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Association between obesity and cancer risk in adults with HIV in Korea

Yoonyoung Jang[a,b], Taehwa Kim[a,c], Yunsu Choi[a], Kyoung Hwan Ahn[a], Jung Ho Kim[d], Hye Seong[e], Youn Jeong Kim[f], Shin-Woo Kim[g], Jun Yong Choi[d], Hyo Youl Kim[h], Joon Young Song[e], Hee Jung Choi[i], Sang Il. Kim[j], Jang Wook Sohn[e], BumSik Chin[k], Bo-Youl Choi[a] and Boyoung Park[a]

Introduction: This study aimed to investigate the association between obesity and cancer risk as well as site-specific cancer risks in adults with HIV using a nationwide health screening database in Korea.

Methods: Of the 16,671 adults with a new diagnosis of HIV from 2004 to 2020, 456 incident cancer cases and 1814 individually matched controls by sex, year of birth, year of HIV diagnosis, and follow-up duration (1 : 4 ratio) were included in this nested case–control study. The association between obesity (BMI $\geq$25 kg/m^2) and cancer risks was estimated and presented as odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results: Of the 456 cancer incident cases, there were 146 AIDS-defining cancer cases and 310 non-AIDS-defining cancer cases. Compared with nonobese adults with HIV, obese adults with HIV were at higher risk of non-AIDS-defining cancer (OR = 1.478, 95% CI = 1.118–1.955). Otherwise, the overall risk of AIDS-defining cancer (OR = 0.816, 95% CI = 0.520–1.279) and each type of AIDS-defining cancer (Kaposi sarcoma and non-Hodgkin's lymphoma) were not high in obese adults with HIV. Of the specific types of non-AIDS-defining cancers, obesity was associated with an increased risk of colorectal cancer (OR = 3.090, 95% CI = 1.110–8.604) and liver, bile duct, and pancreatic cancers (OR = 2.532, 95% CI = 1.141–5.617).

Conclusion: Obesity, which is one of the important health concerns in HIV management, was associated with an increased risk of non-AIDS-defining cancer but not AIDS-defining cancer.

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Keywords: AIDS, AIDS-defining cancer, HIV, non-AIDS-defining cancer, obesity

[a]Department of Preventive Medicine, Hanyang University College of Medicine, [b]Department of Agricultural Economics and Rural Development, Seoul National University, [c]Department of Psychology, Sungkyunkwan University, [d]Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, [e]Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, [f]Division of Infectious Disease, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, [g]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, [h]Division of Infectious Diseases, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, [i]Division of Infectious Diseases, Department of Internal Medicine, Ewha Womans University College of Medicine, [j]Division of Infectious Disease, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, and [k]Division of Infectious Diseases, Department of Internal Medicine, National Medical Center, Seoul, Korea.

Correspondence to Boyoung Park, MD, PhD, Department of Preventive Medicine, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea.

Tel: +82 2 2220 0682; fax: +82 31 2220 0699; e-mail: hayejine@hanmail.net

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Introduction

Since the introduction of highly active antiretroviral therapy (HAART), which suppresses viral replication and improves the immune system, as standard treatment for adults infected with the HIV, the survival and life expectancy of those affected, has increased steadily [1,2]. The increased longevity has resulted in an increased risk of various chronic diseases in these patients, which in turn, has led to a high disease burden among people with HIV/AIDS (PWHA) [3–5]. Regarding cancer, with the use of HAART, the risk of AIDS-defining cancers (cancers that are directly related to the progression of immunodeficiency) has decreased, while the disease burden for non-AIDS-defining cancer has increased [6,7].

Advanced HIV infection was conventionally referred to as a "slimming disease," due to the associated weight loss and muscle wasting. In contrast, by controlling viral replication and reducing metabolic demand, HAART treatment is associated with weight gain. After the introduction of HAART, obesity among PWHA increased, especially among patients who were underweight at the start of HAART [8,9]. Without cost barriers owing to the national health insurance program facilitated through the rare incurable disease system, which covers 100% of HIV-related treatments, people with HIV can receive HAART soon after diagnosis [10].

Obesity is a well known risk factor for chronic diseases [11,12], and recently, the European Commission declared that obesity is a chronic disease and not simply a lifestyle choice [13]. With an increased prevalence of overweight and obesity among PWHA, and the increased risk of chronic diseases, obesity, and weight control have become important issues in the management of PWHA [14]. However, the associations between obesity and various health outcomes in PWHA, especially mortality, have shown inconsistent results [9,15,16]. To the best of our knowledge, there have been only few studies that have examined the association between obesity and cancer risk in PWHA.

