Increasing Incidence of Ophthalmic Lymphoma in Denmark from 1980 to 2005

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Purpose. To evaluate patient characteristics and incidence of ophthalmic lymphoma in Denmark during the period 1980 to 2005.

Methods. All patients in Denmark with a diagnosis of ophthalmic lymphoma during the period 1980 to 2005 were retrieved from three different population-based registries. Specimens from all patients were collected and reclassified according to the World Health Organization (WHO) classification system. Incidence rates were calculated by using Poisson regression models.

Results. A total of 228 patients with a histologically verified diagnosis of ophthalmic lymphoma were included. There was an equal distribution of males and females. The most frequent lymphoma subtype was extranodal marginal zone B-cell lymphoma (MALT [mucosa-associated lymphoid tissue] lymphoma, 55.5%) and most cases were located in the orbit (56.8%). High-grade lymphoma subtypes were found more frequently in males than in females. Incidence rates were highly dependent on the patient's age. For all ages, a statistically significant annual average increase of 3.4% during the 26-year period was found. This increase was primarily due to a rise in the incidence of MALT lymphoma.

Conclusions. In the Danish population ophthalmic lymphoma consists primarily of orbital MALT lymphoma. Although it is a rare disease in mostly elderly patients, the incidence of ophthalmic lymphoma is increasing at a rapid pace. (*Invest Ophthalmol Vis Sci.* 2008;49:3283–3288) DOI:10.1167/iovs.08-1768

Non-Hodgkin lymphoma (NHL) is a malignant neoplasm derived from a clonal proliferation of B or T lymphocytes. It is a heterogenous group of more than 40 different subtypes that can arise both in extranodal tissue and in lymph nodes. The incidence of NHL has risen considerably in Western countries over the past decades.[1,2] In Denmark, NHL represents the seventh most common type of cancer.[3]

Ophthalmic lymphoma (lymphoma localized in the ocular region, i.e., eyelid, conjunctiva, lacrimal sac, lacrimal gland, orbit, or intraocularly) constitutes approximately 10% of all extranodal NHL,[4] and lymphoma is the most common orbital malignancy.[5–9] Most lymphomas arising in the ocular region are low-grade B-cell lymphomas, with a high frequency of extranodal marginal zone B-cell lymphoma (MALT [mucosa-associated lymphoid tissue] lymphoma).[10–12]

The etiology of ophthalmic lymphoma is largely unknown. A possible connection between ocular region MALT lymphoma and *Chlamydia psittaci* (*C. psittaci*) has been suggested.[13] However, results from various studies differ, possibly because of geographic differences.[9,14–16]

Knowledge of both the geographic distribution and time trends of ophthalmic lymphoma may be helpful in formulating new etiologic hypotheses. However, the coexistence of multiple NHL classification systems (e.g., Kiel, Lukes-Collins, Rappaport, Working Formulation) has complicated epidemiologic research in NHL, and incidence data on ophthalmic lymphomas are sparse. Two reports based on register data indicate that the incidence of ophthalmic lymphoma in the United States is increasing at an even higher rate than is NHL in general.[8,17] The implementation of the REAL (revised European-American Lymphoma)[18] and the World Health Organization (WHO)[19] classification systems provides new possibilities for performing reliable epidemiologic studies on ophthalmic lymphoma.

We present a large population-based analysis of all cases of ocular adnexal, orbital, and intraocular lymphoma diagnosed in Denmark from 1980 to 2005. All lymphomas were reclassified according to the WHO classification (2001), and incidences of lymphoma in general and of specific subtypes were calculated to evaluate subtype and time trends in ophthalmic lymphoma.

