Ph.D. Dissertation of Economics

The socioeconomic burden and modifiable risk factors of cancer and HIV

암과 인간면역결핍바이러스로 인한 사회경제적 부담 및 예방 가능한 질병 위험요인

August 2023

Graduate School of Agricultural Economics and Rural Development
Seoul National University
Major in Regional Information Studies

Yoonyoung Jang

The socioeconomic burden and modifiable risk factors of cancer and HIV

Supervisor: Prof. Hong Sok (Brian) Kim

Submitting a Ph.D. Dissertation of Economics

August 2023

Graduate School of Agricultural Economics and Rural Development
Seoul National University
Major in Regional Information Studies

Yoonyoung Jang

Confirming the Ph.D. Dissertation written by Yoonyoung Jang

August 2023

Chair _____(Seal)

Vice Chair _____(Seal)

Examiner _____(Seal)

Examiner _____(Seal)

Examiner _____(Seal)

Abstract

The human immunodeficiency virus (HIV) destroys CD4 cells, which offer protection from bacterial and fungal infections and cancers. Consequently, the symptoms of HIV are similar to those of flu, such as sore throat, fever, muscle pains, and chills lasting for 2–4 weeks. However, the presence of these symptoms does not necessarily indicate an HIV infection. Moreover, some people with HIV remain asymptomatic until the severe stage, thus highlighting the need of undergoing an HIV test in case of exposure or high-risk of exposure to HIV.

Three disease stages are observed in people with HIV who remain untreated. The first stage is a flu-like condition with a high viral load (the quantity of virus present in the blood of a person with an infection). The second stage is chronic HIV infection that is asymptomatic during incubation period; however, virus replication proceeds continuously. This stage is either prolonged for a decade or is short with rapid progression. The third stage is termed as acquired immune deficiency syndrome (AIDS). People with AIDS have a significant viral load and are vulnerable to other severe illnesses. If they remain untreated, their life expectancy reduces to approximately 3 years.

Regarding the patterns of HIV from 1990 to 2019, the highest number of new HIV infections occurred in 1997, with 3.3 million cases, while the highest number of deaths occurred in 2004, with 1.8 million deaths. In 2019, approximately 36.8 million people worldwide were identified to be living with HIV, around 690,000 death cases were due to HIV-related illnesses, and 1.7 million new HIV infections

were confirmed. With the advancement of highly active antiretroviral therapy (HAART), the life expectancy of individuals living with HIV has improved over time. However, there are increasing concerns regarding the costs associated with the long-term handling of the infection. These expenses include obtaining medical care, HIV medications, and addressing comorbid conditions.

In contrast to the global trend, the number of new HIV infections in Korea has been increasing, particularly among young people, since 1986. As of 2019, 1,222 new cases of HIV were confirmed, with 13,857 people confirmed to be living with HIV. This trend is exceptional and mysterious given Korea's good healthcare system, high education level, and efforts from both the government and private sector for prevention and management.

This study was centered on individuals living with HIV, given their increased risk for cancer. While previous investigations in Korea have shown an elevated cancer risk among HIV-positive individuals compared to the general population, specific risk factors within this group remain largely undefined. Notably, in Korea, no study has yet been conducted to pinpoint cancer risk factors among those living with HIV. The rising concerns surrounding obesity and cancer among individuals living with HIV/AIDS cannot be overstated.

Previously, severe HIV infection was often termed a ‘wasting disease’ due to the accompanying weight and muscle loss. However, the narrative has shifted with the introduction of highly active antiretroviral therapy (HAART), which suppresses viral replication, reduces metabolic demand, and often leads to weight gain. Post-

HAART, the prevalence of obesity among those living with HIV/AIDS has risen, especially among those who were underweight when they initiated the therapy. Consequently, recent updates to the treatment protocols for HIV and AIDS have broadened their scope to incorporate the management of both obesity and cancer.

In Korea, the incidence of non-AIDS-related cancer among HIV/AIDS patients has been on the rise. This study's outcomes highlight the association of obesity, a significant issue in HIV care, with an increased risk for non-AIDS-defining cancers. Hence, evaluating and managing obesity during the course of HIV infection is of clinical significance, especially for the prevention of chronic illnesses such as cancer.

Moreover, this study explored the risk factors for thyroid cancer in Korean women over 40 years old, a demographic deemed high-risk. Although most types of cancer present statistically significant elevated risks for HIV-positive individuals compared to the general population, thyroid cancer seems to pose a greater risk for the general populace.

This investigation found a connection between obesity markers such as body mass index (BMI), waist circumference (WC), and waist-height ratio (WHTR), and a heightened risk of thyroid cancer in Korean women. By combining obesity indices like waist circumference (WC), waist-hip ratio (WHR), and waist-height ratio (WHTR) with body mass index (BMI) categories, a notably increased risk of thyroid cancer was identified in women exhibiting both an obesity-level BMI and other obesity indices, compared to women with normal BMI and other obesity

indicators.

Individuals living with HIV are at a higher risk for cancer compared to the general population. However, globally, no studies have been undertaken to measure the strain on the healthcare system due to cancer treatment in HIV patients. this study calculated the healthcare expenses associated with cancer in the first five years post-diagnosis and the final six months of life for individuals living with HIV in Korea. This would provide crucial information about the economic impact linked to cancer in this at-risk group.

The principal findings from this section are as follows. It was discovered that the average yearly medical costs associated with cancer were higher for AIDS-defining cancers compared to non-AIDS-defining cancers. The largest medical expenses in the first year after a cancer diagnosis were typically incurred in the month immediately following the diagnosis. Total medical costs, influenced by both average medical expenses and the number of cancer instances, were higher for non-AIDS-defining cancers as compared to AIDS-defining cancers. Finally, the average monthly total medical expenses for each HIV-positive individual who died after a cancer diagnosis tended to increase as they approached the time of death.

Ultimately, this study calculates the value of a statistical life for HIV, an amount that society is willing to invest in reducing HIV mortality rates. The application of the value of a statistical life method is key to comprehending the socioeconomic consequences of HIV in our community. Simply focusing on the medical or opportunity costs associated with HIV doesn't fully capture its overall

impact. Consequently, this study emphasizes the significance of the value of a statistical life for HIV as an indicator of welfare loss and economic impact within our society. This can provide valuable insight to policymakers when allocating limited medical budgets. If a particular age group invests more in human capital development, they will reap greater welfare benefits from a reduced risk of HIV mortality. Hence, people aged between 30 to 49 with a high level of human capital have a higher value over their extended life expectancy than those younger than 30 or older than 49. Furthermore, as the 45 to 49 age group has a larger population size than any other group and age-specific population sizes were used as weight parameters, the welfare gain for ages 45 to 49 has the highest value.

In conclusion, this study presents three novel findings. First, it identifies obesity as a lifestyle-related risk factor for cancer in individuals with HIV (non-AIDS-defining cancer) and Korean women over the age of 40 (thyroid cancer). Second, it provides first-of-its-kind data on the financial burden associated with cancer treatment during the first five years post-diagnosis and the final six months of life for HIV-infected patients in Korea. Third, the study underscores the importance of the value of a statistical life for HIV as a measure of welfare loss and societal economic impact. This research is hoped to provide valuable insights for medical professionals managing and preventing cancer risk groups, as well as policymakers in charge of decision making in healthcare.

Keyword: Human Immunodeficiency Virus (HIV), Acquired Immune Deficiency Syndrome (AIDS), AIDS-defining Cancer, Non-AIDS-defining Cancer, Cost of Illness (COI), Willingness to Pay (WTP), The Value of a Statistical Life (VSL)

Student Number: 2020-39228

Table of Content

List of Tables

List of Figures

Chapter 1. Introduction

1.1. Study Background

1.1.1. Mechanism of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)

Characteristics of HIV

The human immunodeficiency virus (HIV) destroys CD4 cells, which offer protection from bacterial and fungal infections and cancers. Consequently, the symptoms of HIV are similar to those of flu, such as sore throat, fever, muscle pains, and chills lasting for 2–4 weeks. However, the presence of these symptoms does not necessarily indicate an HIV infection. Moreover, some people with HIV remain asymptomatic until the severe stage, thus highlighting the need of undergoing an HIV test in case of exposure or high-risk of exposure to HIV. The virus can spread via sexual contact, needle sharing, and vertical transmission (mother-to-child) (CDC 2022, WHO 2023). It cannot be transmitted by mosquitoes, other insects, tears or sweat, hugging, shaking hands, sharing dishes, and through air. Furthermore, the virus cannot survive outside the human body (CDC 2021).

AIDS-Defining Conditions

Three disease stages are observed in people with HIV who remain untreated. The first stage is a flu-like condition with a high viral load (the quantity of virus present in the blood of a person with an infection). The second stage is chronic HIV infection that is asymptomatic during incubation period; however, virus replication proceeds continuously. This stage is either prolonged for a decade or is

short with rapid progression. The third stage is termed as acquired immune deficiency syndrome (AIDS). People with AIDS have a significant viral load and are vulnerable to other severe illnesses. If they remain untreated, their life expectancy reduces to approximately 3 years (CDC 2022). In Korea, the criteria for the AIDS stage is CD4 cell count <200 cells/mm^3 or having an AIDS-defining disease such as *Pneumocystis carinii* pneumonia (KDCA 2021).

1.1.2. HIV/AIDS Epidemic

Eradication the public health risk posed by HIV/AIDS by 2030 is a Sustainable Development Goal (SDG) (2021). In 2014, the "90-90-90" strategy was proposed, which aims to ensure that 90% of people with HIV are diagnosed, 90% of them receive antiretroviral therapy (ART), and 90% of those treated achieve viral load suppression, by 2020 (Sidibé, Loures et al. 2016). However, according to the UNAIDS Global HIV and AIDS statistics, globally, only 67% of people with HIV had received ART in 2019.

Although the "90-90-90" goal was not achieved, global efforts toward HIV prevention and treatment have led to a steady decline in the number of new HIV infections over the past decade. Regarding the patterns from 1990 to 2019, based on the Global Burden of Disease Study 2019 (GBD 2019) data resources, the highest number of new HIV infections occurred in 1997 (3.3 million cases), while the highest number of deaths occurred in 2004 (1.8 million). Approximately 36.8 million (16.8 million men and 20.1 million women) people worldwide were diagnosed with HIV, in 2019 (Jahagirdar, Walters et al. 2021). Around 690,000 deaths were due to HIV-related illnesses, and 1.7 million new HIV cases were

confirmed in the same year (Heath, Levi et al. 2021, UNAIDS 2021). The global trend of HIV can be summarized as below (Jahagirdar, Walters et al. 2021) and (Heath, Levi et al. 2021, UNAIDS 2021).

Table 1-1. HIV/AIDS Trend Worldwide

	Details
Global HIV Incidence	• 1.7 million new HIV infections in 2019 (Current) • 3.3 million new HIV infections in 1997 (Worst)
Global HIV Deaths	• 690,000 deaths due to HIV-related illnesses in 2019 (Current) • 1.8 million deaths due to HIV-related illnesses in 2004 (Worst)
Global HIV Prevalence	• 36.8 million people with HIV in 2019

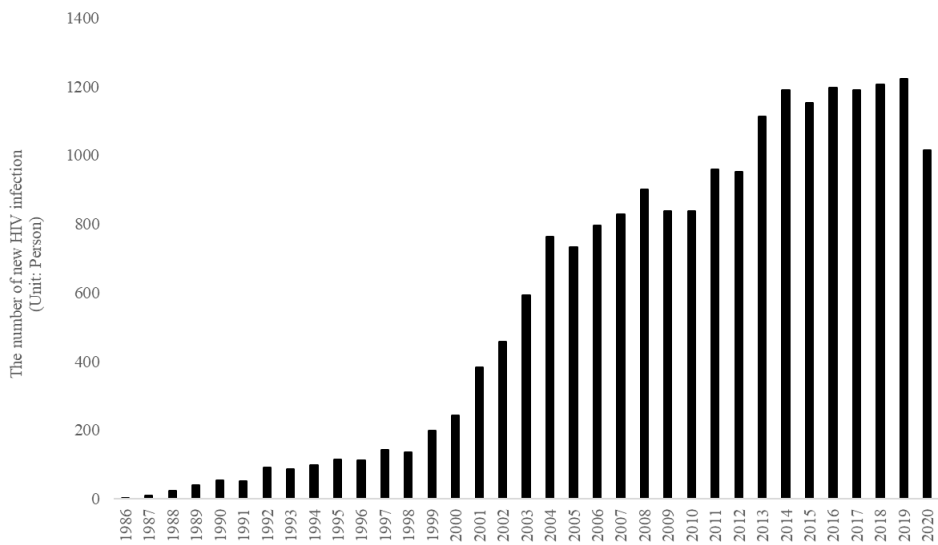
Globally, many countries have experienced a decrease in new HIV infections due to the expanding coverage of HIV treatment. However, based on the data source of the GBD 2019 and UNAIDS from 2010 to 2019 for 204 countries, an upward trend has been observed in countries with high-ranking GDPs, such as the United States (US), Brazil, Spain, and Portugal since 2010. In the US, the incidence rate per 100,000 population increased from 15.6 in 2010 to 20.0 in 2019. However, mortality rates of people with HIV are decreasing worldwide, and it has been forecasted from 11 to 8.5 deaths per 100,000 population by 2040 (Govender, Hashim et al. 2021).

In the US, based on the Census Data and the National HIV Surveillance System, the estimated incidence rate of HIV infection among men who have sex with men (MSM), persons who inject drugs (PWID), heterosexuals from 2010 to 2015 was as follows: MSM, 587.8 to 575.7 per 100,000; PWID, 52.5 to 34.3 per 100,000; and heterosexuals 5.5 to 4.1 per 100,000, respectively (Crepaz, Hess et al.

2019). During these periods, HIV incidence rates reduced among all three groups.

In Taiwan, (Wu, Huang et al. 2022) estimated HIV incidence and prevalence rates in 2012–2019 using the National HIV/AIDS Reporting and Case Management System. Demographic information and risk characteristics for people with HIV were gathered after the diagnosis. Compared with 2012, in 2019 the incidence rates decreased from 9.4 to 7.1 per 100,000 people and prevalence rates increased from 111 to 158 per 100,000 people.

Figure 1-1. Number of new HIV infections, Korea in 1986-2020



Source: Korean Statistical Information Service

Contrary to the global trend, the number of new HIV infections in Korea have been increasing, particularly young people, since 1986. As of 2019, 1,222 new HIV infections and 13,857 people with HIV were confirmed. This trend is exceptional and inexplicable given Korea's excellent health care system, high education level, and efforts from both the government and private sector for prevention and

management (Kim, Choi et al. 2018).

Based on the 2019 Annual Report on the Notified HIV/AIDS in Korea, among 952 Korean men diagnosed with HIV in 2019, 442 and 332 were reported to have been infected with HIV through sexual intercourse with men and women, respectively.

With the advancement of ART, the life expectancy of people with HIV has improved over time (Ray, Logan et al. 2010, Simmons, Ciancio et al. 2013). However, concerns regarding the costs associated with the long-term management of people with HIV have been mounting. Furthermore, the increased life expectancy of people with HIV has led to an increase in the prevalence of HIV-related comorbidities.

According to the healthcare coverage payer data in the US, which includes commercial insurance, Medicaid, and Medicare from 2003 to 2013, people with HIV were more likely to receive treatment for illnesses such as liver and thyroid diseases than the general population (Gallant, Hsue et al. 2017).

(Martínez-Sanz, Serrano-Villar et al. 2022) summarized the discussion of 30 HIV experts to understand HIV-related comorbidities and to develop the strategies on normalizing the health status of people with HIV. The main research topic has changed from AIDS-defining illnesses to non-AIDS-defining illnesses. Moreover, the burden of chronic inflammation in people with HIV are aggravated; however, specialists in the field of HIV research look forward to mitigating this problem in the future through efforts to understand its characteristics.

1.2. Study Purpose

To lessen the socioeconomic impact of cancer, it is essential to understand the disease itself and develop and implement effective cancer prevention and management strategies for those at high risk.

First, this study focuses on the identification of cancer risk factors among HIV-positive individuals in Korea. Understanding how these individuals are at risk of developing cancer can offer crucial insights for healthcare practitioners who provide treatment to patients with HIV (Chapter 2).

Second, this study additionally identifies the risk factors associated with thyroid cancer in Korean women aged 40 and above, a demographic group that constitutes a high-risk group. According to the previous study, general population were more susceptible to thyroid cancer than individuals living with HIV. This additional analysis is devoted to comprehending the increasing prevalence of thyroid cancer in society and formulating preventive strategies. (Chapter 3).

Third, this study analyzes the trend in healthcare expenditures related to cancer treatment over five years post-diagnosis in individuals with HIV. It also estimates the total medical costs, including cancer treatment, during the last six months of life for these patients before death. These insights could be useful to understand the economic burden associated with cancer beyond the impact of HIV infection on people living with this condition. By reducing the risk of cancer incidence in HIV-infected people, society can potentially save on the economic burden related to cancer; therefore, estimated medical costs represent the extent to which preventing cancer incidence can reduce the economic burden (Chapter 4).

Fourth, this study estimates cost of illness (COI) and the value of a statistical

life (VSL) for HIV to understanding the socioeconomic consequences of HIV spread on our society. The long-term increase in new HIV infections in Korea has led to a mounting financial burden on the healthcare system. Life expectancy for people living with HIV also has increased through effective HIV regimens (Ray, Logan et al. 2010, Simmons, Ciancio et al. 2013). The study also analyzed the medical expenditures for people living with HIV based on cost of illness approach. The statistical value of life for those with HIV can indicate a loss of welfare within society due to the disease. This information can aid policymakers in making informed decisions regarding the distribution of scarce medical resources (Chapter 5).

1.3. Structural Concept of Research

1.3.1. Necessity of an Economic and Epidemiologic Approach

Economics is the study of making the best choice to utilize scarce resources. Scarcity and choice are keywords that cannot be separated from economics (Lee 2008). Indefinite availability of resources or budgets will render choice and concentration inconsequential.

The health care sector, which has garnered an increased interest owing to the COVID-19 pandemic, is no exception. The difficulties experienced when the number of COVID-19 cases surged, such as insufficient medical resources, facilities, and medical personnel, are closely related to limited resources.

Even otherwise, the annual national budget is limited; therefore, budgeting its allocation to the health care sector remains an important issue. Considering the amount of money spent on specific diseases, the current status of disease incidence

and mortality, disease prevention strategies, and need for additional budgets are necessary to appropriately utilize limited resources and budgets.

However, an economic approach alone may not suffice for a realistic analysis of the socioeconomic burden and ripple effects of specific diseases. The author believes that realistic research results can be derived when economic and epidemiologic approaches are combined; however, to explain this concept, epidemiology needs to be elucidated.