In Korea, PWHA have shown an increased risk of both AIDS-defining cancer and non-AIDS-defining cancer, such as Hodgkin's lymphoma, oropharyngeal cancer, and anal cancer [17]. Despite the relatively lower obesity prevalence in Korean population than that in the Western population, the prevalence of obesity has been increasing rapidly [18]. This suggests that an increased chronic disease burden in the Korean general population is expected. Therefore, this study investigated the association between obesity and cancer as well as site-specific cancer risks in PWHA in Korea using a nationwide health screening database.

Materials and methods

Study design and population

This study used data from Korea's National Health Insurance Service-National Health Information Database (NHIS-NHID) collected from all persons diagnosed with HIV from 2004 to 2020. The NHIS-NHID contains information on demographic characteristics, healthcare service usage, prescriptions by physicians, general health checkups and cancer screening results, and vital status at least 97% of the Korean population who are covered by the NHIS, a universal and compulsory national health insurance system. Furthermore, a special cost-sharing system is operated by the NHIS to cover diseases with high medical expenses, such as cancer, HIV infection, and rare and incurable diseases.

This study included adults with HIV diagnosed from 2004 to 2020. During this time, adults with HIV infection were covered by the special cost-sharing system. HIV infection was defined as a combination of the ICD-10 codes for HIV infection (B20–B24) and the cost-sharing system codes for HIV treatment from the healthcare utilization database. To identify those with a new HIV diagnosis, those who had medical utilization records from 2002 to 2003 with ICD-10 codes for HIV infection were excluded from this study in line with a previous study [19]. PWHA with a history of cancer diagnosis between 2002 and 2005, as well as those whose cancer diagnosis preceded their HIV diagnosis were excluded from this study. To ensure a minimum follow-up period, participants were excluded if the time between BMI measurement and cancer diagnosis was less than 90 days.

In this study, cancer incidence from 2006 to 2020 was defined by the ICD-10 codes for cancer (C00–C99) and the cost-sharing system codes for cancer from the healthcare utilization database. If a patient with HIV had a medical history of cancer before their initial HIV diagnosis date, they were excluded as prevalent cancer cases. AIDS-defining cancers include Kaposi sarcoma (C46), cervical cancer (C53), and non-Hodgkin's lymphoma (C82–C86, C96). Non-AIDS-defining cancers include other types of cancer [7]. The types of cancer were further classified into colorectal cancer; liver, bile duct, and pancreatic cancer; lung and tracheal cancer; stomach cancer; thyroid cancer; prostate cancer; and anal cancer.

We identified a total of 16 671 cases of new HIV infection from 2004 to 2020. In this nested case–control study, we identified the association between obesity and cancer risk in PWHA (Fig. 1). To construct a nested case–control matching set, we excluded those with a history of cancer before their HIV diagnosis or before 2006 when the cost-sharing system for cancer commenced ($N = 421$).

