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Nonsteroidal anti-inflammatory drug use is associated with cancer risk reduction in chronic dialysis patients

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Previous studies have shown that nonsteroidal anti-inflammatory drug (NSAID) use might be associated with a lower risk of developing cancer in the general population. Patients on dialysis have increased risk for cancer, but there are no studies to determine the relationship between NSAID use and cancer risk in these patients. To identify any association between NSAID use and cancer risk in patients with end-stage renal disease on dialysis, we used Taiwan's National Health Insurance database to conduct a nationwide population-based, propensity score–matched cohort study. All cancers between groups were compared by Cox proportional hazards models. Compared to nonuse of NSAIDs, the use of non-COX-2-selective inhibitors (hazard ratio 0.81, 95% confidence interval 0.67–0.97) or COX-2-selective inhibitors (0.78, 0.62–0.98) was associated with a lower risk of developing cancer. NSAID use reduced the risk of respiratory (0.39, 0.19–0.79), breast (0.41, 0.19–0.89), kidney (0.58, 0.38–0.88), digestive tract (0.64, 0.49–0.85), and bladder cancers (0.73, 0.55–0.96). NSAID use, however, significantly increased risk for upper gastrointestinal bleeding (odds ratio, 1.15, 1.07–1.23) but not adverse cardiac or cerebrovascular events. Thus, NSAID use was associated with a lower risk of developing cancer in chronic dialysis patients; however, they should still be used with caution due to the side effects of gastrointestinal bleeding.

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Nonsteroidal anti-inflammatory drugs (NSAIDs), used since a very long time to relieve fever, inflammation, and pain, are being investigated to determine the nature and extent of their anticancer properties. Overexpression of the inducible cyclooxygenase-2 (COX-2) gene and dysregulation of prostaglandin biosynthesis have an important role in the carcinogenesis and the metastatic potential of many cancers.[1] NSAIDs exert their cancer chemopreventive effect by inhibiting the conversion of arachidonic acid to prostaglandin and thromboxanes by acting on COX enzyme.[2]

Patients on dialysis are potentially at an increased risk of cancer for several reasons, including impaired immune system function, impaired DNA repair, reduced antioxidant defense, accumulation of carcinogenic compounds, and chronic infection and inflammation.[3,4] Previous studies have demonstrated that NSAID use might be associated with a lower risk of developing cancers in the general population.[5,6] Chronic dialysis patients have increased risk for cancer, and thus the role of chemoprevention in these patients might be important. However, data are still lacking regarding whether NSAIDs exert an effect on reducing cancer risk in dialysis patients, and whether these patients should be offered this treatment.

Therefore, we designed a nationwide, population-based case–control study to explore the association between both non-COX-2-selective and COX-2-selective inhibitors and cancer risk. Our intent is to examine the impact of NSAIDs

on the cancer risk, dose response, and adverse outcomes between the users and nonusers in chronic dialysis patients.

RESULTS

Characteristics of the study population before and after matching

Figure 1 shows the flowchart for patient selection. A total of 86,446 chronic dialysis patients were included in our 10-year study cohort. After excluding patients who were under 20 years of age ($n = 585$), those who were on dialysis for <90 days ($n = 12{,}171$), those who had antecedent malignancies ($n = 3430$), those who were diagnosed with cancer within 365 days of enrollment ($n = 941$), and those whose follow-up period was less than 365 days ($n = 13{,}577$), 55,742 patients were enrolled for analysis. Of them, we accrued 12,486 NSAID users and 43,256 nonusers. Before matching, NSAID users were younger, more female predominant, had lower economic status and fewer comorbid conditions, and had received more concomitant medications than non-users. By using the propensity score generated from logistic regression models, conditional on baseline covariates, we matched 11,699 NSAID users with the same numbers of nonusers. Table 1 shows the comparison of the demographic characteristics, dialysis modality, economic status, urbanization, use of aristolochic acid, comorbidities, and concomitant medications between the NSAID users and nonusers before and after matching the propensity scores and *P*-values for the between-group differences (other details are shown in Supplementary Table S1 and Supplementary Figure S1 online).