1.3.2. Definition of Epidemiology

Epidemiology (Celentano, Szklo et al. 2018) is the study of distribution of diseases in the society or in certain populations, and the effects and the factors that determine the distribution of these diseases. Epidemiologists attempt to determine the susceptibility of some people to disease, while others stay healthy, based on the premise that diseases do not occur accidentally within a population.

Epidemiology has four specific purposes. First, it finds the causes and risk factors of diseases. Risk factor is a factor that increases the risk of developing a specific disease. The ultimate goal of epidemiology is to improve people's morbidity and further reduce the risk of disease; therefore, a reasonable basis for disease prevention must be provided.

Second, it attempts to understand the degree of disease burden in the society which is crucial to gauge the appropriate level of required medical resources and manpower.

Third, epidemiology evaluates the existing disease prevention and treatment system and identifies areas to be improved through future investments. For

example, whether the current health care system has effectively protected society from COVID-19 and helped maintain a certain quality of life. At the outset, the possibility of evaluating this aspect needs exploration, and if it is possible, the evaluation methodology will merit consideration as well.

Fourth, epidemiology provides basic data to establish policies to address environmental problems, disease prevention, and health promotion. For example, because the medical system was overburdened due to COVID-19, those with other specific diseases may have not received proper treatment; therefore, questions on the adverse effects experienced by these patients and preventive measures would require answers.

1.3.3. Research Questions

Herein, the key questions of the present research conducted by combining economics and epidemiology are summarized below.

First, people with HIV are more vulnerable to cancer than the general population. What are the risk factors for cancer incidence in people with HIV in Korea? If cancer can be prevented in these people, their quality of life may improve and the socioeconomic burden may be reduced; hence, are there any preventable risk factors? (Chapter 2)

Second, if there is a cancer for which the general population is more vulnerable than people with HIV, what are its risk factors? (Chapter 3)

Third, current treatments for HIV are effective and result in a significantly lower mortality rate and longer life expectancy; however the burden of cancer has increased. How many cases of cancer have been diagnosed and what is the

treatment cost? (Chapter 4)

Fourth, is there a difference between the average annual cancer treatment cost per person for people with HIV and those in the general population? If yes, what are its implications? (Chapter 4)

Fifth, by how much will the mortality rate of people with HIV reduce if they receive proper treatment? (Chapter 5)

Sixth, what is the total cost currently being spent on treating people with HIV and what is the cost per person? (Chapter 5)

Seventh, if people with HIV receive prompt medical services, their mortality rate can significantly decrease. However, this mortality rate is higher than that in the general population; therefore, how much is society willing to pay to increase the survival rate to that as the general population? (Chapter 5)

1.3.4. Differentiation of research

Regarding the answers to the aforementioned questions, the mortality rate of people with HIV, the incidence of HIV infection, and the prevalence of HIV treatments can be accurately confirmed by an epidemiological approach; conversely, the increasing cost of cancer treatments for people with HIV, their treatment expenses, and the cost that society is willing to pay to equalize the survival rate of people with HIV to that of the general population can be confirmed by an economic approach.

Several assumptions will be needed if a study is to be conducted without identifying the characteristics of a disease (transmission route, incidence rate, mortality rate, etc.) through an epidemiological approach. These were limitations

of previous health economics studies.

Economics, a branch of social science, aims to discover the interrelationships between people and society (Lee 2008). It should be preceded by an accurate understanding of current social issues; therefore, this study aims to observe the economic burden and its ripple effect, by first identifying the nature of a disease through an epidemiologic approach.

1.4. Data Source

In this study, data were sourced from the Korean National Health Insurance Service (NHIS) database. The health insurance data was originally collected for health service administration.

The database was first used for academic purposes in July 2014, and the current big data analysis center of the Korean NHIS was established post-April 2016. This database contains the medical information of almost all legal residents in Korea, as all are required to subscribe to health insurance. However, information on non-payment medical services such as cosmetic surgery is not included. However, data such as gender, date of birth, medical treatment, drug prescription, medical expenses, health examination information, and death can be obtained.

Although the database is available for research purposes, it cannot be used for purposes not approved by the Korean NHIS, such as acts that may infringe on the interests of third parties or attempts to identify pseudonymized information. This database is built for administrative purposes; hence, it has the advantage of basic information for the entire population. However, sometimes researchers are unable to check detailed medical information, namely indices such as the stage at the time

of diagnosis for cancer, the amount of virus or immune cells confirmed by blood tests for viral infections, and the severity at the time of diagnosis of a specific disease. Nevertheless, because the database is akin to a population without sampling bias, the author deemed that it is most reliable as data for people with HIV.

Under the national infectious disease monitoring system, when an individual is diagnosed with HIV, it should be mandatorily reported within 24 h of confirmation. Every year, the Korea Centers for Disease Control and Prevention collects and officially announces information on the number of new HIV infections.

A comparison of the number of new HIV diagnoses (HIV cost-sharing system code (V103))—confirmed by the Korean NHIS database—with that reported by the Korea Centers for Disease Control and Prevention revealed that the average error range was approximately 2% annually for 16 years from 2005 to 2019. Therefore, this database was used to conduct the present study.

According to Article 44 of the National Health Insurance Act, “the cost-sharing system reduces the self-burden rate for severely ill, rare, and incurable patients, such as cancer with high medical expenses. If the system benefits are received, the patient pays only 5/100 of the total cost of medical care benefits for outpatient or inpatient treatment.”

Chapter 2. Risk factors for cancer in HIV-infected individuals①

2.1. Study Background

Following the introduction of ART as the standard treatment for HIV infection in adults, the survival rates and life expectancy of people with HIV have improved significantly (Ray, Logan et al. 2010, Simmons, Ciancio et al. 2013). However, the increased life expectancy has resulted in a higher probability of developing various chronic diseases, which has conferred a substantial disease burden in this population (Quiros-Roldan, Magoni et al. 2016, Yang, Beymer et al. 2019, Nanditha, Zhu et al. 2022).

The ART regimen suppresses viral load. People with HIV should begin ART immediately after the diagnosis of HIV. Although ART cannot cure HIV, people with HIV receiving treatment have a longer life expectancy and lead healthy lives. Moreover, people having an undetectable viral load cannot transmit HIV to others (NIH 2021).

Regarding cancer, ART has decreased the risk of AIDS-defining cancers, which are directly linked with progressive immunodeficiency. Nevertheless, the burden of non-AIDS-defining cancers has exhibited an increasing trend (Shiels, Islam et al. 2018, Yarchoan and Uldrick 2018).

Cancer can be defined as a disease where gene changes occur in a cell, causing abnormal changes or excessive multiplication. Cells are the smallest unit of

① This chapter is based on material originally presented in the "Association between obesity and cancer risk in HIV-infected Asians", which was submitted to *The Journal of Global Health* in 2023.

the human body, and cancer does not occur if cells in the body divide, grow, and die, and are maintained at an appropriate level. Cancer is characterized by its ability to spread to surrounding organs or tissues and distant organs, indicating the importance of early diagnosis and prompt and appropriate treatment (NCIC 2023).

According to US National Cancer Institute, AIDS-defining cancers are cancers that develop more frequently in people with HIV, because of their increased vulnerability, than the general population. The development of at least one AIDS-defining cancer indicates that these individuals have reached the AIDS stage. There are three types of AIDS-defining cancers namely Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer(NCI 2023). The remaining cancer types were categorized as non-AIDS-defining cancers.

Historically, advanced HIV infection was frequently called a "wasting disease" because of the associated the loss of weight and muscle mass. In contrast, antiretroviral therapy (ART) treatment, which inhibits viral replication, decreases the metabolic demand, and is associated with weight gain. Following the introduction of antiretroviral therapy (ART), the incidence of obesity among HIV infected people has increased, particularly in patients who were underweight when they started antiretroviral therapy (ART) (Yuh, Tate et al. 2015, Kanters, Renaud et al. 2022). Obesity is a well-established risk factor for chronic diseases (Hyppönen, Mulugeta et al. 2019, Larsson and Burgess 2021), and recently, the European Commission has recognized obesity as a chronic illness, instead of merely a lifestyle-based condition (Burki 2021). With the increased prevalence of overweight and obesity, and the associated increase in the risk of chronic diseases, among HIV infected people, the management of weight and obesity is a crucial aspect of HIV infected people care (Bailin, Gabriel et al. 2020). Nonetheless, in

HIV infected people, the association of obesity with various health outcomes, particularly mortality, remains unclear and inconsistent (Sharma, Hoover et al. 2015, Yuh, Tate et al. 2015, Kumar and Samaras 2018). To our knowledge, only a few studies have explored the association of obesity with cancer risk in people living with HIV.

Regarding smoking, the smoking prevalence among adult men decreased from 45.4% in 2010 to 33.8% in 2018, while that among women slightly decreased from 2.7% to 2.0% during the same period. Regarding alcohol consumption (current drinkers), those who participated in the survey in both 2010 and 2018 usually consumed alcohol more than twice a week in the past year, and the average amount of alcohol consumption per drink was more than 7 cups for men and 5 cups for women. Men's drinking rate decreased to 23.0% in 2018 compared with 26.3% in 2010; however, women recorded the same drinking rate, 3.6%, at both periods (Park 2021).

The prevalence of obesity among Korean men has steadily increased over the past 20 years, from 26.2% in 1998 to 42.8% in 2018, though it has not changed significantly among Korean women during the same period, from 25.1% to 25.5%. Age-wise comparison reveals that both men and women in their 30s and 40s have the highest prevalence of obesity (Nam 2022). Therefore, this study chose obesity index as a main variable in the nested case-control study, and additionally, smoking and alcohol consumption rates, which have recently declined among lifestyle-related cancer risk factors, were used as covariates because >90% of the people with HIV in Korea are men. In Korea, HIV infected people have an increased risk for both AIDS-defining and non-AIDS-defining cancers, including Hodgkin's lymphoma, oropharyngeal cancer, and anal cancer (Park, Ahn et al. 2022). Despite

being comparatively lower than the prevalence in Western populations, the prevalence of obesity in the Korean population has been rapidly increasing (Yang, Han et al. 2022) and associated with an increase in the chronic disease burden in the Korean general population. This study was aimed at examining the relationship between obesity and cancer in Korean people living with HIV based on data obtained from a nationwide health screening database.

2.2. Literature Review

2.2.1. Increased Cancer Risk in People with HIV

(Deeken, Tjen-A-Looi et al. 2012) found that people with HIV had the higher incidence rates of non-AIDS defining cancer than the general population. Despite access to HIV treatment, people with HIV had higher cancer risks than the general population. Furthermore, the study mentioned that the reason for increased non-AIDS-defining cancer risks were unclear. It reviewed several studies from the US, France, the United Kingdom (UK), and Switzerland and demonstrated the standardized incidence rate (SIR) of non-AIDS-defining cancer. The cancer risks for people with HIV were higher than that for the general population (reference group, incidence rate=1) such as Hodgkin's lymphoma (14.7–31.7), leukemia (2.2–2.5), and anal (32.4–42.9), liver (7.0–7.7), head and neck (1.0–4.1), lung (2.2-6.6), and renal (1.8–2.2) cancers (Deeken, Tjen-A-Looi et al. 2012).

(Hernández-Ramírez, Shiels et al. 2017) analyzed the cancer risk for people with HIV compared with the general population. The HIV/AIDS Cancer Match Data (HACM) that was linked with HIV and Cancer Registries in the US was used. Notably, 21,294 patients with cancer among 448,258 people with HIV were

identified from 2006 to 2012. People with HIV were found to be more vulnerable to the cancer incidence than the general population. The incidence rates according to cancer types were as follows: overall cancer (SIR 1.69, 95% CI=1.67–1.72); AIDS-defining cancers such as Kaposi's sarcoma (SIR 498.11, 95% CI: 477.82–519.03), non-Hodgkin's lymphoma (SIR 11.51, 95% CI: 11.14–11.89), and cervical cancer (SIR 3.24, 95% CI: 2.94–3.56); other virus-related cancers such as anal cancer (SIR 19.06, 95% CI: 18.13–20.03), liver cancer (SIR 3.21, 95% CI: 3.02–3.41), and Hodgkin's lymphoma (SIR 7.70, 95% CI: 7.20–8.23); and virus-unrelated cancers such as lung cancer (SIR 1.97, 95% CI: 1.89–2.05) (Hernández-Ramírez, Shiels et al. 2017).

In Korea, (Park, Ahn et al. 2022) analyzed the cancer risk for people with HIV compared with the general population. The study used the Korean NHIS database NHIS and 11,552 cancer-free people (men: 10444 and women: 1108) and 361 patients with cancer (men: 317 and women: 44) during 2006–2018 were identified. The cancer risk for people with HIV was higher for several types of cancers than that for the general population. Overall cancer (SIR 1.68, 95% CI: 1.50–1.87), Kaposi sarcoma (SIR 349.10, 95% CI: 196.10–502.20), anal cancer (SIR 104.20, 95% CI: 55.56–149.90) for men with HIV and overall cancer (SIR 1.26, 95% CI: 0.89–1.64), cervical cancer (SIR 4.98, 95% CI: 1.29–8.66), and non-Hodgkin's lymphoma (SIR 11.78, 95% CI: 1.29–21.21) for women with HIV presented higher cancer risk than that for the general population (Park, Ahn et al. 2022). Despite ART's benefits of a longer life expectancy and improved health, the risk of AIDS-defining cancer remains high for people with HIV, and the burden of non-AIDS-defining cancer has been aggravated.

2.2.2. Risk Factors of Cancer in People with HIV

Risk factors are factors that increase the risk of developing a particular disease. These include behavior, heredity, and exposure to certain environmental hazards. The ultimate purpose of determining the risk factor or cause of the disease is to prevent the occurrence of the disease by reducing exposure to the factor or eliminating the factor itself (Celentano, Szklo et al. 2018).

In the US and Europe, cancer is a major cause of death among people with HIV. Moreover, as mentioned, people with HIV have a higher risk of developing cancer (AIDS-defining and non-AIDS-defining) than the general population. Between 2011 and 2013, 113 papers from Canada, the US, Australia, and Western European countries were meta-analyzed to investigate any difference in the prevalence of modifiable cancer risk factors between people with HIV and the general population in the US (Park, Hernández-Ramírez et al. 2016). Modifiable cancer risk factors considered in the paper were obesity, smoking, alcohol consumption, and hepatitis B virus (HBV) infection. Previous studies, which (Park, Hernández-Ramírez et al. 2016) considered, categorized people with HIV as overall, male, and female groups. The median age of HIV infection in 113 previous studies was 44 years, and the median proportion of males was 75.4%. Among the 113 studies, 59 were on the US and 46 on Western European countries. The US-related results of this study are summarized herein. Regarding current smoking rate, it was approximately 2.5 times higher in overall people (54.0% vs. 20.0%), males (58.0% vs. 23.0%), and females (48.0% vs. 18.0%) with HIV than the general population in the US. Regarding alcohol consumption, each study had a wide range of periods, from the past 30 days to the past 6 months; hence, comparison of people

with HIV with the general population proved to be a limitation. Regarding obesity rate (body mass index (BMI) ≥30.0 kg/m^2), the obesity rates in overall people (17.0% vs. 24.0%) and males (25.0% vs. 32.0%) with HIV were lower than that in the general population; conversely, it was higher in females with HIV (47.0% vs. 36.0%). HBV infection rates were higher in overall people (5.0% vs. 0.3%), males (4.0% vs. 0.4%), and females (5.0% vs. 0.2%) with HIV than that in the general population (Park, Hernández-Ramírez et al. 2016).

To determine the risk factors of cancer in people with HIV in China, (Jin, Liu et al. 2017) conducted a meta-analysis and systematic review of 102 studies. China has been distributing ART nationwide since 2003; however, significantly higher SIRs of AIDS-defining and non-AIDS-defining cancer have been observed in people with HIV than in the general population. Comparison of the characteristics of overall people with HIV and the general population revealed that the prevalence of smoking, alcohol consumption, and viral presence (HBV hepatitis C virus [HCV], human papillomavirus [HPV], Epstein-Barr virus [EBV], human herpesvirus-8 [HHV8]) among people with HIV were higher than those in the general population. Smoking was divided into ever smoker (current and former) and never smoker, and alcohol consumption was divided into former drinker and current drinker. The criteria for overweight and obesity was (BMI ≧24 kg/m^2). Among modifiable behavioral factors, the smoking prevalence rate among people with HIV was higher than that among the general population (Su, Tao et al. 2010, Cheng, Chu et al. 2012); in particular, the current smoking rates among overall people (41.1% vs. 28.3%), males (63.2% vs. 53.3%), and females (3.4% vs. 2.5%) with HIV were higher than those among the general population in China. The rates of overweight and obesity among people with HIV were lower than those among

the general population (22.4 vs. 42.6), which was observed in the previous study in Western countries as well (Park, Hernández-Ramírez et al. 2016). The current alcohol assumption rate among overall people with HIV (30.3% vs. 28.8%) was higher than that among the general population. Regarding HBV infection, the infection rates among overall people (12.5% vs. 7.2%), males (13.4% vs. 8.6%), and females (10.4% vs. 5.7%) with HIV were higher than those among the general population in China (Jin, Liu et al. 2017).

Since the introduction of antiretroviral drugs, many studies worldwide have demonstrated that the risk of non-AIDS-defining cancers has increased among people with HIV. Smoking, chronic inflammation, aging, immunocompromised state, infections caused by viruses such as HBV, HCV, HPV, and EBV) are potential cancer risk factors for people with HIV. Owing to the high smoking rate among people with HIV, high SIRs for lung, pharyngeal, and kidney cancers, which are classified as smoking-related cancers, are being confirmed. The increase in liver cancer that is associated with HBV and HCV infections is well known. Moreover, HPV infection is considered as a risk factor for anal cancer. Owing to the influence of EBV infection, the incidence rate of Hodgkin's lymphoma is high among people with HIV. Although access to treatment for people with HIV has considerably improved over the past few decades, the prognosis for the disease remains worse than that in the general population, if non-AIDS-defining cancers occur (Franzetti, Ricci et al. 2019).

(Nkwonta, Zhang et al. 2023) analyzed the prevalence trend of AIDS-defining and non-AIDS-defining cancers, and cancer risk factors in 11,238 people with HIV in South Carolina in the US using population-based HIV-linked data from 2005 to 2020. The study used the time-dependent proportional hazards model to predict

cancer risk factors in people with HIV.

Among the 11,238 people with HIV, 250 and 454 were diagnosed with AIDS-defining and non-AIDS-defining cancer, respectively. In both cancer types, men (compared with women), old age, hepatitis infection, kidney disease, hypertension, and decreased thyroid function were identified as factors that increased the probability of cancer. A higher viral load (HIV) had a higher probability of developing AIDS-defining cancer, and a higher number of immune cells (CD4 cells) had a lower probability of developing both cancers (Nkwonta, Zhang et al. 2023).

