Long-Term Risk of Cancer in Membranous Nephropathy Patients

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Background: There is a well-known association between membranous nephropathy (MN) and cancer, and patients with MN usually are examined for cancer at the time of diagnosis. The long-term risk of cancer after MN is not well studied.

Study Design: Cohort study with record linkage between the Norwegian Kidney Biopsy Registry and Norwegian Cancer Registry.

Setting & Participants: 161 patients with MN from 1988 to 2003.

Predictor: Patients with MN compared with the age- and sex-adjusted general Norwegian population.

Outcomes: Cancer diagnosis reported through 2003.

Results: Mean duration of follow-up was 6.2 years (range, 0.1 to 15 years). 33 patients developed cancer; including 24 patients with cancer after the diagnosis of MN. Median time from diagnosis of MN to diagnosis of cancer was 60 months (range, 0 to 157 months). Mean annual incidence ratio of cancer was 2.4/100 person-years (2.1/100 person-years in the 0- to 5-year period and 2.8/100 person-years for the 5 to 15 years after kidney biopsy). During the 0 to 15 years after the diagnosis of MN, the expected number of cancers was 10.7, resulting in a standardized incidence ratio of cancer of 2.25 (95% confidence interval, 1.44 to 3.35). In the 5 to 15 years after diagnosis, standardized incidence ratio was 2.30 (95% confidence interval, 1.19 to 4.02). Patients with MN who developed cancer were older (65 versus 52 years; $P < 0.001$). Patients with cancer and MN had a greater mortality rate than patients without cancer (67% versus 26%; $P < 0.001$).

Limitations: Follow-up treatment after MN with cytotoxic and immunosuppressive medications is not known.

Conclusions: An increased risk of developing cancer is observed after the diagnosis of MN, which persists for many years.

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INDEX WORDS: Membranous nephropathy; cancer; nephrotic syndrome; proteinuria.

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in older patients, and the morphological pattern of this renal disease is well recognized by using standard light and electron microscopy.[1]

The concept of paraneoplastic glomerulopathy was introduced in 1922 by Galloway[2] and refers to clinical manifestation of a renal disease that appears to be secondary to malignant tumors and may be caused by secretion of cancer-cell products.[3-8] An association between MN and cancer was described decades ago by Lee et al[9] and later was reported frequently,[8,10-18] although a substantial part of this information was based on case reports.[7,19-28] The frequency of cancer in patients with MN is a matter of debate.[29] In a registry-based analysis, Birkeland and Storm[11] reported a cancer incidence twice as high as expected compared with the general Danish population, whereas in a recent study, Lefaucheur et al[14] reported a risk 10 times greater than expected. The discrepant results may be caused by method differences. However, no study investigated the annual incidence rate of cancer after the renal diagnosis was made. Such information is of

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major importance for follow-up examinations of patients with MN. Generally, the current recommendation regarding the association between MN and cancer[1,11,13,14] is to search for cancer in all patients presenting with MN and nephrotic syndrome. However, if a cancer is not found at the initial workup, an additional search usually is not done in the absence of suggestive symptoms or findings.

In Norway, cases of MN have been recorded in the Norwegian Kidney Biopsy Registry since 1988, and all patients with cancer have been recorded in the Norwegian Cancer Registry since 1953. We linked these 2 registries to study the incidence of cancer in a cohort of patients with MN and compared the incidence of cancer in patients with MN with the expected incidence of cancer in the age- and sex-adjusted general Norwegian population. The annual incidence of cancer in this cohort was studied for 0 to 15 years after the diagnosis of MN was made, an approach that represents much longer follow-up than in previous studies. Our main focus in the present study is to evaluate current diagnostic and follow-up strategies regarding cancer in patients with MN.

METHODS

The study was approved by the local ethical committee, The Norwegian Social Science Data Services, and The Norwegian Data Inspectorate.

The Norwegian Kidney Biopsy Registry was established in 1988. The completeness of registration is estimated to be approximately 90% of all kidney biopsies performed in Norway (population, 4.5 million) since 1988. At the end of 2003, the number of registered biopsies was approximately 6,000. The registry includes extensive morphological, clinical, and laboratory information at the time of kidney biopsy.

The Norwegian Cancer Registry was established in 1953, and registration of cancers in Norway has been based on compulsory reporting of cancer cases by hospital departments and histopathologic laboratories and death certificates from Statistics Norway. The Cancer Registry of Norway gives complete coverage of the population for all cancer sites except basal cell carcinoma of the skin, which was excluded from the present analysis. Completeness of registration is documented to be 98% to 99% for solid tumors.[30,31] Annual incidence rates for cancer and cancer subtypes are available for both sexes, different age groups in 5-year age intervals (ages 50 to 54 years, 55 to 59 years, and so on), and for different calendar periods in 5-year intervals (1985 to 1989, 1990 to 1994, and so on). This information allows calculation of a reliable and accurate estimate of the expected number of cancers in any given cohort.

Identification of Patients

From 1988 to 2003, patients with MN were identified in the Kidney Biopsy Registry by searching for MN and proteinuria.

Identification of Cancer in Patients With MN

We linked the 2 registries by using the unique Norwegian 11-digit personal identification number, making linkage easy and reliable.

Survival data status was obtained from The Peoples Register of Norway, with data updated until October 2006.

Clinical Data at Time of MN Diagnosis

Clinical data at the time of MN diagnosis were obtained from the Norwegian Kidney Biopsy Registry and included age in years, estimated glomerular filtration rate (GFR; 4-variable Modification of Diet in Renal Disease Study equation), serum albumin level in grams per deciliter, and level of proteinuria (protein in grams per 24 hours) in the groups with and without cancer in the post–kidney biopsy follow-up period.

Morphological Data for Kidney Biopsies

Morphological data for kidney biopsies were obtained from the Norwegian Kidney Biopsy Registry and included degree of nephron loss (denoted as none, little, moderate, and severe), glomerular sclerosis (none, little, moderate, and severe), chronic interstitial inflammation (none, acute, and chronic), chronic interstitial fibrosis (none, focal light, focal severe, and diffuse), and glomerular immunodeposits (none, diffuse, and focal) of immunoglobulin A (IgA), IgG, IgM, complement factor 3 (C3), and C1q.

Statistical Analyses

Comparing patients with and without cancer in the follow-up period, independent-samples *t*-test was used with continuous variables and chi-square test was used with categorical variables. Data are presented as mean ± SD of the mean.

Definition of Observation Period

The observation period of patients is defined as the time between kidney biopsy and December 31, 2003; death; or emigration from Norway, whichever came first, and ranged from 0.1 to 15 years (mean, 6.2 years), with a total of 1,005 patient-years of observation.

Calculation of Standardized Incidence Ratio of Cancer After MN

Standardized incidence ratios (SIRs) were calculated as ratios between observed and expected numbers of all cancers, as well as site-specific cancers. The expected number of cases was calculated by multiplying person-years of follow-up by sex-specific national cancer incidence rates in 5-year calendar periods and 5-year age groups. This means that for all person-years of follow-up in 1990 to 1994, 1995 to 1999, and so on, the cancer rate of that particular period was used. For all person-years of follow-up for a patient