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Glomerulonephritis and malignancy: A population-based analysis

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Glomerulonephritis and malignancy: A population-based analysis.

Background. An association between glomerulonephritis and malignant tumors has previously both been found and discarded in clinical series, but to our knowledge never has been tested in a population-based setting.

Methods. The Danish Kidney Biopsy Registry includes all kidney biopsies performed from 1985. Using a unique personal identification number, each person in the registry to the National Population Registry and the Danish Cancer Registry were linked. Cancer occurrence after the biopsy was compared in patients with morphological, glomerular diseases with that of the general Danish population, taking into account sex, age, calendar period and time since biopsy, and the 95% confidence interval (95% CI) for the observed-to-expected rates was calculated, assuming a Poisson distribution. Cancer occurrence was stratified to <1 year, 1 to 4, and ≥5 years after a biopsy.

Results. A total of 102 de novo cancers were found in 1958 patients. These cancers represent a two- to threefold excess of the expected number at <1 and 1 to 4, but not ≥5 years after a biopsy. Non-Hodgkin's lymphomas were observed six to eight times more than expected. Cancer excess was seen in glomerulonephritides with a known or suspected virus etiology.

Conclusions. The excess cancer rate could be the result of underlying undiagnosed tumors whose antigens have initiated glomerulonephritis, or the immunosuppressive therapy that initiated or energized tumor cells. Based on the findings in our study, there is some support for an association to persistent viruses causing first the glomerulonephritides and then the malignancies, perhaps through a common pathogenesis. This calls for other studies to be done that are specifically designed to investigate this issue, with more data on patient characteristics and confounders.

An association between glomerulonephritis (GN) and malignant tumors previously has been found and discarded in clinical series, but to our knowledge has not been tested in a population-based setting [1, 2]. A cancer may be evident before, discovered concomitantly with, or detected well after the development of glomerular lesions. This study concerns de novo malignancies after affirmed glomerular diseases. In Denmark, all kidney biopsies have been registered since 1985 in a central database. Linkage with the Danish Cancer Registry, in existence since 1943, was performed to analyze for a possible excess cancer rate after diagnosed GN. Our study identified cancer cases in the same way as the underlying rates to avoid major ascertainment bias such as that seen in clinical series with an extensive follow-up. Based upon the findings, we discuss explanations for a possible association between glomerulonephritis and malignant tumors.

Key words: kidney biopsy, glomerulonephritis, cancer, virus, non-Hodgkin's lymphoma; cyclin-dependent kinases.

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METHODS

Glomerular diseases are treated in specialized departments for nephrology in Denmark. The Danish Kidney Biopsy Registry includes all kidney biopsies performed in Denmark from 1985 to the present. The registry data include: the patient's personal identification number, date of biopsy, up to four diagnoses of morphology using the WHO classification, results of immunohistology and electron microscopy, and clinical systemic disease and etiology, if known. Our current study was based on the light microscopy diagnoses. While some disease entities such as interstitial nephritis, vascular diseases, diabetes mellitus and hereditary kidney diseases are not systematically biopsied, glomerular diseases are biopsied, according to consensus criteria. These biopsies were evaluated by investigators trained in interpretation of renal biopsies. The reproducibility of the glomerular diagnosis (light microscopy) after the WHO classification has been analyzed with kappa statistics and found acceptable with a kappa value of 0.61 [3]. The biopsies were performed most often before a possible subsequent immunosuppressive therapy. De novo or recurrent GN in a transplanted kidney was excluded.

After the WHO classification, the GN was divided into the following categories: idiopathic/post-infectious (primary) GN, which is minimal change GN; focal, segmental proliferative GN; focal, segmental GN; diffuse membranous GN; diffuse mesangial proliferative GN; diffuse endocapillary GN; diffuse membranoproliferative GN;

Table 1. Observed, expected and observed/expected rate of 102 de novo cancers after glomerulonephritis

Years after entry	Males						Females					
	PYRS	Obs	Exp	O/E	CI low	CI high	PYRS	Obs	Exp	O/E	CI low	CI high
<1	1073	17	7.08	2.4	1.4	3.84	693	10	3.48	2.87	1.37	5.35
1–4	2857	36	18.3	1.97	1.38	2.72	1836	17	9.49	1.79	1.04	2.89
≥5	1508	16	10.37	1.54	0.88	2.5	1145	6	6.41	0.94	0.34	2.06
Total	5438	69	35.75	1.93	1.5	2.44	3674	33	19.39	1.7	1.17	2.39

Abbreviations are: PYRS, person-years; obs, observed; exp, expected; CI, 95% confidence interval (low-high).

diffuse extracapillary GN; diffuse sclerosing GN; and unclassified GN. We concentrated on patients with morphologically-defined glomerular diseases, and used the first diagnosis in those cases where several biopsies existed.

