의학석사 학위논문

Cancer prevalence and risk factors among Korean solid organ transplant recipients

우리나라 고형 장기 이식 환자의 암 발생 현황 및 위험 요인

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민 지 수

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

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With the number of solid organ transplantations (SOT) in Korea increasing, interest in long-term complications in solid organ transplant recipients (SOTRs) is also increasing. Malignancy is one of the leading causes of death in recipients and the use of immunosuppressants or cancer-causing virus infection is considered as risk factors. Also, it is known that the distribution and risk factors of cancers are different from those of the general population. So here we reported prevalence and risk factors of cancers in Korean SOTRs.

Provided personalized National Health Insurance Service-National Health Information Database, we compared incidence of malignancies after SOT to general population by standardized incidence ratios (SIR) and hazard ratio (HR).

Total 25,330 (male:female 15157:10173, median age 48) patients were transplanted from 2003 to 2019, of which 1,392 (5.5%) developed cancers. SOTRs had 2 fold higher risk (SIR 2.31, 95% confidence intervals (CI) 2.19-2.44). The highest risk cancer is Kaposi sarcoma (SIR 159.14, 95% CI 90.96-258.43) followed by non-hodgkin lymphoma (SIR 11.21, 95% CI 9.39-13.29), and non-melanoma skin cancer (SIR 9.94, 95% CI 7.91-12.34). Of 1,304 patients, under 19 years old, 49 (3.8%, SIR 36.31, 95% CI 26.86-48.01) developed cancer at median age 10, of which 35 were non-hodgkin lymphoma (SIR 212.14, 95% CI 147.76-295.03). Cancer incidence was the highest after 1-3 years of transplantation (315 of 1151, SIR 1.84, 95% CI 1.65-2.06). The use of mammalian target of

rapamycin inhibitors, such as sirolimus or everolimus, as maintenance agents increased the cancer risks compared to the use of MMF (HR 1.76, 95%CI 1.01−3.07).

Cancer risks after SOT were higher than general population especially under 19 years old. As types of cancer were different from general population, close monitoring and screening is necessary in SOTRs. Also, other risk factors unanalyzed such as EBV infection should be considered.

Keywords : Malignant neoplasm, Transplant, Immunosuppressant

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Chapter 1. Introduction

With the number of transplantations in Korea doubling during a decade, from 2,472 in 2010 to about 4,200 in 2020(1, 2), interest in long-term complications in transplant recipients is also increasing. Malignancy is one of the major causes of death in solid organ transplant recipients (SOTRs), with cancer-attributable mortality of about 13%(3).

Previous studies suggested some risk factors of malignancies after solid organ transplantation (SOT). Immunosuppressants, whether induction agents such as basiliximab and anti-thymocyte globulin or maintenance agents such as tacrolimus and cyclosporine are the mostly suggested risk factors with pre-existing cancer of donor or recipients, or cancer-causing viral infections (4, 5).

Also, in SOTRs, the distribution of cancers is different from that of the general population (6, 7). SOTRs have a particular higher risk of genital cancer, Kaposi sarcoma, and lymphoma than the general population, however, the type of risk of malignancies varies depending on the regions. Especially, pediatric SOTRs have cancer

risk of more than thirty times and develop cancer in early age compared to non-transplanted population (8, 9). Likewise, they have different types of cancer, commonly non-Hodgkin lymphoma (NHL) known as posttransplant lymphoproliferative disorder (PTLD) and skin cancer, while non-transplanted children developed cancer such as leukemia, brain tumor, and Hodgkin lymphoma (10, 11).

There are several guidelines about cancer screening for SOTRs, but recommendations and evidence levels vary (12, 13). In Korea, there have been no guidelines for cancer surveillance after SOT in adult but also children. So, here, we report risks and risk factors of cancers in Korean SOTRs, as it would be the first step for the guideline after SOT.

Chapter 2. Methods

2.1 Study subjects and design

We provided personalized data from Korea National Health Insurance Sharing Service (NHISS), we compared the incidence of malignancies between SOTRs and general population, and the incidence according to the use of medications among transplant recipients.

From 2002 to 2019, all patients who received SOT were included. To analyze only patients who received organ transplant once, patients who had already received SOT before 2003 or had disease codes suggesting transplant rejection or transplant status were excluded. We excluded patients who were never prescribed immunosuppressants to exclude transplant failure, and who had already diagnosed cancer before transplantation to evaluate de novo malignancies after SOT. (Figure 1) Cancers were grouped according to the similarity of cancer as in Table 1.

This study was approved by the Seoul National University Hospital

institutional review board (IRB No. 2102-053-1196). The informed consent was waived because the NHISS data was provided in anonymized forms and we were unable to obtain the consent.

