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Research Article

Cancer Prevention Research

Orally Active Vitamin D for Potential Chemoprevention of Posttransplant Malignancy

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Abstract

Posttransplant malignancy (PTM) is a limiting factor both for patient and allograft survival in kidney transplant recipients (KTRs). We hypothesized that active vitamin D compounds (AVD) could reduce PTM development in KTRs. Ambulatory KTRs in a Japanese prospective cohort were followed from August 2007 to November 2010. The outcome of interest was newly diagnosed PTM. A propensity score (PS) of having received AVDs was estimated using 26 clinically relevant factors. We used the Cox proportional hazards model with stratification by PS tertiles on the assumption that baseline hazard functions differ among tertiles. As sensitivity analyses, we used inverse probability weighting and PS matching. Among 218 participants, the median age was 50 (interquartile range [IQR], 40 to 59) years, 63.3% were male, median time since transplantation was 11.2 (IQR, 5.2 to 17.1) years, and mean estimated GFR was 41.3 (SD, 15.6) mL/min per 1.73 m^2. At baseline, 42.2% had been treated with AVDs mainly for glucocorticoid-induced osteoporosis. AVDs used were calcitriol (58.7%) and alfacalcidol (41.3%). During follow-up, PTM developed in 5.4% of 92 AVD users and 8.7% of 126 nonusers. Poor vitamin D status was common in the participants, but the serum 25-hydroxyvitamin D level was not significantly associated with PTM in Cox regression analysis. After stratifying patients by PS tertiles, we found that AVDs were significantly associated with a lower risk of PTM (HR 0.25 [0.07 to 0.82]). Sensitivity analyses yielded similar results. AVDs are potential chemopreventive agents against PTM in KTRs. *Cancer Prev Res; 5(10); 1229–35. ©2012 AACR.*

Introduction

Posttransplant malignancy (PTM) is the second to third leading cause of death among kidney transplant recipients (KTRs) after cardiovascular disease and/or infection (1–3). There is a 3- to 5-fold increased incidence of malignancy among KTRs when compared with the age- and sex-matched general population (3, 4). The incidence of death from cancer is now increasing and becoming a limiting factor both for graft and patient survival (2, 3, 5–7). Thus, more effective strategies for disease control and prevention of PTM are needed to improve the outcomes of KTRs (8).

In the Kidney Disease Improving Global Outcomes clinical practice guidelines, an individualized screening plan for PTM is recommended (not graded; ref. 8). However, the growth of cancers in transplant recipients is often more rapid than in the general population and the prognosis is poor (9, 10). This is a significant limitation of disease control with early detection by regular screening and treatment of PTM. Therefore, the most valuable approach to reducing cancer morbidity and mortality should lie in primary prevention.

Poor vitamin D status, defined as low serum concentration of 25-hydroxyvitamin D [25(OH)D], is very common in KTRs (11, 12). Vitamin D deficiency is associated with the development of, and mortality from, various types of cancer, such as colon, pancreas, lung, prostate, breast, ovary, and non-Hodgkin lymphoma (13–17). The pretransplant serum 25(OH)D level has also been shown to be an important determinant for subsequent development of PTM (18). These results have been supported by the findings that extrarenal 1-α-hydroxylase in various tissues contributes to the local production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the most biologically active vitamin D metabolite (19), along with a number of experimental studies reporting

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that $1,25(OH)_2D$ induces cell differentiation and apoptosis, inhibits proliferation and angiogenesis, and decreases metastatic potential (20). Thus, both nutritional and active vitamin D compounds (AVD) are suggested to be potential anticancer therapeutics (21, 22) and are now anticipated as potential chemopreventive agents of PTM in KTRs (15).

There have been 2 reports of subanalyses of randomized controlled trials (RCT) showing a lower incidence of cancer in postmenopausal women receiving nutritional vitamin D and calcium supplementation (23, 24). In addition, oral active vitamin D therapy is associated with reduced mortality from malignancies in hemodialysis patients (25). However, no study has yet described the effect of AVDs as chemopreventive agents against PTM, although they are often prescribed for glucocorticoid-induced osteoporosis or persistent hyperparathyroidism in clinical practice. Here, we hypothesized that AVDs could reduce the incidence of PTM and evaluated their effects in a prospective cohort of ambulatory KTRs.