The Danish Cancer Registry began operations in 1943, covering all cancers in Denmark (2001 population, 5.2 million). The registry has a proven high completeness and validity in the range of 95 to 97% [4]. All cancers in a person are on record and linked to the unique personal identification number introduced in 1968 and used extensively in society.

By the unique personal identification number, each person in the Danish Kidney Biopsy Registry was linked to the National Population Registry and the Danish Cancer Registry, and cancer incidence in the cohort was made available up to the end of 1996, when 2550 kidney-biopsied patients were on file.

The cancer occurrence in patients with morphological, glomerular diseases were compared with that of the general Danish population, taking into account sex, age, calendar period and time since biopsy, and the 95% confidence interval (95% CI) for the observed-to-expected rates was calculated, assuming a Poisson distribution. Person-years at risk and cancer occurrence data were assessed from date of a biopsy until death, transplantation or end of follow-up (Dec. 31, 1996), whichever came first. Patients with a diagnosis of malignancy before the biopsy were excluded. Cancer occurrence was stratified to 0 to <1 year, 1 to 4, and ≥5 years after a biopsy to elucidate the effect of immunosuppressive therapy, if given, and to clarify that a possible excess cancer rate was not observed only in the period immediately following the kidney biopsy as a sign of undetected cancers at the time of biopsy.

RESULTS

All patients with a glomerular disease were identified. They comprised 1958 persons (1190 males and 768 females) accruing 9112 person-years (5438 for males and 3674 for females). In this group 102 cancers were detected (69 in males and 33 in females; Table 1). In both men and women significant excesses of malignancies (2.4 to 3.5-fold) were found at <1 and 1 to 4 years, however, not for five years or more after diagnosis.

Excess cancers were found in the colon (women), lung and skin (men), and lymphatic tissue in both men and women (Table 2). Non-Hodgkin lymphomas were in excess ($N = 9$; 6.6- to 7.4-fold) in both men and women, and so was Hodgkin's disease and myeloma in women and leukemia in men.

The glomerular diseases were subdivided after WHO classification into subgroups as shown in Table 3. Significant excess cancers (1.7- to 4.1-fold) are seen in endocapillary, membranous and mesangioproliferative GN in men and minor change GN in women. A significant excess of cancers in lymphatic and hematopoietic tissue (4.3- to 6.3-fold) was observed in both men and women (Table 4), and excess could be found in minor change, endocapillary, membranous and mesangioproliferative GN, however, the numbers here are small.

DISCUSSION

Studies of a possible excess cancer rate in patients with GN can be biased in several ways, including selection criteria for reference of patients to specialized departments, criteria for diagnosis, and the availability of a relevant cancer registry for comparative analyses.

We have tried to avoid this by a population-based approach. Denmark has a very specialized hospital system and patients with kidney diseases are routinely referred to departments of nephrology. A consensus exists on indications for kidney biopsies, and these are performed if glomerular diseases are suspected.

One may speculate if GN could be a first symptom of a silent cancer and hence give spurious results. Such a mechanism, however, is unlikely since the cancers found are not known as slow growing, and the excess seen in our current study is obvious years after the biopsy leading to a diagnosis of GN. Also, the thorough clinical work-up of the kidney patients speaks against such a relationship. Lymphatic infiltrations in the kidneys, such as seen in non-Hodgkin's lymphomas (NHL), will not be missed by the pathologists, and hence such cases would be excluded from our material.

An analysis of a Danish cohort of patients with end-stage renal diseases, of which some were treated exclusively with dialysis and some were later transplanted,

Table 2. Excess cancers were found in the colon (women), lung and skin (men) and lymphatic tissue in both men and women