Figure 1. Flow chart of study

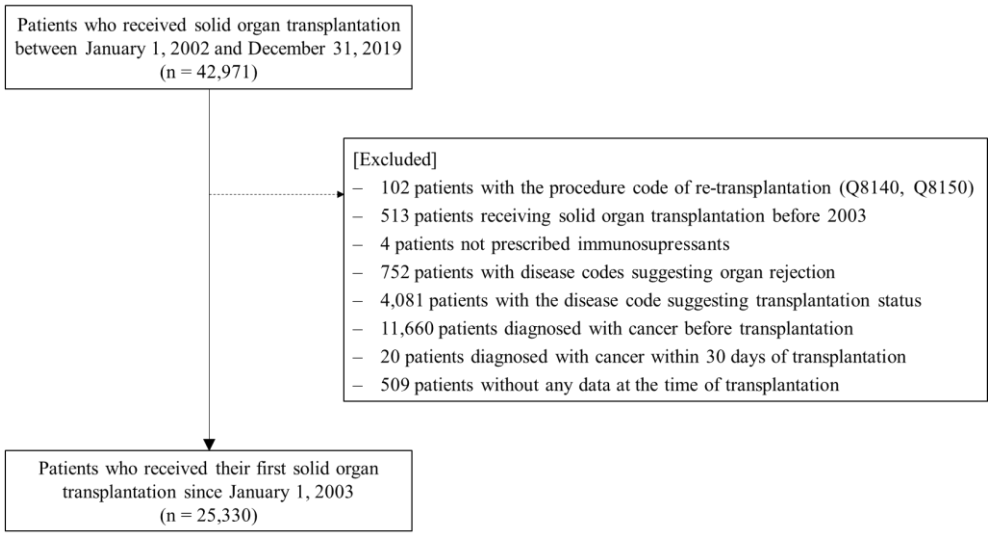


Table 1. Cancer grouping according to the similarity of cancers

Cancer group	ICD-10
Gastric cancer	C16
Colorectal cancer	C18-C20
Hepatobiliary cancer	C22-C25
Lung	C33-C34
Melanoma	C43
Non-melanoma skin cancer	C44
Kaposi sarcoma	C46
Breast cancer	C50
Female-reproductive cancer	C51-58
Prostate	C61
Kidney and other urological cancer	C64-C68
Thyroid cancer	C73
Non-Hodgkin lymphoma	C82-C86, C96
Other hematologic malignancy	C81, C88-C95
Others	
Head and neck cancer	C00-C14
GIT cancer except stomach, colon, and rectum	C15, C17, C21
Other sarcoma	C47, C49
Male-reproductive cancer	C60, C62, C63
Eye & CNS cancer	C69, C70-C72
Endocrine cancer	C74, C75

Abbreviation: CNS, central nervous system; GIT, gastrointestinal tract; ICD, international statistical classification of disease and related health problems

2.2 Data Collection

All data associated with transplant recipients were provided from Korea National Health Insurance Service-National Health Information Database (NHIS-NHID). The baseline clinical parameters such as age at transplantation and cancer diagnosis, sex, the transplanted organ, and the year of transplantation were collected. To analyze risk factors of malignancies after SOT, used immunosuppressants and antiviral agents were collected. A cancer incidence of general population who were not received transplantations, was obtained from Korean Statistical Information Service (KOSIS). These data, surveyed by the Ministry of Health and Welfare, provided incidence counts for 61 cancers by sex, year, cancer site, and 5-year age group.

2.3 Statistical Analysis

The incidence of malignancies in SOTRs was presented as standardized incidences ratios (SIR) with a 95% confidential incidence (95%CI), comparing it to the incidence in general

population and assuming a Poisson distribution. The SIR was calculated as the ratio of the number of observed cases to the expected number of cases. The expected number of cancer cases in the standard population was calculated using data from KOSIS, considering the cancer incidence in same sex, age group, and the year. The incidence rate per 100,000 populations was determined based on the resident registration central population. The SIR was calculated for different age groups, genders, transplanted organs, and follow-up periods after SOT.

Using a Poisson distribution, SIR and corresponding 95%CI according to the immunosuppressants in SOTRs were calculated. P-value was tested using Wilcoxon rank sum test for continuous variables and chi-square test or Fisher's exact test for categorical variables. When the proportional hazard model was satisfied, according to the use of immunosuppressants, the hazard ratio (HR) and 95%CI was calculated through Cox proportional hazard model. Statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, North Carolina).

Results

3.1 Baseline Characteristics of population

Among total 42,971 patients who were transplanted from 2002 to 2019, 17,641 were excluded (11,660 had cancer before SOT, 5,448 were not first transplantation, 509 had no available data, 20 developed a cancer within 30 days, and 4 did not prescribe immunosuppressants ever) and finally 25,330 were included in analysis (Figure 1).

Table 2 shows the baseline characteristics of entire patients. Of 25,330 SOTRs, 15,157 (59.8%) patients were male. They received transplantation at median 48 [Interquartile range (IQR), 37–56] years of age, of whom children under 19 years old were 1,304 (5.15%). About three quarters of entire patients were recipients of kidney transplant (18,554 patients, 74.4%), about a fifth were those of liver transplant (4,828 patients, 19.1%), and the remains were those of heart, lung, pancreas, and small bowel (heart 1,108 patients, 4.4%; lung 469 patients, 1.9%; pancreas 524 patients, 2.1%; and small bowel 9 patients, 0.04%).

From 2003 to 2006, a total of 2,532 (10.0%) patients received transplantations, and the number of SOTRs increased by more than 4 times to 10,866 (42.9%) from 2015 to 2019. Nevertheless, the number of patients who developed cancer decreased from 320 (23.0%) in 2003–2006 to 250 (18.0%) in 2015–2019.

Among 25,330 SOTRs, 1,392 (5.5%) diagnosed cancer at the median age of 55 (IQR 46–62) years. SOTRs with cancer are older than those without cancer at transplantation, as median age 50 (IQR, 41–57) years old.

There was no difference in cancer development according to the transplanted organ except for pancreatic transplantation. Patients who were receive pancreas less developed cancer (P=0.013).

Table 2. Baseline characteristics of entire patients.

	Entire population (n=25,330)	With cancer (n=1,392)	Without cancer (n=23,938)	P-value
Age at transplantation (years) [median (Q1, Q3)]	48 (37, 56)	50 (41, 57)	48 (37, 56)	<.0001
0-19 (n, [%])	1304 (5.2)	49 (3.5)	1255 (5.2)	
20-29 (n, [%])	1846 (7.3)	55 (4.0)	1791 (7.5)	
30-39 (n, [%])	4176 (16.4)	192 (13.8)	3984 (16.6)	
40-49 (n, [%])	6624 (26.2)	377 (27.1)	6265 (26.2)	
50-59 (n, [%])	7745 (30.6)	469 (33.7)	7276 (30.4)	
60-69 (n, [%])	3303 (13.0)	221 (15.9)	3082 (12.9)	
70-79 (n, [%])	312 (1.2)	29 (2.1)	283 (1.2)	
80- (n, [%])	2 (0.01)	0	2 (0.01)	
Sex				0.696
Male (n, [%])	15157 (59.8)	826 (59.3)	14331 (59.9)	
Female (n, [%])	10173 (40.2)	566 (40.7)	9607 (40.1)	
Year at first transplantation				<0.001
2003-2006 (n, [%])	2532 (10.0)	320 (23.0)	2212 (9.2)	
2007-2010 (n, [%])	5048 (19.9)	414 (29.7)	4634 (19.4)	
2011-2014 (n, [%])	6884 (27.2)	408 (29.3)	6476 (27.1)	
2015-2019 (n, [%])	10866 (42.9)	250 (18.0)	10616 (44.4)	
Organ type				
Kidney (n, [%])	18554 (74.4)	1055 (75.8)	17799 (74.4)	0.233
Liver (n, [%])	4828 (19.1)	277 (20.0)	4551 (19.0)	0.412