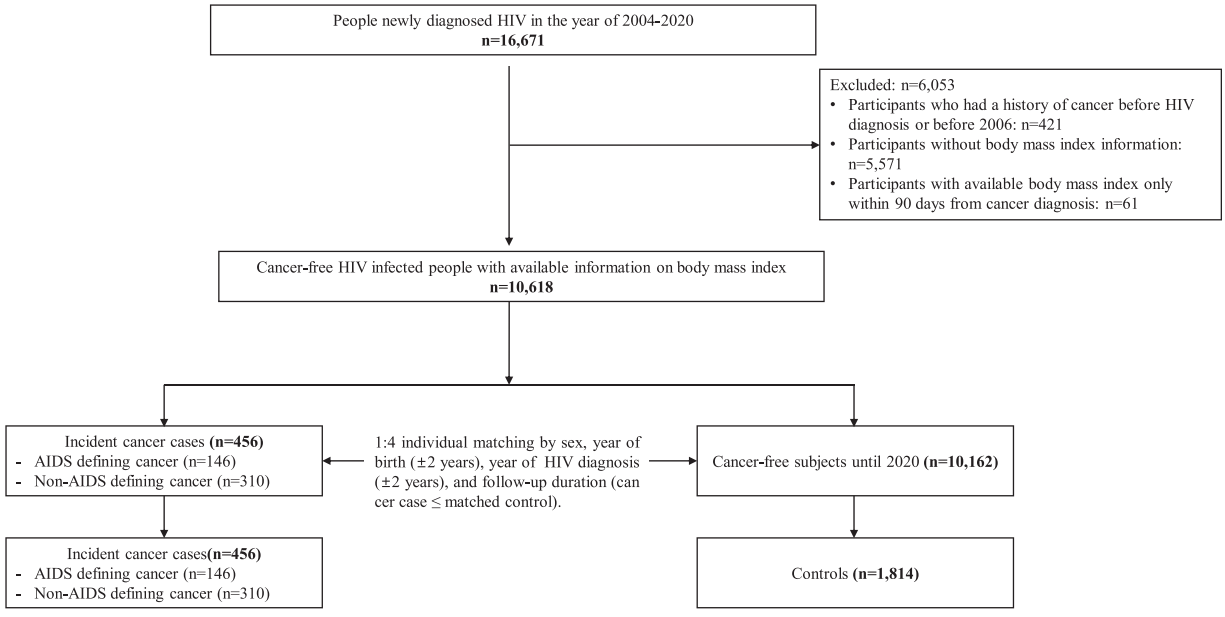

Fig. 1. Participant selection flowchart.

Moreover, data on BMI were recorded by the NHIS-NHID when people participated in the national health screening program. Hence, those who had never participated in the national health screening program ($N = 5569$) were excluded. Furthermore, BMI data were missing for two individuals despite their participation in the national health screening program; therefore, they were excluded. To avoid reverse causation, of the individuals with incident cancer, those with a recorded BMI from their health screening within 90 days of their cancer diagnosis, were also excluded ($N = 61$) because the BMI may have been influenced by cancer. After the application of these exclusion criteria, 10 618 adults with HIV remained. Those who did not develop cancer after their HIV diagnosis until December 31, 2020, were matched to individuals with incident cancer by sex, year of birth (±2 years), year of HIV diagnosis (±2 years), and follow-up duration (defined as the number of days from the date of HIV diagnosis to the date of cancer diagnosis, death, or December 31, 2020, whichever came first). The follow-up duration of the matched controls was set to be the same or longer than that of each of the cancer incident case in a ratio of 1 : 4.

This study was approved by the Institutional Review Board of Hanyang University, Korea (Approval no: HYUIRB-202111-005). We obtained permission to utilize and analyze the pseudonymized NHIS-NHID through the National Health Insurance Sharing Service system for our research. The consent waiver was obtained for this present study. The study was conducted in compliance with protocols of the Reporting of Observational Studies in Epidemiology for cohort studies.

BMI assessment

During the national health screening program, trained medical staff measured each individual's height and weight. BMI was calculated by weight (kg) divided by height in meters squared. We focused on BMI at HIV diagnosis considering universal HAART for HIV-infected people; thus, if a person infected with HIV participated in national health screening more than once, the results closest to the date of HIV diagnosis were applied. Individuals were classified into two groups based on their BMI according to the Asia–Pacific classification: obese (BMI $\geq$25 kg/m^2) and normal to overweight (BMI $<$25 kg/m^2) [20]. The median difference from the date of BMI assessment to the date of HIV diagnosis was 44 days.

Covariates assessment

Responses from the self-administered questionnaire, including health behaviors, medical history diagnosed by physicians, family history of chronic diseases, and anthropometric measurements, were obtained from the national health screening records of the NHIS-NHID. Based on the self-reported questionnaire responses recorded at BMI assessment, smoking status (never, former, or current), drinking frequency during the last year (never, less than 1 day per week, 1–2 days per week, 3–4 days per week, or 5–7 days per week), physical activity (none, 1–6 days per week or 7 days per week), and a history of stroke, heart disease, hypertension, diabetes, dyslipidemia, family history of strokes, heart diseases, hypertension, and diabetes, were applied to the analyses as adjusted variables. As a surrogate of the progression of HIV, diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis was defined based on the ICD-10 code in the health utilization data

and attendance at minimum three clinics due to the same disease within 1 year after the date of the initial diagnosis of AIDS-defining diseases. In terms of AIDS-defining diseases, candidiasis, extra-pulmonary cryptococcus, cytomegalovirus, tuberculosis, chronic ulcers due to herpes simplex, recurrent pneumonia, *Pneumocystis jirovecii* pneumonia, progressive multifocal leukoencephalopathy, *Toxoplasma gondii*, and wasting syndrome due to HIV were considered [21]. As cancer was the study outcome, we did not consider AIDS-defining cancer. On the basis of the prescription information, we also considered the prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis (none, less than 60 days, and 60–90 days).