Materials and Methods

Study participants

This study examined a prospective cohort of KTRs at the outpatient department of kidney transplantation in Inoue Hospital, Osaka, Japan. Between August 2007 to May 2008, 262 ambulatory KTRs at more than 1 year after transplantation were enrolled in the prospective registry and followed up until November 2010. Patients excluded were those with acute kidney injury at enrollment ($n = 5$), subsequent transplantation ($n = 5$), active cancer ($n = 2$), and documented nonadherence ($n = 3$). Also excluded were patients with a history of parathyroidectomy ($n = 15$), all of whom had received AVDs for the management of hypocalcemia; those with type 1 diabetes ($n = 9$), all of whom had not received AVDs; and those who were pregnant or who wished to become pregnant ($n = 4$) to whom AVD administration required extra care. As a result, 218 (83.2%) patients were included in this study. Patients were considered lost to follow-up if no contact could be documented for more than 3 months. We continued to follow up of the participants even if they restarted dialysis for allograft failure. Patients were censored at death or when considered to be lost to follow-up from the date of the last documented contact. Patients were also censored if they stopped or started to use AVDs.

We adhered to the Declaration of Helsinki throughout this study. The ethics committee of Inoue Hospital approved the study protocol, and all of the patients provided written informed consent to participate in all aspects of the study.

Data collection

The primary exposure of interest was baseline AVDs defined as calcitriol and alfacalcidol. None of the patients received falecalcitriol or paricalcitol. We did not prescribe cholecalciferol, ergocalciferol, or calcium bicarbonate for these patients. Other baseline clinical variables included age, sex, body mass index (BMI), season of measurement, time since transplantation, dialysis vintage before transplantation, as well as history of diabetes, HCV infection, and malignancy. Also included were donor information (donor age at transplantation, and living or cadaveric donor), histocompatibility (ABO compatibility), and the type of prescribed immunosuppressants (tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, mizoribine, and predonisolone). None of the patients received everolimus. We also included seasonality as a covariate because serum 25(OH)D levels change with seasonal variation in solar ultraviolet-B (UV-B), the major source of vitamin D. According to the mean monthly cumulative UV-B dose during 1994 to 2008 (26), we divided the season of measurement into 3 categories: low season (November, December, January, and February), middle season (March, April, September, and October), and high season (May, June, July, and August). Additional baseline laboratory variables were serum levels of albumin, creatinine, calcium corrected for albumin (27), phosphate, intact parathyroid hormone (iPTH), 25(OH)D, and presence or absence of proteinuria [defined as the dipstick test $\geq(1+)$]. We used the Japanese equation for GFR estimation [estimated GFR (eGFR) (mL/min per 1.73 m^2) $194 \times \text{Serum creatinine}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female)] (28).

The primary outcome of interest was the time to the development of PTM, defined as the time from the enrollment date to the documented date of diagnosis. We recommended that patients undergo annual cancer screening tests: abdominal ultrasonography, plain chest and abdominal computed tomography, gastrointestinal fiberscopy, and detection of fecal occult blood and tumor markers. We also carried out neck ultrasonography every year because this prospective cohort study was originally begun to evaluate persistent hyperparathyroidism after kidney transplantation. All patients with suspected PTM were referred to Osaka University Hospital or Sumitomo Hospital for confirmation and management of PTM.

25(OH)D levels

Peripheral blood was collected from each participant at inclusion. Serum samples were isolated and stored at −30°C for later analysis. In August 2011, the samples were sent to Kyowa Medex, Inc. and assayed for 25(OH)D using the DiaSorin LIAISON 25-hydroxy OH Vitamin D TOTAL Assay (DiaSorin, Inc.), a direct competitive chemiluminescence immunoassay. This assay was shown to be an accurate and precise automated tool for the determination of the serum 25(OH)D levels (29).

Statistical analysis

Values with normal distribution were expressed as mean ± SD; they were compared using unpaired Student *t* test or 1-way ANOVA. If values were not normally distributed, they were expressed as the median (interquartile range, IQR) and were compared using Mann–Whitney *U* test or Kruskal–Wallis test. Comparisons for nominal variables among groups were assessed with a χ^2 test. The cumulative

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incidence for the outcome was estimated using the Kaplan–Meier method and compared using the log-rank test.