Heart (n, [%])	1108 (4.4)	47 (3.4)	1061 (4.4)	0.061
Lung (n, [%])	469 (1.9)	18 (1.3)	451 (1.9)	0.112
Pancreas (n, [%])	524 (2.1)	16 (1.2)	508 (2.1)	0.013
Small bowel (n, [%])	9 (0.04)	1 (0.07)	8 (0.03)	0.399*
Age at cancer diagnosis (years) [median (Q1, Q3)]		55 (46,62)		
0–19 (n, [%])		39 (2.8)		
20–29 (n, [%])		25 (1.8)		
30–39 (n, [%])		114 (8.2)		
40–49 (n, [%])		285 (20.5)		
50–59 (n, [%])		464 (33.3)		
60–69 (n, [%])		373 (26.8)		
70–79 (n, [%])		87 (6.25)		
80– (n, [%])		5 (0.4)		

Categorical variables were presented as n (%), and continuous variables were shown as median with interquartile range.

* Fisher's exact test

3.2 Cancer risk among transplant recipients

Table 3 showed that SOTRs have more than two times of cancer risk than expected (SIR 2.31, 95%CI 2.19−2.44). Of all cancers, Kaposi sarcoma had the highest risk (SIR 159.14, 95%CI 90.96−258.43), followed by NHL (SIR 11.21, 95%CI 9.39−13.29), non-melanoma skin cancer (NMSC, SIR 9.94, 95%CI 7.91−12.34) and kidney and urological cancer (SIR 7.12, 95% CI 6.15−8.20). Colorectal cancer in SOTRs had similar risk with general population (SIR 1.07, 95%CI 0.85−1.34, P>0.05)

Among all age groups, children and adolescents under the age of twenty had the highest risk of cancer with SIR 36.31 (95%CI 26.86−48.01). As the patients' age increased, the risk of cancer decreased and then increased in their seventies (SIR 2.06, 95%CI 1.38−2.96). (Table 4)

As time passed after the transplantation, the risk of developing cancer gradually increased from SIR 1.84 (95%CI 1.65−2.05) between one and three years after transplantation to SIR 3.83 (95%CI 3.26−4.47) at 10 years after transplantation, except during

the first year immediately after transplantation (SIR 2.23, 95%CI 1.96-2.53).

Table 3. Standardized incidence ratio according to the cancer type

Cancer site	Entire population			
	Expected Cancer Cases	Observed Incidence cases	SIR	95%CI
All cancers	601.57	1392	2.31*	2.19-2.44
Gastric cancer	84.06	131	1.56*	1.30-1.85
Colorectal cancer	71.72	77	1.07	0.85-1.34
Hepatobiliary	72.40	161	2.22*	1.89-2.60
Lung	50.15	72	1.44*	1.12-1.81
Melanoma	1.40	3	2.14	0.44-6.24
Non-melanoma skin cancer	8.25	82	9.94*	7.91-12.34
Kaposi sarcoma	0.10	16	159.14*	90.96-258.43
Breast cancer	67.22	83	1.23	0.98-1.53
Female-reproductive	27.67	56	2.02*	1.53-2.63
Prostate	22.13	50	2.26*	1.68-2.98
Kidney and other urological	26.98	192	7.12*	6.15-8.20
Thyroid	114.43	161	1.41*	1.20-1.64
Non-Hodgkin lymphoma	11.86	133	11.21*	9.39-13.29
Other hematologic malignancy	16.42	56	3.41*	2.58-4.43
Others	31.20	71	2.28*	1.78-2.87

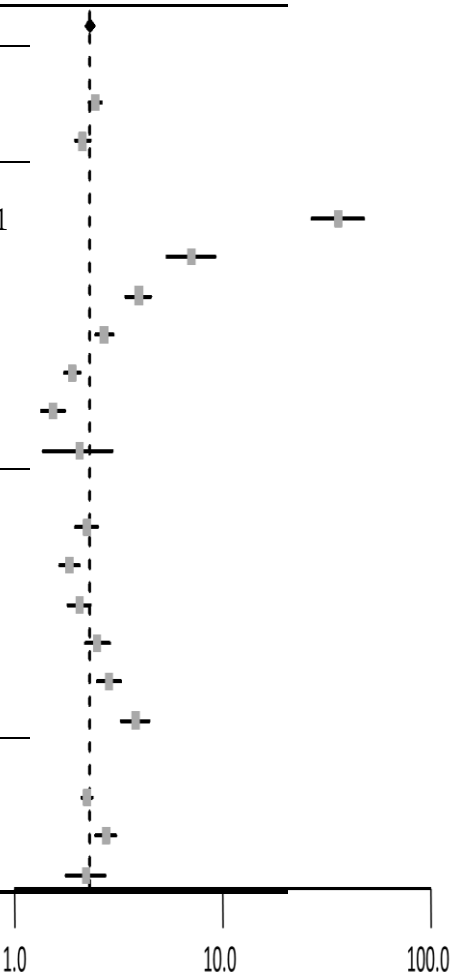
*significance level: <0.05

Cancer types were grouped as indicated in Table 1.

Abbreviation: CI, confidential incidence; SIR, Standardized incidence ratio

Table 4. Standardized incidence ratio with forest plot for all cancer

	SIR	95%CI	Forest plot
Total	2.31*	2.19–2.44	
Sex type			
Male	2.46*	2.29–2.63	
Female	2.13*	1.96–2.32	
Age group			
0–19	36.31*	26.86–48.01	
20–29	7.15*	5.39–9.31	
30–39	3.97*	3.42–4.57	
40–49	2.70*	2.44–2.99	
50–59	1.90*	1.74–2.08	
60–69	1.54*	1.34–1.75	
70–79	2.06*	1.38–2.96	
After organ transplantation			
< 1 year	2.23*	1.96–2.53	
1 year ≤ < 3 years	1.84*	1.65–2.06	
3 years≤ <5 years	2.06*	1.81–2.33	
5 years≤ <7 years	2.51*	2.19–2.87	
7 years≤ <10 years	2.86*	2.49–3.27	
10 years ≤	3.83*	3.26–4.47	
Organ type			
Kidney	2.23*	2.10–2.37	
Liver	2.76*	2.45–3.11	
Others†	2.22*	1.77–2.75	



