GI) tract (15%), prostate cancer (11%), and leukemia (8%). Number and percentage of each cancer type after diagnosis of biopsy-proven GCA are given in Table 2. Nineteen patients (10 females) were diagnosed with more than 1 cancer, 14 (7 females) with 2, and 5 (3 females) with 3 cancer diagnoses or more. Only the first cancer per organ system was included in our analysis.

SIR. The expected number of cancers among the patients with GCA, based on data from the background Swedish population, was 121. Accordingly, the overall risk for cancer was not increased among patients with biopsy-proven GCA (SIR 0.98, 95% CI 0.81-1.17). However, there was an increased risk for leukemia with SIR of 2.31 (95% CI

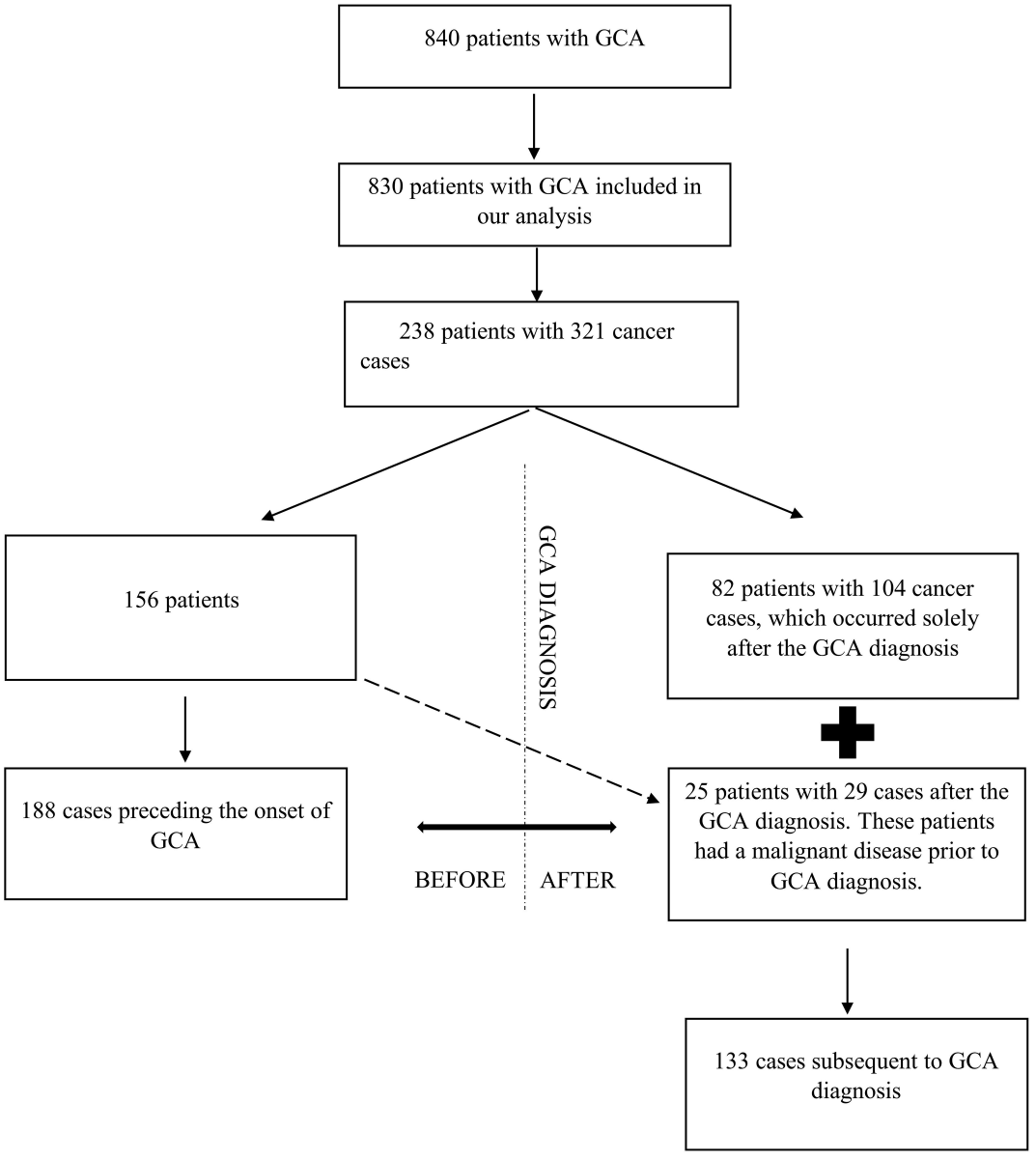

Figure 1. Flowchart illustrating the patients from a population-based cohort in southern Sweden who developed cancer before and after giant cell arteritis (GCA) diagnosis.

Table 2. Malignancies subsequent to giant cell arteritis diagnosis, in descending order.

