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Original Investigation

Association of Rosacea With Risk for Glioma in a Danish Nationwide Cohort Study

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IMPORTANCE Rosacea, a common facial skin disorder, has a poorly understood pathogenesis in which increased matrix metalloproteinase activity might play an important role. Glioma accounts for 80% of all primary malignant tumors in the central nervous system, and these tumors also show upregulation of certain matrix metalloproteinases.

OBJECTIVE To investigate the association between rosacea and the risk for glioma.

DESIGN, SETTING, AND PARTICIPANTS Nationwide cohort study of the Danish population from individual-level linkage of administrative registers. All Danish citizens 18 years or older from January 1, 1997, to December 31, 2011, were eligible for inclusion. A total of 5 484 910 individuals were eligible for analysis; of these, 68 372 had rosacea and 5 416 538 constituted the reference population. Data were analyzed from July 14 to August 10, 2015.

MAIN OUTCOMES AND MEASURES The outcome of interest was a diagnosis of glioma. Incidence rates per 10 000 person-years were calculated, and incidence rate ratios adjusted for age, sex, and socioeconomic status were estimated by Poisson regression distribution models.

RESULTS Of the 5 484 910 individuals in the study population, 21 118 individuals developed glioma during the study period, including 20 934 of the 5 416 538 individuals in the reference population (50.4% women; mean [SD] age, 40.8 [19.7] years) and 184 of the 68 372 patients with rosacea (67.3% women; mean [SD] age, 42.2 [16.5] years). The incidence rate (95% CI) of glioma was 3.34 (3.30-3.39) in the reference population and 4.99 (4.32-5.76) in patients with rosacea. The adjusted incidence rate ratio (95% CI) of glioma in patients with rosacea was 1.36 (1.18-1.58) in our primary analysis. When analyses were limited to patients with a primary diagnosis of rosacea by a hospital dermatologist (n = 5964), the adjusted incidence rate ratio was 1.82 (1.16-2.86).

CONCLUSIONS AND RELEVANCE Rosacea was associated with a significantly increased risk for glioma in a nationwide cohort. This association may be mediated, in part, by mechanisms dependent on matrix metalloproteinases. Increased focus on neurologic symptoms in patients with rosacea may be warranted.

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Rosacea is a common chronic inflammatory skin condition characterized primarily by transient or persistent centrofacial erythema with concomitant telangiectasia, papules, and pustules.[1] Several subtypes of rosacea exist, and these subtypes often overlap in the same patient. Neurogenic rosacea is characterized by neurologic or neuropsychiatric symptoms, such as complex regional pain syndrome, depression, essential tremor, and obsessive-compulsive disorder, which suggest cerebral involvement.[2,3] A significant relationship between rosacea and migraine has also been established, further indicating a relationship between rosacea and the brain.[4] Matrix metalloproteinases (MMPs) are enzymes that are involved in tissue remodeling, organ development, and regulation of inflammatory processes. Increased activation and expression of certain MMPs in skin with rosacea, in particular in ocular and phymatous rosacea, have been identified previously.[1,5] Increased expression of MMPs has also been associated with neuroinflammation and gliomas.[6,7] Matrix metalloproteinases appear to play an important part in glioma invasion, dissemination, and angio-genesis.[8,9] Gliomas are the most frequent primary brain tumors in adults, accounting for 70% of all brain cancers.[10] Very recently, data from the US Nurses' Health Study II[11] showed an increased risk for thyroid cancer in patients with rosacea. However, that study was limited to women, and otherwise, to our knowledge, no substantial reports are available on a potential association between rosacea and malignant neoplasms. We hypothesized that shared pathogenic mechanisms dependent on increased MMP activity could provide a link between rosacea and glioma and we therefore investigated this association in a nationwide cohort of the Danish population.

Methods

Data Sources and Study Population

The Danish Civil Registration System assigns a permanent and unique 10-digit personal identification number to all citizens at birth or immigration, which allows for unambiguous linkage across nationwide registers.[12] Moreover, the Danish Civil Registration System contains information such as date of birth, sex, and vital status, and Statistics Denmark records information on tax-reported household income.[13] The Danish National Patient Register contains information on all inpatient and outpatient (ambulatory) hospital contacts since 1978 according to the *International Classification of Diseases, Eighth Revision* (*ICD-8*) before 1994, and the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) was used thereafter. For administrative reasons, the *International Classification of Diseases, Ninth Revision*, was never used in Denmark. Hospital treatment interventions, surgical procedures, and hospital-administered pharmacotherapy are coded as treatment procedure codes.[14] Since 1994, all pharmacy-dispensed prescriptions in Denmark have been recorded accurately in the Register of Medicinal Product Statistics, and all drugs are classified according to the Anatomical Therapeutical Chemical (ATC) classification.[15] Study approval was obtained from the Danish Data Protection Agency. Review of an ethics committee is not required for register studies in Denmark. Conduct of this study was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[16] Informed consent is not required for administrative registry studies in Denmark. All data were encrypted and rendered anonymous when used for research purposes.