*Significance level: <0.05
†This includes heart, lung, pancreas, and small bowel.
Abbreviation: CI, confidential incidence; SIR, Standardized incidence ratio

3.2.1 According to transplanted organ

Table 5 showed SIR according to the transplanted organ. Liver transplant recipients had the highest risk of cancer than other SOTRs (SIR 2.76, 95%CI 2.45-3.11). The cancer with the highest risk in liver transplant recipients was NHL (SIR 13.49, 95%CI 8.96-19.49), followed by NMSC (SIR 8.57, 95%CI 4.56-14.65), hepatobiliary cancer (SIR 6.48, 95%CI 5.19-8.01), and hematologic malignancy other than NHL (SIR 5.25, 95%CI 2.94-8.65). Total 277 (of 4828, 5.74%) patients among liver transplant recipients developed cancers. Hepatobiliary cancer was the most common cancer among them with 86 (of 277, 31.04%) patients, compared to 74 (of 1055, 7.01%) in kidney transplant recipients and 4 (of 82, 4.88%) in other SOTRs.

The kidney transplantation recipients also had higher risk than general population (SIR 2.23, 95%CI 2.10-2.37). Among them, Kaposi sarcoma had the highest risk with SIR 194.43 (95%CI 108.82-320.67), followed by NMSC (SIR 10.04, 95%CI 7.71-12.84), NHL (SIR 9.77, 95%CI 7.86-12.01), and kidney and other urological cancer (SIR 8.79, 95%CI 7.56-10.17). Of 1055 (of 18854, 5.6%)

patients who had developed cancers after kidney transplantations, the most common cancer was the kidney and urological cancer, developed in 181 (of 1055, 17.16%) patients, while in 10 (of 277, 3.61%) among liver transplant recipients and 4 (of 82, 4.88%) among other SOTRs.

Other SOTRs, including heart, lung, pancreas, and small bowel transplant recipients, had the risk of cancer with SIR 2.22 (95%CI 1.77−2.75). Although Kaposi sarcoma had the highest risk of cancer with SIR 139.8 (95%CI 3.54−788.9), but the cancer developed in only one patient (of 82, 1.22%). NHL had the second highest risk of cancer with SIR 29.79 (95%CI 18.67−45.10), and was the most common cancer, observed in 22 (of 82, 26.83%) patients, while in 90 (of 1055, 8.53%) among kidney transplant recipients and in 28 (of 277, 10.11%) among liver transplant recipients. NMSC had the risk of cancer with SIR 12.55 (95%CI 5.05−25.86) and observed in 7 (of 82, 8.54%) patients, more compared to 63 (of 1055, 5.97%) among kidney transplant recipients and 13 (of 277, 4.69%) among liver transplant recipients.

Table 5. Standardized incidence ratio according to the transplanted organ

Cancer site	Kidney			Liver			Others†		
	Observed cases	SIR	95%CI	Observed cases	SIR	95%CI	Observed cases	SIR	95%CI
All cancers	1055	2.23*	2.10–2.37	277	2.76*	2.45–3.11	82	2.22*	1.77–2.75
Gastric cancer	98	1.52*	1.23–1.85	25	1.65*	1.07–2.43	8	1.49	0.64–2.94
Colorectal cancer	55	1.00	0.75–1.30	19	1.46	0.88–2.28	5	1.09	0.36–2.55
Hepatobiliary	74	1.34*	1.05–1.68	86	6.48*	5.19–8.01	4	0.85	0.23–2.17
Lung	57	1.51*	1.14–1.95	8	0.88	0.38–1.72	8	2.16	0.93–4.25
Melanoma	3	2.75	0.57–8.03	0	0.00	0.00–12.19	0	0.00	0.00–34.88
Non–melanoma skin cancer	63	10.04*	7.71–12.84	13	8.57*	4.56–14.65	7	12.55*	5.05–25.86
Kaposi sarcoma	15	194.43*	108.82–320.67	0	0.00	0.00–170.76	1	139.80*	3.54–778.91
Breast cancer	74	1.33*	1.05–1.67	7	0.72	0.29–1.48	3	0.95	0.20–2.79
Female–reproductive	44	1.93*	1.40–2.59	10	2.48*	1.19–4.56	2	1.50	0.18–5.42
Prostate	39	2.39*	1.70–3.27	9	2.26*	1.03–4.30	2	0.97	0.12–3.50
Kidney and other urological	181	8.79*	7.56–10.17	10	2.03	0.97–3.74	4	2.20	0.60–5.64
Thyroid	147	1.56*	1.32–1.83	12	0.73	0.38–1.28	4	0.68	0.19–1.74
Non–Hodgkin lymphoma	90	9.77*	7.86–12.01	28	13.49*	8.96–19.49	22	29.79*	18.67–45.10

Other hematologic malignancy	37	2.89*	2.04−.3.99	15	5.25*	2.94−8.65	6	5.95*	2.18−12.95
Others	45	1.87*	1.36−2.50	23	4.18*	2.65−6.28	3	1.49	0.31−4.35

*significance level: <0.05

†This includes heart, lung, pancreas, and small bowel.

Cancer types were grouped as indicated in Table 1.

