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Malignancy after Kidney Transplantation in Korea

Yongjung Park
Gangnam Severance Hospital, Yonsei University, Republic of Korea

According to the KONOS statistics, 21,977 kidney transplantations (KTs) were conducted during the 16 years from 2002 to 2017, with a consistent increase in number from 741 in 2002 to 2,163 in 2017. Although the use of immunosuppressive drugs increases graft survival, it also leads to considerable complications such as cardiovascular disease and cancer. Cancer incidence in KT recipients was reported to be three to five times higher than in the general population. The development of post-transplantation malignancy is one of the primary causes of morbidity and mortality in KT patients. The types of cancer reported to occur in KT patients vary across study populations. In Western countries, non-melanoma skin cancer, Kaposi sarcoma, lip cancer, and post-transplant lymphoproliferative disorder (PTLD) are relatively common. In Asian countries, renal cancer, gastric cancer, non-Hodgkin lymphoma, and transitional cell carcinoma occur more frequently in KT recipients. Our study was based on the National Health Information Database (NHID) containing all records of healthcare utilization by KT recipients. We investigated the types and risk factors of post-KT de novo cancer in a population cohort of the NHID in South Korea from 2002 to 2017. Data from 21,191 single-organ KTs performed in South Korea during the 16 years from 2002 to 2017 were reviewed, and among them, a total of 14,842 patients were finally evaluated to identify the incidence of various de novo cancers. We divided male and female patients in age groups with 5-year intervals in order to make a comparison with the annual report of the Korea Central Cancer Registry (KCCR). Cancer incidence during the follow-up period after KT between 2002 and 2017 was compared to the data from the KCCR, which is operated by the National Cancer Information Center (NCIC) and includes the age-adjusted cancer incidence per 100,000 person-years. The standardized incidence ratio (SIR) was calculated as follows: Standardized incidence ratio = Observed cancer incidence / Age-adjusted expected cancer incidence The observed cancer incidence was calculated by dividing the observed cancer cases by death-censored person-years during the study period. The age-adjusted expected cancer incidence was calculated by adjusting the 2017 annual cancer incidence of the KCCR according to the age-groups with 5-year intervals with the person-years according to the same age-group of our data. The number of KT patients of our data per year constantly increased from 452 in 2002 to 1454 in 2017. Among the total 14,842 patients included, 8729 (58.8%) were male, the mean age at the time of KT was

46.0 ± 12.4 years, and those aged between 50 and 59 accounted for the largest portion (30.3%), followed by those in their 40s (27.4%) and 30s (19.3%). A median follow-up period was 66 months. During the study period, 1,050 (7.6%) de novo cancer cases among 13,912 death-censored patients developed, including 605 cases in males and 445 cases in females. The overall SIRs of KT patients decreased as age increased. In male patients, the SIRs for the age groups 5–9, 10–14, 15–19, 20–24 showed statistically significant high values over 25.0. In female patients, the same age groups showed a significantly high SIR over 15.0. Overall, the age-adjusted cancer risk of KT patients was higher than that of the general population. The SIR for all cancers was 2.5 in males and 2.6 in females. The highest SIR was shown for Kaposi's sarcoma in both males and females. In males, prostate cancer (*n* = 104, 17.2%), renal cancer (*n* = 97, 16.0%), liver cancer (*n* = 83, 13.7%), and non-Hodgkin lymphoma (*n* = 64, 10.6%) were the most commonly developed cancers. In females, thyroid cancer (*n* = 105, 23.6%), breast cancer (*n* = 61, 13.7%), liver cancer (*n* = 43, 9.7%), and non-Hodgkin lymphoma (*n* = 37, 8.3%) were the most commonly developed cancers. **Table.** Age-adjusted standardized incidence ratio by de novo primary cancer types after kidney transplantation during 16 years.