Material and Methods

Patients

The study included all biopsy-verified cases of primary and secondary lymphoma in the ocular region in Denmark during the period from 1980 to 2005. Patients were enrolled by using three different population-based registries: (1) the Eye Pathology Institute Registry, (2) the

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Danish Registry of Pathology, and (3) The Danish Lymphoma Group Registry. From the registries, we searched for all patients with a diagnosis of ophthalmic lymphoid lesions. Histopathologic descriptions from all patient records were reviewed. Specimens with evident descriptions of pseudolymphoma, or the now preferred term reactive lymphoid hyperplasia, were identified but not further analyzed in this study. All specimens with any suspicion of lymphoid malignancy were reviewed by histology and immunohistochemistry.

Classification of Cases

Formalin-fixed, paraffin-embedded tissue from patients with a suspected ophthalmic lymphoma diagnosis was collected from the Eye Pathology Institute and from all Danish pathology departments. Sections were heated in a microwave oven in a TEG buffer (pH: 9) for 15 minutes, and a primary immunohistochemical panel was applied with antibodies directed against CD3, CD5, CD20, and CD79α, to differentiate between B- and T-cell lymphomas. The B-cell neoplasms were also immunophenotyped with antibodies directed against bcl-2, bcl-6, CD10, CD23, CD30, Cyclin D1, MUM-1, and κ- and λ light-chains. T-cell lymphomas were immunophenotyped with CD4, CD8, CD30, CD56, ALK-1, TIA, and granzyme B. In all cases, the mitotic rate was investigated with MIB-1. The stainings were performed with an immunochemical staining system (Techmate 500 Immunostainer; Dako, Glostrup, Denmark) that included a secondary antibody (Envision K5007; Dako). The sections were examined independently by two of the authors (LDS and ER) and were reviewed in consensus, to reclassify the lymphomas according to the WHO classification.[19]

Clinical Data

Clinical records and prebiopsy pathology requisition forms were reviewed with particular reference to year of diagnosis, sex, age, prior history of lymphoma, and sites of involvement.