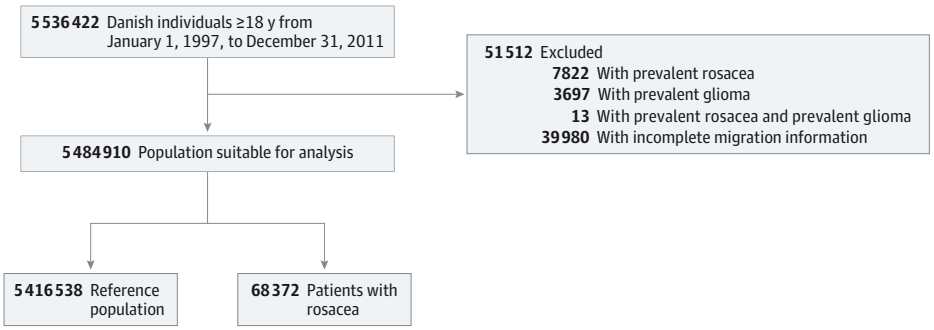
All 5 536 422 Danish citizens 18 years or older on January 1, 1997, or the subsequent day they reached 18 years of age were included in the cohort. Individuals were followed up until December 31, 2011, migration, a diagnosis of glioma, or death due to any cause, whichever came first. At baseline, patients with prevalent rosacea or glioma were excluded to enable examination of the temporal relationship between exposure and outcome and to ensure accurate risk-time allocation. Patients with rosacea were identified by a hospital (inpatient or outpatient) diagnosis of rosacea (*ICD-8* code 695.3 and *ICD-10* code L71) or when they were dispensed their second prescription of topical metronidazole (ATC D06BX01), whichever came first. Metronidazole is the preferred first-line treatment for rosacea and very infrequently used for other skin conditions in Denmark. The primary end point was a hospital diagnosis of glioma (*ICD-8* code 191 and *ICD-10* codes C71, D33, and D43) recorded in the Danish National Patient Register. Use of this registry for identification of cancer and tumor diagnoses has been described previously with an accuracy of greater than 90%.[17] The end point was decided a priori, and we did not examine the association with other types of cancers.

Statistical Analysis

Data were analyzed from July 14 to August 10, 2015. Baseline characteristics were presented as frequencies with percentages for categorical variables and means with SDs for continuous variables. Incidence rates were summarized per 10 000 person-years at risk. Any diagnosis of glioma after the study started, but before the onset of rosacea, was assigned to the reference population (n = 5 416 538) to obtain a more accurate allocation of exposure time. We used Poisson regression distribution models to calculate crude and adjusted incidence rate ratios (IRRs). Given that the causes of glioma are largely unknown, we included age, sex, and socioeconomic status in the adjusted models. Socioeconomic status was calculated as an index from 0 (lowest) to 4 (highest) based on the mean gross annual income (standardized by age) during a 5-year period before study inclusion.

For sensitivity analyses, we retrieved information on prescriptions for tetracycline hydrochloride (ATC J01A), which is the standard oral medication prescribed for rosacea in Denmark, to obtain a reasonably valid estimate of rosacea severity. Thus, patients were classified as having mild disease from the onset of rosacea and until they fulfilled the criteria for moderate to severe disease (ie, initiation of oral tetracycline therapy), if appropriate. In these analyses, patients contributed risk time in the mild rosacea group until they fulfilled the criteria for moderate to severe rosacea, if appropriate. Patients were assumed to have predominantly ocular rosacea if they had claimed a prescription for hypromellose eyedrops (ATC code S01XA20) that are often used to treat xeropthalmia in rosacea, and we identified patients with rhinophyma

Figure. Study Flowchart



All Danish citizens 18 years or older were eligible for the study.

Table 1. Baseline Characteristics of Study Population

Characteristic	Reference Population (n = 5 416 538)	Patients With Rosacea (n = 68 372)
Age, mean (SD), y	40.8 (19.7)	42.2 (16.5)
Women, No. (%)	2 732 029 (50.4)	45 994 (67.3)
Men, No. (%)	2 684 509 (49.6)	22 378 (32.7)
Socioeconomic status, mean (SD)[a]	2.0 (1.4)	2.5 (1.3)

[a] Calculated as an index from 0 (lowest socioeconomic status) to 4 (highest socioeconomic status) based on the mean gross annual income (standardized by age) during a 5-year period before study inclusion.