Statistical analysis

Baseline characteristics between incident cancer cases after HIV diagnosis and matched cancer-free controls are shown as proportions or means and compared using the Chi-square test (categorical variables) and Student's *t*-test (continuous variables). Baseline characteristics with a chi-square *P* value less than 0.20 in terms of their association with cancer incidence were selected as covariates. Initially, the association between obesity and cancer risk was assessed by simple logistic regression. A multiple logistic regression model was applied to identify the associations between obesity and cancer incidence, adjusting for variables other than the matching variables (physical activity per week, smoking status, drinking frequency during the last year, medical history of tuberculosis, diagnosis of Candida, recurrent pneumonia, *T. gondii* within 3 months of HIV diagnosis, and prescription of HAART therapy within 3 months of the initial HIV diagnosis). The association between obesity and each type of cancer was also assessed by multiple logistic regression. The statistical significance criterion was set as a two-sided *P* value. A *P* value less than 0.05 was considered statistically significant. SAS software (version 9.4; SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analyses.

Results

Table 1 summarizes the baseline characteristics of adults with HIV (cancer incident cases and matched controls) included in this study. Of the 456 cancer incident cases, there were 391 men (87.1%) and 59 women (12.9%). The proportions of participants in the age group of the 50 s, 40 s, and 60 s were 29.4, 27.6, and 22.4%, respectively. Compared with the matched controls, the cancer incident cases included a higher proportion of people who never engaged in physical activity and consumed alcohol 5–7 days per week. In contrast, prescription of highly active antiretroviral therapy within 3 months of the initial HIV diagnosis was lower among the cancer incident cases than that among the matched controls. Regarding the diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis, the proportions of candida infection and recurrent pneumonia were higher in cancer incident cases than those in the matched controls and the differences showed a borderline significance ($P = 0.0627$ and 0.0538, respectively).

Of the 456 cancer incident cases, there were 146 AIDS-defining cancer cases, including 25 Kaposi sarcoma, four cervical cancer, and 117 non-Hodgkin's lymphoma (Fig. 1). There were 310 non-AIDS defining cancer cases, including 32 colorectal cancer; 44 liver, bile duct, and pancreatic cancer; 38 lung and tracheal cancer; 39 stomach cancer; 28 thyroid cancer; 21 prostate cancer; 16 anal cancer; and 91 other types of cancers (Fig. 2).

The results of the simple logistic regression analysis on the association between obesity and cancer are summarized in Table 2. Table 2 and Fig. 3 demonstrate the association between obesity and cancer, in terms of odds ratio (OR) after adjusting for covariates. The adjusted OR of overall cancer associated with obesity was 1.203 (95% CI = 0.953–1.519). Compared with nonobese adults with HIV, obese adults with HIV were at a higher risk of non-AIDS-defining cancer (OR = 1.478, 95% CI = 1.118–1.955). On the contrary, the overall risk of AIDS-defining cancer and the risk of each type of AIDS-defining cancer (Kaposi sarcoma and non-Hodgkin's lymphoma) was not increased in obese adults with HIV. Of the specific types of non-AIDS-defining cancers, obesity was associated with an increased risk of colorectal cancer (OR = 3.090, 95% CI = 1.110–8.604) and liver, bile duct, and pancreatic cancers (OR = 2.532, 95% CI = 1.141–5.617). Although the results were not statistically significant, the OR was increased for stomach cancer, thyroid cancer, and prostate cancer but decreased for lung and trachea cancer and anal cancer.

Discussion

Obesity and cancer are emerging health issues among PWHA. Considering this, the recently revised guidelines for HIV and AIDS have expanded the contents regarding obesity management and cancer [22]. When the cancer risk associated with obesity was evaluated in PWHA in Korea, obesity was associated with increased risk of non-AIDS-defining cancer in adults with HIV, especially colorectal cancer and liver, bile duct, and pancreatic cancers. The association between obesity and AIDS-defining cancer was not statistically significant.

Weight gain and obesity are well established risk factors not only for cancer but also for various chronic diseases in the general population [23,24]. Insulin resistance, glucagon metabolism dysregulation, high leptin level, adipokines, and chronic inflammation have been

Table 1. Baseline characteristics of cancer incident cases and matched controls in a cohort of cancer-free adults with HIV.