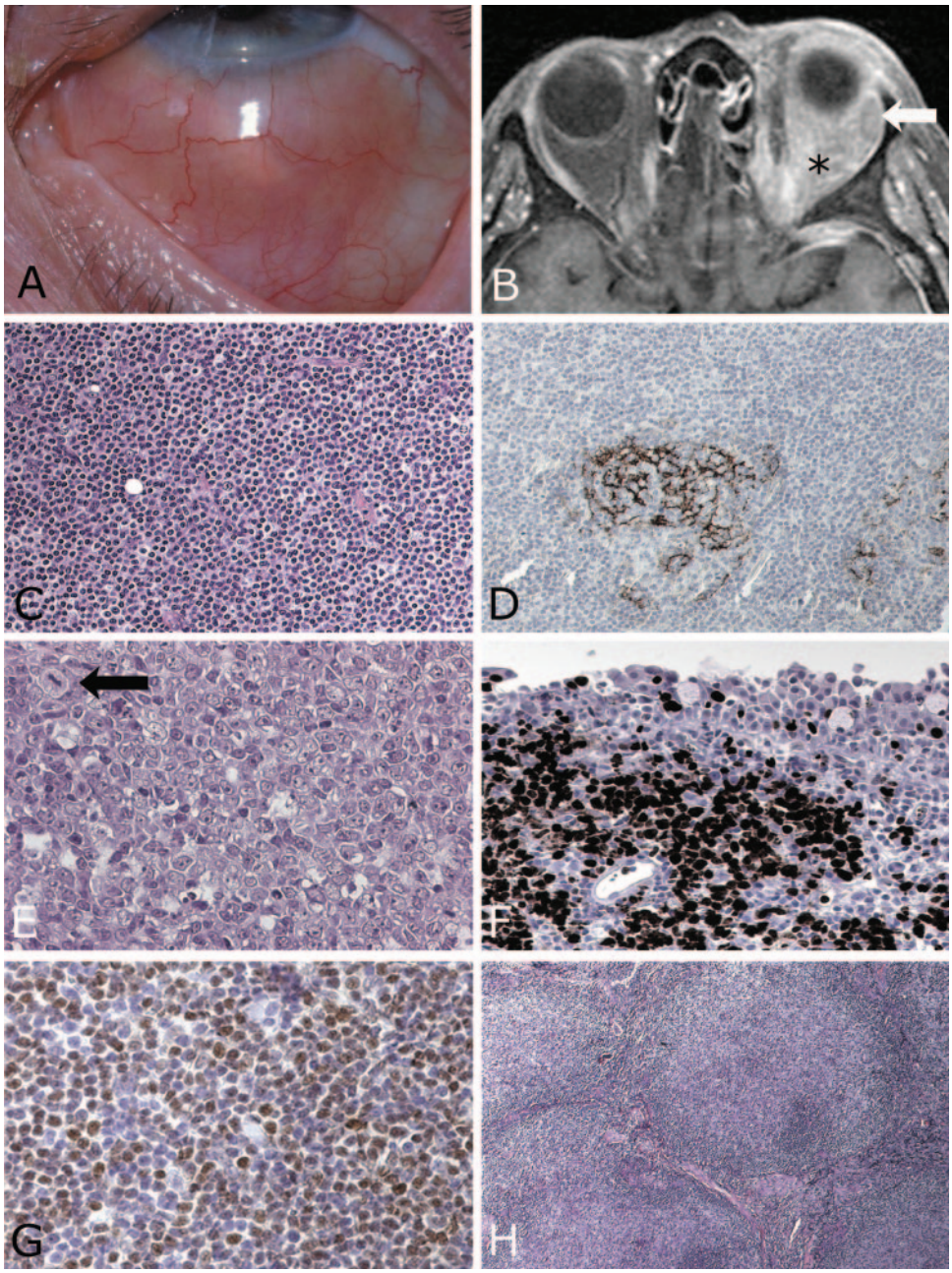

Figure 1. (**A**) Typical conjunctival lymphoma presenting as a painless salmon-colored tumor in the conjunctiva of a 65-year-old male. (**B**) Magnetic resonance image of the eye of a 65-year-old female with a 2-year history of proptosis. The tumor spread from the left lacrimal gland (*arrow*) and infiltrated the orbit diffusely (✻). On histopathologic examination, the tumor was found to be a MALT lymphoma. (**C**) Orbital MALT lymphoma characterized by a diffuse pattern of small centrocyte-like cells in an 81-year-old female. Hematoxylin-eosin stain. (**D**) MALT lymphoma (same patient as **C**) with preserved germinal centers shown by CD23 staining (*brown*) of the follicular dendritic cells. CD23 staining. (**E**) Diffuse large B-cell lymphoma in the right lower eyelid. The tumor cells have pleomorphic nuclei with irregularly distributed chromatin and up to three nucleoli. Mitoses (*arrow*) are frequently seen. The 80-year-old male died 6 months after diagnosis (hematoxylin-eosin; ×400). (**F**) Diffuse large B-cell lymphoma in the conjunctiva of a 73-year-old female. The mitotic activity was high as shown by the MIB-1 nuclear staining (*brown*). (**G**) Cyklin D1 positivity in an orbital MCL in a 85-year-old male, with no prior history of lymphoma. Subsequent staging revealed involvement of the bone marrow and axillary and inguinal lymph nodes. Cyklin D1 staining. (**H**) Typical nodular pattern in a follicular lymphoma in a 45-year-old female. A full-body CT-scan exposed a retroperitoneal tumor, and chemotherapeutic treatment was initiated. Hematoxylin-eosin. Magnification: (**C**, **D**, **F**) ×200; (**E**, **G**) ×400; (**H**) ×100.