Abbreviation: CI, confidential incidence; SIR, Standardized incidence ratio

3.2.2 According to age

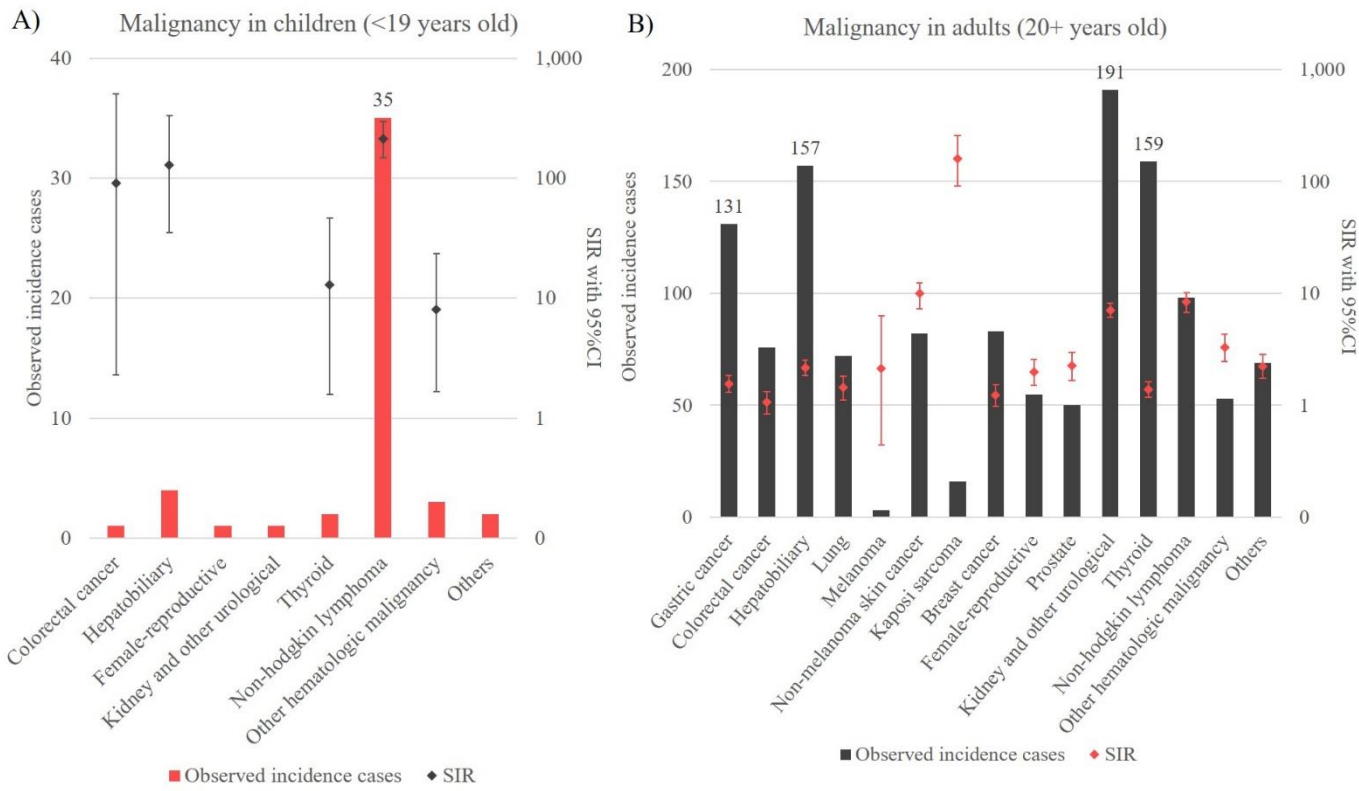
As shown in Table 4, except for patients over 70 years of age, the younger the patients were who received the SOT, the higher the risk of cancers was. Especially, in children under the age of twenty, SOTRs had more than 36 times increased cancer risk than general population (SIR 36.31, 95%CI 26.86−48.01). Cancer risk decreased as the age of SOTRs increasing, to SIR 1.54 (95%CI 1.34−1.75) in the 60s but increased back to SIR 2.06 (95%CI 1.38−2.96) in SOTRs over 70.

Figure 2 shows the risk of cancers by children under the age of 20 and adults over 20 years old at SOT. Children's cancers after SOT developed in median 10 (IQR 3−18) years old. Compared to adults (1343 of 24026, 5.59%, SIR 2.24 95%CI 2.12−2.36), children had fewer cases (49 of 1304, 3.76%) but much a higher risk. In children, NHL had a risk more than two hundred times higher (SIR 212.14, 95%CI 147.78−295.03) than the general population, and was the most common cancer, occurring in 71.43% (35 of 49) of cases. Other than that, hepatobiliary cancer, hematologic malignancies, and thyroid

cancer were developed in children with higher risk, more than eight times.

Unlike children, in adult, kidney and other urological cancer was the most common, observed in 191 patients (14.2%), followed by thyroid cancer (159 patients, 11.8%), hepatobiliary cancer (157 patients, 11.7%), and gastric cancer (131 patients, 9.8%). But, Kaposi sarcoma had the highest risk cancer with SIR 159.38 (95%CI 91.1−258.83). NMSC showed a higher risk, with SIR 9.95 and 95%CI 7.29−12.36, and NHL also showed a higher risk, with SIR 8.38 and 95%CI 6.8−10.21.

Figure 2. Standardized incidence ratio and numbers of patients by age



*Statistically insignificant, $P>0.05$

3.3 Cancer risk according to medications

We compared the cancer incidence among SOTRs depending on whether the mediations were used and presented as HR and 95%CI (Table 6). After adjusting for sex, age, the number of transplanted organs, and the type of transplanted organ, most of medications did not satisfy the proportional hazard model; all induction agents, glucocorticoid, tacrolimus, mycophenolate mofetil (MMF), antiviral agents including acyclovir and ganciclovir, and rituximab used before transplantations.

The impact of mammalian target of rapamycin inhibitors (mTORi), such as sirolimus or everolimus, on cancer development was contrary to expectations. The use of mTORi was associated with increased cancer risks compared to the use of MMF (HR 1.76, 95%CI 1.01–3.07, P=0.045). However, the increase was not statistically significant compared to non-users (HR 1.44, 95%CI 0.86–2.41, P=0.163) or the use of azathioprine (HR 1.98, 95%CI 0.26–15.34, P=0.515).

Table 6. Hazard ratios according to the type of medications among transplant recipients

	Number (Cancer/Total)	Crude			Adjusted*		
		HR	95%CI	p-value	HR	95%CI	p-value
Induction agents†	1093/22235						
ATG†	148/3722						
Basiliximab†	1004/19657						
No induction agents†	223/3082			ref.			
Maintenance agents†							
Glucocorticoid† (ref. no glucocorticoid)	474/12353 (458/8863)						
Tacrolimus† (ref. no tacrolimus)	708/18207 (230/3009)						
Tacrolimus† (ref. cyclosporine)	702/18193 (198/2407)						
MMF (ref. no MMF)†	669/16681 (263/4535)						
Sirolimus or everolimus (ref. no sirolimus or everolimus)	17/457 (219/10038)	1.60	0.98-2.63	0.061	1.44	0.86-2.41	0.163
Sirolimus or everolimus (ref. MMF)	14/335 (173/8503)	1.96	1.14-3.39	0.015	1.76	1.01-3.07	0.045
Sirolimus or everolimus (ref. Azathioprine)	17/456 (1/43)	1.77	0.23-13.35	0.580	1.98	0.26-15.34	0.515
Antiviral agents† (ref. no antiviral agents)	88/1266 (1228/24051)						
ACV (ref. no ACV)†	80/1007 (1236/24310)						
GCV (ref. no GCV)†	8/259 (1308/25058)						
Rituximab†‡ (ref. no rituximab)	175/2139 (1141/23178)						

*Adjusted for sex, age, the number of transplanted organ, and transplanted organ

†HR was not calculated as they did not satisfy the proportional hazard model.