Sex	Type/Site of Cancer	ICD-10	KCCR Incidence[1]	Observed (N)	Expected (N)	SIR	95% CI	*p*-Value
Male								
	All primary cancers	C00–C96	478.1	605	239.8	2.5	(2.2–2.8)	<0.0001
	Prostate	C61	50.0	104	20.0	5.2	(3.6–7.4)	<0.0001
	Kidney	C64	14.1	97	8.7	11.3	(6.8–18.7)	<0.0001
	Liver	C22	45.0	83	26.2	3.2	(2.3–4.5)	<0.0001
	Non-Hodgkin lymphoma	C82–C86, C96	10.6	64	5.3	12.2	(6.4–23.1)	<0.0001
	Stomach	C16	77.9	62	43.1	1.4	(1.1–2.0)	0.0129
	Thyroid	C73	23.6	49	15.6	3.1	(2.0–4.8)	<0.0001
	Lung	C34	72.9	39	30.2	1.3	(0.9–1.9)	0.1003
	Colon	C18	37.1	34	18.9	1.8	(1.1–2.8)	0.0066
	Skin, except malignant melanoma	C44	9.8	34	4.2	7.9	(3.8–16.5)	<0.0001

	Pancreas	C25	14.6	26	7.1	3.6	(1.9–6.9)	<0.0001
	Bladder	C67	13.8	21	5.7	3.7	(1.8–7.5)	0.0002
	Rectum	C19, C20	28.0	19	15.7	1.2	(0.7–2.1)	0.2567
	Kaposi's sarcoma	C46	0.2	11	0.1	184.5	(23.8–1428.9)	<0.0001
	Gallbladder	C23, C24	13.9	8	5.5	1.4	(0.6–3.4)	0.2316
	Myeloid leukemia	C92–C94	5.2	7	2.6	2.5	(0.8–7.3)	0.0539
Female								
	All primary cancers	C00–C96	428.6	445	173.7	2.6	(2.3–2.9)	<0.0001
	Thyroid	C73	78.5	105	40.0	2.6	(2.0–3.4)	<0.0001
	Breast	C50	86.9	61	46.4	1.3	(1.0–1.8)	0.0387
	Liver	C22	15.2	43	4.4	9.4	(5.1–17.5)	<0.0001
	Non-Hodgkin lymphoma	C82–C86, C96	8.0	37	2.7	13.2	(6.1–28.2)	<0.0001
	Stomach	C16	38.1	33	13.3	2.5	(1.6–3.9)	<0.0001
	Kidney	C64	6.6	33	2.7	11.7	(5.4–25.4)	<0.0001
	Colon	C18	28.2	30	8.6	3.6	(2.1–6.1)	<0.0001
	Ovary	C56	10.5	25	4.8	5.1	(2.6–9.8)	<0.0001
	Cervix uteri	C53	13.5	19	6.3	3.0	(1.6–5.7)	0.0004
	Rectum	C19, C20	16.5	17	5.7	3.0	(1.5–6.0)	0.0007
	Skin, except malignant melanoma	C44	12.6	16	2.3	6.5	(2.7–15.8)	<0.0001

Pancreas	C25	12.9	14	3.1	4.4	(1.9–10.2)	0.0003
Bladder	C67	3.3	14	0.8	19.9	(4.5–87.6)	<0.0001
Lung	C34	32.5	13	9.8	1.3	(0.7–2.6)	0.2038
Kaposi's sarcoma[2]	C46	0.1	4	0.0	341.3	(38.1–3053.0)	<0.0001