Characteristics	Cancer incident cases		Controls[a]		
	N	%	*N*	%	*P*
Age at HIV diagnosis (Mean/SD)	50.3 (12.4)	49.7 (12.5)	0.3872		
Age group					
29	21	4.6	87	4.8	0.8418
30–39	73	16.0	330	18.2	
40–49	126	27.6	476	26.2	
50–59	134	29.4	514	28.3	
≥60	102	22.4	407	22.5	
Sex					
Men	397	87.1	1581	87.2	0.9572
Women	59	12.9	233	12.8	
BMI (Mean/SD)	23.5 (3.3)	23.3 (3.0)	0.2362		
Obesity status					
Normal and Overweight (<25 kg/m^2)	317	69.5	1334	73.5	0.0847
Obese (≥25 kg/m^2)	139	30.5	480	26.5	
Physical activity per week					
Never	157	34.4	519	28.6	0.0305
1–6 days/week	181	39.7	817	45.0	
7 days/week	105	23.0	450	24.8	
Missing	13	2.9	28	1.6	
Smoking status					
Never smoked	200	43.8	799	44.1	0.1957
Former smokers	62	13.6	307	16.9	
Current smokers	185	40.6	684	37.7	
Missing	9	2.0	24	1.3	
Drinking frequency during the last year					
Never	236	51.8	969	53.4	0.0258
Less than 1 day per week	33	7.2	109	6.0	
1–2 days per week	117	25.7	519	28.6	
3–4 days per week	33	7.2	139	7.7	
5–7 days per week	28	6.1	57	3.1	
Missing	9	2.0	21	1.2	
Medical history[b]					
Stroke	4	0.9	21	1.2	0.6079
Heart diseases	9	2.0	39	2.2	0.8151
Hypertension	52	11.4	220	12.1	0.6703
Diabetes mellitus	38	8.3	135	7.4	0.5214
Dyslipidemia	11	2.4	40	2.2	0.7895
Tuberculosis	5	1.1	38	2.1	0.1621
Positive family history					
Stroke	31	6.8	111	6.1	0.5924
Heart diseases	18	4.0	55	3.0	0.3219
Hypertension	53	11.6	226	12.5	0.6270
Diabetes mellitus	50	11.0	186	10.3	0.6564
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	18	4.0	43	2.4	0.0627
Extra-pulmonary cryptococcus	2	0.4	6	0.3	0.6653
Cytomegalovirus (CMV)	21	4.6	67	3.7	0.3673
Tuberculosis (TB)	66	14.5	247	13.6	0.6350
Chronic ulcers due to herpes simplex	15	3.3	41	2.3	0.2053
Recurrent pneumonia	81	17.8	257	14.2	0.0538
Pneumocystis jirovecii pneumonia	28	6.1	90	5.0	0.3107
Progressive multifocal leukoencephalopathy (PML)	5	1.1	13	0.7	0.3831
Toxoplasma gondii	34	7.5	103	5.7	0.1541
Wasting syndrome due to HIV	2	0.4	9	0.5	0.9999
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	240	52.6	608	33.5	<.0001
Incomplete[c]	65	14.3	275	15.2	
Complete[c]	151	33.1	931	51.3	

Statistically significant findings are highlighted in bold ($P < 0.05$).
[a]Controls were matched to cancer cases by sex, year of birth (±2 years), year of HIV diagnosis (±2 years), and follow-up duration (defined as the number of days from the date of HIV diagnosis to the date of cancer diagnosis, death, or December 31, 2020, whichever came first). The follow-up duration of the matched controls was set to be the same or longer than that of each cancer incidence case with 1 : 4 ratio.
[b]Defined as ever diagnosed by clinicians.
[c]If the date of prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis was <60 days, it was considered incomplete. Otherwise, if the date of prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis was ≥60 days, it was considered complete.

