CLINICAL RESEARCH STUDY

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Risk and Prognosis of Cancer in Patients with Nephrotic Syndrome

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ABSTRACT

BACKGROUND: Nephrotic syndrome may be a marker of occult cancer, but population-based studies of this association are lacking. Therefore, we examined the risk and prognosis of cancer in patients with nephrotic syndrome.

METHODS: We conducted this population-based cohort study in Denmark, including all individuals diagnosed with nephrotic syndrome between 1980 and 2010 without a preceding cancer history. We computed the 5-year risk of cancer accounting for competing risk by death and standardized incidence ratios (SIRs) of cancer in patients with nephrotic syndrome relative to the general population. We compared the 5-year mortality for patients with cancer after nephrotic syndrome with that for a cancer cohort without a history of nephrotic syndrome using Cox regression adjusted for age, gender, and comorbidity.

RESULTS: Of 4293 individuals with nephrotic syndrome, 338 developed an incident cancer during a median follow-up of 5.7 years. The 5-year risk of any cancer was 4.7% in patients with nephrotic syndrome, a 73% increased risk (SIR, 1.73; 95% confidence interval [CI], 1.55-1.92). The association was most pronounced for lung cancer, kidney cancer, lymphoma, and multiple myeloma. It was highest within 1 year of nephrotic syndrome diagnosis (SIR, 4.49; 95% CI, 3.68-5.42), but remained increased beyond 1 year (SIR, 1.34; 95% CI, 1.17-1.53). The 5-year mortality after cancer was 68.5% in patients with cancer with nephrotic syndrome and 63.4% in the cancer comparison cohort (adjusted hazard ratio, 1.20; 95% CI, 1.02-1.42).

CONCLUSIONS: Nephrotic syndrome is a marker of occult solid tumors and hematologic malignancies and is associated with a worsened cancer prognosis.

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KEYWORDS: Cohort studies; Mortality; Neoplasms; Nephrotic syndrome; Prognosis; Risk

Nephrotic syndrome, defined by proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia, is a rare condition, with an incidence of 3 per 100,000 person-years in adults.[1] Nephrotic syndrome is most often caused by membranous glomerulonephritis, minimal change disease, or other glomerular disease but also can be secondary to diabetes mellitus, amyloidosis, use of certain drugs, or some infections.[1] For several decades, case reports and case series have suggested a link between nephrotic syndrome and occult cancer.[2-20] However, these case series were small (1-200 study subjects), and the lack of a comparison group hampers their interpretation. Some evidence of cancer risk in patients with membranous nephropathy and other glomerular disease also exists, but there is only a limited understanding of these relations at a population level.[21-23]

There are no formal epidemiologic studies of the association between nephrotic syndrome and cancer in a population-based setting. Accurate estimates of the cancer risk in patients with nephrotic syndrome are needed to confirm the suggested association, to understand the clinical course of nephrotic syndrome, and to improve the care of

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affected patients. Although cancer is associated with a 2- to 8-fold increased mortality in patients with glomerulonephritis,[22,23] there are no data on the impact of nephrotic syndrome on mortality in patients with cancer.

To clarify these issues, we examined the risk of cancer after hospitalization or specialist care for nephrotic syndrome and compared it with that in the general population. Furthermore, we compared mortality of cancer after nephrotic syndrome with patients with cancer without a history of nephrotic syndrome.

CLINICAL SIGNIFICANCE

- We found that nephrotic syndrome is a marker of occult cancer and associated with a worsened cancer prognosis.
- Lung cancer and multiple myeloma may be the focus of targeted clinical workups based on clinical suspicion of co-occurring signs or symptoms in patients with nephrotic syndrome.

METHODS

Study Population and Data Sources

We conducted this nationwide cohort study in Denmark within a cumulative population of 7,821,778 people in the study period between January 1, 1980, and December 31, 2010.[24] The Danish National Health Service provides free tax-funded medical care for all Danish residents.[25] Therefore, hospital services are essentially population-based. The unique civil registration number assigned to every Danish citizen and included in all Danish medical databases allowed us to electronically link several medical databases.[24,25]

Nephrotic Syndrome

We used the Danish National Registry of Patients to establish a cohort of individuals with an incident inpatient or outpatient clinic diagnosis of nephrotic syndrome in the study period among Danes without prior cancer.[26] Incident cases of nephrotic syndrome were ascertained through the universal referral system to secondary and tertiary care existing in Denmark.[27] We eliminated prevalent cases with a diagnosis of nephrotic syndrome during 1977-1979.

The Danish National Registry of Patients has recorded information from all acute, nonpsychiatric hospitalizations since 1977 and from all hospital specialist clinic and emergency department visits since 1995, including virtually all acute and specialist medical care in Denmark.[26] The information includes, among other elements, dates of admission and discharge or dates of service, and up to 20 diagnoses, classified according to the International Classification of Diseases, 8th revision (ICD-8) through 1993 and to the 10th revision (ICD-10) thereafter. For the ICD-10 period (1994-2010), in which glomerular disease was classified uniformly, we searched for potential underlying glomerular disease diagnosed within ±6 months of nephrotic syndrome. Codes for nephrotic syndrome and potential underlying glomerular diseases are provided in **Appendix Table 1**, online. Patients with nephrotic syndrome were followed until a first cancer was reported, an emigration or death occurred, or the end of the follow-up period (December 31, 2010). Data on death were obtained from the Danish Civil Registration System, which has maintained data on civil registration number, residence, migration, vital status (dead or alive), and exact date of death for all Danish residents since 1968.[24]

Cancer

Through linkage with the Danish Cancer Registry (DCR), we identified incident cancers after a diagnosis of nephrotic syndrome. The DCR has recorded all incident cancer cases in Denmark since 1943.[28] Data include, among others, the month/year or exact date of diagnosis and cancer site reclassified to the Danish version of the ICD-10. Details of the DCR protocols and practices have been published.[28-30] Comprehensive validation has shown that the registry is 95% to 98% complete and valid.[29]

Mortality in Patients with Cancer with and Without Preceding Nephrotic Syndrome

We compared the mortality of incident cancers in patients with nephrotic syndrome with that in patients with cancer without any previous nephrotic syndrome diagnosis using a cancer comparison cohort. We created the comparison cohort by matching each nephrotic syndrome patient with cancer to 5 patients with cancer with no history of nephrotic syndrome. This comparison cohort was identified from the DCR with matching on cancer site, age at time of cancer diagnosis (in 5-year age groups), sex, and year of cancer diagnosis (in 5-year calendar time groups). Data on all-cause mortality were obtained from the Civil Registration System.[24] We used the Charlson Comorbidity Index score to adjust for confounding by comorbid diseases.[31,32] For each study patient, we computed the Index score using inpatient or outpatient clinic diagnoses recorded in the National Registry of Patients within the last 5 years before the cancer diagnosis. The 5-year period was chosen to capture comorbidity similarly for all patients included during the 30-year study period and because patients with considerable chronic conditions are likely to have a hospital contact within a 5-year period. Three levels of comorbidity were defined: low (for patients with no recorded underlying comorbid conditions); moderate (Index score of 1-2); and high (Index score of 3+). Diagnoses of cancer and renal diseases were excluded from the Index because they respectively defined our study cohorts and exposure variable.

Statistical Analysis

We started follow-up at the diagnosis of nephrotic syndrome and estimated the 5-year risks of incident cancer as the

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