Abbreviations: KCCR, Korea Central Cancer Registry; SIR, standardized incidence ratio; CI, confidence interval. [1] 2017 annual cancer incidence per 100,000 persons, age-unadjusted; [2] Not listed in order of incidence. The cumulative cancer incidence at 12, 24, 60, 120, and 180 months after KT was 1.4%, 2.3%, 5.6%, 11.2%, and 18.4%, respectively. Until 157 months after KT, the cumulative cancer incidence rate increased linearly with the length of the follow-up period. The equation was determined as follow from our data, which had an R^2 of 0.9988: Cumulative cancer incidence (%) = 0.09295 x months after KT + 0.12285 (95% confidence intervals for the slope and y-intercept of 0.09245 to 0.09345 and 0.07737 to 0.16834, respectively) We analyzed types of post-KT de novo cancers, including different types occurring in the same patient. A total of 13,912 (8,142 male and 5,770 female) death-censored KT recipients were analyzed. The most common cancer type occurred in the thyroid, accounting for a total of 154 cases, with an incidence of 1.1%. In addition, a total of 130 kidney cancers corresponded to an incidence of 0.9%. Non-Hodgkin lymphoma was diagnosed in 99 KT recipients, with an incidence of 0.7%. Additionally, a total of 15 cases of Kaposi's sarcoma corresponded to an incidence of 0.1%. According to the Korean NCIC data for 2017, the most common type of cancer in the general Korean population was stomach cancer, followed by colon, lung, and thyroid cancers. Compared to patients younger than 20, patients older than 39 had a higher cancer risk. Patients treated with (methyl)prednisolone as the initial steroid regimen compared to deflazacort had a higher risk of being diagnosed with cancer. Meanwhile, a national survey in Japan showed that PTLD, kidney, stomach, colon, and lung cancer were most common in solid organ transplantation recipients (*Surg Today* 2018;48:618–24.). In addition, single-center data and meta-review from China reported that urothelial transitional cell carcinoma, hepatocellular carcinoma, gastrointestinal cancer, renal cell carcinoma, and lymphoma were most common (*Med Oncol* 2014;31:32.). This study reported somewhat lower cancer incidence of 2.19% comparing with other studies of different Asian countries. Heo Jaesung et al. (*BMC Nephrol* 2018;19(1):311.) reported Korean data in the year 2018. They investigated 1,343 KT recipients and 7.7% of them developed cancer. Our data showed similar overall cancer incidence of 7.6%. Thyroid, kidney, and stomach cancers were most common in male and thyroid, breast, and cervix cancers were most common in female in their study. Kidney cancer in male and thyroid and breast cancers in female were also common in our data but prostate and liver cancers, and non-Hodgkin lymphoma were more frequent in our data. SIR for all cancers were 3.54 in this study, which is higher than our data. Similar to our results, they reported high SIRs for kidney cancer and non-Hodgkin lymphoma. Park Boyoung et al. (*Sci Rep* 2019;9(1):17202.) also reported another Korean data in the year 2019. The advantage of this study is inclusion

of liver recipients and they analyzed the cancer incidences for each organ. This study estimated *de novo* cancer incidence in kidney and liver recipients between 2008 and 2015 in Korea using nationwide data. The study population was comprised of 10,085 kidney recipients and 3,822 liver recipients. Compared with the general population, the cancer risk increased by 3.19-fold in male and 2.56-fold in female kidney recipients. By cancer type, a notably increased SIR was observed for Kaposi sarcoma, renal cancer, skin cancer, and non-Hodgkin's lymphoma in male and for bladder cancer, renal cancer, and non-Hodgkin's lymphoma in female kidney recipients. In liver recipients, the SIR of all cancers was 3.43 in males and 2.30 in females. In male liver recipients, the SIRs for Kaposi sarcoma, non-Hodgkin's lymphoma, myeloid leukemia, and skin cancer and in female recipients those for non-Hodgkin's lymphoma and liver cancer were prominent. Unlike the previous study, SIRs were higher in male than in female in their study. In our data, thyroid cancer was the most common in female KT recipients, followed by breast and liver cancers, non-Hodgkin lymphoma, and stomach and kidney cancers. Bladder cancer, non-Hodgkin lymphoma, and kidney cancer showed higher SIRs in females. In male KT patients, prostate cancer was the most common, followed by kidney and liver cancers, non-Hodgkin lymphoma, and stomach cancer. In male, the risk of developing non-Hodgkin lymphoma and kidney cancer was higher compared to the general population. Considering the SIR, the incidence of Kaposi's sarcoma increased the most in both male and female KT patients compared to the general population. Considering that the types of cancer occurring in the general population and KT recipients were dissimilar, different approaches from typical cancer screening methods are recommended to monitor cancer development in KT recipients. The high incidence of thyroid cancer in Korean females is unique among the Asian countries previously studied. Although there are still opposing opinions, the highest incidence of prostate cancer in males was observed in our study. According to Sherer et al. (*Int Braz J Urol* 2017;43:1021–32.), the use of older immunosuppressants such as cyclosporine, azathioprine, and tacrolimus may increase the risk of developing prostate cancer compared to the use of newer agents such as the mTOR inhibitor. Careful prostate monitoring for male KT patients would be helpful. In addition, we were able to derive an equation to estimate the cumulative cancer incidence according to the length of the follow-up period, owing to the large dataset utilized. According to our model, the cumulative cancer incidence in KT recipients under immunosuppressive conditions increases by approximately 0.1% each month. This may help clinicians to predict the approximate cancer incidence risk when monitoring KT recipients. It is expected that this trend in cumulative cancer incidence can be referenced in determining the frequency of cancer screening for long-term follow-up patients. Furthermore, clinicians need a better prevention to lessen the linear occurrence or risk of an increase in cancer incidence.