Possible risk factors of non-AIDS-defining cancer include HIV itself, oncogenic viruses, and tobacco exposure (Deeken, Tjen-A-Looi et al. 2012). People with HIV are more sensitive and vulnerable to the effects of environmental carcinogens (Altavilla, Caputo et al. 2000, Altavilla, Caputo et al. 2004). Finally, HIV infection itself can enhance tumor progression and metastasis (Corallini, Sampaolesi et al. 2002).

Table 2-1. The Summary of Literature Review

Reference	Research Participants	Summary
Nkwonta, Zhang et al. 2023 Time-Dependent Proportional Hazards Model	People with HIV in South Carolina, US; using population-based HIV-linked data from 2005 to 2020	► Risk factors of cancer Men (compared with women), old age, hepatitis, kidney disease, hypertension, and decreased thyroid function identified as factors that increased the probability of cancer. ► AIDS-defining and non-AIDS-defining cancers The higher the viral load, the higher the probability of developing AIDS-defining cancer, and the higher the number of immune cells (CD4 cells), the lower the probability of developing both cancers.
Franzetti, Ricci et al. 2019	Review Paper (Worldwide)	► Risk factors of AIDS-defining cancer Smoking, chronic inflammation, aging, immunocompromised state, and

		infections with viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), and Epstein-Barr virus (EBV)
Jin, Liu et al. 2017 Meta-analysis And Systematic Review	102 papers from China that were published from 2006 to 2015 *Including only two papers from before 2010	Comparison of prevalence rates between people with HIV and the general population. ► Current smoking • Overall people with HIV (41.1%) > general population (28.3%) • Males with HIV (63.2%) > general male population (53.3) • Females with HIV (3.4%) > general female population (2.5%) * Smoking prevalence rate of people with HIV was higher than that of the general population (Su, Tao et al. 2010, Cheng, Chu et al. 2012) ► Overweight and obesity (BMI ≥ 24.0 kg/m^2) • Overall people with HIV(22.4%) < general population (42.6%) ► Current drinker • Overall people with HIV(30.3%) > general population (28.8%) ► Hepatitis B virus (HBV) • Overall people with HIV(12.5%) > general population (7.2%) • Males with HIV(13.4%) > general male population (8.6%) • Females with HIV(10.4%) > general female population (5.7%) * This study compared the characteristics of people with HIV and the general population in China.
Park, Hernndez-Ramrez et al. 2016. Meta-analysis and systematic review	113 studies from Western countries that were published from 2011 to 2013 *The US (59 studies), Canada, Australia, and Western European countries (46 studies)	Comparison of prevalence rates between people with HIV and general population. ► Obesity (BMI ≥ 30.0 kg/m^2) • Overall people with HIV(17.0%) < general population (34.0%) • Males with HIV(25.0%) < general male population (32.0%) • Females with HIV(47.0%) > general female population (36.0%) ► Current smoking • Overall people with HIV(54.0%) > general population (20.0%) • Males with HIV(58.0%) > general male population (23.0%) • Females with HIV(48.0%) > general female population (18.0%) ► Current drinker Each study had a wide range of periods, from the past 30 days to the past 6 months, which was a limitation when comparing people with HIV and the general population. ► Hepatitis B virus (HBV)

		• Overall people with HIV(5.0%) > general population (0.3%) • Males with HIV(4.0%) > general male population (0.4%) • Females with HIV(5.0%) > general female population (0.2%) * This study compared the prevalence of people with HIV with the published prevalence estimates in US adults.
Deeken, Tjen-A-Looi et al. 2012	Invited article	► Risk factors for non-AIDS-defining cancer HIV itself, which means that the infection itself enhance tumor progression and metastasis; tobacco exposure; and oncogenic viruses (HBV, HCV, HPV, and EBV)

Liver cancer is related to infection, with chronic HBV infection being the primary cause of liver cancer in Korea (accounting for more than 60% and 10% of liver and bile duct cancers, respectively) (Shin, Park et al. 2011). Notably, the main transmission route of chronic HBV is mother-to-child perinatal infection (vertical transmission) (Yim and Kim 2019). In Korea, chronic HBV in adulthood is primarily transmitted sexually and is less likely to be associated with decreased immunity in people with HIV. Moreover, the liver cancer incidence in people with HIV did not differ significantly from that in the general population in Korea (Park, Ahn et al. 2022), where HBV is endemic (Yim and Kim 2019). Obesity was independently linked to liver cancer in individuals with chronic HBV (Kim, Choi et al. 2018).

2.2.3. Obesity issues in people with HIV

Obesity and cancer have become important health concerns among people with HIV. Therefore, recent updates to the management guidelines for people with HIV/AIDS include management strategies for obesity and cancer (Ryom, De

Miguel et al. 2022).

Earlier, HIV was referred to as a “slimming disease” because of the weight and muscle loss experienced by people with HIV. However, since the introduction of effective HIV treatments that inhibit viral replication, obesity in people with HIV who were underweight at treatment initiation have been increasing (Yuh, Tate et al. 2015, Kanters, Renaud et al. 2022). In 2021, the European AIDS Clinical Society Guidelines included obesity and cancer in the health care management of people with HIV (Ryom, De Miguel et al. 2022).

Weight gain and obesity are well-recognized risk factors of cancer and various chronic diseases in the general population (Kyrgiou, Kalliala et al. 2017, Fang, Wei et al. 2018). Insulin resistance, impaired glucagon metabolism, elevated levels of leptin and other adipokines, and chronic inflammation have been identified as the factors that connect obesity and a higher risk for cancer (Stone, McPherson et al. 2018). T-helper 1 and T-helper 17 cells, subtypes of CD4+ or T-cells, contribute to the development of chronic inflammation and hyperglycemia; this is another factor in the association between obesity and cancer (Ip, Cilfone et al. 2016). Consequently, these helper cells have been proposed as connectors between inflammatory status and disrupted glucose metabolism secondary to obesity and carcinogenesis (Alizadeh, Katsanis et al. 2013, De Simone, Pallone et al. 2013). The decline of CD4+ cells in adults with HIV (Okoye and Picker 2013) has led to a hypothesis of the association between T-cell changes in adipose tissue, HIV infection, and cancer has been proposed (Lewis, Lysaght et al. 2019).

In people with HIV, obesity or weight gain presents a contradictory impact, often described as a “double-edged sword” (Kumar and Samaras 2018). Obesity or

weight gain can serve as an indicator of viral suppression and CD4+ cell recovery, which is followed by the normalization of resting energy expenditure. Thus, weight gain after ART was considered a “return to health” marker (Tate, Willig et al. 2012). However, it has become less common because the number of adults with HIV-associated wasting syndrome has decreased (Kumar and Samaras 2018). However, excessive weight gain or obesity is linked to a higher risk of diabetes and other metabolic comorbidities in people with HIV (Kumar and Samaras 2018, Nansseu, Bigna et al. 2018, Chang 2022), similar to that in the general population.

Since the introduction of antiretroviral drugs, overweight or obesity in people with HIV has increased, and excessive increase in fat can cause metabolic dysfunction, especially in those who are aging. Restoring normal weight through HIV treatment is associated with a decrease in mortality; however, obesity and overweight in people with HIV increase the risk of diabetes and cardiovascular and liver diseases (Bailin, Gabriel et al. 2020).

Among people with HIV, the relationship between obesity or weight gain and major chronic diseases, including cardiovascular disease or mortality, remains unclear, with inconsistent research results and dependence on the initial weight status (Kumar and Samaras 2018, Chang 2022).

2.2.4. Well-known Risk Factors of Cancer

Age (time from birth (WHO 1992)) is a most-studied risk factor for cancer in epidemiological research. Cancer can be considered an age-related disease because the incidence of cancer increases with age. Modifiable chronic diseases (obesity and diabetes) tend to increase in middle age (45–64 years), a phenomenon that is related to a higher risk of cancer and a lower survival rate of patients with cancer

(White, Holman et al. 2014). Middle-aged adults are considerably affected by smoking, malnutrition, lack of exercise, alcohol consumption, and certain chronic infections that are known risk factors of cancer (Ott, Ullrich et al. 2011, Prasad, Sung et al. 2012).

Diabetes is associated with an increased risk of breast (in menopausal women), colon, and pancreatic cancers (La Vecchia, Giordano et al. 2011). Moreover, it causes side effects that accelerate aging in humans (Cowie, Rust et al. 2009).

Overweight is a factor that increases the risk of various cancer types, including thyroid, pancreatic, esophageal, gallbladder, colon, breast, cervical c, and kidney cancers (Wolin, Carson et al. 2010, La Vecchia, Giordano et al. 2011). Overweight is associated with an increased risk of metabolic syndrome, which is associated with an increased risk of developing cancer (Trinchieri 2012, Gilbert and Slingerland 2013). Metabolic syndrome issues include high blood pressure, dyslipidemia, insulin resistance and hyperglycemia, inflammatory conditions, and platelet reduction (Grundy 2016).

Furthermore, a link between sleep disorders and cancer risk has been observed, suggesting that mitigation of sleep disorders can help prevent cancer (Blask 2009, White, Holman et al. 2014). Increased physical activity and reduced sitting time have benefits as well (Ory, Anderson et al. 2014).

According to International Agency for Research on Cancer (IARC), carcinogens are individually categorized by risk levels because exposure to harmful chemicals in daily life can increase the risk of cancer. Twelve carcinogens, including trichloroethylene, benzene, and vinyl chloride, are well-known carcinogens (Lim, Kim et al., 2018). Apart from heredity and chronic infection, environmental pollution is considered as a cause of cancer as well (Alavanja and

Bonner 2012, Zhivin, Laurier et al. 2013)

In addition, health literacy is garnering attention. Analyses of the relationship between health information literacy and cancer prevention behavior for people below the poverty line reveals that providing information on cancer prevention guidelines according to the literacy levels of different people can improve their understanding of health promotion information. Improving awareness of health in people with relatively low literacy may induce them to engage in cancer prevention behavior (Kim and Kim 2021). Improving the older adult population's understanding of health information is vital, especially for those in rural areas (Hwang 2016).

2.3. Materials and Methods

The Korea National Health Insurance Service database

This study utilized data from the National Health Insurance Service-National Health Information database (NHIS-NHID) in Korea that collected information on all individuals who were diagnosed with HIV between 2004 and 2020. The NHIS-NHID includes data on demographics, healthcare service utilization, physician prescriptions, health examinations, cancer screening results, and death of more than 97% of the Korean population who are covered by the NHIS – a universal and mandatory national health insurance system. Moreover, the NHIS operates a special cost-sharing system for diseases with high medical expenditure, such as cancer, HIV infection, or rare, incurable diseases.

Case-control study

First, the definition of a case-control study and the reason for the conduct of the case-control study are explained herein. While summarizing data on people with HIV in Korea, it was confirmed that the people with HIV who developed cancer were exposed to a specific cancer risk factor. Consequently, the researcher established a study hypothesis on whether this risk factor was related to an increase in cancer development in people with HIV. Since a meaningful conclusion cannot be derived by simply looking at the degree of exposure to the risk factor in the patients with cancer group, a comparative study with a matched control group needs to be conducted, i.e., comparison of the exposure to risk factors ratio in the patient and control groups. If exposure to a specific risk factor is associated with cancer incidence, the risk factor exposure proportion in the patient group will be higher than that in the control group.

Individual Matching

This section defines individual matching and explains the reason for performing the analysis by individual matching. Individual matching is a method of ensuring that each individual case (patient) and control has a similar distribution for a particular variable when conducting a case-control study. For example, since gender and age are important variables in the occurrence of diseases, the distribution of gender and age between the case (patient) and control groups need to be matched, i.e., if a specific patient with cancer is a 30-year-old male, a 30-year-old male without cancer is selected as the patient's control. Consequently, the researcher can identify the quantitative difference between the case (patient) and control groups in the degree of exposure to the risk factors.

Study Design and Population

The eligible participants were adults who were diagnosed with HIV from 2004 to 2020 – a period wherein as adults with HIV infection were covered by the special cost-sharing system. HIV infection was identified using a combination of ICD-10 codes for HIV infection (B20–B24) and the cost-sharing system codes (V103) for HIV treatment from the healthcare utilization database. To identify incident HIV cases, individuals with medical utilization records for 2002–2003 that contained ICD-10 codes for HIV infection were excluded from the study, in accordance with the method followed in a previous study (Park, Choi et al. 2022).

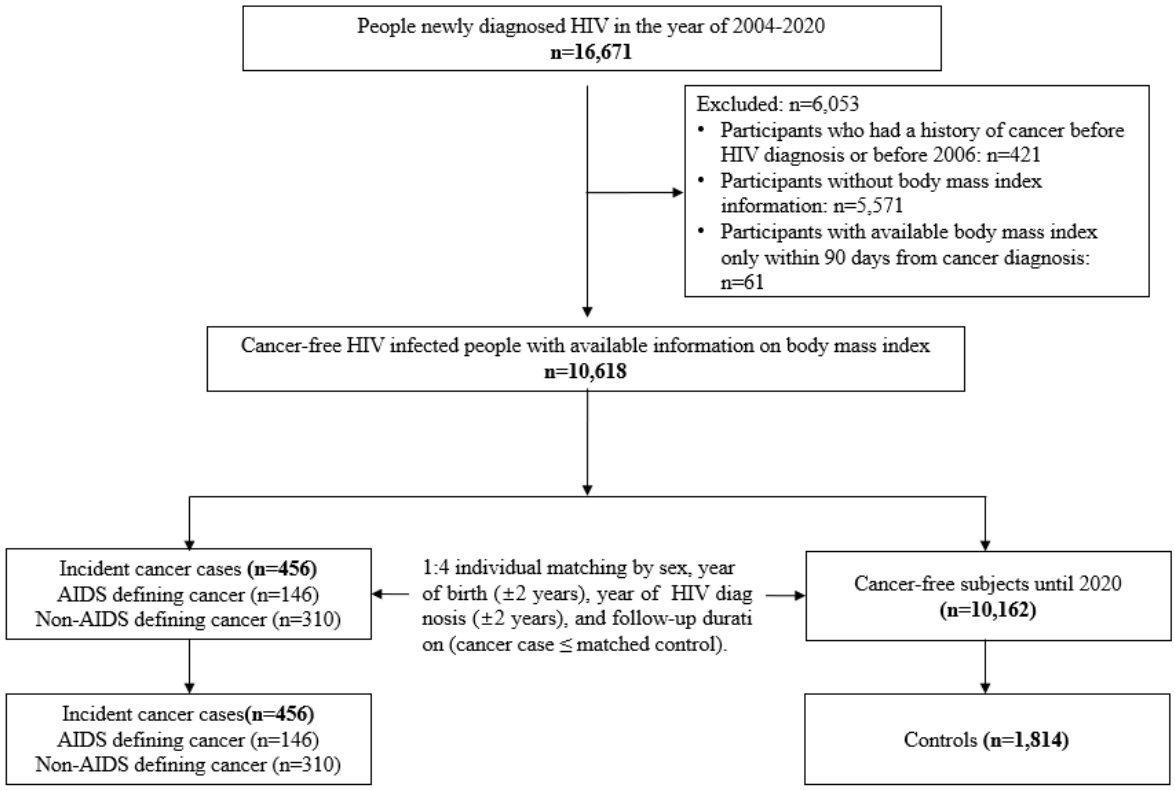
In this study, the cancer incidence from 2006 to 2020 was determined using the ICD-10 codes for cancer (C00–C99) and the cost-sharing system codes (V193, V194, or V027) for cancer from the healthcare utilization database. Patients with a medical history of cancer before the HIV diagnosis were considered as prevalent cancer cases and excluded. AIDS-defining cancers include Kaposi sarcoma (C46), cervical cancer (C53), and non-Hodgkin's lymphoma (C82–C86, C96). Non-AIDS-defining cancers include the other cancer types (Yarchoan and Uldrick 2018), which were categorized as colorectal cancer; liver, bile duct, and pancreatic cancer; lung and tracheal cancer; stomach cancer; thyroid cancer; prostate cancer; and anal cancer.

From 2004 to 2020, a total of 16,671 incident HIV infection cases were identified. In this nested case–control study, the association between obesity and cancer risk in HIV infected people was examined (Figure 2-1). To create a nested case-control matched set, individuals with a history of cancer before their HIV diagnosis or those who were diagnosed with cancer before 2006, when the cancer cost-sharing system began (N=421), were excluded. Additionally, as the National

Health Insurance Service-National Health Information database (NHIS-NHID) recorded body mass index (BMI) data during participation in the national health screening program, individuals who had never participated in the program (N=5,569) were excluded as were two individuals whose BMI data were missing, despite participation in the health screening program. To prevent reverse causation, individuals with incident cancer whose BMI was recorded within 90 days of their cancer diagnosis were excluded (N=61) as their BMI might have been influenced by cancer. After the application of these exclusion criteria, a dataset of 10,618 adults with HIV was obtained. Individuals, without a cancer diagnosis before their HIV diagnosis, and diagnosed with HIV until December 31, 2020 were matched to those with incident cancer (1:4 ratio) 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 occurred first). The follow-up duration of matched controls was set to be equal to or longer than that of each incident cancer case.

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.

Figure 2-1. Participant selection flowchart



Variable Definition

During the national health screening program, trained medical staff obtained height and weight measurements for each individual. The BMI was calculated as the weight (kg) divided by height, in meters, squared. For HIV-infected individuals with multiple participations in the national health screening program, the results nearest to their HIV diagnosis date were considered. The participants were categorized according to the Asia–Pacific BMI classification into two groups: one group was classified as obese (BMI ≥25 kg/m^2) whereas the other was deemed normal to overweight (BMI <25 kg/m^2). The median difference from the date of BMI assessment to the date of HIV diagnosis was 44 days. 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.

Information from the self-reported questionnaire responses recorded during the BMI assessment, including smoking status (never, former, or current); drinking frequency in the past 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); history of stroke, heart disease, hypertension, diabetes, dyslipidemia; and family history of stroke, heart disease, hypertension, and diabetes, was included as adjusted variables in the analyses. A diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis was ascertained based on the ICD-10 code in the health utilization data and attendance at a minimum of three clinics for the same disease within 1 year after the initial diagnosis of AIDS-defining diseases, which included candidiasis, extrapulmonary cryptococcus, cytomegalovirus, tuberculosis, chronic ulcers due to herpes simplex, recurrent pneumonia, pneumocystis carinii pneumonia, progressive multifocal leukoencephalopathy, toxoplasma gondii infection, and HIV-related wasting syndrome (Brodt, Kamps et al. 1997). As cancer was the dependent variable, AIDS-defining cancer was not included in the analysis. Based on the prescription-related information, antiretroviral therapy (ART) prescription within 3 months of HIV diagnosis was evaluated (none, less than 60 days, and 60–90 days).