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Statistical Analyses

Population data stratified by sex, age, and period were obtained from Statistics Denmark.[3] NHL incidence rates, expressing the number of new cases per 100,000 person-years were calculated for the whole population and for population subgroups according to lymphoma subtype, localization, sex, age, and period. Age was grouped in ten 10-year age groups, and period in five 5-year groups. Due to a low number of cases of the NHL subtypes diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and follicular lymphoma, it was necessary to pool periods (1980–1992 and 1993–2005). For the estimation of the effects of age, sex, and period on NHL incidence rates, we used a Poisson regression model.[20] The models were checked for interaction terms, and a goodness-of-fit test was used based on the deviance. Differences in the patients' characteristics in NHL groups were tested with the Fisher exact test. All statistical analyses were performed with commercial software (SAS ver. 9.1; SAS, Cary, NC).

Ethics

The investigation adhered the tenets of the Declaration of Helsinki and was approved by the local scientific ethics committee (journal no. KF 01-262201) and the Danish Protection Agency (journal no. 2005-41-5098).

Results

A total of 228 Danish patients with a biopsy-reviewed verified diagnosis of ocular adnexal, orbital, or intraocular lymphoma were identified from the total 462 enrolled patients and were included in this study. Thirty-five cases were originally diagnosed as ophthalmic lymphoma, but were excluded from the study for technical reasons (18 cases) or because an ophthalmic location or a lymphoma diagnosis could not be confirmed (17 cases). The remaining 199 cases were identified as reactive lymphoid hyperplasia from the original histopathologic descriptions.

Lymphoma Subclassification

Histopathologic review of the specimens showed that four lymphoma subtypes predominated: MALT lymphoma (126, 55%), DLBCL (29, 13%), MCL (20, 9%), and follicular lymphoma (17, 8%, Fig. 1). Twenty-one patients (9%) had B-cell lymphoma that could not be further classified because of lack of tissue specimens to perform a full immunohistochemical examination. Other subtypes found were: peripheral T-cell lymphoma, unspecified (n = 4, 2%), small lymphocytic lymphoma–chronic lymphocytic lymphoma (n = 3, 1%), Burkitt lymphoma (n = 3, 1%), precursor B-lymphoblastic lymphoma (n = 3, 1%), and anaplastic large T-cell lymphoma (n = 2, 1%; Table 1).

Patient Characteristics

Most patients were elderly with a median age of 69 years (95% confidence interval [CI], 66–71; range, 5–96); 75% were older than 59 years. There was an almost equal distribution of males and females (males: 116, 51%, Table 2). Most lymphomas were localized in the orbit (n = 129, 57%) and the second most frequent localization was in the conjunctiva (n = 57, 25%), whereas lacrimal sac lymphoma was very rare (n = 3, 1%, Table 1).

Intraocular lymphoma was diagnosed in 12 cases (5%). Of these, 10 (83%) were located in the uvea (8 in the choroid and 2 in the iris). The remaining two cases were retinal DLBCL (17%, Table 3). Concurrent cerebral disease was found in one of these patients.

Ocular lymphoma was the first presenting symptom in the majority of patients (n = 184, 81%, Table 2). More than half of them (n = 102, 65%) had involvement only of the ocular region (stage I). Ten (6%) patients had disease involving regional lymph nodes (stage II), 8 (5%) had involvement of the lymph nodes below the diaphragm (stage III), and 35 (23%) patients had affected bone marrow at the time of diagnosis (stage IV; Tables 3, 4). The remaining 44 cases were secondary (i.e., there was a prior history of systemic lymphoma), including 7 of 12 intraocular lymphoma cases (58%, Table 3).

Bilateral disease was significantly more common in MCL (9/20, 45%) than in MALT lymphoma (13/127, 10%, P = 0.0004; Table 1) or all other lymphoma subtypes (6/81, 7%, P = 0.0002).

MCL occurred only in patients older than 60 years (P = 0.005), whereas acute leukemias and Burkitt lymphoma occurred only in patients younger than 60 years ($P < 0001$). The high-grade lymphoma subtypes were significantly more frequent intraocularly than in the remaining ocular region (P = 0.0035, Table 1).