Because the frequency of PTM development was not large enough to adjust for the baseline clinical characteristics (30), a propensity score (PS) of having received AVDs was estimated as a data reduction technique using logistic regression with the 26 factors given above. Natural log numerical values transformed in this regression were body mass index, time since transplantation, and dialysis vintage as well as serum levels of creatinine, phosphate, 25(OH)D, and iPTH. The C-index of this model was 0.841. The Cox proportional hazards model to estimate the effect of AVD treatment was stratified according to the PS tertiles, assuming that baseline hazard functions are different. As sensitivity analyses, we used 4 additional models: (i) adjustment for the logit of the PS (31), (ii) stratification for PS quartiles (31), (iii) optimal matching within the caliper of 25% or 30% of the standard deviation of the logit of the PS in which the maximum AVD user: nonuser ratio is 2:1 (32), and (iv) inverse probability weighting (33). The validities of the proportional hazard assumption and the linearity assumption were checked by adding time-dependent interaction variables and quadratic terms for each of the predictors in the models, respectively. A P value of less than 0.05 for 2-sided tests was considered significant, and CIs reported are 95% intervals. All analyses were conducted using STATA/SE 11.1 for Windows (STATA Corp. LP).

Results

Baseline patient characteristics are listed in Table 1. For the 218 subjects, median age was 50 (interquartile range [IQR], 40 to 59) years, 63.3% were male, median time since transplantation was 11.2 (IQR, 5.2 to 17.1) years, and mean eGFR was 41.3 (SD, 15.6) mL/min per 1.73 m^2. At baseline, 92 (42.2%) had received AVDs mainly for treatment of glucocorticoid-induced osteoporosis. Of these, 56 patients (58.7%) had been given calcitriol and 41 (41.3%) alfacalcidol. The median doses were 0.5 (IQR, 0.5 to 0.5) μg and 0.5 (IQR, 0.25 to 1.0) μg for calcitriol and alfacalcidol users, respectively. According to the Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines (34), 83 patients (38.1%) were deficient in vitamin D, 128 insufficient (58.7%), and only 7 sufficient (3.2%; Fig. 1). AVD users, compared with nonusers, were significantly younger, had higher serum creatinine levels, and had had longer periods since transplantation. In AVD users, the serum iPTH levels were significantly lower and serum 25(OH)D levels were marginally higher than those in nonusers. During a median follow-up of 2.9 (IQR, 2.1 to 3.0) years, 4 AVD users and 4 nonusers died, and 5 AVD users and eleven nonusers developed PTM. The incidence rates of PTM were 2.1 (95% CI, 0.9 to 5.1)/100 patient-years and 3.5 (95% CI, 2.0 to 6.4)/100 patient-years for AVD users and nonusers, respectively. Only 1 patient was lost to follow-up. Table 2 shows the types of PTM developed during the study period. No skin cancer including melanoma developed in our patients.

The estimated incidence of PTM in a crude analysis was not significantly different between AVD users and nonusers ($P = 0.344$ by log-rank test; Fig. 2A). Also, there was no significant association between PTM and 25(OH)D level (HR, 1.00; 95% CI, 0.92 to 1.08). To adjust for the different baseline characteristics between AVD users and nonusers, we stratified the patients according to the PS tertiles and found that all observed variables were successfully balanced in each stratum except for serum iPTH levels in the highest tertile (median 41.3 [IQR, 28.1 to 57.7] pg/mL for AVD users versus median 55.6 [IQR, 41.5 to 63.1] pg/mL for nonusers, $P = 0.029$; Supplementary Table). We also confirmed that eGFR and the doses of each immunosuppressant were not statistically different. Cox proportional hazard regression with stratification by the PS tertiles revealed that AVD users had a significantly lower risk of PTM development (HR, 0.21; 95% CI, 0.07 to 0.65). After optimal matching based on PS within the caliper of 25% of the standard deviation of the logit of the PS, the Kaplan–Meier curve showed that the estimated incidence of PTM in AVD users was significantly lower than in nonusers ($P = 0.033$ by log-rank test; Fig. 2B), with a HR of 0.31 (95% CI, 0.10 to 0.97; Table 3). All other sensitivity analyses yielded similar results (Table 3). Further adjustment for natural log transformed serum iPTH, where we found a significant difference between AVD users and nonusers within the highest PS tertile, did not affect these results, as expected biologically.