Regarding HIV treatment, to avoid immortal time bias, the compliance variable used was treatment initiated within 90 days of HIV diagnosis. Immortal time bias is an error that can overestimate or underestimate the effectiveness of a drug because the tracking time prescribed for the drug itself varies across studies.

In studies including patients with cancer and controls, patients with cancer are tracked from the time of HIV diagnosis to the time of cancer; however, the control group is tracked from the time of HIV diagnosis to the time of death or the end of the study period. When matching a total patient group with a control group, researchers normally utilize the option that the follow-up period for the control group should be equal to or longer than that for the patient group. Therefore, if researchers consider only the effect of HIV treatment prescriptions on cancer prevention, the longer the follow-up period of the control group, the longer the treatment can be prescribed, resulting in an overestimation of the cancer prevention effect of HIV treatment (Dekkers and Groenwold 2020).

Statistical Analysis

Baseline characteristics of both incident cancer cases after HIV diagnosis and matched cancer-free controls are presented as proportions or means and compared using the chi-square test and the t-test. Regarding covariates, forward selection or backward elimination were utilized to consider their association with cancer incidence. The relationship between obesity and cancer risk was evaluated through simple logistic regression and then a multiple logistic regression model was used to determine the associations between obesity and cancer incidence (adjusted with forward selection or backward elimination considering weekly physical activity; smoking status; drinking frequency; medical history of stroke, heart diseases, hypertension, diabetes mellitus, dyslipidemia, tuberculosis; positive family history of stroke, heart diseases, hypertension, diabetes mellitus; diagnosis of candidiasis, extra-pulmonary cryptococcus, cytomegalovirus (CMV), tuberculosis (TB), chronic ulcers due to herpes simplex, recurrent pneumonia, pneumocystis carinii pneumonia (PCP), progressive

multifocal leukoencephalopathy (PML), toxoplasma gondii, wasting syndrome due to HIV; prescription of antiretroviral therapy (ART) within 3 months of the initial HIV diagnosis). The interrelationship between obesity and each cancer type was examined using multiple logistic regression. The criterion for statistical significance was set as a two-sided *p*-value, with $p<0.05$ deemed statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.4. Results

Of the 456 cases of incident cancer, 146 had AIDS-defining cancer, including 25 cases of Kaposi sarcoma, 4 cases of cervical cancer, and 117 of non-Hodgkin's lymphoma. There were 310 cases of non-AIDS-defining cancer, including 32 cases of colorectal cancer; 44 cases of liver, bile duct, and pancreatic cancer; 38 cases of lung and tracheal cancer; 39 cases of stomach cancer; 28 cases of thyroid cancer; 21 cases of prostate cancer; 16 cases of anal cancer; and 92 cases of other specific types of cancer.

Figure 2-2. Proportions of incident cancer types in adults with HIV in Korea.

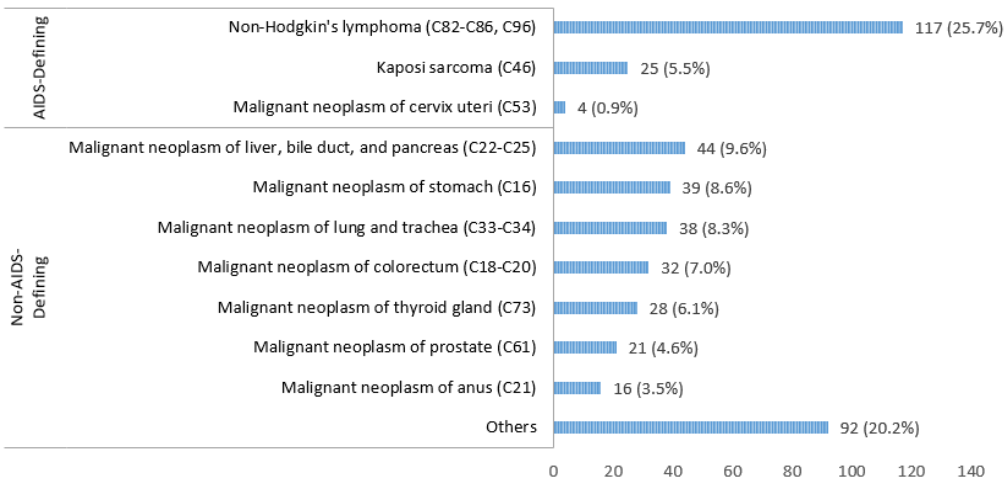


Table 2-2 presents the incident cases for cancer types which were categorized as overall, AIDS-defining, and non-AIDS-defining cancers. This present study's aim is to identify the risk factor depending on the categorized cancer type and sex (male or female).

Table 2-2. Proportions of incident cancer types in men and women with HIV in Korea

Cancer Type	Overall	Men	Women
Overall cancer	456 (100)	397 (87.1)	59 (12.9)
AIDS-defining cancer	146 (100)	133 (91.1)	13 (8.9)
Kaposi sarcoma	25 (100)	25 (100)	0 (0)
Cervical cancer	4 (100)	0 (0)	4 (100)
Non-Hodgkin's lymphoma	117 (100)	108 (92.3)	9 (7.7)
Non-AIDS-defining cancer	310 (100)	264 (85.2)	46 (14.8)
Malignant neoplasm of colorectum	32 (100)	29 (90.6)	3 (9.4)
Malignant neoplasm of liver, bile duct, and pancreas	44 (100)	38 (86.4)	6 (13.6)
Malignant neoplasm of lung and trachea	38 (100)	33 (86.8)	5 (13.2)
Malignant neoplasm of stomach	39 (100)	33 (84.6)	6 (15.4)
Malignant neoplasm of thyroid gland	28 (100)	19 (67.9)	9 (32.1)
Malignant neoplasm of prostate	21 (100)	21 (100)	0 (0)
Malignant neoplasm of anus	16 (100)	16 (100)	0 (0)
Others	92 (100)	75 (81.5)	17 (18.5)

Table 2-3. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (overall cancer: both men and women)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	
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	
30–39	73	16.0	330	18.2	
40–49	126	27.6	476	26.2	0.8418
50–59	134	29.4	514	28.3	
≥60	102	22.4	407	22.5	

Characteristics	Cancer incident cases		Controls [1]		P-value
Sex					
Men	397	87.1	1581	87.2	0.9572
Women	59	12.9	233	12.8	
Body mass index (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 [2]					
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 carinii pneumonia (PCP)	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

Characteristics	Cancer incident cases		Controls [1]		P-value
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	
Incomplete [3]	65	14.3	275	15.2	<.0001
Complete [3]	151	33.1	931	51.3	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-4**.** The association of risk factors and cancer incidence in HIV-infected people (overall cancer: both men and women)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (1.00-1.01)	0.3871	1.00 (0.99-1.01)	0.7265	1.00 (0.99-1.01)	0.5952
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**1.22 (0.97-1.53)**	**0.0850**	**1.18 (0.94-1.49)**	**0.1625**	**1.21 (0.95-1.52)**	**0.1178**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.73 (0.58-0.93)	0.0111	0.75 (0.58-0.95)	0.0196	0.76 (0.59-0.97)	0.0295
7 days/week	0.77 (0.58-1.02)	0.0667	0.81 (0.61-1.08)	0.1531	0.84 (0.63-1.13)	0.2514
Smoking status						
Never smoked	Ref (1)					
Former smokers	0.81 (0.59-1.10)	0.1801			0.82 (0.59-1.13)	0.2213
Current smokers	1.08 (0.86-1.35)	0.4990			1.12 (0.87-1.42)	0.3815
Drinking frequency during the last year						
Never	Ref (1)					
Less than 1 day per week	1.24 (0.82-1.88)	0.3036			1.19 (0.77-1.84)	0.4278
1–2 days per week	0.93 (0.72-1.18)	0.5379			0.97 (0.75-1.26)	0.8197
3–4 days per week	0.98 (0.65-1.46)	0.9017			0.99 (0.65-1.51)	0.9559
5–7 days per week	2.02 (1.26-3.24)	0.0037			1.80 (1.10-2.94)	0.0204
Medical history [1]						
Stroke	0.76 (0.26-2.21)	0.6093				
Heart diseases	0.92 (0.44-1.91)	0.8151				

Hypertension	0.93 (0.68-1.29)	0.6703				
Diabetes mellitus	1.13 (0.78-1.65)	0.5216				
Dyslipidemia	1.10 (0.56-2.15)	0.7896				
Tuberculosis	0.52 (0.20-1.32)	0.1695				
Positive family history						
Stroke	1.12 (0.74-1.69)	0.5925				
Heart diseases	1.31 (0.76-2.26)	0.3231				
Hypertension	0.92 (0.67-1.27)	0.6271				
Diabetes mellitus	0.18 (0.77-1.50)	0.6565				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	1.69 (0.97-2.96)	0.0655	1.83 (1.02-3.28)	0.0413	1.85 (1.03-3.32)	0.0400
Extra-pulmonary cryptococcus	1.33 (0.27-6.60)	0.7290				
Cytomegalovirus (CMV)	1.26 (0.76-2.08)	0.3681				
Tuberculosis (TB)	1.07 (0.80-1.44)	0.6351				
Chronic ulcers due to herpes simplex	1.47 (0.81-2.68)	0.2074	1.59 (0.85-2.99)	0.1467	1.63 (0.86-3.07)	0.1327
Recurrent Pneumonia	1.31 (1.00-1.72)	0.0543	1.48 (1.11-1.98)	0.0085	1.50 (1.12-2.00)	0.0070
Pneumocystis carinii pneumonia (PCP)	1.25 (0.81-1.94)	0.3115				
Progressive multifocal leukoencephalopathy (PML)	1.54 (0.55-4.33)	0.4164	2.21 (0.77-6.34)	0.1391	2.20 (0.76-6.37)	0.1468
Toxoplasma gondii	1.34 (0.90-2.00)	0.1552	1.50 (0.98-2.29)	0.0631	1.50 (0.98-2.31)	0.0639
Wasting syndrome due to HIV	0.88 (0.19-4.10)	0.8744				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.60 (0.44-0.82)	0.0011	0.55 (0.40-0.75)	0.0002	0.54 (0.40-0.75)	0.0002
Complete [2]	0.41 (0.33-0.52)	<.0001	0.38 (0.30-0.48)	<.0001	0.39 (0.30-0.49)	<.0001

[1] Defined as a diagnosis by medical professionals.
[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-3 presents the baseline characteristics of adults with HIV (overall cancer incident cases and matched controls for both men and women) who were included in this study. Of the 456 participants with incident cancer, 397 were men (87.1%) and 59 were women (12.9%). The proportions of participants in their 50s, 40s, and over 60s were 29.4%, 27.6%, and 22.4% respectively. Compared to matched controls, incident cancer was detected in a higher proportion of

individuals who were living with obesity (not significant), never engaged in physical activity or consumed alcohol 5-7 days per week. In contrast, the frequency of antiretroviral therapy (ART) prescription within 3 months of the initial HIV diagnosis was lower among the group with incident cancer as compared to the matched controls. With regard to the diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis, the proportions of candidiasis infection and recurrent pneumonia were higher in the group with incident cancer than in matched controls, with borderline significance (p = 0.0627 and 0.0538, respectively).

The results of multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-4 (overall cancer incident cases and matched controls for both men and women), which indicates the relationship between obesity and cancer in terms of the odds ratio (OR) after adjusting for covariates. The adjusted OR of overall cancer linked with obesity was 1.21 (95% CI: 0.95–1.52, P=0.1178, backward elimination) compared with adults with HIV without obesity. Furthermore, alcohol consumption for 5–7 days/week (reference group: non-drinkers) and diagnosis of an AIDS-defining disease (candidiasis and recurrent pneumonia) were associated with increased risk of overall cancer incidence. Conversely, physical activity for 1–6 days/week (reference group: no activity at all) and high compliance with HIV treatment 3 months after HIV diagnosis were related to a decreased risk of overall cancer incidence.

The results of forward selection and backward elimination were almost identical; however, the alcohol consumption frequency variable was not included in the forwarding selection.

Table 2-5. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (overall cancer: men)

Characteristics	Cancer incident cases		Controls[1]		P-value
	N	%	N	%	
Age at HIV diagnosis (Mean/SD)	49.9 (12.4)		49.3 (12.5)		0.3620
Age group					
-29	18	4.5	76	4.8	
30–39	67	16.9	305	19.3	
40–49	113	28.5	424	26.8	0.7758
50–59	117	29.5	438	27.7	
≥60	82	20.7	338	21.4	
Body mass index (Mean/SD)	**23.3 (3.1)**		**23.4 (3.0)**		**0.9801**
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**284**	**71.5**	**1159**	**73.3**	**0.4775**
Obese (≥25 Kg/m^2)	**113**	**28.5**	**422**	**26.7**	
Physical activity per week					
Never	134	33.8	440	27.8	
1–6 days/week	161	40.6	715	45.2	0.0476
7 days/week	91	22.9	399	25.2	
Missing	11	2.8	27	1.7	
Smoking status					
Never smoked	148	37.3	583	36.9	
Former smokers	62	15.6	301	19.0	0.2790
Current smokers	180	45.3	675	42.7	
Missing	7	1.8	22	1.4	
Drinking frequency during the last year					
Never	194	48.9	779	49.3	
Less than 1 day per week	33	8.3	104	6.6	
1–2 days per week	109	27.5	489	30.9	0.0603
3–4 days per week	29	7.3	133	8.4	
5–7 days per week	25	6.3	56	3.5	
Missing	7	1.8	20	1.3	
Medical history[2]					
Stroke	3	0.8	19	1.2	0.5972
Heart diseases	5	1.3	31	2.0	0.3500
Hypertension	44	11.1	184	11.6	0.7568
Diabetes mellitus	34	8.6	116	7.3	0.4090
Dyslipidemia	9	2.3	31	2.0	0.6984
Tuberculosis	4	1.0	35	2.2	0.1222
Positive family history					
Stroke	24	6.0	102	6.5	0.7670
Heart diseases	16	4.0	50	3.2	0.3894
Hypertension	46	11.6	194	12.3	0.7091
Diabetes mellitus	41	10.3	162	10.2	0.9622
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	16	4.0	38	2.4	0.0754
Extra-pulmonary cryptococcus	2	0.5	6	0.4	0.6651
Cytomegalovirus (CMV)	19	4.8	64	4.0	0.5121
Tuberculosis (TB)	60	15.1	230	14.5	0.7758
Chronic ulcers	15	3.8	37	2.3	0.1094

Characteristics	Cancer incident cases		Controls[1]		P-value
due to herpes simplex					
Recurrent Pneumonia	74	18.6	235	14.9	0.0639
Pneumocystis carinii pneumonia (PCP)	24	6.0	87	5.5	0.6746
Progressive multifocal leukoencephalopathy (PML)	5	1.3	12	0.8	0.3593
Toxoplasma gondii	30	7.6	97	6.1	0.3016
Wasting syndrome due to HIV	2	0.5	9	0.6	1.0000
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	200	50.4	492	31.1	
Incomplete[3]	60	15.1	251	15.9	<.0001
Complete[3]	137	34.5	838	53.0	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-6. The association of risk factors and cancer incidence in HIV-infected people (overall cancer: men)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (1.00-1.01)	0.3619	1.00 (0.99-1.01)	0.4648	1.00 (0.99-1.01)	0.4648
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**1.09 (0.86-1.40)**	**0.4775**	**1.07 (0.83-1.37)**	**0.6215**	**1.07 (0.83-1.37)**	**0.6215**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.74 (0.57-0.96)	0.0219	0.76 (0.58-1.00)	0.0458	0.76 (0.58-1.00)	0.0458
7 days/week	0.75 (0.56-1.01)	0.0578	0.79 (0.58-1.08)	0.1333	0.79 (0.58-1.08)	0.1333
Smoking status						
Never smoked	Ref (1)	-				
Former smokers	0.81 (0.59-1.13)	0.2111				
Current smokers	1.05 (0.82-1.34)	0.6927				
Drinking frequency during the last year						
Never	Ref (1)					

Less than 1 day per week	1.27 (0.84-1.94)	0.2605				
1–2 days per week	0.90 (0.69-1.16)	0.4041				
3–4 days per week	0.88 (0.57-1.35)	0.5459				
5–7 days per week	1.79 (1.09-2.95)	0.0213				
Medical history [1]						
Stroke	0.63 (0.19-2.13)	0.4538				
Heart diseases	0.64 (0.25-1.65)	0.3550				
Hypertension	0.95 (0.67-1.34)	0.7569				
Diabetes mellitus	1.18 (0.79-1.76)	0.4094				
Dyslipidemia	1.16 (0.55-2.46)	0.6986				
Tuberculosis	0.45 (0.16-1.27)	0.1321	0.45 (0.16-1.29)	0.1382	0.45 (0.16-1.29)	0.1382
Positive family history						
Stroke	0.93 (0.59-1.48)	0.7670				
Heart diseases	1.29 (0.72-2.28)	0.3904				
Hypertension	0.94 (0.67-1.32)	0.7091				
Diabetes mellitus	1.01 (0.70-1.45)	0.9621				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	1.71 (0.94-3.09)	0.0786	1.72 (0.92-3.20)	0.0888	1.72 (0.92-3.20)	0.0888
Extra-pulmonary cryptococcus	1.33 (0.27-6.61)	0.7280				
Cytomegalovirus (CMV)	1.19 (0.71-2.01)	0.5126				
Tuberculosis (TB)	1.05 (0.77-1.42)	0.7737				
Chronic ulcers due to herpes simplex	1.64 (0.89-3.02)	0.1120	1.91 (1.00-3.62)	0.0484	1.91 (1.00-3.62)	0.0484
Recurrent Pneumonia	1.31 (0.98-1.75)	0.0645	153 (1.13-2.08)	0.0067	153 (1.13-2.08)	0.0067
Pneumocystis carinii pneumonia (PCP)	1.11 (0.69-1.76)	0.6747	0.42 (0.13-1.31)	0.1388	0.42 (0.13-1.31)	0.1388
Progressive multifocal leukoencephalopathy (PML)	1.67 (0.59-4.77)	0.3382	2.49 (0.86-7.26)	0.094	2.49 (0.86-7.26)	0.094
Toxoplasma gondii	1.25 (0.82-1.91)	0.3024	2.91 (1.02-8.33)	0.0466	2.91 (1.02-8.33)	0.0466
Wasting syndrome due to HIV	0.88 (0.19-4.11)	0.8754				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.59 (0.42-0.82)	0.0014	0.53 (0.38-0.74)	0.0002	0.53 (0.38-0.74)	0.0002
Complete [2]	0.40 (0.32-0.51)	<.0001	0.36 (0.29-0.47)	<0.0001	0.36 (0.29-0.47)	<0.0001

[1] Defined as a diagnosis by medical professionals.