Table 1. Distribution of Lymphoma within the Ophthalmic Region According to Lymphoma Subtype

Lymphoma Subtype	*n*	Bilateral *n* (%, CI)	Eyelid *n* (%, CI)	Conj. *n* (%, CI)	Lacr. Sac *n* (%, CI)	Lacr. Gland *n* (%, CI)	Orbit *n* (%, CI)	Intraocular *n* (%, CI)
All lymphomas	228	28 (12, 8–17)	11 (5, 2–8)	57 (25, 19–30)	3 (1, 0–3)	16 (7, 4–10)	129 (57, 50–63)	12 (5, 2–8)
Low-grade types	147	14 (10, 5–14)	7 (5, 1–8)	44 (30, 23–37)	2 (1, 0–3)	10 (7, 3–11)	83 (56, 48–64)	0
MALT	126	13 (10, 5–17)	5 (4, 0–7)	40 (31, 23–40)	1 (1, 0–2)	6 (5, 2–8)	74 (58, 50–67)	0
FL	17	1 (6, 0–17)	1 (6, 0–17)	4 (24, 3–44)	0	3 (18, 0–36)	9 (53, 29–77)	0
SLL/CLL	3	0	1 (33, 0–87)	0	1 (33, 0–87)	1 (33, 0–87)	0	0
High-grade types	61	10 (16, 7–26)	4 (7, 0–13)	9 (15, 6–24)	1 (2, 0–5)	4 (7, 0–13)	35 (57, 45–70)	8 (13, 5–22)*
DLBCL	29	1 (3, 0–10)	1 (3, 0–10)	2 (7, 0–16)	0	3 (10, 0–21)	19 (66, 48–83)	4 (14, 1–26)
MCL	20	9 (45, 23–67)†	0	7 (35, 14–65)	1 (5, 0–15)	1 (5, 0–15)	11 (55, 33–77)	0
PTL, NOS	4	0	2 (50, 1–99)	0	0	0	1 (25, 0–67)	1 (25, 0–67)
BL	3	0	0	0	0	0	1 (33, 0–87)	2 (67, 13–100)
B-ALL	3	0	0	0	0	0	2 (67, 13–100)	1 (33, 0–87)
T-ALCL	2	0	1 (50, 0–100)	0	0	0	1 (50, 0–100)	0
BCL, uncl.	21	4 (20, 2–38)	0	4 (20, 2–38)	0	2 (10, 0–23)	11 (55, 33–77)	4 (15, 0–31)

B-ALL, precursor B-cell lymphoblastic lymphoma; BCL, uncl., B-cell lymphoma, unclassified; BL, Burkitt lymphoma; CI, 95% confidence interval; Conj., conjunctiva; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; Lacr., lacrimal; MALT, extranodal marginal zone B-cell lymphoma (MALT lymphoma); MCL, mantle cell lymphoma; PTL, NOS, peripheral T-cell lymphoma, unspecified; SLL/CLL, small lymphocytic lymphoma; T-ALCL, anaplastic large T-cell lymphoma.

* The frequency of high-grade lymphoma intraocularly was significantly higher as compared to the remaining ocular region; P = 0.0035.

† Bilateral affection was significantly more common in MCL compared to MALT lymphoma; P = 0.0004.

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TABLE 2. Clinical Data According to Lymphoma Subtype