†This rituximab was used for desensitization before transplantation.
Abbreviation: ACV, acyclovir; ATG, anti-thymocyte globulin; CI, confidential incidence; GCV, ganciclovir; HR, hazard ratios; MMF, mycophenolate mofetil

Discussion

NHIS-NHID is a database based on national health insurance and long-term care insurance. As all patients who receive medical treatment in Korea are covered by health insurance, the NHISS can provide the public data. The KOSIS database, which contains incidence counts for cancers, is annually announced by the Ministry of Health and Welfare. This database is based on the national Cancer Registration Statistics Program, which aims to widely utilize the data for policy development and cancer research. Therefore, the data were representative and suitable for the analysis.

Malignancies after SOT are thought to be associated with chronic immune suppression, viral infection, exposure to immunosuppressants, and, although rare, transmission from the

donor. (4, 14) Immune system dysregulation has been linked to cancer development, as immune cells play a critical role in identifying and eliminating damaged cells.(15) Also, chronically immune-suppressed patients were thought to be unable to effectively combat viral infections.(15) As a results, cancers that are common in immunocompromised patients are usually associated with viral infections; NHL and Hodgkin's lymphoma [Epstein-Barr virus (EBV)], Kaposi sarcoma (human herpes virus 8), and squamous cell cancer (human papilloma virus).(16) Patients with primary immunodeficiency have a higher risk of NHL, Hodgkin's disease, and leukemia(17), and patients with acquired immunodeficiency syndrome have a higher risk of Kaposi sarcoma and NHL(18). Similarly, SOTRs on persistent immunosuppression have a higher risk of Kaposi sarcoma, NMSC, and NHL.(7, 19, 20) Especially in SOTRs, the association between EBV and PTLD is well recognized. *Yanik* et al. reported that EBV-seronegative children before transplantation were likely to develop cancer three times more

than EBV-seropositive children.(21) *Sampaio* et al. also reported EBV-seronegative recipients had more than 5 times cancer risk.(22) In this study, we demonstrated a higher risk of Kaposi sarcoma and NHL in STORs, which is consistent with previous studies. However, due to the absence of titer or serology status of EBV in the available public data, we were unable to confirm the association between EBV and cancer after SOT.

Immunosuppressants used to maintain allograft function after SOT have diverse effects on cancer growth. Typically, these medications serve to prevent organ rejection; however, they can also hinder the recognition of cancer cells, thereby contributing to the development of cancers.(14) The use of anti-lymphocyte antibodies used when induction or treating acute rejection, could increase the incidence of cancers.(23, 24) Calcineurin inhibitors (CNIs) promote the cytokine associated B-cell growth or angiogenesis resulting in tumor growth.(25)

Rodríguez-Perálvarez et al. suggested that the cumulative exposure to CNIs was the sole predictor of malignancies after SOT, and a higher exposure to CNI was associated with an increased risk of developing cancer.(26) On the other hand, mTORi inhibit cell proliferations including lymphocytes, endothelial cells, and even tumor cells.(25) *Lim* et al. reported a lower risk of cancer development after converting maintenance agents from CNIs to mTORi.(27) The effect of MMF on cancer development after SOT is controversial. A prospective cohort of Europe, United States, and New Zealand reported that MMF users had a similar risk of cancer but a tendency for cancer to occur at a later stage compared to MMF non-users.(23) The effects of glucocorticoid on cancer have not been established.(25) In our study, the effects of most medications on cancer were unknown. However, the use of mTORi (sirolimus or everolimus) seemed to increase cancer risks. In Korea, national health insurance has covered sirolimus for kidney transplant recipients since 2010, and everolimus for

heart transplant recipients since 2014, liver transplant recipients since 2015, and kidney transplant recipients since 2022. Therefore, we analyzed the hazard based on the use of mTORi after 2014. This represents the first possibility of these results, the relative short follow-up period. The second possibility is that the number of patients who used mTORi was too small, compared to those who used other immunosuppressants. Although we were unable to assess high-risk factors for malignancies, such as viral infection status, due to the limitations of the database providing only the diagnostic codes, it is worth considering that patients with EBV viremia or a higher likelihood of developing cancer may have switched to mTORi, as part of the strategy to reduce immunosuppression intensity.(5, 28)

SOTRs who received organs from deceased donor with advanced ages, hypertension, or cerebrovascular disease were found to have a higher risk of cancers compared to those who

received organs from other donor types.(29) However, the risk of cancer transmission from organ donors could vary depending on the type and pathology of the cancer, necessitating risk evaluation and clinical assessment prior to transplantation.(30) Typically, donors with active malignancy should be excluded, while donors with certain cancers, such as skin cancers or small renal cell cancers, could be considered for transplantation after risk evaluation and obtaining informed consents.(30, 31) In Korea, the history of previous cancers and current infection status are assessed through history taking and laboratory tests prior to transplantation.