Cancer Categories	Frequency	%
Skin cancer (without BC)	45	33.8
Lower gastrointestinal tract	20	15
Prostate	15	11.3
Leukemia	10	7.5
Female reproductive system	9	6.8
Respiratory system	8	6
Breast cancer	6	4.5
Urinary tract	6	4.5
Unspecified type	5	3.8
Lymphoma	3	2.3
Kidneys and renal pelvis	2	1.5
Multiple myeloma	2	1.5
Upper gastrointestinal tract	1	0.8
Myelofibrosis	1	0.8
Total	133	100

BC: basal cell.

1.06–4.39). The risk of breast cancer was lower among patients with GCA compared to background population with SIR of 0.33 (95% CI 0.12–0.72). Similarly, there was a lower risk for cancer of the upper GI tract, SIR of 0.16 (95% CI 0.00–0.91). Table 3 shows the SIR for observed cancer in 830 patients with biopsy-proven GCA. There was not a single case of cancer of the liver, gallbladder, pancreas, or peritoneum, compared to 4 expected cases.

Site-specific malignancies. Nine cases were diagnosed with upper GI tract cancer, but only 1 case (11%) out of those 9 was diagnosed after the onset of GCA. By contrast, 9 of the 12 (75%) myeloid leukemia cases developed subsequently to the onset of GCA. All the 9 patients diagnosed with leukemia had a myeloid leukemia, 5 of them an acute myeloid leukemia (AML), and 4 of them a myeloid leukemia that was classified as unspecified (World Health Organization classification: 4 patients diagnosed with AML with recurrent genetic abnormalities, 2 with AML with myelodysplasia-related changes, and 3 with AML not otherwise categorized). Three patients developed their leukemia during the first 2 years after the GCA diagnosis (2 during the first year). All the patients who developed a myeloid leukemia died within 2 years after the leukemia was diagnosed. Of the 34 cases of breast cancer, only 6 (18%) developed after the GCA diagnosis (Table 2 and Supplementary Table 3, available with the online version of this article). Supplementary Figure 1 illustrates the frequency and differences in the 10 most common types of cancer before and after the GCA diagnosis.

Temporal concurrence of GCA and cancer. Of all malignancies diagnosed in controls, 9.2% occurred within 2 years before the index date. The corresponding figure for cases was 5.5%. For the time period within 2 years after index date, 7.5% of malignancies in controls were diagnosed compared to 13.1% for patients with GCA (Supplementary Figure 2, available with the online version of this article). The distribution of malignancies across time periods was significantly different in GCA cases and controls (p = 0.009).

Table 3. Observed and expected cases of cancer after the onset of giant cell arteritis (GCA) in a cohort of 830 patients with GCA in southern Sweden diagnosed between 1997 and 2010.

Category	Observed	Expected	SIR	95% CI
Upper GI tract	1	6.14	0.16	0.00–0.91
Lower GI tract	18	18.14	0.99	0.59–1.57
Liver, gallbladder, pancreas, peritoneum	0	4.01	NA	NA
Respiratory	8	10.43	0.76	0.33–1.51
Breast	6	18.13	0.33	0.12–0.72
Female reproductive system	8	7.31	1.09	0.47–2.16
Prostate	15	11.52	1.30	0.73–2.15
Male reproductive system	0	0.17	NA	NA
Kidneys	2	2.07	0.96	0.12–3.49
Urinary tract without kidneys	6	7.08	0.84	0.31–1.85
Skin	34	24.93	1.36	0.94–1.91
Eyes	0	0.18	NA	NA
CNS	1	1.3	0.76	0.02–4.29
Endocrine system	0	1.7	NA	NA
Sarcomas	0	0.75	NA	NA
Unspecified	4	4.95	0.80	0.22–2.07
Lymphoma	3	4.32	0.69	0.14–2.03
Multiple myeloma	2	1.7	1.17	0.14–4.25
Leukemia	9	3.89	2.31	1.06–4.39
Myelofibrosis	1	0.47	2.12	0.05–11.85
Total	118	120.8	0.98	0.81–1.17

SIR: standardized incidence ratio; GI: gastrointestinal; CNS: central nervous system; NA: not applicable.

DISCUSSION

In this large population-based cohort of patients with biopsy-proven GCA, there was no increased overall risk of malignancies after the onset of GCA. However, the risk of leukemia was significantly higher among patients with GCA compared to the background Swedish population. On the other hand, our study showed lower risk of upper GI malignancies and breast cancer compared to the risk among background population.

Our findings regarding the overall risk for cancer were comparable to what have been shown in previous studies from Australia, Minnesota, Norway, and Spain[18,19,23,24]. Those studies also included only patients with biopsy-proven GCA, although they included fewer GCA cases, and the study from Norway[23] included both patients with temporal arteritis and patients with PMR.

The association between malignancies and systemic vasculitis has been studied previously. For AAV, such associations were variable. While Rahmatulla, *et al* showed an increase in non-melanoma skin cancer but no other cancer[25], other studies showed much higher cancer risk among patients with AAV[16,26]. Differences in the pathophysiology, the magnitude of inflammation, the multiple organs that are affected by AAV, and the different treatment options (e.g., cyclophosphamide for AAV) may explain the differences in risk for cancer in patients with GCA in comparison with AAV.