Lymphoma Subtype	Number (%, CI)	Males *n* (%, CI)	Median Age Both Sexes, y (Range)	Patients with Ophthalmic Lymphoma as First Presenting Symptom *n* (%, CI)
All lymphomas	228 (100)	116 (51, 44–57)	69 (5–96)	184 (81, 76–86)
Low-grade types	147 (64, 58–70)	66 (45, 37–55)	69 (8–96)	127 (88, 80–91)
MALT	126 (55, 49–62)	58 (46, 37–54)	69 (8–92)	116 (92, 85–96)
FL	17 (7, 4–11)	7 (41, 18–65)	63 (45–96)	11 (65, 42–87)
SLL/CLL	3 (1, 0–3)	1 (33, 0–87)	75 (62–75)	0
High-grade types	61 (27, 21–33)	42 (69, 57–80)*	72 (5–95)	42 (69, 57–80)
DLBCL	29 (13, 8–17)	13 (45, 27–63)	77 (17–95)	23 (79, 59–89)
MCL	20 (9, 5–12)	17 (85, 69–100)†	75 (60–90)	11 (55, 33–77)
PTL, NOS	4 (2, 0–3)	3 (75, 33–100)	61 (31–77)	3 (75, 33–100)
BL	3 (1, 0–3)	2 (67, 13–100)	41 (34–55)	1 (33, 0–87)
B-ALL	3 (1, 0–3)	2 (67, 13–100)	9 (5–34)	2 (67, 13–100)
T-ALCL	2 (1, 0–2)	2 (100, 90–100)	45 (35–55)	2 (100, 90–100)
BCL, uncl.	21 (9, 5–12)	11 (55, 33–77)	63 (18–77)	15 (71, 50–90)

Abbreviations are defined in Table 1.

* Males were more likely to present with high-grade lymphoma than were female; $P = 0.0022$.

† In MCL, a predominance of males was found; $P = 0.0017$.

The males were more likely to present with high-grade lymphoma than were the females ($P = 0.0022$, Table 2). Especially MCL affected males predominantly ($P = 0.0017$). No differences in distribution according to site of ophthalmic lymphoma were found between the males and females.

Among the patients with MALT lymphoma, six (5%) had a preceding history of autoimmune disease.

Incidence Data

Age-Specific Incidence Rates by Sex. Incidence rates were highly dependent on patient age ($P < 0.0001$, Fig. 2). For both sexes, the age-specific incidence, during the period 2001 to 2005 was below 0.5 per 100,000 until age 60 years, increasing progressively with each decade until a maximum of 2.6 cases per 100,000 for males at age 90 years and 1.0 per 100,000 for females at age 80 years. Differences in incidence between males and females were not statistically significant.

Time Trends in Incidence Rates. The number of patients and incidence rates in different calendar periods are shown in Table 5. Incidence rates of ophthalmic lymphoma for the whole population increased from 0.086 in 1981 to 1985 to 0.249 per 100,000 in 2001 to 2005. Adjustment for differences in the age distribution over the period confirmed this increasing tendency ($P = 0.0068$). The estimated changes in incidence corresponded to an annual average increase in the 26-year period of 3.4% ($P < 0.0007$, Table 5).

TABLE 3. Intraocular Lymphoma

Subtype	Stage	Retina (*n*)	Uvea (*n*)
DLBCL	I	1	0
	III	0	1
	Ns	1	0
	Sec. intraoc.	0	1
PTL, NOS	IV	0	1*
BL	Sec. intraoc.	0	2
B-ALL	Sec. intraoc.	0	1*
BCL, uncl.	I	0	1
	Sec. intraoc.	0	3

Lymphoma subtype, localization, and staging of 12 patients. Ns, not stated; Sec. intraoc., secondary intraocular lymphoma. The remaining abbreviations are defined in Table 1.

* Localized in the iris.

For comparison, the number of cases of reactive lymphoid hyperplasia also increased with distribution according to period, as follows: 1981 to 1985, 20 cases; 1986 to 1990, 38 cases;

TABLE 4. Extraocular Ophthalmic Lymphoma

Lymphoma Subtype/Stage	Orbit (*n*)	Ocular Adnexa (*n*)
MALT		
I	45	28
II	1	1
III	3	0
IV	12	6
Ns	9	11
FL		
I	3	3
II	0	1
III	1	2
Ns	1	0
DLBCL		
I	9	1
II	0	2
IV	3	0
Ns	4	1
MCL		
II	0	2
IV	7	2
PTL, NOS		
I	0	1
II	1	0
BL		
II	1	0
B-ALL		
IV	2	0
T-ALCL		
I	0	1
III	1	0
BCL, uncl.		
I	5	4
II	1	0
IV	1	1
Ns	1	1

Stage of disease at diagnosis according to lymphoma subtype and localization in 179 patients with ophthalmic lymphoma as first presenting symptom. Abbreviations are defined in Table 1.