[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-5 presents the baseline characteristics of people with HIV (overall cancer incident cases and matched controls for males) who were included in this study. The proportions of 397 participants in their 40s, 50s, and over 60s were 28.5%, 29.5%, and 20.7% respectively. Compared with matched controls, cancer was detected in a higher proportion of individuals who were obese (not significant), consumed alcohol 5–7 days/week, or never engaged in physical activity. In contrast, the frequency of ART prescription within 3 months of the initial HIV diagnosis was lower among the cancer group than among the matched controls. Regarding the diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis, the proportions of candidiasis and recurrent pneumonia were higher in the cancer group than in the matched controls, with borderline significance (P=0.0754 and P=0.0639, respectively).

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-6 (overall cancer incident cases and matched controls for men), which indicates the relationship between obesity and cancer in terms of the OR after adjusting for covariates. The adjusted OR of overall cancer linked with obesity was 1.07 (95% CI: 0.83–1.37, P =0.6215) compared with non-obese men with HIV. Furthermore, a diagnosis of an AIDS-defining disease (chronic ulcers due to herpes simplex, recurrent pneumonia, and toxoplasmosis) was associated with increased risk of overall cancer incidence for men. Conversely, physical activity 1–6 days/week (reference group: no activity at all) and high compliance with HIV treatment within 3 months after HIV diagnosis were related to decreased risk of overall cancer incidence for men. The results of forward selection and backward elimination were identical.

Table 2-7. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (overall cancer: women)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	
Age at HIV diagnosis (Mean/SD)	52.7 (12.4)		52.7 (12.4)		0.9738
Age group					
-29	3	5.1	11		
30–39	6	10.2	25		
40–49	13	22.0	52		0.9709
50–59	17	28.8	76		
≥60	20	33.9	69		
Body mass index (Mean/SD)	**24.4 (4.2)**		**22.8 (3.2)**		**0.0080**
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**33**	**55.9**	**175**	**75.1**	**0.0037**
Obese (≥25 Kg/m^2)	**26**	**44.1**	**58**	**24.9**	
Physical activity per week					
Never	23	39.0	79	33.9	
1–6 days/week	20	33.9	102	43.8	0.4714
7 days/week	14	23.7	51	21.9	
Missing	2	3.4	1	0.4	
Smoking status					
Never smoked	52	88.1	216	92.7	
Former smokers	0	0.0	6	2.6	0.1540
Current smokers	5	8.5	9	3.9	
Missing	2	3.4	2	0.9	
Drinking frequency during the last year					
Never	42	71.2	190	81.5	
Less than 1 day per week	0	0.0	5	2.1	
1–2 days per week	8	13.6	30	12.9	0.0176
3–4 days per week	4	6.8	6	2.6	
5–7 days per week	3	5.1	1	0.4	
Missing	2	3.4	1	0.4	
Medical history [2]					
Stroke	1	1.7	2	0.9	0.4933
Heart diseases	4	6.8	8	3.4	0.2700
Hypertension	8	13.6	36	15.5	0.7168
Diabetes mellitus	4	6.8	19	8.2	1.0000
Dyslipidemia	2	3.4	9	3.9	1.0000
Tuberculosis	1	1.7	3	1.3	1.0000
Positive family history					
Stroke	7	11.9	9	3.9	0.0245
Heart diseases	2	3.4	5	2.1	0.6321
Hypertension	7	11.9	32	13.7	0.7061
Diabetes mellitus	9	15.3	24	10.3	0.2830
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	2	3.4	5	2.1	0.6321
Extra-pulmonary cryptococcus	0	0.0	0	0.0	-
Cytomegalovirus (CMV)	2	3.4	3	1.3	0.2662
Tuberculosis (TB)	6	10.2	17	7.3	0.4279

Characteristics	Cancer incident cases		Controls [1]		P-value
Chronic ulcers due to herpes simplex	0	0.0	4	1.7	0.5862
Recurrent Pneumonia	7	11.9	22	9.4	0.5784
Pneumocystis carinii pneumonia (PCP)	4	6.8	3	1.3	0.0327
Progressive multifocal leukoencephalopathy (PML)	0	0.0	1	0.4	1.0000
Toxoplasma gondii	4	6.8	6	2.6	0.1208
Wasting syndrome due to HIV	0	0.0	0	0.0	-
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	40	67.8	116	49.8	
Incomplete [3]	5	8.5	24	10.3	0.0411
Complete [3]	14	23.7	93	39.9	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-8. Th**e** association of risk factors and cancer incidence in HIV-infected people (overall cancer: women)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (0.98-1.02)	0.9737	1.00 (0.97-1.02)	0.7604	1.00 (0.97-1.02)	0.8213
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**2.38 (1.31-4.30)**	**0.0042**	**2.17 (1.13-4.18)**	**0.0197**	**2.27 (1.19-4.33)**	**0.0132**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.67 (0.35-1.31)	0.2457				
7 days/week	0.94 (0.45-2.00)	0.8782				
Smoking status						
Never smoked	Ref (1)					
Former smokers	-					
Current smokers	2.31 (0.74-7.18)	0.1485				
Drinking frequency during the last year						

Never	Ref (1)					
Less than 1 day per week	-					
1–2 days per week	1.21 (0.52-2.82)	0.6648	1.28 (0.52-3.17)	0.5888	1.24 (0.50-3.05)	0.6409
3–4 days per week	3.02 (0.82-11.16)	0.0982	3.22 (0.77-13.45)	0.1098	3.13 (0.75-13.02)	0.1168
5–7 days per week	13.57 (1.38-133.71)	0.0255	10.29 (0.99-106.99)	0.0509	9.97 (0.96-104.00)	0.0546
Medical history [1]						
Stroke	1.99 (0.18-22.34)	0.5766				
Heart diseases	2.05 (0.59-7.04)	0.2564				
Hypertension	0.86 (0.38-1.96)	0.717				
Diabetes mellitus	0.82 (0.27-2.51)	0.7266				
Dyslipidemia	0.87 (0.18-4.15)	0.8648				
Tuberculosis	1.32 (0.14-12.94)	0.8105				
Positive family history						
Stroke	3.35 (1.19-9.41)	0.0218	3.03 (0.95-9.67)	0.0611	2.98 (0.94-9.49)	0.0644
Heart diseases	1.60 (0.30-8.46)	0.5795				
Hypertension	0.85 (0.35-2.02)	0.7064				
Diabetes mellitus	1.57 (0.69-3.58)	0.2856				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	1.60 (0.30-8.46)	0.5795				
Extra-pulmonary cryptococcus						
Cytomegalovirus (CMV)	2.69 (0.44-16.48)	0.2846	3.45 (0.48-24.53)	0.2169		
Tuberculosis (TB)	1.44 (0.54-3.83)	0.4660				
Chronic ulcers due to herpes simplex						
Recurrent Pneumonia	1.29 (0.52-3.19)	0.5791				
Pneumocystis carinii pneumonia (PCP)	5.57 (1.21-25.63)	0.0273	7.54 (1.38-41.02)	0.0195	7.29 (1.35-39.5)	0.0213
Progressive multifocal leukoencephalopathy (PML)						
Toxoplasma gondii	2.75 (0.75-10.09)	0.1267				
Wasting syndrome due to HIV						
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.60 (0.22-1.69)	0.3368	0.52 (0.16-1.62)	0.2555	0.51 (0.16-1.60)	0.2486
Complete [2]	0.44 (0.22-0.85)	0.0149	0.44 (0.21-0.92)	0.0287	0.46 (0.22-0.95)	0.0362

[1] Defined as a diagnosis by medical professionals.

[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the

prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-7 presents the baseline characteristics of people with HIV (overall cancer incident cases and matched controls for women) who were included in this study. The proportions of 59 participants in their 40s, 50s, and over 60s were 22.0%, 28.8%, and 33.9% respectively. Compared to matched controls, cancer was detected in a higher proportion of obese individuals who consumed alcohol 5–7 days/week. In contrast, the frequency of ART prescription within 3 months of the initial HIV diagnosis was lower among the cancer group than among the matched controls. Regarding the diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis, the proportion of *PCP* was higher in the cancer group than that in the matched controls. Moreover, the proportion of family history of stroke was higher in the cancer group than that in the matched controls.

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-8 (overall cancer incident cases and matched controls for women), which indicates the relationship between obesity and cancer in terms of OR after adjusting for covariates. The adjusted OR of overall cancer linked with obesity for women was 2.27 (95% CI: 1.19–4.33, P=0.0132, backward elimination) compared with non-obese women with HIV. Furthermore, diagnosis of an AIDS-defining disease (PCP) was associated with increased risk of overall cancer incidence for women. Conversely, high compliance with HIV treatment within 3 months after HIV diagnosis was related to decreased risk of overall cancer incidence for women. The results of forward selection and backward elimination were almost identical to each other; diagnosis of cytomegalovirus (CMV) infection, an AIDS-defining disease, within 3 months of

HIV diagnosis was not included in the backward elimination.

Table 2-9. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (AIDS-defining cancer: both men and women)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	
Age at HIV diagnosis (Mean/SD)	46.5 (12.1)		46.0 (12.2)		0.6843
Age group					
-29	9	6.2	39	6.7	
30–39	34	23.3	161	27.6	
40–49	50	34.2	170	29.2	0.7387
50–59	31	21.2	130	22.3	
≥60	22	15.1	83	14.2	
Sex					
Men	133	91.1	532	91.3	0.9524
Women	13	8.9	51	8.7	
Body mass index (Mean/SD)	**23.1 (3.2)**		**23.4 (3.3)**		**0.4053**
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**110**	**75.3**	**414**	**71.0**	**0.2980**
Obese (≥25 Kg/m^2)	**36**	**24.7**	**169**	**29.0**	
Physical activity per week					
Never	39	26.7	151	25.9	
1–6 days/week	64	43.8	272	46.7	0.9189
7 days/week	37	25.3	151	25.9	
Missing	6	4.1	9	1.5	
Smoking status					
Never smoked	66	45.2	225	38.6	
Former smokers	21	14.4	97	16.6	0.2950
Current smokers	56	38.4	255	43.7	
Missing	3	2.1	6	1.0	
Drinking frequency during the last year					
Never	79	54.1	285	48.9	
Less than 1 day per week	8	5.5	46	7.9	
1–2 days per week	42	28.8	194	33.3	0.6249
3–4 days per week	12	8.2	40	6.9	
5–7 days per week	3	2.1	13	2.2	
Missing	2	1.4	5	0.9	
Medical history [2]					
Stroke	1	0.7	4	0.7	1.0000
Heart diseases	2	1.4	5	0.9	0.6321
Hypertension	7	4.8	62	10.6	0.0311
Diabetes mellitus	10	6.8	35	6.0	0.7041
Dyslipidemia	1	0.7	16	2.7	0.2185
Tuberculosis	2	1.4	8	1.4	1.0000
Positive family history					
Stroke	8	5.5	31	5.3	0.9379
Heart diseases	5	3.4	20	3.4	0.9972

Characteristics	Cancer incident cases		Controls [1]		P-value
Hypertension	17	11.6	82	14.1	0.4450
Diabetes mellitus	14	9.6	64	11.0	0.6274
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	8	5.5	16	2.7	0.1170
Extra-pulmonary cryptococcus	0	0.0	2	0.3	1.0000
Cytomegalovirus (CMV)	12	8.2	34	5.8	0.2887
Tuberculosis (TB)	29	19.9	78	13.4	0.0477
Chronic ulcers due to herpes simplex	5	3.4	15	2.6	0.5723
Recurrent Pneumonia	29	19.9	97	16.6	0.3567
Pneumocystis carinii pneumonia (PCP)	14	9.6	29	5.0	0.0343
Progressive multifocal leukoencephalopathy (PML)	1	0.7	2	0.3	0.4891
Toxoplasma gondii	16	11.0	34	5.8	0.0284
Wasting syndrome due to HIV	1	0.7	3	0.5	1.0000
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	97	66.4	198	34.0	
Incomplete[3]	17	11.6	87	14.9	<.0001
Complete[3]	32	21.9	298	51.1	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-10. The association of risk factors and cancer incidence in HIV-infected people (AIDS-defining cancer: both men and women)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (0.99-1.02)	0.6839	1.01 (0.99-1.02)	0.4569	1.01 (0.99-1.02)	0.4569
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**0.80 (0.53-1.22)**	**0.2986**	**0.83 (0.53-1.29)**	**0.4096**	**0.83 (0.53-1.29)**	**0.4096**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.91 (0.58-1.42)	0.6815				
7 days/week	0.95 (0.57-1.57)	0.8375				
Smoking status						

Never smoked	Ref (1)	-				
Former smokers	0.74 (0.43-1.27)	0.2753				
Current smokers	0.75 (0.50-1.12)	0.1547				
Drinking frequency during the last year						
Never	Ref (1)					
Less than 1 day per week	0.63 (0.29-1.38)	0.2486				
1–2 days per week	0.78 (0.52-1.18)	0.2447				
3–4 days per week	1.08 (0.54-2.16)	0.8226				
5–7 days per week	0.83 (0.23-2.99)	0.7789				
Medical history [1]						
Stroke	1.00 (0.11-9.01)	1.0000				
Heart diseases	1.61 (0.31-8.36)	0.5731				
Hypertension	0.42 (0.19-0.95)	0.0360				
Diabetes mellitus	1.15 (0.56-2.38)	0.7043				
Dyslipidemia	0.24 (0.03-1.86)	0.1734				
Tuberculosis	1.00 (0.21-4.75)	0.9983				
Positive family history						
Stroke	1.03 (0.46-2.30)	0.9374				
Heart diseases	1.00 (0.37-2.71)	0.9972				
Hypertension	0.81 (0.46-1.41)	0.4458	0.40 (0.17-0.93)	0.0336	0.40 (0.17-0.93)	0.0336
Diabetes mellitus	0.86 (0.47-1.58)	0.6277				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	2.05 (0.86-4.90)	0.1044	2.30 (0.90-5.83)	0.0889	2.30 (0.90-5.83)	0.0889
Extra-pulmonary cryptococcus	-	-				
Cytomegalovirus (CMV)	1.45 (0.73-2.87)	0.2907				
Tuberculosis (TB)	1.61 (1.00-2.57)	0.0492	1.56 (0.84-2.91)	0.1611	1.56 (0.84-2.91)	0.1611
Chronic ulcers due to herpes simplex	1.34 (0.48-3.76)	0.5742				
Recurrent Pneumonia	1.24 (0.78-1.97)	0.3573				
Pneumocystis carinii pneumonia (PCP)	2.03 (1.04-3.94)	0.0376				
Progressive multifocal leukoencephalopathy (PML)	2.00 (0.18-22.25)	0.5716				
Toxoplasma gondii	1.99 (1.07-3.71)	0.0310	1.87 (0.83-4.24)	0.1320	1.87 (0.83-4.24)	0.1320
Wasting syndrome due to HIV	1.33 (0.14-12.91)	0.8038				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.40 (0.23-0.71)	0.0017	0.32 (0.18-0.58)	0.0002	0.32 (0.18-0.58)	0.0002
Complete [2]	0.22 (0.14-0.34)	<.0001	0.20 (0.13-0.31)	<0.0001	0.20 (0.13-0.31)	<0.0001

[1] Defined as a diagnosis by medical professionals.

[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-9 presents the baseline characteristics of people with HIV (AIDS-defining cancer incident cases and matched controls for both men and women) who were included in this study. Among the 146 participants with cancer, 133 were men (91.1%) and 13 were women (8.9%). The proportions of participants in their 30s, 40s, and 50s were 23.3%, 34.2%, and 21.2% respectively. Cancer was detected in a lower proportion of individuals with obesity than in the matched controls (not significant). The non-significant association between obesity and AIDS-defining cancer may be attributed to improved immunity or less severe AIDS progression in people with HIV. Higher proportion of past medical history of hypertension in matched controls than that in the AIDS-defining cancer group may be related to the obesity proportion because both obesity and hypertension are part of metabolic syndrome. The lack of statistical significance might be attributable to the small number of incident cases. Furthermore, the frequency of antiretroviral therapy (ART) prescription within 3 months of the initial HIV diagnosis was lower among the AIDS-defining 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 tuberculosis (TB), PCP, and toxoplasmosis were higher in the AIDS-defining cancer incident cases than in the matched controls.

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-10 (AIDS-defining cancer incident cases and matched controls for both men and women), which indicates the relationship between obesity and cancer in terms of OR after adjusting for covariates. The adjusted OR of AIDS-defining cancer with obesity was 0.83 (95% CI: 0.53–1.29, P=0.4096). Furthermore, a past medical history of hypertension and high compliance with HIV treatment within 3 months after HIV diagnosis were

associated with a decreased risk of AIDS-defining cancer incidence. Conversely, a diagnosis of an AIDS-defining disease (candidiasis) was associated with an increased risk of AIDS-defining cancer incidence. The results of forward selection and backward elimination were identical.