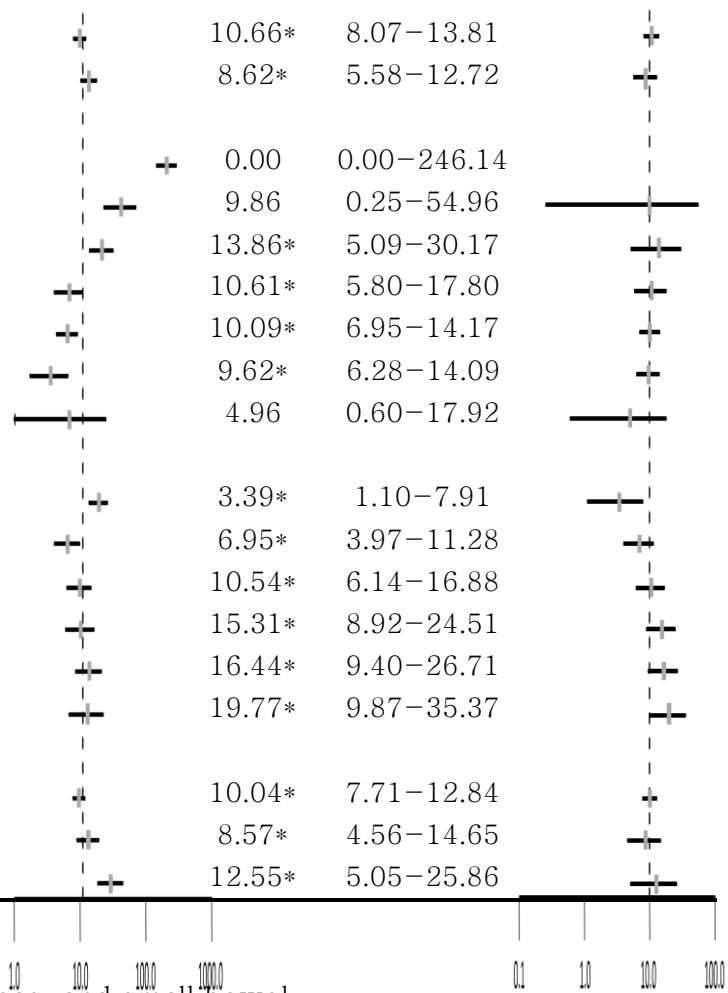
PTLD exhibited the highest risk in the immediate year following transplantation and decreased thereafter.(8, 32, 33) Conversely, the risk of NMSC development showed a gradual increase over time after SOT.(33, 34) Our study yielded similar results (Table 7). Typically, early de novo malignancies after SOT were attributed to intense immunosuppression and viral

infections.(32) In contrast, late de novo malignancies after SOT were influenced by chronic immunosuppression and other environmental factors, such as sunlight exposure.(32, 34)

It appeared that SOTRs who underwent transplantation between 2015 and 2019 had a lower occurrence of cancer events compared to those who underwent transplantation earlier. However, Figure 3 demonstrated that there was no difference in the incidence of cancer events based on the year of transplantation. The lower incidence may be attributed to the relatively shorter follow-up periods.

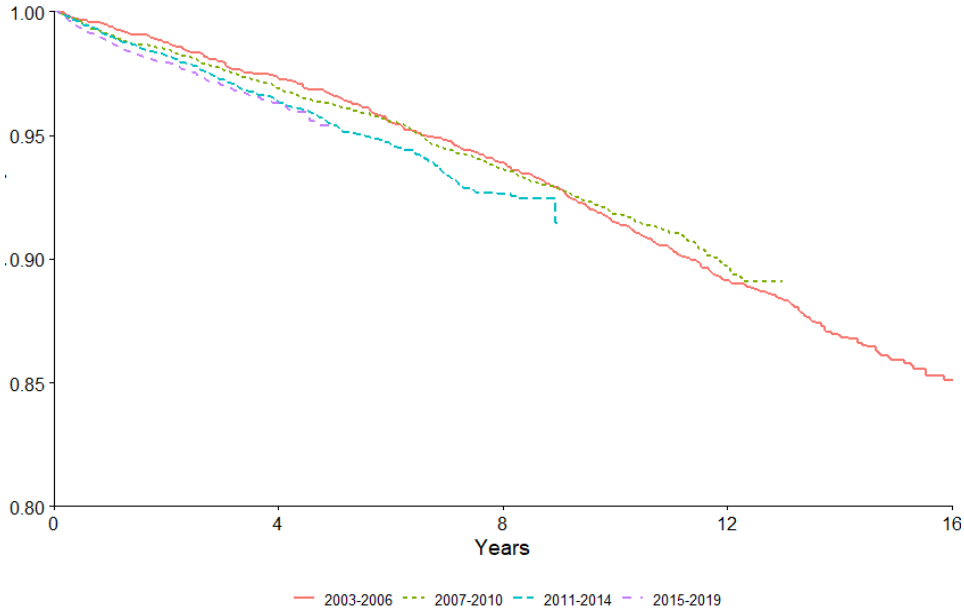
Table 7. Standardized incidence ratio with forest plot for non-Hodgkin lymphoma and non-melanoma skin cancer

	Non-Hodgkin lymphoma			Non-melanoma skin cancer		
	SIR	95%CI	Forest plot	SIR	95%CI	Forest plot
Sex type						
Male	10.01*	7.95-12.44		10.66*	8.07-13.81	
Female	13.80*	10.30-18.09		8.62*	5.58-12.72	
Age group						
0-19	212.14*	147.76-295.03		0.00	0.00-246.14	
20-29	42.54*	23.26-71.38		9.86	0.25-54.96	
30-39	21.75*	13.93-32.36		13.86*	5.09-30.17	
40-49	6.91*	4.09-10.91		10.61*	5.80-17.80	
50-59	6.51*	4.39-9.29		10.09*	6.95-14.17	
60-69	3.63*	1.74-6.67		9.62*	6.28-14.09	
70-79	6.96	0.84-25.14		4.96	0.60-17.92	
After organ transplantation						
< 1 year	19.55*	13.91-26.73		3.39*	1.10-7.91	
1 year ≤ <3 years	6.58*	4.07-10.06		6.95*	3.97-11.28	
3 years≤ <5 years	9.97*	6.32-14.96		10.54*	6.14-16.88	
5 years≤ <7 years	10.35*	6.03-16.58		15.31*	8.92-24.51	
7 years≤ <10 years	13.99*	8.66-21.39		16.44*	9.40-26.71	
10 years ≤	13.17*	6.81-23.01		19.77*	9.87-35.37	
Organ type						
Kidney	9.77*	7.86-12.01		10.04*	7.71-12.84	
Liver	13.49*	8.96-19.49		8.57*	4.56-14.65	
Others†	29.79*	18.67-45.10		12.55*	5.05-25.86	



*Significance level: <0.05
†This includes heart, lung, pancreas, and small bowel.
Abbreviation: CI, confidential incidence; SIR, Standardized incidence ratio

Figure 3. Kaplan Meier survival curves for cancer development based on the year of transplantation