Discussion

In this study, we showed a lower risk of PTM development in KTRs with AVDs using the Cox regression analysis adjusting for the baseline characteristics with stratification by PS tertiles. Among 228 KTRs with a time period since transplantation of over 1 year, vitamin D status was generally poor. During a median follow-up period of 2.9 (IQR, 2.1 to 3.9) years, 18 patients developed PTM. The incidence of PTM in this study was as high as 2.9 [95% CI, 0.2 to 4.8]/100 patient-years as a whole, consistent with previous reports (4, 9, 35–37). The significant association between AVD usage and a decreased incidence of PTM remained almost the same with several sensitivity analyses. Our preliminary results suggest a novel potential strategy to prevent PTM using a usual dose of AVDs with their well-known safety profiles, which are readily available and inexpensive.

KTRs are exposed to various kinds of risk factors for malignancy (9). In addition to conventional factors such as aging, sun exposure, cigarette smoking, and previous malignancy, factors such as chronic renal failure and the use of immunosuppressants contribute to PTM through their negative impacts on immunosurveillnce. We hypothesized that poor vitamin D status in KTRs may play a role as another risk factor and that AVDs could offer prevention against PTM. Although the relationship between vitamin D status and cancer has been reported both in the general population and pretransplant KTRs (18, 38), we could not find a significant association in our patients. This apparently conflicting result may have come from the decreased 1-α

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Table 1. Baseline characteristics of the participants

	Patients with AVDs ($n = 92$)	Patients without AVDs ($n = 126$)	*P* value
Basic information			
Age (y)	46.5 ± 11.2	51.6 ± 12.3	0.001
Male (%)	62.0%	64.3%	0.725
Body mass index	21.0 (19.4–23.0)	22.1 (19.7–24.5)	0.075
Time since transplant (y)	13.0 (7.4–17.0)	9.7 (3.5–17.2)	0.027
Dialysis vintage (y)	2.3 (1.1–4.9)	2.1 (0.8–5.1)	0.350
ABO incompatibility			0.106
Compatible (%)	82.6%	70.6%	
Incompatible (%)	8.7%	17.5%	
No information (%)	8.7%	11.9%	
Living donor (%)	82.6%	86.5%	0.428
Donor age (y)	51 (43–58)	51 (40–60)	0.679
Past history			
Diabetes			0.008
Type 2 (%)	2.2%	3.2%	
NODAT (%)	5.4%	19.8%	
Hepatitis C virus (%)	3.3%	4.0%	0.784
Previous cancer (%)	9.8%	7.1%	0.484
Medication			
Calcineurin inhibitor			0.393
Cyclosporine (%)	58.7%	52.4%	
Tacrolimus (%)	29.4%	38.1%	
None (%)	12.0%	9.5%	
Antiproliferative agent			0.028
Azathioprine (%)	31.5%	15.9%	
Mycophenolate mofetil (%)	44.6%	60.3%	
Mizoribine (%)	17.4%	16.7%	
None (%)	7.6%	8.7%	
Predonisolone (%)	97.8%	97.6%	0.920
AVD analogues			N/A
Calcitriol (%)	58.7%	N/A	
(μg/day)	0.5 (0.5–0.5)	N/A	
Alfacalcidol (%)	41.3%	N/A	
(μg/day)	0.5 (0.25–1.0)	N/A	
Laboratory data			
Albumin (mg/dL)	4.2 ± 0.3	4.3 ± 0.2	0.057
Creatinine (mg/dL)	1.54 (1.17–2.00)	1.35 (1.02–1.74)	0.011
eGFR (mL/min per 1.73 m^2)	38.6 ± 15.2	43.3 ± 15.6	0.014
Corrected calcium (mg/dL)	9.3 ± 0.5	9.2 ± 0.5	0.787
Phosphate (mg/dL)	3.2 (2.8–3.6)	3.1 (2.7–3.4)	0.241
Intact PTH (pg/mL)	54.0 (36.7–85.1)	72.7 (56.2–103.0)	<0.001
25(OH)D (ng/mL)	18.0 (13.8–21.7)	15.5 (11.7–21.1)	0.051
Urinary protein ≥30 mg/dL (%)	54.4%	45.2%	0.184
Season of measurement			0.006
High UV-B season (%)	45.7%	63.5%	
Middle UV-B season (%)	43.5%	29.4%	
Low UV-B season (%)	10.9%	7.1%	

NODAT, new-onset diabetes after transplantation; eGFR, estimated glomerular filtration rate.

hydroxylase activity and megalin expression in the allograft kidney with moderately impaired function (mean eGFR, 41.3 [SD, 15.6] mL/min per 1.73 m^2) due to the long period of time after transplantation (39). Moreover, the uptake of 25(OH)D by nonrenal cells expressing 1-hydroxylase is blunted in CKD patients (40). In contrast, AVDs, which have direct anticancer effects, showed a significant preventive effect against PTM.