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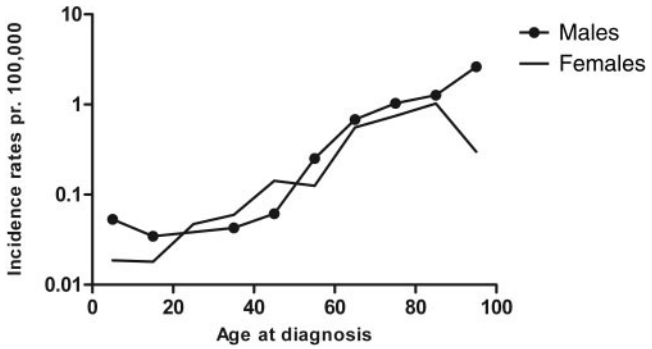

FIGURE 2. Age-specific ophthalmic lymphoma incidence rates for males and females in Denmark during the period 2001 to 2005. The rates are calculated based on all data in a Poisson regression model adjusted for period. Incidence rates in the 5-year periods from 1981 to 2000 were proportional to the ones depicted here, although lower, as shown in Table 3. Incidence rates were highly dependent on patient age ($P < 0.0001$) with a maximum incidence rate of 2.6 per 100,000 for males and 1.0 per 100,000 for females. Differences in incidence between males and females were not statistically significant ($P = 0.766$).

1991 to 1995, 28 cases; 1996 to 2000, 52 cases; and 2001 to 2005, 57 cases.

The increase in incidence of ophthalmic lymphoma was found, both in patients with limited disease (stages I and II) and in patients with more advanced lymphomas (stages III and IV or secondary lymphoma; age-adjusted rate-ratio [RR] = 2.15, $P = 0.0002$ and age-adjusted RR = 1.85, $P = 0.0043$, respectively), between the 1980 to 1992 and the 1993 to 2005 period.

When the lymphomas were subdivided into the four most common lymphoma subtypes, the increasing incidence was found only in the low-grade lymphomas, MALT lymphoma (age-adjusted RR, 1993 to 2005 vs. 1980 to 1992 = 1.6, $P = 0.009$) and follicular lymphoma (age-adjusted RR, 1993 to 2005 vs. 1980 to 1992 = 4.1, $P = 0.02$), whereas there was no statistically significant increase over time for the high-grade lymphoma types DLBCL and MCL.

Furthermore, when incidence rates were analyzed according to anatomic localization in the ocular region, there was a statistically significant increase in orbital (age-adjusted RR, 1993 to 2005 vs. 1980 to 1992 = 1.6, $P = 0.007$) and all other extraocular lymphomas (age-adjusted RR = 1.6, $P = 0.028$), whereas the incidence of intraocular lymphoma remained stable between the periods 1980 to 1992 and 1993 to 2005 (age-adjusted RR = 0.93, $P = 0.028$).

DISCUSSION

In this study, we reclassified all lymphomas diagnosed in the Danish population during the period 1980 to 2005. Analyzing 263 cases, we found that 228 could be verified to be ophthalmic lymphoma. Lymphoma in the ocular region is relatively uncommon with an annual incidence of ~2 per 100,000 in the population older than 80 years.

In our study, there was an equal distribution between the males and females; and, consistent with other studies, ocular adnexal lymphoma was primarily MALT lymphoma, localized in the orbit,[11,12,16,21,22] whereas intraocular lymphomas were predominantly high-grade lymphomas.[23–26] More than 80% of the patients had the first presentation of disease in the ocular region.