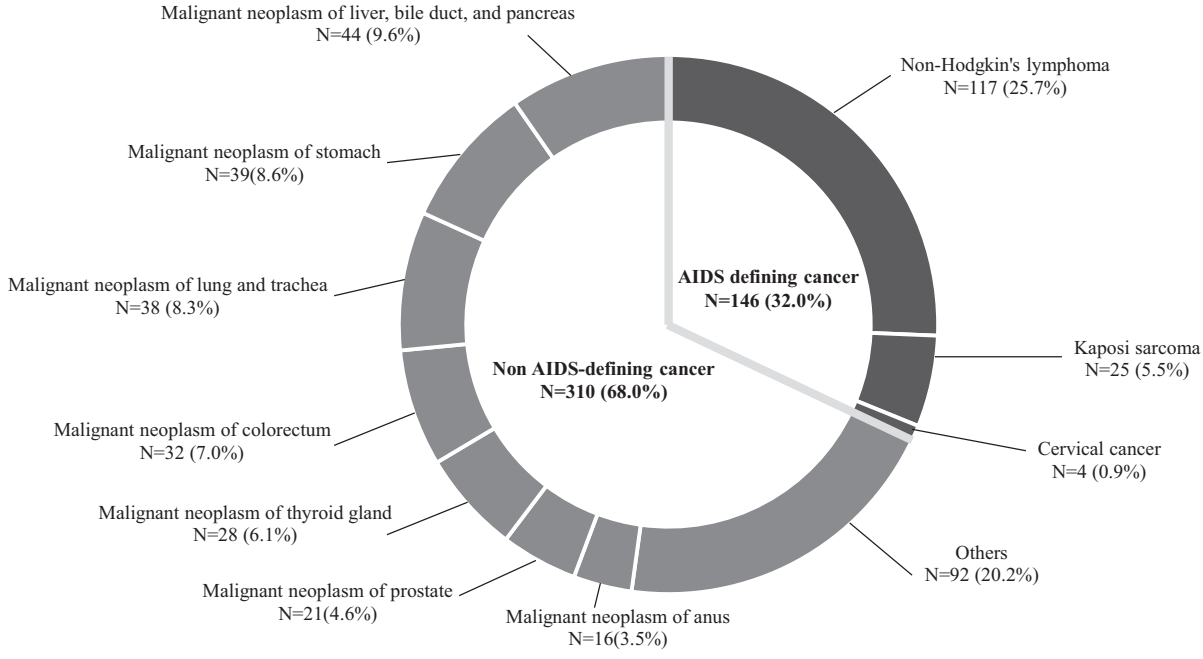

Fig. 2. Proportion of incident cancer types in adults with HIV in Korea.

conventionally identified as the underlying mechanisms linking obesity to an increased cancer risk [25]. Regarding the impact of chronic inflammation (caused by obesity) on cancer, helper T1 and helper T17-cell as subtypes of $CD4^+$ T-cell have been observed to contribute to the development of inflammation and hyperglycemia [26]. Thus, these two helper cells have been suggested to represent one of the links between inflammation status and disordered glucose metabolism following obesity and carcinogenesis [27,28]. Considering the progressive $CD4^+$ T-cell depletion in adults with HIV [29], a hypothesis to link T cell alteration in adipose tissue, HIV infection, and cancer has been proposed [30].

Among PWHA, obesity or weight gain has a conflicting impact; therefore, this is referred to as a double-edged sword [15]. Obesity or weight gain may be the representative indicator of viral suppression and $CD4^+$ T-cell recovery, followed by normalization of resting energy expenditure. With this implication, weight gain after HAART is recognized as a "return to health" [31]. In contrast, excess weight gain or obesity is associated with an increased risk of diabetes and other metabolic comorbidities in PWHA [15,32,33] as is in the general population. It has been suggested that weight gain as a marker of "return to health" has become less prevalent as the initial HIV treatment using HAART has become the

Table 2. Associations between obesity[a] and overall and site-specific cancer risks compared with nonobese[b] adults with HIV.

	Crude OR	*P*	Adjusted OR[c]	*P*
Overall cancer	1.219 (0.973–1.526)	0.0850	1.203 (0.953–1.519)	0.1208
AIDS-defining cancer	0.802 (0.529–1.216)	0.2986	0.816 (0.520–1.279)	0.3747
Kaposi sarcoma	0.899 (0.324–2.495)	0.8377	1.229 (0.251–6.023)	0.7992
Non-Hodgkin's lymphoma	0.822 (0.519–1.302)	0.404	0.864 (0.523–1.428)	0.5696
Non-AIDS defining cancer	1.472 (1.125–1.927)	0.0048	1.478 (1.118–1.955)	0.0061
Malignant neoplasm of the colorectum	2.007 (0.878–4.590)	0.0988	3.090 (1.110–8.604)	0.0308
Malignant neoplasm of the liver, bile duct, and pancreas	2.500 (1.261–4.957)	0.0087	2.532 (1.141–5.617)	0.0224
Malignant neoplasm of the lung and trachea	0.534 (0.207–1.373)	0.1928	0.421 (0.144–1.232)	0.1144
Malignant neoplasm of the stomach	1.700 (0.823–3.515)	0.1519	1.679 (0.755–3.734)	0.2037
Malignant neoplasm of the thyroid gland	1.749 (0.721–4.242)	0.2162	1.838 (0.652–5.181)	0.2494
Malignant neoplasm of the prostate	1.409 (0.503–3.945)	0.5137	1.625 (0.468–5.638)	0.4444
Malignant neoplasm of the anus	0.638 (0.162–2.517)	0.5210	0.496 (0.084–2.939)	0.4399

Statistically significant findings are highlighted in bold ($P < 0.05$). CI, confidence interval; OR odds ratio.
[a]Obesity was defined as a BMI of $\geq 25\,kg/m^2$.
[b]Non-obese was defined as a BMI of $<25\,kg/m^2$.
[c]Adjusted for physical activity, smoking status, drinking frequency during the last year, medical history (tuberculosis), diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis (Candida, recurrent pneumonia, toxoplasma), and prescription of highly active antiretroviral therapy (HAART) within 3 months of HIV diagnosis.