Incidence rates and HRs for cancer according to NSAID dose in the chronic dialysis cohort

A total of 2217 cancers occurred in dialysis patients during the follow-up period of 220,756 person-years. The overall incidence rate was 1004.5 cancers per 100,000 person-years. Among the male and female patients, the cancer incidences were 988.9 and 1017.9 per 100,000 person-years, respectively. Compared with the general population, chronic dialysis patients had a higher risk for cancer (standardized incidence ratios 1.62, 95% confidence interval (CI) 1.55–1.68). The details are shown in Supplementary Table S2 online.

Compared with NSAID nonusers, NSAID users had a significantly lower risk for cancer (crude hazard ratio (HR), 0.58; 95% CI 0.52–0.64), and the results remained consistent after adjusting for different covariates in the propensity score–matching model (Table 2 and Supplementary Table S3 online). As shown in Table 2, we observed a dose-response relationship between NSAID use and cancer risk after controlling for confounders. The HRs in the propensity score–matched Cox proportional hazards model were 0.82 (95% CI 0.68–0.99), 0.78 (95% CI 0.67–0.92), and 0.55 (95% CI 0.41–0.75) for NSAID cumulative defined daily doses (cDDDs) of 28–90, 91–365, and >365, respectively, relative to no NSAID use (<28 cDDDs). In a subanalysis according to NSAID subtypes, compared with nonuse of NSAIDs, the use of both non-COX-2-selective inhibitors (HR 0.81; 95% CI 0.67–0.97; $P = 0.019$) and COX-2-selective-inhibitors (HR 0.78; 95% CI 0.62–0.98; $P = 0.034$) was associated with a lower risk of developing cancer.

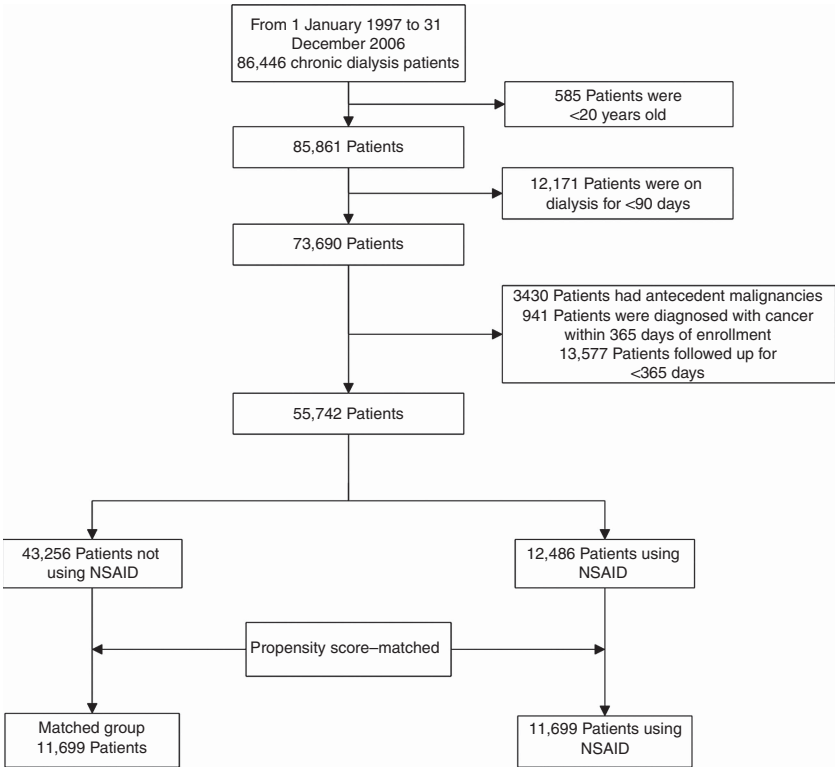

Figure 1 | Patient selection flowchart. NSAID, nonsteroidal anti-inflammatory drug.