	Males					Females				
Cancer diagnosis	obs	exp	O/E	CI low	CI high	obs	exp	O/E	CI low	CI high
153. Colon, incl recto-sigmoid	4	2.5165	1.59	0.43	4.07	**5**	**1.354**	**3.69**	**1.19**	**8.62**
162.0,1 Lung primary, trachea	**14**	**6.0299**	**2.32**	**1.27**	**3.9**	1	1.7291	0.58	0.01	3.22
191 Other skin (than melanomas)	**17**	**5.9243**	**2.87**	**1.67**	**4.59**	5	2.9087	1.72	0.55	4.01
198-199 Secondary and unspecified sites	3	0.9951	3.01	0.61	8.81	**3**	**0.5556**	**5.4**	**1.09**	**15.78**
200-205 Lymphatic and hemopoietic tissue	**15**	**2.3848**	**6.29**	**3.52**	**10.37**	**9**	**0.9651**	**9.33**	**4.26**	**17.7**
200, 202 Non-Hodgkin lymphoma	**6**	**0.9096**	**6.6**	**2.41**	**14.36**	**3**	**0.4036**	**7.43**	**1.49**	**21.72**
201 Hodgkin's disease	1	0.1717	5.82	0.08	32.41	**3**	**0.0747**	**40.18**	**8.08**	**117.4**
203 Multiple myoloma	1	0.4038	2.48	0.03	13.78	2	0.1591	12.57	1.41	45.38
204 Leukemia	**7**	**0.8746**	**8**	**3.21**	**16.49**	1	0.322	3.11	0.04	17.28

Numbers heading the cancer diagnosis are from the International Classification of Disease. Bold script indicates significant excess. Abbreviations are: obs, observed; exp, expected; CI, 95% confidence interval (low-high).

Table 3. Cancers in relation to the glomerular diseases subdivided into subgroups after WHO classification

	Males					Females				
140–205 All malignant neoplasms	obs	exp	O/E	CI low	CI high	obs	exp	O/E	CI low	CI high
1 Minor change	3	1.2679	2.37	0.48	6.91	**5**	**1.2287**	**4.07**	**1.31**	**9.5**
2 Focal segm. prolif.	8	4.7391	1.69	0.73	3.33	1	2.4635	0.41	0.01	2.26
3 Focal segmental sclerosis	4	1.4343	2.79	0.75	7.14	1	0.3806	2.63	0.03	14.62
4 Membranoproliferative	2	1.5874	1.26	0.14	4.55	2	1.257	1.59	0.18	5.74
5 Extracapillary	10	5.4802	1.82	0.87	3.36	5	2.3432	2.13	0.69	4.98
6 Endocapillary	**4**	**1.0128**	**3.95**	**1.06**	**10.11**	1	0.4963	2.02	0.03	11.21
7 Diffuse membranous	**13**	**7.28**	**1.79**	**0.95**	**3.05**	7	3.5455	1.97	0.79	4.07
8 Diffuse mesangial proliferative	**13**	**7.1**	**1.83**	**0.97**	**3.13**	8	4.5713	1.75	0.75	3.45
9 Diffuse sclerosis	3	1.5139	1.98	0.4	5.79	—	0.5198	—	—	5.76
10 Unclassified	**9**	**4.3373**	**2.08**	**0.95**	**3.94**	3	2.5837	1.16	0.23	3.39
Total	**69**	**35.753**	**1.93**	**1.5**	**2.44**	**33**	**19.3897**	**1.7**	**1.17**	**2.39**

Bold script indicates significant excess. Abbreviations are: obs, observed; exp, expected; CI, 95% confidence interval (low-high).

Table 4. Excess cancers in lymphatic tissue in relation to the glomerular diseases subdivided in subgroups after WHO

	Males					Females				
200–205 Lymphatic and hemopoietic tissue	obs	exp	O/E	CI low	CI high	obs	exp	O/E	CI low	CI high
1 Minor change	**2**	**0.1035**	**19.32**	**2.17**	**69.74**	**2**	**0.0677**	**29.55**	**3.32**	**106.7**
6 Endocapillar	**2**	**0.07**	**28.72**	**3.23**	**103.7**	—	0.0259	—	—	115.6
7 Diffuse membranous	**4**	**0.4644**	**8.61**	**2.32**	**22.05**	—	0.1692	—	—	17.7
8 Diffuse mesangial proliferative	2	0.5122	3.9	0.44	14.1	**4**	**0.2374**	**16.85**	**4.53**	**43.14**
Total (all groups)	**15**	**2.3848**	**6.29**	**3.52**	**10.37**	**9**	**0.9651**	**9.33**	**4.26**	**17.7**

Bold script indicates significant excess. Abbreviations are; obs, observed; exp, expected; CI, 95% confidence interval (low-high).

showed that excess cancer risk in such patients occurred after transplantation and not during dialysis [5].