* The results were adjusted for physical activity per week, smoking status, drinking frequency during the last year, medical history (tuberculosis), diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis (candida, recurrent pneumonia, toxoplasma), and prescription of highly active antiretroviral therapy (HAART) within 3 months of HIV diagnosis

** Statistically significant, in boldface (p<0.05)

Type of Cancer	Normal & Overweight (< 25Kg/m²)	Conf.int	Obesity (≥ 25Kg/m²)	P-value
Cancer (all types)	**1 (ref)**		1.203 (0.953-1.519)	0.1208
AIDS defining cancer	**1 (ref)**		0.816 (0.520-1.279)	0.3747
Kaposi sarcoma	1 (ref)		1.229 (0.251-6.023)	0.7992
Non-Hodgkin's lymphoma	1 (ref)		0.864 (0.523-1.428)	0.5696
Non-AIDS defining cancer	**1 (ref)**		1.478 (1.118-1.955)	0.0061
Malignant neoplasm of colorectum	1 (ref)		3.090 (1.110-8.604)	0.0308
Malignant neoplasm of liver, bile duct, and pancreas	1 (ref)		2.532 (1.141-5.617)	0.0224
Malignant neoplasm of lung and trachea	1 (ref)		0.421 (0.144-1.232)	0.1144
Malignant neoplasm of stomach	1 (ref)		1.679 (0.755-3.734)	0.2037
Malignant neoplasm of thyroid gland	1 (ref)		1.838 (0.652-5.181)	0.2494
Malignant neoplasm of prostate	1 (ref)		1.625 (0.468-5.638)	0.4444
Malignant neoplasm of anus	1 (ref)		0.496 (0.084-2.939)	0.4399

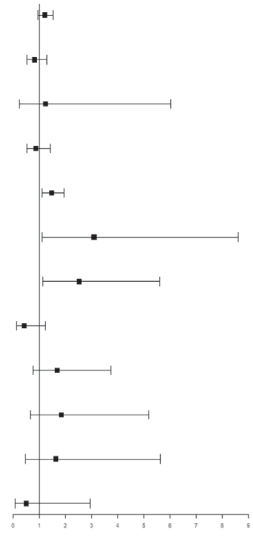

Fig. 3. Odds ratio and 95% confidence interval for the association between obesity and overall cancer risk and site-specific cancer risks compared with nonobese adults with HIV. The results were adjusted for physical activity per week, smoking status, drinking frequency during the last year, medical history (tuberculosis), diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis (candida, recurrent pneumonia, toxoplasma), and prescription of highly active antiretroviral therapy (HAART) within 3 months of HIV diagnosis.

standard practice worldwide; thus, adults with HIV who experienced wasting syndrome became few [15]. The association between obesity or weight gain and major chronic diseases, including cardiovascular disease or mortality, is less understood, with inconsistent results among the studies and according to the initial weight status [15,33].

To the best of our knowledge, this is the first study to assess the association between obesity and cancer risk in PWHA. Considering unintentional weight loss as a symptom of HIV-associated wasting syndrome, an AIDS-defining condition [34], the nonsignificant association between obesity and AIDS-defining cancer may be due to improved immunity or less AIDS deterioration in PWHA. The lack of statistical significance may be due to the small number of incident cancer cases. The results of this study showed decreased point estimates of AIDS-defining cancer risk in obese PWHA compared with nonobese PWHA. The decreased risk of anal cancer (statistically insignificant), which is one of the non-AIDS defining cancers, and human papillomavirus infection [7] were detected in obese PWHA in this study and also in a previous study [35]. This also reflects a delayed progression of HIV infection.