Table 2-11. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (AIDS-defining cancer: men)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	
Age at HIV diagnosis (Mean/SD)	46.0 (11.8)		45.5 (11.9)		0.6685
Age group					
-29	7	5.3	32	6.0	
30–39	33	24.8	156	29.3	
40–49	48	36.1	165	31.0	0.7820
50–59	28	21.1	109	20.5	
≥60	17	12.8	70	13.2	
Body mass index (Mean/SD)	**23.2 (3.2)**		**23.5 (3.3)**		**0.3512**
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**99**	**74.4**	**372**	**69.9**	**0.3060**
Obese (≥25 Kg/m^2)	**34**	**25.6**	**160**	**30.1**	
Physical activity per week					
Never	34	25.6	132	24.8	
1–6 days/week	58	43.6	256	48.1	0.8023
7 days/week	35	26.3	135	25.4	
Missing	6	4.5	9	1.7	
Smoking status					
Never smoked	54	40.6	176	33.1	
Former smokers	21	15.8	96	18.0	0.2244
Current smokers	55	41.4	254	47.7	
Missing	3	2.3	6	1.1	
Drinking frequency during the last year					
Never	69	51.9	245	46.1	
Less than 1 day per week	8	6.0	43	8.1	
1–2 days per week	41	30.8	186	35.0	0.7523
3–4 days per week	10	7.5	40	7.5	
5–7 days per week	3	2.3	13	2.4	
Missing	2	1.5	5	0.9	
Medical history [2]					
Stroke	0	0.0	3	0.6	1.0000
Heart diseases	1	0.8	3	0.6	1.0000
Hypertension	7	5.3	51	9.6	0.1140
Diabetes mellitus	10	7.5	31	5.8	0.4681
Dyslipidemia	1	0.8	14	2.6	0.3258
Tuberculosis	1	0.8	7	1.3	1.0000
Positive family history					

Characteristics	Cancer incident cases		Controls [1]		P-value
Stroke	6	4.5	30	5.6	0.6072
Heart diseases	4	3.0	20	3.8	0.8003
Hypertension	16	12.0	77	14.5	0.4674
Diabetes mellitus	12	9.0	61	11.5	0.4201
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	7	5.3	14	2.6	0.1599
Extra-pulmonary cryptococcus	0	0.0	2	0.4	1.0000
Cytomegalovirus (CMV)	12	9.0	34	6.4	0.2847
Tuberculosis (TB)	26	19.5	75	14.1	0.1172
Chronic ulcers due to herpes simplex	5	3.8	14	2.6	0.5583
Recurrent Pneumonia	26	19.5	94	17.7	0.6141
Pneumocystis carinii pneumonia (PCP)	11	8.3	29	5.5	0.2212
Progressive multifocal leukoencephalopathy (PML)	1	0.8	2	0.4	0.4886
Toxoplasma gondii	13	9.8	34	6.4	0.1733
Wasting syndrome due to HIV	1	0.8	3	0.6	1.0000
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	88	66.2	169	31.8	
Incomplete [3]	15	11.3	81	15.2	<.0001
Complete [3]	30	22.6	282	53.0	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-12. The association of risk factors and cancer incidence in HIV-infected people (AIDS-defining cancer: men)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (0.99-1.02)	0.6679	1.00 (0.98-1.02)	0.8280	1.00 (0.98-1.02)	0.8280
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**0.80 (0.52-1.23)**	**0.3066**	**0.80 (0.50-1.27)**	**0.3396**	**0.80 (0.50-1.27)**	**0.3396**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.88 (0.55-1.41)	0.5947				

7 days/week	1.01 (0.59-1.71)	0.9808				
Smoking status						
Never smoked	Ref (1)					
Former smokers	0.71 (0.41-1.25)	0.2381				
Current smokers	0.71 (0.46-1.08)	0.1054				
Drinking frequency during the last year						
Never	Ref (1)					
Less than 1 day per week	0.66 (0.3-1.47)	0.3103				
1–2 days per week	0.78 (0.51-1.2)	0.2651				
3–4 days per week	0.89 (0.42-1.87)	0.7532				
5–7 days per week	0.82 (0.23-2.96)	0.7610				
Medical history [1]						
Stroke	-	-				
Heart diseases	1.34 (0.14-12.95)	0.8026				
Hypertension	0.52 (0.23-1.18)	0.1196				
Diabetes mellitus	1.31 (0.63-2.75)	0.4692				
Dyslipidemia	0.28 (0.04-2.15)	0.2215				
Tuberculosis	0.57 (0.07-4.66)	0.5985				
Positive family history						
Stroke	0.79 (0.32-1.94)	0.6080				
Heart diseases	0.79 (0.27-2.36)	0.6783				
Hypertension	0.81 (0.45-1.44)	0.4681				
Diabetes mellitus	0.77 (0.40-1.47)	0.4214	1.90 (0.82-4.37)	0.1331	1.90 (0.82-4.37)	0.1331
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	2.06 (0.81-5.20)	0.1280	2.60 (0.96-6.99)	0.0591	2.60 (0.96-6.99)	0.0591
Extra-pulmonary cryptococcus	-	-				
Cytomegalovirus (CMV)	1.45 (0.73-2.89)	0.2867				
Tuberculosis (TB)	1.48 (0.90-2.43)	0.1186	1.63 (0.94-2.83)	0.0836	1.63 (0.94-2.83)	0.0836
Chronic ulcers due to herpes simplex	1.45 (0.51-4.09)	0.4869				
Recurrent Pneumonia	1.13 (0.70-1.84)	0.6143	1.55 (0.90-2.66)	0.1137	1.55 (0.90-2.66)	0.1137
Pneumocystis carinii pneumonia (PCP)	1.57 (0.76-3.22)	0.2239				
Progressive multifocal leukoencephalopathy (PML)	2.01 (0.18-22.31)	0.5705				
Toxoplasma gondii	1.59 (0.81-3.10)	0.1765				
Wasting syndrome due to HIV	1.34 (0.14-12.95)	0.8026				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.40 (0.23-0.71)	0.0017	0.27 (0.14-0.51)	<0.0001	0.27 (0.14-0.51)	<0.0001
Complete [2]	0.22 (0.14-0.34)	<.0001	0.18 (0.11-0.28)	<0.0001	0.18 (0.11-0.28)	<0.0001

[1] Defined as a diagnosis by medical professionals.

[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-11 presents the baseline characteristics of people with HIV (AIDS-defining cancer incident cases and matched controls for men) who were included in this study. The proportions of 133 participants in their 30s, 40s, and 50s were 24.8%, 36.1%, and 21.1% respectively. Cancer was detected in a lower proportion of individuals with obesity (not significant), similar to that in Table 2-9. Moreover, the frequency of ART prescription within 3 months of the initial HIV diagnosis was lower among the AIDS-defining cancer incident cases than in the matched controls.

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-12 (AIDS-defining cancer incident cases and matched controls for men), which indicates the relationship between obesity and cancer in terms of OR after adjusting for covariates. The adjusted OR of overall cancer linked with obesity was 0.8 (95% CI, 0.50–1.27, *P*=0.3396). A diagnosis of an AIDS-defining disease (candidiasis and TB) was associated with increased risk of AIDS-defining cancer incidence for men. Conversely, high compliance with HIV treatment within 3 months after HIV diagnosis were related to a decreased risk of AIDS-defining cancer incidence for men. The results of forward selection and backward elimination were identical.

Table 2-13. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (non-AIDS-defining cancer: both men and women)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	
Age at HIV diagnosis (Mean/SD)	52.1 (12.2)		51.4 (12.2)		0.4360
Age group					
-29	12	3.9	48	3.9	
30–39	39	12.6	169	13.7	0.9628
40–49	76	24.5	306	24.9	

Characteristics	Cancer incident cases		Controls [1]		P-value
50–59	103	33.2	384	31.2	
≥60	80	25.8	324	26.3	
Sex					
Men	264	85.2	1049	85.2	0.9809
Women	46	14.8	182	14.8	
Body mass index (Mean/SD)	**23.7 (3.4)**		**23.2 (2.9)**		**0.0455**
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**207**	**66.8**	**920**	**74.7**	**0.0047**
Obese (≥25 Kg/m^2)	**103**	**33.2**	**311**	**25.3**	
Physical activity per week					
Never	118	38.1	368	29.9	0.0158
1–6 days/week	117	37.7	545	44.3	
7 days/week	68	21.9	299	24.3	
Missing	7	2.3	19	1.5	
Smoking status					
Never smoked	134	43.2	574	46.6	0.0498
Former smokers	41	13.2	210	17.1	
Current smokers	129	41.6	429	34.8	
Missing	6	1.9	18	1.5	
Drinking frequency during the last year					
Never	157	50.6	684	55.6	0.0019
Less than 1 day per week	25	8.1	63	5.1	
1–2 days per week	75	24.2	325	26.4	
3–4 days per week	21	6.8	99	8.0	
5–7 days per week	25	8.1	44	3.6	
Missing	7	2.3	16	1.3	
Medical history [2]					
Stroke	3	1.0	17	1.4	0.7804
Heart diseases	7	2.3	34	2.8	0.6222
Hypertension	45	14.5	158	12.8	0.4341
Diabetes mellitus	28	9.0	100	8.1	0.6043
Dyslipidemia	10	3.2	24	1.9	0.1716
Tuberculosis	3	1.0	30	2.4	0.1102
Positive family history					
Stroke	23	7.4	80	6.5	0.5619
Heart diseases	13	4.2	35	2.8	0.2213
Hypertension	36	11.6	144	11.7	0.9668
Diabetes mellitus	36	11.6	122	9.9	0.3772
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	10	3.2	27	2.2	0.2885
Extra-pulmonary cryptococcus	2	0.6	4	0.3	0.3475
Cytomegalovirus (CMV)	9	2.9	33	2.7	0.8298
Tuberculosis (TB)	37	11.9	169	13.7	0.4070
Chronic ulcers due to herpes simplex	10	3.2	26	2.1	0.2459
Recurrent Pneumonia	52	16.8	160	13.0	0.0845
Pneumocystis carinii pneumonia (PCP)	14	4.5	61	5.0	0.7481
Progressive multifocal leukoencephalopathy (PML)	4	1.3	11	0.9	0.5191

Characteristics	Cancer incident cases		Controls [1]		P-value
Toxoplasma gondii	18	5.8	69	5.6	0.8909
Wasting syndrome due to HIV	1	0.3	6	0.5	1.0000
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	143	46.1	410	33.3	
Incomplete [3]	48	15.5	188	15.3	<.0001
Complete [3]	119	38.4	633	51.4	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-14. The association of risk factors and cancer incidence in HIV-infected people (non-AIDS-defining cancer: both men and women)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (0.99-1.01)	0.4357	1.00 (0.99-1.02)	0.5100	1.00 (0.99-1.02)	0.5100
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**1.47 (1.13-1.93)**	**0.0048**	**1.47 (1.11-1.94)**	**0.0073**	**1.47 (1.11-1.94)**	**0.0073**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.67 (0.50-0.89)	0.0063	0.68 (0.50-0.91)	0.0105	0.68 (0.50-0.91)	0.0105
7 days/week	0.71 (0.51-0.99)	0.0445	0.74 (0.52-1.06)	0.0966	0.74 (0.52-1.06)	0.0966
Smoking status						
Never smoked	Ref (1)					
Former smokers	0.84 (0.57-1.23)	0.3617	0.86 (0.57-1.28)	0.4522	0.86 (0.57-1.28)	0.4522
Current smokers	1.29 (0.98-1.69)	0.0683	1.39 (1.03-1.87)	0.0299	1.39 (1.03-1.87)	0.0299
Drinking frequency during the last year						
Never	Ref (1)					
Less than 1 day per week	1.73 (1.05-2.84)	0.0301	1.67 (0.99-2.82)	0.0526	1.67 (0.99-2.82)	0.0526
1–2 days per week	1.01 (0.74-1.36)	0.9725	1.04 (0.75-1.44)	0.8220	1.04 (0.75-1.44)	0.8220
3–4 days per week	0.92 (0.56-1.53)	0.7580	0.88 (0.53-1.48)	0.6346	0.88 (0.53-1.48)	0.6346
5–7 days per week	2.48 (1.47-4.17)	0.0006	2.30 (1.34-3.93)	0.0025	2.30 (1.34-3.93)	0.0025
Medical history [1]						
Stroke	0.70 (0.20-2.40)	0.5681				
Heart diseases	0.81 (0.36-1.85)	0.6228				
Hypertension	1.15 (0.81-1.65)	0.4344				

Diabetes mellitus	1.12 (0.72-1.74)	0.6045				
Dyslipidemia	1.68 (0.79-3.54)	0.1761	1.89 (0.88-4.06)	0.1049	1.89 (0.88-4.06)	0.1049
Tuberculosis	0.39 (0.12-1.29)	0.1233	0.36 (0.11-1.24)	0.1045	0.36 (0.11-1.24)	0.1045
Positive family history						
Stroke	1.15 (0.71-1.87)	0.5621				
Heart diseases	1.50 (0.78-2.86)	0.2236				
Hypertension	0.99 (0.67-1.46)	0.9669				
Diabetes mellitus	1.19 (0.81-1.77)	0.3777				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	1.49 (0.71-3.11)	0.2909	1.71 (0.80-3.66)	0.1707	1.71 (0.80-3.66)	0.1707
Extra-pulmonary cryptococcus	1.99 (0.36-10.93)	0.4275				
Cytomegalovirus (CMV)	1.09 (0.51-2.29)	0.8298				
Tuberculosis (TB)	0.85 (0.58-1.25)	0.4074				
Chronic ulcers due to herpes simplex	1.55 (0.74-3.24)	0.2487	1.69 (0.78-3.67)	0.1821	1.69 (0.78-3.67)	0.1821
Recurrent Pneumonia	1.35 (0.96-1.90)	0.0852	1.59 (1.11-2.27)	0.0120	1.59 (1.11-2.27)	0.0120
Pneumocystis carinii pneumonia (PCP)	0.91 (0.50-1.64)	0.7482				
Progressive multifocal leukoencephalopathy (PML)	1.45 (0.46-4.59)	0.5267				
Toxoplasma gondii	1.04 (0.61-1.77)	0.8898				
Wasting syndrome due to HIV	0.66 (0.08-5.51)	0.7022				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.73 (0.51-1.06)	0.0982	0.71 (0.48-1.04)	0.0788	0.71 (0.48-1.04)	0.0788
Complete [2]	0.54 (0.41-0.71)	<.0001	0.54 (0.41-0.72)	<.0001	0.54 (0.41-0.72)	<.0001

[1] Defined as a diagnosis by medical professionals.

[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-13 presents the baseline characteristics of people with HIV (non-AIDS-defining cancer incident cases and matched controls for both men and women) who were included in this study. Among the 310 participants with cancer, 264 were men (85.2%) and 46 were women (14.8%). The proportions of participants in their 40s, 50s, and over 60s were 24.5%, 33.2%, and 25.8% respectively. The incidence of non-AIDS-defining cancer was detected in a higher

proportion of individuals with obesity who never engaged in physical activity, smoked currently, or consumed alcohol 5–7 days/week. In contrast, the frequency of ART prescription within 3 months of the initial HIV diagnosis was lower among the non-AIDS-defining cancer incident cases than in the matched controls. Regarding the diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis, recurrent pneumonia was higher in the non-AIDS-defining cancer incident cases than that in the matched controls, with borderline significance (*P*=0.0845).

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-14 (non-AIDS-defining cancer incident cases and matched controls for both men and women), which indicates the relationship between obesity and cancer in terms of OR after adjusting for covariates. The adjusted OR of non-AIDS-defining cancer linked with obesity was 1.47 (95% CI: 1.11–1.94, *P*=0.0073). Furthermore, current smoking (reference group: never smoking), consuming alcohol 5–7 days/week (reference group: no drinking at all) and a diagnosis of an AIDS-defining disease (recurrent pneumonia) were associated with increased risk of non-AIDS-defining cancer incidence. Conversely, physical activity 1–6 days/week (reference group: no activity at all) and high compliance with HIV treatment within 3 months after HIV diagnosis were related to a decreased risk of non-AIDS-defining cancer incidence. The results of forward selection and backward elimination were identical.

Table 2-15. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (non-AIDS-defining cancer: men)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	

Characteristics	Cancer incident cases		Controls [1]		P-value
Age at HIV diagnosis (Mean/SD)	51.9 (12.2)		51.2 (12.3)		0.4105
Age group					
-29	11	4.2	44	4.2	
30–39	34	12.9	149	14.2	
40–49	65	24.6	259	24.7	0.9509
50–59	89	33.7	329	31.4	
≥60	65	24.6	268	25.5	
Body mass index (Mean/SD)	23.4 (3.1)		23.2 (2.9)		0.4717
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**185**	**70.1**	**787**	**75.0**	**0.1012**
Obese (≥25 Kg/m^2)	**79**	**29.9**	**262**	**25.0**	
Physical activity per week					
Never	100	37.9	308	29.4	
1–6 days/week	103	39.0	459	43.8	0.0248
7 days/week	56	21.2	264	25.2	
Missing	5	1.9	18	1.7	
Smoking status					
Never smoked	94	35.6	407	38.8	
Former smokers	41	15.5	205	19.5	0.0814
Current smokers	125	47.3	421	40.1	
Missing	4	1.5	16	1.5	
Drinking frequency during the last year					
Never	125	47.3	534	50.9	
Less than 1 day per week	25	9.5	61	5.8	
1–2 days per week	68	25.8	303	28.9	0.0075
3–4 days per week	19	7.2	93	8.9	
5–7 days per week	22	8.3	43	4.1	
Missing	5	1.9	15	1.4	
Medical history [2]					
Stroke	3	1.1	16	1.5	0.7799
Heart diseases	4	1.5	28	2.7	0.2771
Hypertension	37	14.0	133	12.7	0.5632
Diabetes mellitus	24	9.1	85	8.1	0.6030
Dyslipidemia	8	3.0	17	1.6	0.1341
Tuberculosis	3	1.1	28	2.7	0.1426
Positive family history					
Stroke	18	6.8	72	6.9	0.9791
Heart diseases	12	4.5	30	2.9	0.1642
Hypertension	30	11.4	117	11.2	0.9229
Diabetes mellitus	29	11.0	101	9.6	0.5095
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	9	3.4	24	2.3	0.2982
Extra-pulmonary cryptococcus	2	0.8	4	0.4	0.3473
Cytomegalovirus (CMV)	7	2.7	30	2.9	0.8549
Tuberculosis (TB)	34	12.9	155	14.8	0.4325
Chronic ulcers due to herpes simplex	10	3.8	23	2.2	0.1388
Recurrent Pneumonia	48	18.2	141	13.4	0.0499
Pneumocystis carinii pneumonia (PCP)	13	4.9	58	5.5	0.6977

Characteristics	Cancer incident cases		Controls [1]		P-value
Progressive multifocal leukoencephalopathy (PML)	4	1.5	10	1.0	0.4987
Toxoplasma gondii	17	6.4	63	6.0	0.7923
Wasting syndrome due to HIV	1	0.4	6	0.6	1.0000
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	112	42.4	323	30.8	
Incomplete [3]	45	17.0	170	16.2	0.0005
Complete [3]	107	40.5	556	53.0	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-16. The association of risk factors and cancer incidence in HIV-infected people (non-AIDS-defining cancer: men)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.01 (0.99-1.02)	0.4102	1.01 (0.99-1.02)	0.3367	1.01 (0.99-1.02)	0.3206
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**1.28 (0.95-1.73)**	**0.1017**	**1.28 (0.94-1.75)**	**0.1196**	**1.27 (0.93-1.74)**	**0.1281**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.69 (0.51-0.94)	0.0198	0.70 (0.51-0.97)	0.0316	0.69 (0.50-0.95)	0.0237
7 days/week	0.65 (0.45-0.94)	0.0227	0.69 (0.47-1.01)	0.0533	0.68 (0.47-1.00)	0.0512
Smoking status						
Never smoked	Ref (1)					
Former smokers	0.87 (0.58-1.30)	0.4846	0.89 (0.59-1.36)	0.6016	0.92 (0.60-1.40)	0.6869
Current smokers	1.29 (0.95-1.74)	0.1011	1.36 (0.99-1.87)	0.0618	1.38 (1.00-1.90)	0.0528
Drinking frequency during the last year						
Never	Ref (1)					
Less than 1 day per week	1.75 (1.06-2.90)	0.0296	1.63 (0.96-2.77)	0.0690	1.67 (0.98-2.83)	0.0592
1–2 days per week	0.96 (0.69-1.33)	0.8007	0.97 (0.68-1.37)	0.8435	0.96 (0.68-1.36)	0.8303
3–4 days per week	0.87 (0.51-1.48)	0.6151	0.81 (0.47-1.39)	0.4449	0.82 (0.47-1.41)	0.4690
5–7 days per week	2.19 (1.26-3.79)	0.0053	1.98 (1.13-3.50)	0.0179	2.01 (1.14-3.54)	0.0161
Medical history [1]						
Stroke	0.74 (0.22-2.57)	0.6377				