The risk of cancer in allograft was found to be higher in SOTRs. Our study, consistent with findings from the Swiss transplant cohort(35), showed an increased risk of kidney and other urological cancers among kidney transplant recipients, as well as a higher risk of hepatobiliary cancers among liver transplant recipients. These findings can be attributed to the effects of chronic inflammation, which can arise as a consequence of chronic antigenic stimulation of transplanted organ or recurrent infections.(36) And, it is well recognized that chronic immune activation is associated with the development of cancer.(37) Also, cancers could arise when renal transplanted patients had acquired cystic kidney disease in their native kidneys.(32) Hepatocellular carcinomas in liver transplanted patients were usually associated with recurrence of previous hepatocellular carcinoma.(13) However, because we excluded the patients who had cancers before transplantation, our study have a meaning that we showed liver transplanted patients have a higher risk of de novo hepatobiliary cancers after SOT (SIR

6.48, 95%CI 5.19-8.01), especially in children (SIR 328.38, 95%CI 89.47-840.77).

Children who underwent SOT had a significantly higher risk of developing cancers than adults, and their distribution differs from non-transplanted children (11). The majority malignancies in SOTRs were PTLD, and this was more common in younger recipients (21). Due to the lower levels of EBV antibodies in children compared to adults (38), intense immunosuppression following SOT could potentially affect EBV infection or reactivation, resulting in a higher risk of PTLD.

Outcomes of malignancies in SOTRs are worse than those of malignances in patients not transplanted (39). So, early detection and treatment are needed and for this, regular screening after SOT could play an important role. Annual skin examination by a dermatologist or frequent self-exam is recommended to screen for skin cancers, which are the highest risky in SOTRs.(12, 13) Although there is insufficient evidence,

routine exams same as the general population are suggested to screen for cervical cancer, colorectal cancer, and breast cancer.(12, 13, 40) However, there is no accepted consensus about screening for PTLD. The American society of Transplantation recommended a physical exam and complete history taking to suggest involvement of PTLD, at least every 3 months during the first year after transplantation and annually thereafter.(41) Although the EBV burden in peripheral blood may be associated with the development of PTLD (42), there is a lack of evidence measuring EBV titer as a screening tool for PTLD.(41) Although there have been no specific guidelines for cancer screening in Korean SOTRs until now, it is necessary to develop our own strategies for post-transplant malignancies as cancers can vary across regions or races,

There were several limitations to this study. First, as our follow-up period was less than twenty years, the long-term effects of SOT in children or young adults, who have a longer

remaining life expectancy and are more likely to experience long-term complications, may be unknown or may have been undervalued. Secondly, we were unable to analyze risk factors such as the severity of infections or the extent of immunosuppression, as NHIS-NHID only provides diagnostic codes and drug codes.

In conclusion, SOTRs were at a higher risk of developing compared to general population, and the distribution of cancer types were also different, with higher risk of Kaposi sarcoma, NMSC, and NHL. Children had a higher risk, particularly for NHL. Cancer incidences were more likely to occur within the first year after SOT and increased over time. Also, a risk of cancers in transplanted organs were higher. However, cancers in SOTRs, generally have poorer prognosis compared to non-transplanted patients. Therefore, early diagnosis and treatment are crucial, along with comprehensive and precise screening specially tailored for high-risk and common cancer types in

SOTRs.

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요약 (국문초록)

최근 국내 장기 이식 시행 건수가 증가하면서, 장기 이식 수혜자의 장기적인 합병증에 대한 관심도 증가하고 있다. 악성 종양은 장기 이식 수혜자들의 주요 사망 원인 중 하나로, 면역억제제의 사용과 암 유발 바이러스 감염 등이 위험 요인으로 꼽힌다. 이러한 장기 이식 수혜자들에서는 자주 발생하는 암과 그 위험요인은 일반 인구와 다르다고 알려져 있다. 따라서 본 연구에서는 한국인 장기 이식 수혜자에서의 암 발생 현황과 그 위험 요인에 대해 보고하고자 한다.

국민건강보험자료를 이용해 일반 인구와 장기 이식 수혜자 간의 암 발생 빈도를 비교하고 표준화 발생 비(standardized incidence ratios, SIR)와 95% 신뢰구간 (95% confidence intervals, 95%CI), 위험비(harzard ratio, HR)로 제시하였다.

2003년부터 2019년까지 총 25,330명 (남:여 15,157:10,173, 중간 연령 48세)의 환자가 장기 이식을 받았고, 그 중 1,392명(5.5%)에서 암이 발생하였다. 장기 이식 수혜자들은 일반 인구 대비 암이 발생할 위험이 2배 이상 높았다. (SIR 2.31 95%CI 2.19-2.44) 가장 발생 위험이 높은 암은 Kaposi 육종이었고 (SIR 159.14, 95% CI 90.96-258.43),

그 다음으로 비호지킨림프종 (SIR 11.21, 95% CI 9.39−13.29)과 비흑색종피부암 (SIR 9.94, 95% CI 7.91−12.34)이었다.

19세 이하 소아 1,304명이 장기 이식을 받았고 그 중 49명 (3.8%)에서 암이 발생하였고 SIR 36.31 (95% CI 26.86−48.01)이 확인되었다. 이 중 35명이 비호지킨림프종 (SIR 212.14, 95% CI 147.76−295.03)이었다. 암 발생빈도는 이식 후 1−3년 후에 가장 높았으며, 1,151명 중 315명에서 암이 발생하였고 SIR 1.84, 95%CI 1.65−2.06에 해당하였다. mammalian target of rapamycin 억제제를 사용하는 경우 mycophenolate mofetil을 사용했을 때와 비교해 암 발생 위험률이 증가하였다 (HR 1.76, 95%CI 1.01−3.07).

장기 이식 후 암 발생 위험은 일반 인구이 비해 높았으며, 특이 19세 이하 소아 환자에서 높았다. 장기 이식 수혜자에서는 일반 인구와 암 발생 분포가 다르기 때문에, 주의 깊은 모니터와 스크리닝이 필요하며, 본 연구에서 확인하지 못한 Ebstein−barr virus 감염과 같은 다른 위험 요인에 대한 추가적인 연구가 필요하다.

주요어: 암, 악성종양, 이식, 면역억제제
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