Table 2. Incidence Rates of Glioma per 10 000 Person-years

Group	Incidence of Glioma	
	Reference Population	Patients With Rosacea
Overall		
No. of events	20 934	184
Person-years	62 584 210	369 031.1
Incidence rate (95% CI)	3.34 (3.30-3.39)	4.99 (4.32-5.76)
Women		
No. of events	10 877	108
Person-years	31 830 047	251 123.8
Incidence rate (95% CI)	3.42 (3.35-3.48)	4.30 (3.56-5.19)
Men		
No. of events	10 057	76
Person-years	30 754 164	117 907.3
Incidence rate (95% CI)	3.27 (3.21-3.33)	6.45 (5.15-8.07)

by *ICD-10* code L71.1. We performed a sensitivity analysis where we used a hospital diagnosis of rosacea (*ICD-10* code L71) by an inpatient or outpatient dermatologist as the exposure variable. In addition, to rule out misclassification of patients with seborrheic dermatitis as having rosacea, we performed sensitivity analyses in which patients with rosacea were excluded if they had ever (before, during, or after the study period) received treatment with ketoconazole in shampoo or topical form (ATC code D01AC08) or topical corticosteroids (ATC code D07A), which are the typical treatment modalities for seborrheic dermatitis in Denmark.

Model assumptions, including absence of interactions between model covariates, were tested and found to be valid unless otherwise indicated. We found a significant interaction between rosacea and sex ($P < .001$); therefore, overall and sex-stratified estimates are described. Two-tailed $P < .05$ was considered statistically significant, and results were reported with 95% CIs where applicable. All statistical analyses were performed with the STATA (version 11.0; StataCorp) and SAS (version 9.2; SAS Institute Inc) statistical software.

Results

From January 1, 1997, to December 31, 2011, the study population consisted of 5 536 422 Danish citizens 18 years or older. After excluding 51 512 individuals with prevalent rosacea or glioma and with incomplete information on migration, the final cohort consisted of 5 484 910 individuals with a maximum follow-up of 15 years. The study flowchart is shown in the **Figure**, and the baseline characteristics of the study population are given in **Table 1**. Of note, 67.3% of the patients with rosacea were women.

During the study period, a total of 20 934 and 184 patients with glioma were identified among the reference population and the patients with rosacea, respectively. The incidence rate of glioma per 10 000 person-years was 3.34 (95% CI, 3.30-3.39) in the reference population and 4.99 (95% CI, 4.32-5.76) in patients with rosacea, with increased incidence rates of glioma in men vs women among the patients with rosacea (**Table 2**).

The crude and adjusted IRRs of glioma in patients with rosacea were 1.49 (95% CI 1.29-1.72), and 1.36 (95% CI 1.18-1.58), respectively, and stratification for sex yielded similar results, as shown in **Table 3**. Among patients with a primary *ICD-10* diagnosis of rosacea by a hospital dermatologist, the crude and adjusted IRRs of glioma were 1.93 (95% CI 1.23-3.02) and 1.82 (95% CI 1.16-2.86), respectively. In analyses in which patients were classified by severity of rosacea based on systemic treatment with tetracycline, the adjusted IRRs for mild and moderate to severe rosacea were 1.43 (95% CI 1.18-1.73) and 1.44 (95% CI 1.14-1.82), respectively (eTable in the Supplement). The mean (SD) time from onset of rosacea to diagnosis of glioma was 4.3 (3.3) and 5.8 (5.6) years, for mild and severe

Table 3. IRRs of Glioma in Patients With Rosacea

Patients With Rosacea	Crude IRR (95% CI)	*P* Value[a]	Adjusted IRR (95% CI)[b]	*P* Value[a]
Overall	1.49 (1.29-1.72)	<.001	1.36 (1.18-1.58)	<.001
Women	1.26 (1.04-1.52)	.02	1.27 (1.05-1.54)	.01
Men	1.97 (1.57-2.47)	<.001	1.47 (1.17-1.84)	<.001

Abbreviation: IRR, incidence rate ratio.

[a] Calculated using the 2-tailed test.