A novel finding in our study is the lower risk for breast cancer as well as upper GI tract cancer among patients with GCA. Breast cancer is the second most common cancer in the world and by far the most frequent cancer among women[27]. It is difficult to conclude whether the decreased risk for breast cancer depends on the reduced prevalence of traditional risk factors for breast cancer among patients with GCA or whether other mechanisms, such as circulating cytokines, chemokines, the immunosuppressive treatment, and specific immunological cellular response might contribute to the reduced risk. In several studies, a lower body mass index (BMI) has been associated with a higher risk of developing GCA[28,29,30,31]. A low BMI may reflect a reduced estrogen exposure during the postmenopausal period[32]. Further, early menopause and longterm breastfeeding have been reported to be independent risk factors for developing GCA, suggesting that longer periods with reduced exposure to female sex hormones correlate with a higher risk for GCA[31]. Additionally, interleukin 6, which is important in the pathogenesis of GCA, has been found to inhibit lipid biosynthesis by adipocytes, increasing the rate of lipid catabolism[33,34]. Thus, traditional risk factors for breast cancer such as obesity[35] and late menopause[36] seem to be less prominent in patients with GCA.

To our knowledge, there have been no previous reports on associations between GCA and upper GI tract cancer. In our cohort, only 1 patient developed upper GI tract cancer (oral cavity — lip) while the expected number in the background population was 6 cases. Obesity and excess of adipose tissue have been described as risk factors for some GI cancers such as esophageal and gastric cancer[37,38,39]. A possible complex interplay between adipokines (leptin and adiponectin) with inflammatory cytokines and cancer cells has been implicated as one of the many mechanisms that contribute to the pathogenesis of GI tract cancer[40]. Further, hyperglycemia and diabetes have been described as risk factors for GI cancer[37,38,40]. Given the reported negative association between BMI and GCA[28,30] and the reduced prevalence of diabetes at GCA onset[41], limited exposure to metabolic risk factors may explain the reduced rate of GI tract cancer in patients with GCA.

In accordance with the observations in our study, autoimmune diseases have been associated with an increased risk for hematological malignancies[11], including myelodysplastic syndromes[42] and myeloid malignancies[43]. Anderson, *et al* showed in a population-based case-control study of hematopoietic malignancies that the OR for developing a myeloid malignancy was 1.61 (1.14–2.27) for patients with GCA and 1.73 (1.43–2.09) for those with PMR[44]. Further, another study performed in the Swedish population showed an increased risk for leukemia and particularly for acute myeloid leukemia in patients with PMR and GCA[45].

GCA and other inflammatory disorders could be linked to leukemia development through an effect of inflammation on hematopoietic stem cells (HSC). HSC are a type of bone marrow cells that are responsible for the constant renewal of blood cells. They are usually in a latent-inactive state and are activated upon certain stimuli, e.g., cytokines[46]. In GCA, there is a high inflammatory activity with a high number of circulating cytokines. These cytokines could activate the HSC and cause functional changes. The continuous activation of HSC, owing to the inflammatory process, could lead to HSC exhaustion, causing bone marrow failure, which in turn leads to preleukemic states and leukemia through the accumulation of genetic and epigenetic changes[46].

In our study, we observed a temporal relationship between the date of GCA diagnosis and the diagnosis of cancer. When the cases were compared to the randomly selected controls from the background population, a higher proportion of patients with GCA were diagnosed with malignancies within 2 years after their date of diagnosis. However, this was a secondary objective and our study was not designed to address this question. A possible explanation for this co-occurrence would be the effect of the inflammatory activity as a risk factor for development or progression of cancer[47]. Alternatively, this pattern may be due to surveillance of patients who were carefully monitored after initiation of therapy for GCA. We do not believe that the treatment given to patients with GCA contributes to an increased risk for cancer because cytotoxic drugs, which are known to increase the risk for developing cancer[16,26,48], are not

commonly recommended for treating GCA. The present data do not support routine screening for cancer after the diagnosis of GCA. More studies and observations on the temporal relation between GCA and cancer are needed.

Strengths of our study include the population-based setting and the large sample size. To our knowledge, this is the largest study that has investigated the relationship between cancer and GCA. In addition, the diagnosis of GCA was confirmed by biopsy, limiting the risk of incorrect classification. The use of a validated cancer register also adds to the strengths of this study[49].

Limitations include the lack of data on traditional cancer risk factors such as smoking and exposure to other carcinogens. Further, the small number of observed cancer cases in some categories limited the precision of the estimates of site-specific cancer rates and contributed to the wide CI. Given the large number of analyses of site-specific cancers, we cannot exclude that the associations were due to chance. Finally, the study included only patients with biopsy-proven GCA, and the results cannot be generalized to those with biopsy-negative GCA and those with isolated large-vessel GCA.

Our study demonstrated a similar risk for malignancy in patients with GCA compared to the background population. However, there was an increased risk for leukemia and a decreased risk for breast cancer and upper GI tract cancer. Potential explanations include effects of chronic inflammation and exposures that predispose to GCA and should be further studied.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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