The increased risk of non-AIDS-defining cancer in obese PWHA compared with nonobese PWHA was comparable with that of the general population. Due to the small number of each type of cancer included as non-AIDS-defining cancer, a statistically significant increment associated with obesity was only observed for colorectal cancer and hepatobiliary/pancreatic cancer. Obesity is a well established risk factor for colorectal cancer in the general population, with hormonal systems associated with insulin regulation and adipokines as potential mechanisms [36]. The hormonal systems also underpin the association between obesity and cancer in PWHA as well. Obesity is also a risk factor for hepatobiliary and pancreatic cancer, with obesity-induced insulin-resistance and type 2 diabetes as the most commonly suggested mechanisms [37–39]. Liver cancer is infection-related, with chronic hepatitis B virus infection being the major cause in Korea (contributing to more than 60% of liver cancer and 10% of bile duct cancer) [40]. Interestingly, the major transmission route of chronic hepatitis B virus infection is perinatal infection from mother to infant [41]. In Korea, chronic hepatitis B in adulthood is mainly transmitted sexually and is less associated with decreased immunity among patients with HIV. Furthermore, the liver cancer incidence in PWHA was not significantly different compared with that in the general population in Korea [17], where hepatitis B infection is endemic [41]. Obesity was independently associated with liver cancer in those with chronic hepatitis B infection [42]. For PWHA, the association between

obesity and hepatobiliary and pancreatic cancer, without consideration of hepatitis virus infection, would be explainable. Further studies with a relatively larger number of incident cancer cases for each type of cancer are required to determine the association between obesity and cancer in PWHA with sufficient power.

This study has several limitations. First, although weight change after HAART is an important issue, many of the previous studies did not include baseline weight measurements [27]. This study did not consider weight or BMI trajectories before and after HAART as the number of participants decreased if repeated measures were considered. Moreover, the number of repeated BMI measurements during health checkups and the time between checkups varied among individuals, making it difficult to find a suitable analysis model. Further studies with follow-up of BMI at regular intervals are required. Second, for the temporal relationship, we considered the BMI that was at least 90 days before cancer diagnosis and closest to the date of HIV diagnosis. This latent period would not be long enough for temporal association, and reverse causation (weight change after cancer diagnosis and its effect on the association) would be possible. Considering that weight loss is one of the nonspecific cancer symptoms [43], if there had been reverse causation, it would underestimate the association because incident cancer cases who had already lost weight were included among the cancer cases. Therefore, the observed results would be toward the null hypothesis, which is suggestive of conservative results. Third, PWHA with no results from the national health screening program were excluded due to unavailable BMI data, which resulted in the exclusion of approximately 33% of the study participants. Hence, the study population may not be representative of all PWHA. To increase validity, we adopted a nested case–control study design. Both the incident cancer cases and matched controls (matched by age, sex, and year of HIV diagnosis) were selected from PWHA who had participated in the national health screening program. Fourth, due to the properties of the claims-based data, clinical information, such as $CD4^+$ T-cell count or viral load, was not available. Instead of this information, we identified the health status at the time of HIV diagnosis by considering the presence of AIDS-defining diseases. Fifth, although several covariates were adjusted for the independent association between obesity and cancer risk, possible confounders, such as a family history of cancer, were not considered due to unavailable information. Sixth, several regimens of HAART have been prescribed to treat HIV; however, this study did not consider the effect of each regimen on weight change. Further research is needed to determine the association between the type of HAART, obesity, and cancer development. Last, owing to the small number of cancer sites, different cancer types in adjacent organs were grouped in the analysis to distinguish between subtypes according to the ICD-10 classification.

Conclusion

PWHA are at an increased risk of both AIDS-defining cancer and non-AIDS-defining cancer. The disease burden due to non-AIDS-defining cancer has progressively increased. The results of this study identified that obesity, which is one of the important health concerns in HIV management, was associated with an increased risk of non-AIDS-defining cancer but not AIDS-defining cancer. The question of how to evaluate and manage obesity during HIV progression is of clinical relevance, especially in terms of the prevention of chronic diseases, including cancer. Further prospective studies with a larger number of incident cancer cases, information on weight or BMI trajectories over the course of the disease, relevant clinical information, and confounders are required to further characterize the exact relationship between obesity and cancer risk.

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B.P. and Y.J. performed the research. T.K., Y.C., and K.H. A. analyzed the data. S.W.K., J.Y.C., and H.Y.K. were responsible for data acquisition and verification. J.H.K., H.S., and YJK designed the research. J.Y.S., H.J.C., and K.S.I. planned the statistical analyses. J.W.S., B.S.C., and B.Y.C. visualized the results. All authors contributed to writing the original draft and the interpretation of the research.

The data that support the findings of this study are available on the website of the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/). We accessed the database after submitting the study protocol, the IRB approval document, and the reviewed request form from the relevant committee. Further information is available from the corresponding author upon request.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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