[b] Adjusted for age, sex, and socioeconomic status.

rosacea, respectively (*P* = .002). When all patients with rosacea who had ever filled a prescription for treatment of seborrheic dermatitis (ketoconazole [shampoo or topical formulation] or topical corticosteroids) were excluded, the crude and adjusted IRRs of glioma were 1.67 (95% CI, 1.27-2.21) and 1.59 (95% CI, 1.20-2.09), respectively. The adjusted IRR of glioma in patients with rosacea (excluding those with predominant ocular rosacea as defined by prescription of viscous eyedrops), was 1.32 (95% CI, 1.12-1.55); in patients with ocular rosacea, the adjusted IRR was 1.55 (95% CI, 1.14-2.11). Among patients with rhinophyma, we found 3 cases of glioma, and the adjusted IRR was 1.71 (95% CI, 0.55-5.31; *P* = .35). Additional subanalyses are shown in the eTable in the Supplement.

Discussion

Primary Findings

In this nationwide study of the Danish population, we observed a significantly increased risk for glioma in patients with rosacea. The results remained significant in sensitivity analyses and after adjustment for potential confounding factors. Notably, the rosacea-associated increased risk for glioma was greater in men than in women, whereas gliomas and rosacea were generally more common among women.

Strengths and Limitations

Several strengths and limitations apply to the interpretation of the present results. The high accuracy of the Danish registers and the available information on socioeconomic status allow for large-scale nationwide analyses in which selection and recall bias are minimized. We used *ICD-10* codes and prescriptions of topical metronidazole and tetracycline for rosacea identification and severity classification, respectively. Tetracycline is used routinely in the treatment of acne vulgaris and certain infections, but because topical metronidazole therapy is not used for these conditions, any misclassification related to the use of tetracycline in this specific cohort is likely negligible. Minocycline is not marketed in Denmark. However, results of our sensitivity analysis, where the exposure was a hospital diagnosis of rosacea, were generally in accordance with those of our primary analysis, with the risk for bias owing to misclassification of patients with rosacea likely to be low as also indicated by the sensitivity analysis, with exclusion of patients treated with agents for seborrheic dermatitis.

Some patients may not seek medical treatment for rosacea. This situation would have led to an underestimation of rosacea diagnoses and rosacea events in the registries, and thereby have attenuated the true rosacea-related risk for glioma. The Danish population is primarily white, which may limit extrapolation to other ethnicities because rosacea is common in fair-skinned individuals, and white race is an established risk factor for glioma.[18,19] The observational nature of our study does not allow establishment of causation and is open to the influence of unmeasured confounders. In addition, the apparent lack of a rosacea severity–dependent risk for glioma was mediated by the use of tetracycline, and this notion may be supported by the apparent longer time from rosacea onset to glioma diagnosis in patients with severe rosacea (ie, individuals treated with tetracyclines).

Although some but not all tetracyclines penetrate the blood-brain barrier, previous studies[20-22] have shown that tetracycline (in particular, minocycline) inhibits tumorogenesis, particularly through antiangiogenic mechanisms involving inhibition of MMPs. Minocycline has been used experimentally for its antitumor effects; in 1 study in a rodent brain tumor model,[23] local treatment with minocycline contributed to extended median survival.

Interpretation

Although speculative, mechanisms dependent on MMPs may contribute to the link between rosacea and the risk for glioma. Thus, MMPs, and in particular MMP-9, play a pivotal role in rosacea and regulation of the invasiveness of malignant glioma cells, and 1 study[24] found increased expression of MMP-9 in tumor tissue specimens from 76% of patients with glioblastoma, the most common and aggressive malignant form of glioma.[24-26] A role for antimicrobial peptides in the natural history of glioma has not been reported, but the apparent joint contribution of MMPs to the pathophysiologic mechanisms of the 2 diseases, and, for example, recent evidence indicating activation of interleukin 17–dependent inflammatory pathways in rosacea and glioma, clearly suggest that such shared pathophysiologic mechanisms may contribute to the epidemiologic association observed in the present study.[27-29] In addition, studies have suggested that the HLA class II histocompatibility antigen, DR α chain (HLA-DRA), is a prominent genetic component in rosacea, and *HLA-DRA* gene expression also appears to be important for interferon-γ expression and responsivity in glioblastoma multiforme.[30-32]

Conclusions

Rosacea is associated with a significantly increased risk for glioma. This association may be mediated, in part, by mechanisms dependent on MMPs. Increased focus on neurologic symptoms (eg, headaches, memory loss, seizures, loss of muscle control, visual symptoms, dysarthria, cognitive decline, and personality changes) in patients with rosacea and timely referral to relevant specialists may be warranted.

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Study concept and design: Egeberg, Thyssen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Egeberg.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Egeberg, Gislason.
Administrative, technical, or material support: Egeberg, Gislason.
Study supervision: Hansen, Gislason, Thyssen.

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