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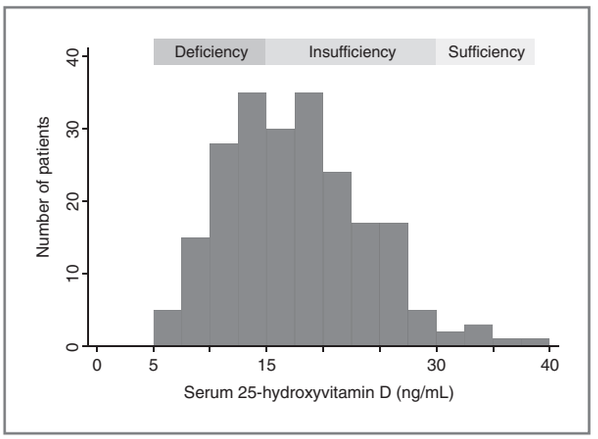

Figure 1. Vitamin D status according to the KDOQI guidelines.

Table 2. Types of posttransplant malignancy developed during the study period

Patients without AVDs ($n = 11$)	
Breast cancer	3
Renal cell calcinoma	2
Papillary thyroid carcinoma	2
Colon cancer	1
Bladder carcinoma	1
Uterine corpus carcinoma	1
Malignant lymphoma	1
Patients with AVDs ($n = 5$)	
Esophageal carcinoma	1
Malignant mesothelioma	1
Renal pelvic cancer[a]	1
Origin unknown	2

[a]Donor origin.

Another established risk factor of PTM is chronic virus infection: Epstein–Barr virus for non-Hodgkin lymphoma, hepatitis viruses B and C for hepatocellular carcinoma, and human papilloma viruses for cancers of the cervix, penis, vulva, vagina, anus, skin and oropharynx including the tonsils (9). In this study, we observed the development of malignant lymphoma. Our previous study also reported malignant lymphoma, uterine cancer, and liver cancer in Japanese KTRs (41). Conversely, there were no skin cancers, oropharynx cancers and Kaposi's sarcoma both in this study and our previous study. These results agreed with nationwide surveys of the Japanese renal transplant registry in 2003 and 2006 (5, 6) but not with reports from other countries (35–37, 42). With respect to Kaposi's sarcoma, this discrepancy can be explained by the difference in the prevalence of human herpes 8 infection (43). However, it remains unclear for skin cancers and oropharynx cancers because there has been no large epidemiological study on the prevalence of human papilloma virus infection in Japan.

Despite the enthusiasm for use of AVDs in chemotherapy against established cancer, clinical trials have failed to show definite benefits thus far (13). These results can be explained by the fact that the vitamin D receptor decreases with cancer development (21, 44), and experimental studies suggest that a very high dose of calcitriol is necessary for an anticancer effect on malignant cells (20). Therefore, AVDs would be ineffective against established cancers and may only work in the early stages of cancer or in prevention (13). There have been reports of nutritional vitamin D with or without calcium supplementation reducing the incidence of cancer in 2 subanalyses of RCTs (23, 24) and several meta-analyses for colorectal adenoma and breast cancer (45–47). The effect size of AVDs in our study (HR, 0.21) was very similar to that reported for cholecalciferol in the subanalysis of RCT by Lappe and colleagues (HR, 0.23; ref. 24). It also should be noted that a significant preventive effect was observed with usual doses of AVDs. The well-known safety profile of AVDs and their definite cost-effectiveness would ensure their application and thus enhance the importance of our findings.