MCL was seen only in patients older than 60 years, whereas Burkitt lymphoma and acute leukemia were found only in patients younger than 60. Of note, high-grade lymphoma, in general, and MCL in particular were more common in the males than in the females, and MCL was frequently bilateral. These observations are in accordance with those of other studies.[21,27]

The incidence rates found in this study are comparable with those in previous studies from Western countries based on cancer registry analyses.[8,17] The use of three different population-based registries and the fact that all specimens were reviewed and reclassified gives a very reliable result in our investigation.

We observed an increase in the incidence of orbital and ocular adnexal lymphoma, as was also found by others.[8,17] This increase could be due to a change in classification systems (i.e., some cases formerly classified as reactive lymphoid hyperplasia would be classified as MALT lymphoma, according to the REAL or WHO classification). However, we found an increase in the total number of cases of both reactive lymphoid hyperplasia and MALT lymphoma. In addition, even though MALT lymphoma was not a described entity until 1983,[28] the diagnosis went into practical use in the early 1990s, and thus the increase found from the mid-1990s to 2005 can be considered reliable.

During the period from 1980 to 2005, we found that the annual age-adjusted incidence rate more than doubled. The increase was consistent in both males and females, and applies for the lymphoma subtypes MALT lymphoma and follicular lymphoma and for all ophthalmic localizations except intraocular lymphoma. For the lymphoma subtypes DLBCL and MCL, which are more likely to be part of a systemic disease, we found no statistically significant increase. During the same interval, the incidence rate of NHL in general has risen as well, but at a slower rate than reported in this study, and the increase seems to have stabilized during the late 1990s.[2,29]

The increasing incidence rate of ophthalmic lymphoma calls for further studies to elucidate its etiology and especially that of ophthalmic MALT lymphoma, accounting for more than 50% of the cases. MALT lymphoma arises in aggregates of lymphocytes at sites of chronic inflammation in persistent infection.[30] Microbial species do not directly transform lymphoid cells, but persistent infection induces a sustained lymphoid proliferation, thus increasing the risk of chromosomal alterations leading to malignant transforma-

TABLE 5. Incidence of Ophthalmic Lymphoma from 1981 to 2005 in Denmark

Period	Patients (*n*)	Incidence per 100,000 (CI)	Age-Adjusted Rate Ratio (CI)*
1981–1985	22	0.086 (0.057–0.131)	1.00 (1.00–1.00)
1986–1990	44	0.171 (0.128–0.231)	1.58 (0.94–2.70)
1991–1995	38	0.147 (0.107–0.202)	1.60 (0.94–2.71)
1996–2000	50	0.189 (0.143–0.249)	1.78 (1.06–2.98)
2001–2005	69	0.249 (0.196–0.316)	2.41 (1.47–3.93)

During the period, there was an average increase of 3.4% per year (95% CI: 1.4%–5.4%, $P = 0.0007$).
* $P = 0.0068$.

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tion.[30] In the gastrointestinal tract MALT lymphoma has been linked to infection with *Helicobacter pylori* (*H. pylori*),[31] and during the past few years, several studies of a possible association between ocular lymphoma and *C. psittaci* infection have been conducted, with inconclusive results.[9,13–16,32,33] Other infectious agents have been investigated in ocular MALT lymphoma, such as hepatitis C virus (HCV) and *H. pylori*, without success.[34–36] Thus, whether a specific infectious agent triggers ocular MALT lymphoma is still controversial.

In conclusion, we performed a large population-based study reclassifying all cases of ophthalmic lymphoma in Denmark through a 26-year-period. We analyzed patient characteristics, lymphoma subtypes, and incidences and found that, in the Danish population, ophthalmic lymphoma consists primarily of orbital MALT lymphoma. Although a rare disease of elderly patients, the incidence of ocular adnexal lymphoma is increasing at a rapid rate in Denmark.

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