Since not all patients with kidney diseases proceed to terminal uremia with the possibility for renal replacement therapy, we found it of interest to analyze a cohort of patients with biopsy-verified kidney diseases who were followed from the day of biopsy, that is, from an early phase. We focused on glomerular diseases, since they are systematically biopsied and most develop as a result of immune dysregulation, either an inappropriate immune response to self-antigens occurring through a failure of tolerance (autoimmunity) or an ineffectual response to a foreign antigen. Viruses may play a role in both circumstances. At the time of biopsy immunosuppressive therapies normally are not given.

Glomerulonephritis may be primary, restricted in clinical manifestations to the kidney, or it may be part of a multi-system disease, most frequently systemic lupus or vasculitis. The etiologies in most GN are still unknown, however, much evidence now suggests that infectious agents such as bacteria or virus induce GN by triggering an autoimmune response, leading to the formation of immune complex deposits in glomeruli, or evoke a cell-mediated immune response to antigens in or of the glomerulus [reviewed in 10].

We found an overall significant excess of malignancies

in both men and women for the entire group of GN patients. The excess was found in both the <1 and 1 to 4 year groups, however, not in the ≥5 year group, after diagnosis. This could be taken as an argument against a long-term effect of immunosuppression; however, our study did not allow a further analysis of the possible influence of immunosuppression. The absence of an increased risk after five years is probably due to the sample size, but could be taken as an argument against an association between glomerulonephritis and malignancy. However, if a virus etiology causes first the glomerulonephritis and then the malignancy, this would be seen in the first years and not so much in the long run, as learned from the literature on malignancy after organ transplantation, especially concerning the non-Hodgkin lymphomas.

The excess was mostly seen in sites where a virus etiology was suspected, and consequently such an effect may be emphasized further by immunosuppression. Most evident was the cancer excess in lymphatic and hematopoietic tissue with observed/expected (O/E) rates of six to nine in men and women. This corresponds very well to findings after transplantation where viruses from the herpes group have been suspected culprits.

If divided into morphological subgroups of GN, the numbers of malignancies are small. From the earlier kappa-statistical study performed in the same cohort as analyzed in our current study [3] we know that reproducibility between different observers varied between crescentic (0.81) to membranoproliferative (0.40) GN, which could be the reason for not finding more subgroup-specific cancer excess. Another point is the timing of a biopsy, since many glomerulonephritides over time change from one category to another and, furthermore, many have one or more different morphological components. On the other hand, the study comprises 1958 persons with 100 to 200 in each group, making it the biggest ever performed, so the reason also could be that excess cancer in GN is not so much linked to specific morphological subgroups (membranous GN has often been mentioned, based on the findings of four cancers among 107 membranous GN [2]) as to the glomerular disease per se. In any case, it is noteworthy that minimal change, endocapillary, membranous, and mesangial proliferative GN show excess cancers in lymphatic tissue (Tables 3 and 4).

A common virus etiology for both the glomerular disease and the malignancies could be due either to an oncogenic effect of the viruses *per se* or a disturbed clearance of biological mediators of importance for both virus effects and oncogenesis, which are normally cleared in the glomeruli. In this aspect it is important that the glomeruli have a special position in the body, inasmuch as the kidneys receive 25% of the cardiac output.

Within an infected host viruses can establish long-term persistence. Three general conditions must be fulfilled. The virus must be able to infect host cells without killing them. There must be mechanisms for maintaining the viral genome in host cells. Finally, the virus must avoid detection and elimination by the host's immune system. Viruses that persist in humans include cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B (HBV) and -C (HCV) viruses, human papilloma virus (HPV), parvovirus B19, human immune deficiency virus (HIV) and polyoma virus. Most of these are known to be able to cause cancer in immune deficient patients [7], but some (EBV, HBV, HCV, parvovirus B19, HIV) are known also to be able to cause GN, and still more nephritogenic/oncogenic viruses doubtless remain to be detected.

Hepatitis B virus, especially in its chronic form, can cause GN and polyarteritis nodosa [8]. The GN is often membranous (<5% of adults are HBV associated), but membranoproliferative GN, mesangioproliferative GN and even IgA and minimal change GN also can be seen. HCV is often associated with a cryoglobulinemic membranoproliferative GN, however, mesangioproliferative and membranous GN forms can be seen [reviewed in 9]. This etiology is underlined by the occurrence of a de novo membranoproliferative GN in HCV infected kidney transplanted patients [10].