This study has several limitations. First, our results might be biased to some extent as is true with all observational

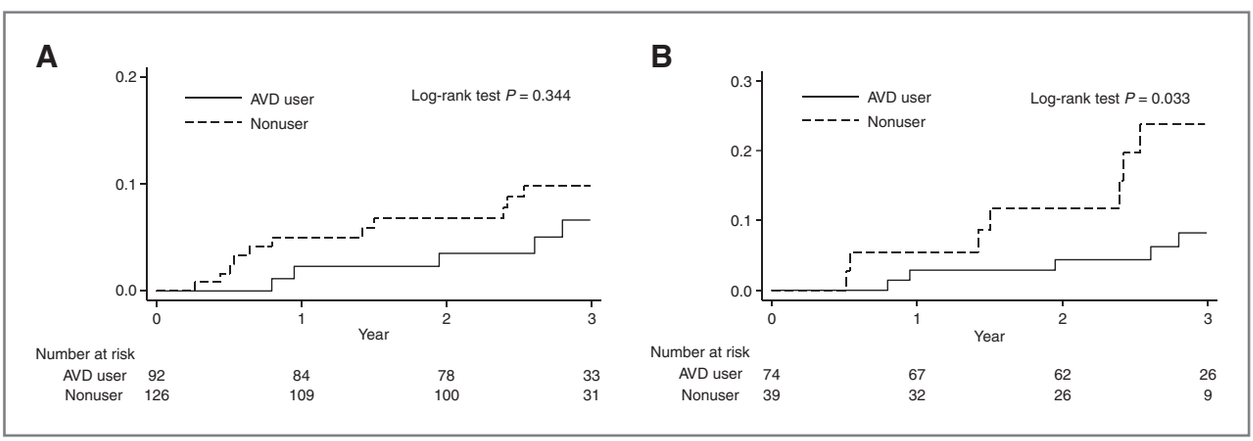

Figure 2. Estimated incidence of posttransplant malignancy in (A) the entire cohort and (B) the propensity-score matched patients.

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Table 3. Estimated effect of active vitamin D compounds

	HR	95% CI	*P* value
Stratification			
PS tertiles	0.25	(0.07–0.82)	0.022
PS quartiles	0.25	(0.08–0.82)	0.022
Adjustment for Logit (PS)			
	0.23	(0.07–0.76)	0.016
Optimal matching			
Caliper: 25% of Logit (PS)	0.31	(0.10–0.97)	0.044
Caliper: 30% of Logit (PS)	0.30	(0.10–0.95)	0.041
Inverse probability weighting			
	0.30	(0.10–0.90)	0.032

studies. Second, residual confounding may exist although we tried to adjust rigorously for the observed factors using a PS-based approach. Third, we could not adjust for unobserved factors such as smoking status, genetic disposition and human papilloma virus infection. As we did not administer the diet history questionnaire, dietary vitamin D may also remain a residual confounder. However, this is unlikely the case because we adjusted for serum 25(OH)D levels, which reflect dietary vitamin D intake if we take seasonality into account. Moreover, the estimated effect size of AVDs was similar in several sensitivity analyses, which suggests the robustness of our results. Another major limitation is limited statistical power. We could not show who would benefit most from AVDs or which type of cancer AVDs could prevent. The association between cancer development and AVD treatment or vitamin D status may depend on the cancer type (21).

In conclusion, we suggest a novel potential strategy to prevent PTM using a usual dose of AVDs. Further studies including randomized clinical trials evaluating the effect of AVD therapy as chemoprevention against cancer are needed.

Disclosure of Potential Conflicts of Interest

S. Takahara, Y. Tsubakihara, N. Ichimaru, J. Kaimori and T. Hamano belong to their respective departments receiving research grants from Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan), a company that is marketing calcitriol and alfacalcidol. T Hamano has served as a consultant to Kyowa Medex Co., Ltd. (Tokyo, Japan). These companies were not involved in the analysis of the results or in writing the manuscript. The other authors revealed no potential conflicts of interest.

Authors' Contributions

Conception and design: Y. Obi, N. Ichimaru, T. Hamano, K. Tomida, I. Matsui, K. Yazawa, Y. Kokado
Development of methodology: Y. Obi, N. Ichimaru, T. Hamano, K. Tomida
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Obi, T. Hamano, K. Tomida, N. Fujii, J.-ya Kaimori, Y. Kokado, N. Nonomura
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Obi, T. Hamano, I. Matsui
Writing, review, and/or revision of the manuscript: Y. Obi, N. Ichimaru, T. Hamano, I. Matsui, Y. Isaka
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Ichimaru, K. Tomida, M. Okumi
Study supervision: N. Ichimaru, T. Hamano, I. Matsui, M. Okumi, Y. Tsubakihara, H. Rakugi, S. Takahara, Y. Isaka

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Kyowa Medex Co., Ltd. measured serum 25-hydroxyvitamin D (Tokyo, Japan).

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