Heart diseases	0.56 (0.20-1.61)	0.2835				
Hypertension	1.12 (0.76-1.66)	0.5633				
Diabetes mellitus	1.13 (0.71-1.82)	0.6032				
Dyslipidemia	1.90 (0.81-4.45)	0.1405	2.03 (0.85-4.83)	0.1101	2.07 (0.87-4.92)	0.1016
Tuberculosis	0.42 (0.13-1.39)	0.1550	0.36 (0.11-1.24)	0.1064	0.36 (0.11-1.25)	0.1077
Positive family history						
Stroke	0.99 (0.58-1.70)	0.9792				
Heart diseases	1.62 (0.82-3.21)	0.1671	1.63 (0.79-3.34)	0.1837	1.65 (0.80-3.39)	0.1727
Hypertension	1.02 (0.67-1.56)	0.9225				
Diabetes mellitus	1.16 (0.75-1.79)	0.5098				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	1.51 (0.69-3.28)	0.3008				
Extra-pulmonary cryptococcus	1.99 (0.36-10.95)	0.4269				
Cytomegalovirus (CMV)	0.93 (0.40-2.13)	0.8550				
Tuberculosis (TB)	0.85 (0.57-1.27)	0.4329				
Chronic ulcers due to herpes simplex	1.76 (0.83-3.74)	0.1437	2.16 (0.98-4.76)	0.0547	2.20 (1.00-4.83)	0.0507
Recurrent Pneumonia	1.43 (1.00-2.05)	0.0506	1.63 (1.12-2.38)	0.0117	1.65 (1.12-2.43)	0.0112
Pneumocystis carinii pneumonia (PCP)	0.89 (0.48-1.64)	0.6979			0.21 (0.05-0.94)	0.0414
Progressive multifocal leukoencephalopathy (PML)	1.60 (0.50-5.14)	0.4301				
Toxoplasma gondii	1.08 (0.62-1.87)	0.7924			4.39 (1.12-17.19)	0.0337
Wasting syndrome due to HIV	0.66 (0.08-5.52)	0.7025				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.76 (0.52-1.13)	0.1774	0.74 (0.49-1.10)	0.1374	0.73 (0.49-1.10)	0.1306
Complete [2]	0.56 (0.41-0.75)	0.0001	0.57 (0.41-0.77)	0.0003	0.56 (0.41-0.77)	0.0003

[1] Defined as a diagnosis by medical professionals.
[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-15 presents the baseline characteristics of people with HIV (non-AIDS-defining cancer incident cases and matched controls for men) who were included in this study. The proportions of 264 participants in their 40s, 50s, and over 60s were 24.6%, 33.7%, and 24.6% respectively. The incidence of non-AIDS-defining cancer for men was detected in a higher proportion of individuals with

obesity (not significant) who never engaged in physical activity, smoked currently, or consumed alcohol 5–7 days/week. In contrast, the frequency of ART prescription within 3 months of the initial HIV diagnosis was lower among the non-AIDS-defining cancer incident cases than among the matched controls. Regarding the diagnosis of AIDS-defining diseases within 3 months of the initial HIV diagnosis, the proportion of recurrent pneumonia was higher among the non-AIDS-defining cancer incident cases than among the matched controls.

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-16 (non-AIDS-defining cancer incident cases and matched controls for men), which indicates the relationship between obesity and cancer in terms of OR after adjusting for covariates. The adjusted OR of non-AIDS-defining cancer linked with obesity for men was 1.28 (95% CI: 0.94–1.75, *P*=0.1196, forward selection). Furthermore, current smoking (reference group: never smoking), consuming alcohol 5–7 days/week (reference group: no drinking at all) and a diagnosis of an AIDS-defining disease (recurrent pneumonia, PCP, toxoplasmosis) were associated with an increased risk of non-AIDS-defining cancer incidence for men. Conversely, physical activity 1–6 days/week (reference group: no activity at all) and high compliance with HIV treatment within 3 months after HIV diagnosis were related to a decreased risk of non-AIDS-defining cancer incidence. The results of forward selection and backward elimination were almost identical; however, the variables of diagnosis of an AIDS-defining disease (PCP, and toxoplasmosis) were not included in the forward selection.

Table 2-17. Baseline characteristics of incident cancer cases and matched controls in a cohort of cancer-free adults with HIV (non-AIDS-defining cancer: women)

Characteristics	Cancer incident cases		Controls [1]		P-value
	N	%	N	%	
Age at HIV diagnosis (Mean/SD)	53.1 (12.0)		53.0 (11.9)		0.9671
Age group					
-29	1	2.2	4	2.2	
30–39	5	10.9	20	11.0	
40–49	11	23.9	47	25.8	0.9989
50–59	14	30.4	55	30.2	
≥60	15	32.6	56	30.8	
Body mass index (Mean/SD)	**24.9 (4.4)**		**23.0 (3.1)**		**0.0058**
Obesity status					
Normal and Overweight (<25 Kg/m^2)	**22**	**47.8**	**133**	**73.1**	**0.0010**
Obese (≥25 Kg/m^2)	**24**	**52.2**	**49**	**26.9**	
Physical activity per week					
Never	18	39.1	60	33.0	
1–6 days/week	14	30.4	86	47.3	0.1617
7 days/week	12	26.1	35	19.2	
Missing	2	4.3	1	0.5	
Smoking status					
Never smoked	40	87.0	167	91.8	
Former smokers	0	0.0	5	2.7	0.2644
Current smokers	4	8.7	8	4.4	
Missing	2	4.3	2	1.1	
Drinking frequency during the last year					
Never	32	69.6	150	82.4	
Less than 1 day per week	0	0.0	2	1.1	
1–2 days per week	7	15.2	22	12.1	0.0542
3–4 days per week	2	4.3	6	3.3	
5–7 days per week	3	6.5	1	0.5	
Missing	2	4.3	1	0.5	
Medical history [2]					
Stroke	0	0.0	1	0.5	-
Heart diseases	3	6.5	6	3.3	0.3904
Hypertension	8	17.4	25	13.7	0.5290
Diabetes mellitus	4	8.7	15	8.2	1.0000
Dyslipidemia	2	4.3	7	3.8	1.0000
Tuberculosis	0	0.0	2	1.1	-
Positive family history					
Stroke	5	10.9	8	4.4	0.1447
Heart diseases	1	2.2	5	2.7	1.0000
Hypertension	6	13.0	27	14.8	0.7576
Diabetes mellitus	7	15.2	21	11.5	0.4970
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis					
Candidiasis	1	2.2	3	1.6	1.0000
Extra-pulmonary cryptococcus					
Cytomegalovirus (CMV)	2	4.3	3	1.6	0.2654
Tuberculosis (TB)	3	6.5	14	7.7	1.0000
Chronic ulcers	-	-	3	1.6	-

Characteristics	Cancer incident cases		Controls [1]		P-value
due to herpes simplex					
Recurrent Pneumonia	4	8.7	19	10.4	1.0000
Pneumocystis carinii pneumonia (PCP)	1	2.2	3	1.6	1.0000
Progressive multifocal leukoencephalopathy (PML)	-	-	1	0.5	-
Toxoplasma gondii	1	2.2	6	3.3	1.0000
Wasting syndrome due to HIV					
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis					
Never	31	67.4	87	47.8	
Incomplete [3]	3	6.5	18	9.9	0.0593
Complete [3]	12	26.1	77	42.3	

[1] Controls were paired with cancer cases based on 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 occurred first). The follow-up duration for matched controls was set 1:4, to be equal to or longer than that of each cancer incidence case.

[2] Defined as a diagnosis by medical professionals.

[3] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-18. The association of risk factors and cancer incidence in HIV-infected people (non-AIDS-defining cancer: women)

Variable	-		Forward selection (20%)		Backward elimination (20%)	
	Crude Odds Ratio	P-value	Adjusted Odds Ratio	P-value	Adjusted Odds Ratio	P-value
Age at HIV Diagnosis	1.00 (0.97-1.03)	0.9669	0.99 (0.96-1.02)	0.5825	0.99 (0.96-1.02)	0.5825
Obesity status						
Normal and Overweight (<25 Kg/m2)	**Ref (1)**					
Obese (≥25 Kg/m2)	**2.96 (1.52-5.76)**	**0.0014**	**2.86 (1.40-5.84)**	**0.0039**	**2.86 (1.40-5.84)**	**0.0039**
Physical activity per week						
Never	Ref (1)					
1–6 days/week	0.54 (0.25-1.18)	0.1208	0.47 (0.21-1.07)	0.0717	0.47 (0.21-1.07)	0.0717
7 days/week	1.14 (0.49-2.65)	0.7557	1.31 (0.54-3.18)	0.5501	1.31 (0.54-3.18)	0.5501
Smoking status						
Never smoked	Ref (1)					
Former smokers	-	-				
Current smokers	2.09 (0.60-7.28)	0.2481				
Drinking frequency during the last year						
Never	Ref (1)					
Less than 1 day per week	-	-				
1–2 days per week	1.49 (0.59-3.79)	0.4006				

3–4 days per week	1.56 (0.30-8.10)	0.5949				
5–7 days per week	14.06 (1.42-139.58)	0.0240				
Medical history [1]						
Stroke	-	-				
Heart diseases	2.05 (0.49-8.51)	0.3248				
Hypertension	1.32 (0.55-3.16)	0.5299				
Diabetes mellitus	1.06 (0.34-3.36)	0.9207				
Dyslipidemia	1.14 (0.23-5.66)	0.8760				
Tuberculosis	-	-				
Positive family history						
Stroke	2.65 (0.83-8.53)	0.1017	3.96 (1.11-14.06)	0.0334	3.96 (1.11-14.06)	0.0334
Heart diseases	0.79 (0.09-6.90)	0.8286				
Hypertension	0.86 (0.33-2.23)	0.7578				
Diabetes mellitus	1.38 (0.55-3.47)	0.4982				
Diagnosis of AIDS-defining diseases within 3 months of HIV diagnosis						
Candidiasis	1.33 (0.14-13.05)	0.0585				
Extra-pulmonary cryptococcus	-	-				
Cytomegalovirus (CMV)	2.71 (0.44-16.73)	0.2824				
Tuberculosis (TB)	0.84 (0.23-3.05)	0.7874				
Chronic ulcers due to herpes simplex	-	-	-	-		
Recurrent Pneumonia	0.82 (0.26-2.53)	0.7261				
Pneumocystis carinii pneumonia (PCP)	1.33 (0.14-13.05)	0.8088				
Progressive multifocal leukoencephalopathy (PML)	-	-				
Toxoplasma gondii	0.65 (0.08-5.55)	0.6959				
Wasting syndrome due to HIV	-	-				
Prescription of highly active antiretroviral therapy within 3 months of HIV diagnosis						
Never	Ref (1)					
Incomplete [2]	0.47 (0.13-1.7)	0.2480	0.41 (0.10-1.66)	0.2120	0.41 (0.10-1.66)	0.2120
Complete [2]	0.44 (0.21-0.91)	0.0271	0.52 (0.24-1.15)	0.1054	0.52 (0.24-1.15)	0.1054

[1] Defined as a diagnosis by medical professionals.
[2] If the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was less than 60 days, the treatment was deemed incomplete. In contrast, if the prescription date of highly active antiretroviral therapy within 3 months of HIV diagnosis was 60 days or more, it was considered complete.

Table 2-17 presents the baseline characteristics of people with HIV (non-AIDS-defining cancer incident cases and matched controls for women) who were included in this study. The proportions of the participants in their 40s, 50s, and

over 60s were 23.9%, 30.4%, and 32.6% respectively. The incidence of non-AIDS-defining cancer for women was detected in a higher proportion of women with obesity. In contrast, the frequency of ART prescription within 3 months of the initial HIV diagnosis was lower among the non-AIDS-defining cancer incident cases than in the matched controls.

The results of the multiple logistic regression analysis of the association between obesity and cancer are listed in Table 2-18 (non-AIDS-defining cancer incident cases and matched controls for women), which indicates the relationship between obesity and cancer in terms of OR after adjusting for covariates. The adjusted OR of non-AIDS-defining cancer linked with obesity for women was 2.86 (95% CI: 1.40–5.84, *P*=0.0039). Furthermore, a family medical history of stroke was associated with an increased risk of non-AIDS-defining cancer incidence for women. High compliance with HIV treatment within 3 months after HIV diagnosis had a decreased risk of non-AIDS-defining cancer for women, though not statistically significant. The results of forward selection and backward elimination were identical.

Table 2-19. Summary of cancer related risk factors in HIV-infected people

Cancer type	Both men and women	Men	Women
Overall cancer	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 1.18 (95% CI 0.94–1.49)	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 1.07 (95% CI 0.83–1.37)	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 2.17 (95% CI 1.13–4.18)
Increased risk factor	Heavy drinking and AIDS-defining disease (candidiasis, recurrent pneumonia, and toxoplasmosis)	AIDS-defining disease (candidiasis, chronic ulcers due to herpes simplex, recurrent pneumonia, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML))	AIDS-defining disease (*Pneumocystis carinii* pneumonia (PCP)), the family history of stroke
Decreased risk factor	High compliance with HIV treatment and physical activity	High compliance with HIV treatment and physical activity	High compliance with HIV treatment

AIDS-defining cancer	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 0.83 (95% CI 0.53–1.29)	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 0.80 (95% CI 0.50–1.27)	-
Increased risk factor	AIDS-defining disease (candidiasis)	AIDS-defining disease (candidiasis and, tuberculosis)	-
Decreased risk factor	High compliance with HIV treatment and family history of hypertension	High compliance with HIV treatment	-
Non-AIDS-defining cancer	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 1.47 (95% CI 1.11–1.94)	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 1.28 (95% CI 0.94–1.75)	Adjusted OR of obesity (Ref: BMI ≦25.0 kg/m^2) 2.86 (95% CI 1.40–5.84)
Increased risk factor	Currently smoking, heavy drinking, and AIDS-defining disease (recurrent pneumonia)	Currently smoking, heavy drinking, and AIDS-defining disease (chronic ulcers due to herpes simplex, recurrent pneumonia, *Pneumocystis carinii* pneumonia, toxoplasmosis)	Family history of stroke
Decreased risk factor	High compliance with HIV treatment and physical activity	High compliance with HIV treatment and physical activity	Physical activity

Three criteria summarize Table 2-19. First, regarding the estimation result of BMI, when the coefficients of the multiple regression model using backward elimination and forward selection were different, the estimate of the forward selection was entered. However, no significant difference in the results of obesity estimation in the two variable selection methods was observed. Second, if either of the results determined by the two variables-selection method was *P*-value <10%, the variables were included as risk factors for cancer.

Until recently, HIV has been referred to as “slimming disease”; however, it has been linked to a statistically significant increased risk of non-AIDS-defining cancer in both overall (men and women) and women. According to previous study, owing to effective HIV treatments, recovering immune cells can reduce the risk of AIDS-defining cancer, while a similar benefit for non-AIDS-defining cancer has not yet been confirmed. However, the present study found that increased

compliance with HIV treatment is related to the decreased risk of both AIDS-defining and non-AIDS-defining cancer through a case-control study with individual matching for gender, age, year of diagnosis for HIV, and follow-up duration.

2.5. Conclusion and Discussion

This study investigated the relationship between obesity and cancer risk. Unintentional weight loss is a symptom of HIV-associated wasting syndrome, an AIDS-defining condition (Siddiqui, Samuel et al. 2022); therefore, the non-significant association between obesity and AIDS-defining cancer may be attributed to improved immunity or less severe AIDS progression in people with HIV. The lack of statistical significance might be attributable to the small number of incident cases of cancer. The study's findings revealed lower point estimates of AIDS-defining cancer risk in people with HIV and obesity than in people with HIV and without obesity. In a previous study (Guiot, Muñoz-Massó et al. 2018), the reduced risk of anal cancer, a non-AIDS-defining cancer associated with HPV infection (Yarchoan and Uldrick 2018), was observed in people with HIV and obesity, which may be associated with a slower progression of HIV infection as well.

The increased risk of non-AIDS-defining cancer in obese HIV infected people compared to non-obese people living with HIV is similar to that observed in the general population. Due to the limited numbers of each subtype non-AIDS-defining cancer, this study could not identify the association between obesity and the cancer incidence for subtypes of cancer. In the general population, obesity is a

well-established risk factor for colorectal cancer, with potential mechanisms involving hormonal systems related to insulin regulation and adipokines (Ma, Yang et al. 2013) that may underlie the connection between obesity and cancer in HIV infected people. Furthermore, obesity is a risk factor for hepatobiliary and pancreatic cancer, wherein obesity-induced insulin resistance and type 2 diabetes constitute the most commonly proposed mechanisms (Preziosi, Oben et al. 2014, Li, Gan et al. 2016, Sohn, Lee et al. 2021).

This study has a few limitations. First, although weight change following antiretroviral therapy (ART) is a crucial issue, many studies did not include baseline weight measurements (Alizadeh, Katsanis et al. 2013). This study did not account for weight or BMI trajectories either before or after antiretroviral therapy (ART). However, when we considered the timing of antiretroviral therapy (ART) introduction (mid-1990s), the high treatment rate, and the high viral suppression rate among HIV infected people in Korea (Choi 2020), and the study period (adults newly diagnosed with HIV between 2004 and 2020), it is likely that many participants began receiving antiretroviral therapy (ART) shortly after their HIV diagnosis. Second, we considered BMI measurements taken at least 90 days before cancer diagnosis and those that were closest to the date of the HIV diagnosis to ascertain the temporal relationship. This latent period might not be sufficient for a temporal association, and the possibility of reverse causation (weight change after cancer diagnosis and its impact on the association) exists. Given that weight loss is a nonspecific cancer symptom (Nicholson, Hamilton et al. 2018), the existence of reverse causation would lead to an underestimation of the association because participants with incident cancer who had already experienced weight loss would have been included among the cancer cases. Therefore, the observed results would

tend toward the null hypothesis, and this suggest conservative results. Third, due to unavailability of BMI data, HIV infected people without results from the national health screening program were excluded, and this led to the exclusion of approximately 33% of the potential participants. Thus, the study population may not be representative of all HIV infected people. To increase validity, we used a nested case-control study design, by selecting both incident cancer cases and matched controls (matched by age, sex, and year of HIV diagnosis) from HIV infected people who had participated in the national health screening program. Fourth, as is characteristic of claim-based data, clinical information, such as the CD4 T-cell count or viral load, was unavailable. Thus, the obesity status could not be differentiated from the "normal" immune status. Fifth, although several covariates were adjusted to determine the independent association between obesity and cancer risk, potential confounders, including a family history of cancer, were not considered due to the unavailability of the relevant information.