Viruses from the herpes group also have been postulated as causing GN. Those are CMV linked to membranoproliferative GN [11], EBV linked to IgA GN, membranous GN, minimal change GN, focal sclerosing GN and immune complex-mediated GN [12].

Epstein-Barr virus has been linked to non-Hodgkin lymphomas [13, 14] and the same has been disputed for HCV [reviewed in 15]. Furthermore, EBV persistence seems to be associated with a far greater spectrum of malignancies than previously anticipated [13, 14].

For some tumors, such as gastric mucosa-associated lymphoid tissue (MALT) lymphoma and non-Hodgkin lymphoma after bone marrow transplantation and organ transplantation, tumor regression has been observed when the infection was treated [16] and/or the immunosuppression was decreased or ceased. Similar observations have been made in cases of CMV [17], HBV [18] and HCV-induced GN [19] and lymphoma [20].

Recurrence of GN after transplantation has been evaluated in an extensive series [21] with rates for histologic/clinical recurrence on 25/25% for membranous GN, 25/12.5% for membranoproliferative GN type I, and 85/5% for type II. There are also reports of the repetitive recurrence of membranous GN in successive transplants [22]. It is striking that those GN that recur under the extensive post-transplant immunosuppressive regime are the same as those where the effect of that therapy is most disputed when they occur in the native kidneys, and it can be speculated that the culprit is not so much the immunologic feature of GN as an underlying cause, which very well may be a virus. Along this line of thought, it is

noteworthy that most recurrences are seen in GN of known or suspected virus etiology. This theory is further emphasized by the findings of resolution by antiviral drugs of some, but not all, of the GN caused by CMV [17] using ganciclovir and HBV [23] and HCV [24] by α-interferon (alone or combined with ribavirin), which has been found to be effective even in some cases of post-transplant lymphoproliferative disease (PTLD) [17, 20]. Reports on the resolution of hepatitis B [25] and -C [26] virus-related membranoproliferative glomerulonephritis after orthotopic liver transplantation is in agreement with this theory.

Cellular proliferation is regulated by several kinasic complexes associated with cyclins and their catalytic subunits, cyclin-dependent kinases (CDKs), which trigger and co-ordinate the cell division cycle phases and the passage through the restriction point into the S-phase of the cell cycle. The activities of CDKs are constrained by CDK inhibitory proteins. These factors play a role both in glomerulonephritis and neoplasia. The restriction point is deregulated in many tumor cells and upon infection with DNA tumor viruses. HHV-8, which causes Kaposi's sarcoma and body cavity lymphoma, encodes viral cyclin complexes with CDKs that are resistant to CDK inhibitors [27]. CDK1 and cyclin A expression is linked to cell proliferation and associated with a prognosis in non-Hodgkin's lymphomas [26, 28]. The proliferation of mesangial cells is a common feature of many glomerular diseases. The transcription factor E2F1 is overexpressed, which facilitates the mesangial cell cycle and later induces apoptosis. It up-regulates G_1 cyclins and hence CDKs 4 and 2 [28, 29]. A viral induced imbalance in CDKs/CDK-inhibitors then could be hypothesized as a common cause for the association of GN and lymphoproliferation.

Although a certain proportion of glomerulonephritides seem to be caused by viruses, not all are initiated by them, and those viruses in question only induce GN in a proportion of the infected individuals, and even fewer proceed to malignancy. Thus, other factors are necessary, such as the immunosuppression regimen, genetics of the infected individuals, or simply a disturbance of the fine balance in CDK and CDK-inhibitors.

The findings in our current study seem very similar to what has been learned from transplantation, where prophylaxis against herpes virus concomitant with the immunosuppressive treatment seems to diminish the risk for virus infections and post-transplant lymphomas [30]. If further substantiated, the hypothesis of a virus etiology for most GN and particularly the neoplastic complication could lead to an altered therapy, in which anti-virus drugs such as acyclovir could be of value.

In conclusion, the excess cancer rate in patients with biopsy-proven glomerulonephritis could be the result of several factors. It could be underlying undiagnosed tumors whose antigens have initiated glomerulonephritis, or the result of immunosuppressive therapy that initiated or energized tumor cells. Based on our findings, there is some support for a virus etiology, with the hypothesis that infections with persistent viruses of the herpes and hepatitis groups first caused the glomerulonephritides and then the malignancies. This could be through a common pathogenesis of disturbed cyclin kinase/inhibitor balance. This hypothesis calls for other studies to be done that are specifically designed to investigate this issue, and that will utilize more data on patient characteristics and confounders.

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