HIV infected people have increased risks for both AIDS-defining and non-AIDS-defining cancers. The burden of non-AIDS-defining cancer has been steadily increasing. This study's findings revealed that obesity, which is a significant health concern in HIV management, was associated with a higher risk of non-AIDS-defining, 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.

The author reviewed previous studies and confirmed that the general population had a higher risk of developing thyroid cancer than people with HIV. The high incidence of thyroid cancer in the general population was related to overdiagnosis; hence, lower risk of thyroid cancer among people with HIV can be attributed to limited access to medical services. However, people with HIV had a higher risk of developing breast and prostate cancers than the general population, despite overdiagnosis. Therefore, attributing the trend of thyroid cancer only to overdiagnosis was considered a limitation (Park, Ahn et al. 2022).

When previous studies estimated the age-standardized incidence rate (ASR) per 100,000 women and men for thyroid cancer, the ASR for women was more than three times higher than that for men (10.1:3.1) worldwide (Sung, Ferlay et al. 2021).

Therefore, in Chapter 3, the Health Examine Study (HEXA) database, a part of the Korean Genome and Epidemiology Study (KoGES), was used to investigate thyroid cancer risk factors for Korean women aged ≥40 years. The HEXA database included variables such as oral contraceptives use, hysterectomy, and childbirth, which are associated with the occurrence of thyroid cancer in women; hence, the data can be considered as an appropriate source to analyze thyroid cancer risk factors in women in the general population.

Chapter 3. Risk factors for thyroid cancer[②]

3.1. Study Background

The author reviewed previous studies and confirmed that the risk of thyroid cancer in the general population was higher than that of people with HIV (Park, Ahn et al. 2022). This trend is inexplicable; hence, this study identifies the risk factors of thyroid cancer in the general population by focusing on women aged >40 years as a thyroid cancer risk group in this chapter.

Worldwide, in 2020, 19.3 million incident cancer cases were diagnosed and resulted in 10 million deaths. With 586,000 cases, thyroid cancer was the ninth most common cancer. A noteworthy feature of thyroid cancer is its higher incidence in women than in men [global age-standardized incidence rate (ASR) 10.1 vs. 3.1 per 100,000 women and men, respectively]. The incidence of thyroid cancer is higher in developed nations, compared to developing countries. In particular, compared to women in developing countries, those in developed countries have a 5.5 times greater likelihood of being diagnosed with thyroid cancer (Sung, Ferlay et al. 2021).

In Korea, thyroid cancer is the most common type of cancer. Despite a significant reduction in the number of thyroid cancer cases between 2012 and 2015 due to concern about overdiagnosis, the frequency of thyroid cancer has shown an upward trend since 2015. The increase in thyroid cancer cases in Korea has been mainly associated with the incidence in women. Overdiagnosis is a key factor in the high incidence of thyroid cancer in Korea, which has been supported by a

② This chapter is based on material that was originally presented in the "Association between Obesity Indexes and Thyroid Cancer Risk in Korean Women: Nested Case-Control Study", which was published in *Cancers* in 2022.

relative survival rate of more than 100%, a robust link between screening rates and the incidence of thyroid cancer, and a substantial period effect (Ahn, Kim et al. 2014, Kang, Won et al. 2022).

Despite the increasing awareness of the role of overdiagnosis in cases of thyroid cancer, the exact causes of thyroid cancer remain unclear. Although exposure to ionizing radiation in childhood is a well-known risk factor, additional factors, including iodine intake, obesity, diabetes, estrogen, reproductive aspects, autoimmune thyroiditis, and various lifestyle factors, have been suggested as possible contributors of the thyroid cancer risk. Nonetheless, definitive proof establishing a connection between these factors and the risk of thyroid cancer has not been confirmed yet (Liu, Su et al. 2017).

In the Korean population, wherein thyroid cancer constitutes an epidemic, studies have identified family history, obesity, non-smoking, non-drinking, and low income as potential risk factors for thyroid cancer (Myung, Lee et al. 2017, Cho, Chang et al. 2018, An, Kim et al. 2020). Among these risk factors, the association between obesity and thyroid cancer risk has been researched considerably. However, the majority of the research comprises case-control studies, which have mainly focused on body mass index (BMI), which cannot help distinguish between fat and muscle composition. Therefore, the association of body fat with thyroid cancer risk has not been definitively established (Shin, Jee et al. 2017, Son, Lee et al. 2018, Hoang, Song et al. 2021).

Consequently, this study was conducted prospectively to investigate the relationship between various obesity indices, including waist circumference (WC), waist-hip ratio (WHR), and waist-height ratio (WHTR), along with BMI as well as their combinations, in relation to thyroid cancer among Korean women. This

research aimed to ascertain the association between thyroid cancer and various obesity indicators within the Korean population.

3.2. Literature Review

(Myung, Lee et al. 2017) identified 802 patients with thyroid cancer from among 34,211 cohort participants using data collected by the National Cancer Center of Korea from 2002 to 2012. The patient group (802 patients) was compared with two control groups to conduct a study on the intergroup differences. In the first control group, age and residential area were matched (1:1) and in the second control group, age, residential area, and gender were matched (1:1). Compared with the first control group, the risk of thyroid cancer was increased in women rather than men in the patient group, while a higher income, was associated with a lower risk of thyroid cancer in former or current smokers. Compared with the second control group, alcohol consumption and a family history of cancer (excluding thyroid cancer) were associated with a decreased risk of thyroid cancer, although BMI and family history of thyroid cancer were associated with the risk of thyroid cancer in the patient group. Finally, the study suggested that obesity (BMI >25.0 kg/m^2), a family history of thyroid cancer, non-drinking, non-smoking, and low income were associated with an increased risk of thyroid cancer. In particular, adjusted OR of BMI was estimated to be 1.42 (95% CI 1.09–1.85) for obesity (BMI ≥25.0 kg/m^2) and 1.28 (95% CI 0.98–1.68) for overweight (23.0≤ BMI <25.0 kg/m^2) compared with the normal weight (BMI <23.0 kg/m^2).

(An, Kim et al. 2020) A study was conducted to identify risk factors for thyroid cancer using the national health examinations of people aged ≥40 years

(NHIS database from 2002 to 2013). For 4,977 patients with thyroid cancer, 19,908 (1:4 ratio) controls were matched by gender, age, residence, and income level, and the Charlson Comorbidity Index (CCI). The CCI estimates the 10-year mortality for a person who may have a range of multi-morbidities. The results of the case-control study revealed that smoking and drinking were associated with a lower risk of thyroid cancer, and obesity, with an increased risk. In the previous study, obesity was defined as follows: 25.0≤ BMI <30.0 kg/m^2 and BMI ≥30.0 kg/m^2. Both obesity criteria have been confirmed to increase the incidence of thyroid cancer. The OR of BMI ≥30 kg/m^2 (1.24, 95% CI: 1.04–1.47) was higher than that for 25.0≤ BMI <30 kg/m^2 (1.13, 95% CI: 1.05–1.22) as a result of the adjusted logistic regression analysis between thyroid cancer incident cases and matched controls.

(Cho, Chang et al. 2018) selected 96,855 people with no major missing variables among those who underwent health checkups between 2006 and 2014 at the health screening center of the Kangbuk Samsung Hospital. A total of 1,250 newly diagnosed patients with thyroid cancer have been confirmed since the first medical examination. In this study, risk factors for thyroid cancer were analyzed using Cox's proportional hazards regression model. The result of the analysis, which adjusted covariates such as age, drinking, and exercise, indicated that smoking was associated with a decreased risk of thyroid cancer. Subsequently, obesity (BMI ≥25 kg/m^2) and thyroid stimulating hormone (TSH) values were added as covariates, and the analysis was repeated. The results were similar to those obtained previously, i.e., smoking continued to be associated with a lower risk of thyroid cancer.

(Hoang, Song et al. 2021) conducted a case-control study using patient data from the National Cancer Center in Korea to determine the risk factors of

thyroid cancer. A total of 41,109 cohort participants' data on economic and social characteristics and lifestyles from 2002 to 2014 were retrieved. This study focused on the effect of obesity on thyroid cancer. The standard for obesity was defined as BMI ≥ 25.0 kg/m^2, overweight as 23.0≤ BMI <25.0 kg/m^2, and normal weight as BMI <23.0 kg/m^2. The potential controls for the 702 patients with thyroid cancer was 37,236 participants with no history of thyroid-related diseases.

After a 1:1 matching between the patients and potential controls using gender and age variables, the data of 702 patients with thyroid cancer and 702 controls were analyzed. Family history of thyroid cancer, marital status, education level, occupation, income level, and smoking status were used as covariates. The analysis confirmed that the adjusted OR for obesity (BMI ≥25.0 kg/m^2) was 1.62 (95% CI: 1.23–2.14) and that for overweight (23.0≤ BMI <25.0 kg/m^2) was 1.46 (95% CI: 1.10–1.93) compared with the normal weight (BMI <23.0 kg/m^2). Obesity was identified to be significantly associated with an increased risk of thyroid cancer.

(Son, Lee et al. 2018) used the National Sample Cohort (NSC) database in the Korean NHIS to identify the risk factors for thyroid cancer incidence. The NSC database included 351,402 participants aged >20 years who had undergone health checkups from 2003 to 2008. (Son et al., 2018) identified 3,308 thyroid cancer incident cases and subsequently, utilized Cox's proportional hazard ratio model to determine the association between obesity and thyroid cancer incidence. This study defined normal weight (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), and obesity (30.0 kg/m^2) using the BMI. Compared with normal weight, the adjusted hazard ratio of overweight was 1.211 (95% CI: 1.133–1.351) and that of obesity was 1.274 (1.048–1.548). Gender, age, smoking status, exercise, alcohol

consumption, history of diabetes, and history of dyslipidemia were used as covariates. Smoking, drinking, and exercise exhibited an inverse correlation with thyroid cancer incidence.

(Lee, Chai et al. 2021) conducted a meta-analysis of 24 studies worldwide that analyzed the association between smoking and thyroid cancer because although smoking is a well-known cancer risk factor, smoking and thyroid cancer incidence are negatively correlated. The meta-analysis stratified gender, detailed types of thyroid cancer, smoking status of patients, and smoking amount. The analysis identified that smoking was associated with a decreased risk of thyroid cancer in both men and women. However, (Lee, Chai et al. 2021) suggested that further studies with sufficient sample size, depending on detailed types of thyroid cancer, are needed.

In 2014, an epidemiological survey was conducted in the Jiangsu region of China in 2014 to confirm the link between metabolic syndrome and thyroid nodules. In this investigation, a total of 6,494 people underwent thyroid ultrasonography to detect thyroid nodules. (Feng et., 2017) confirmed that WC, fasting blood sugar, high blood pressure, and smoking were positively correlated with the prevalence of thyroid nodules (adjusted by age and sex) using the collected data (from the database of the epidemiological investment in Jiangsu, China). Abdominal obesity in Chinese women was defined as WC >80 cm. The adjusted OR of obesity (WC ≥80 cm) was 1.264 (95% CI 1.091–1.466).

(Kabat, Kim et al. 2012) analyzed thyroid cancer risk factors in postmenopausal women using the Women's Health Initiative database. This database contains information on physical measurements and clinical trials for the general population conducted at 40 US medical institutions from 1993 to 1998.

Among the 144,219 postmenopausal women in the cohort data, 294 had thyroid cancer. The results revealed that BMI, WC, hip circumference (HC), and WHR were not associated with thyroid cancer incidence. Conversely, tall height was significantly associated with an increased risk of thyroid cancer. The risk of thyroid cancer was 1.15 (95% CI 1.04–1.27) per 5 cm height increment, compared with the height of the baseline group (<157.7 cm).

(Rinaldi, Lise et al. 2012) conducted an analysis of thyroid cancer risk factors using the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort database. The EPIC cohort first collected health surveys and body measurement information for 150,000 individuals aged 35–39 years in 10 European countries (including the UK, Germany, and France) between 1991 and 2000, and further updated participant information until 2009. A total of 343,765 women participated in the baseline survey, and repeated surveys confirmed 508 incident cases of thyroid cancer. If the WC was ≥83.5 cm compared with the reference group (<74.0 cm), the hazard ratio was 1.34 (95% CI: 1.00–1.79), which was associated with a high-risk of thyroid cancer. Obesity (BMI ≥30.0 kg/m^2) was not related with an increased risk of thyroid cancer incidence compared with the reference group (normal: BMI 18.5–23.0 kg/m^2). A WHR ≥0.815 among the participants was associated with an increased risk of thyroid cancer (hazard ratio=1.42, 95% CI: 1.42–1.91) compared with the reference group (WHR <0.758). The WHR is calculated by dividing the WC by the HC.

The biological mechanisms underlying thyroid cancer and obesity have not yet been clearly identified. Resistance to insulin, altered adipocytokine components, inflammatory response, and their combinations have been suggested as

mechanisms underlying the relationship between obesity and thyroid cancer risk. Endocrine disorders and inflammation of central obesity-related adipose tissue were observed in obese individuals, leading to insulin resistance. High thyrotropin hormone levels have been identified in overweight and obese individuals, and thyrotropin is associated with mitogenic effects. In addition, high levels of serum tumor necrosis factor-alpha (TNF-α), interleukin-6, TNF-α immuno-reactivity, and leptin hormone in thyroid tissues have been demonstrated in patients with thyroid cancer (Shin, Cho et al. 2022).

(Bogović Crnčić, Ilić Tomaš et al. 2020) summarized well-known risk factors of thyroid cancer such as iodine intake, hereditary conditions, estrogen, obesity, lifestyle, environmental toxic pollutants, and exposure to ionizing radiation in childhood.

Table 3-1. The Summary of Literature Review

Reference	Risk factors for thyroid cancer	Data source
(Hoang, Song et al. 2021) Korea case-control study	► Risk factors: obesity (BMI ≥ 25.0 kg/m^2) * Sample size = 702 patients with thyroid cancer and 702 matched controls * 1:1 matched by gender and age	Patient cohort data from the National Cancer Center; 2002–2014
(An, Kim et al. 2020) Korea case-control study	► Risk factors: obesity (25.0 kg/m^2 ≤ BMI <30.0 kg/m^2 or 30.0 kg/m^2 ≤BMI), non-smoking, and non-drinking * Sample size = 4,977 patients with thyroid cancer and 19,908 matched controls * 1:4 matched by gender, age, residential area, income level, and the Charlson Comorbidity Index (CCI)③	National health examination data of people aged >40 years from 2002 to 2013, the Korea National Health Insurance Service (NHIS)
(Son, Lee et al. 2018)	► Risk factors: obesity (25.0 kg/m^2 ≤ BMI <30.0 kg/m^2) and overweight (23.0–24.9 kg/m^2)	National sample cohort (NSC)

③ CCI is the estimator of the 10-year mortality for a person who may get a range of comorbid health statuses.

Korea Cox's professional hazards regression	* Sample size = 3,308 patients with thyroid cancer among 351,402 participants * Covariates (gender, age, smoking status, exercise, alcohol consumption, and history of diabetes and dyslipidemia) * Smoking, drinking, and exercise exhibited an inverse correlation with the incidence of thyroid cancer	database; 2003–2008; the Korea National Health Insurance Service (NHIS)
(Cho, Chang et al. 2018) Korea Cox's proportional hazards regression	► Risk factors: non-smoking and obesity (BMI ≥25 kg/m^2) * Sample size = 1,250 newly diagnosed patients with thyroid cancer 96,855 participants * Covariates: age, year of health examination, alcohol consumption, exercise, and TSH levels (thyroid stimulating hormone)	Health examination database; between 2006 and 2014; health screening center at the Kangbuk Samsung Hospital
(Myung, Lee et al. 2017) Korea case-control study	► Risk factors: obesity (BMI>25.0 kg/m^2), family history of thyroid cancer, non-drinking, non-smoking, and low income * Sample size = 802 patients with thyroid cancer and 802 matched controls * 1:1 matched by gender, age (±2 years), and residential area	Cohort data in the National Cancer Center of Korea (2002–2012)
(Lee, Chai et al. 2021) meta-analysis	► Controversial association between smoking and thyroid cancer incidence * A reduced risk of thyroid cancer in both men and women was identified. However, (Lee, Chai et al. 2021) suggested that further studies with sufficient sample size depending on detailed types of thyroid cancer were needed	Previous 24 studies (published during 1990–2019) on the association between smoking and thyroid cancer incidence
(Feng et., 2017) Jiangsu, China logistic regression	► Risk factors of thyroid nodules④: waist circumference (WC ≥90 cm in men and WC ≥80 cm in women), fasting blood sugar, high blood pressure, and smoking * Sample size = 1,150 patients with thyroid nodules among 6,494 participants * Covariates: gender and age	Epidemiological survey conducted in the Jiangsu region of China (2014)
(Rinaldi, Lise et al. 2012) 10 European countries Cox's proportional hazards	► Risk factors: waist circumference (WC >83.5 cm), waist-hip ratio (WHR >0.815) * Sample size = 508 patients with thyroid cancer among 343,765 female participants * Obesity, based on BMI, was not associated with an increased risk of thyroid cancer. * Smoking status was adjusted for Cox's proportional hazards regression	EPIC cohort (the European Prospective Investigation into Cancer and Nutrition), data collected from 1991 to 2000 and

④Thyroid nodule refers to a lump in the thyroid gland caused by excessive proliferation of thyroid cells.

regression		updated until 2009.
(Kabat, Kim et al. 2012) US Cox's proportional hazards regression	► The risk of thyroid cancer was 1.15 (95% CI 1.04–1.27) per 5 cm height increment compared with the height of the reference group (<157.7 cm) * Sample size = 294 patients with thyroid cancer among 144,219 postmenopausal women * BMI, WC, hip circumference (HC), and WHR were not associated with thyroid cancer incidence	The Women's Health Initiative database in the US (1993–1998)
(Bogović Crnčić, Ilić Tomaš et al. 2020) review	► Well-known risk factors to date: low or high iodine intake, hereditary conditions, estrogen, obesity, lifestyle, environmental toxic pollutants, and exposure to ionizing radiation in childhood	Review paper
(Huxley, Mendis et al. 2010), (Liu, Tong et al. 2011), (Zhou, Li et al. 2021), (Ke, Wang et al. 2022)	These studies suggest that central obesity indices, such as WC, WHR, and waist-height ratio (WHTR) are more accurate indicators of abdominal fat than BMI and are more strongly associated with an increased risk of disease	

3.3. Materials and Methods

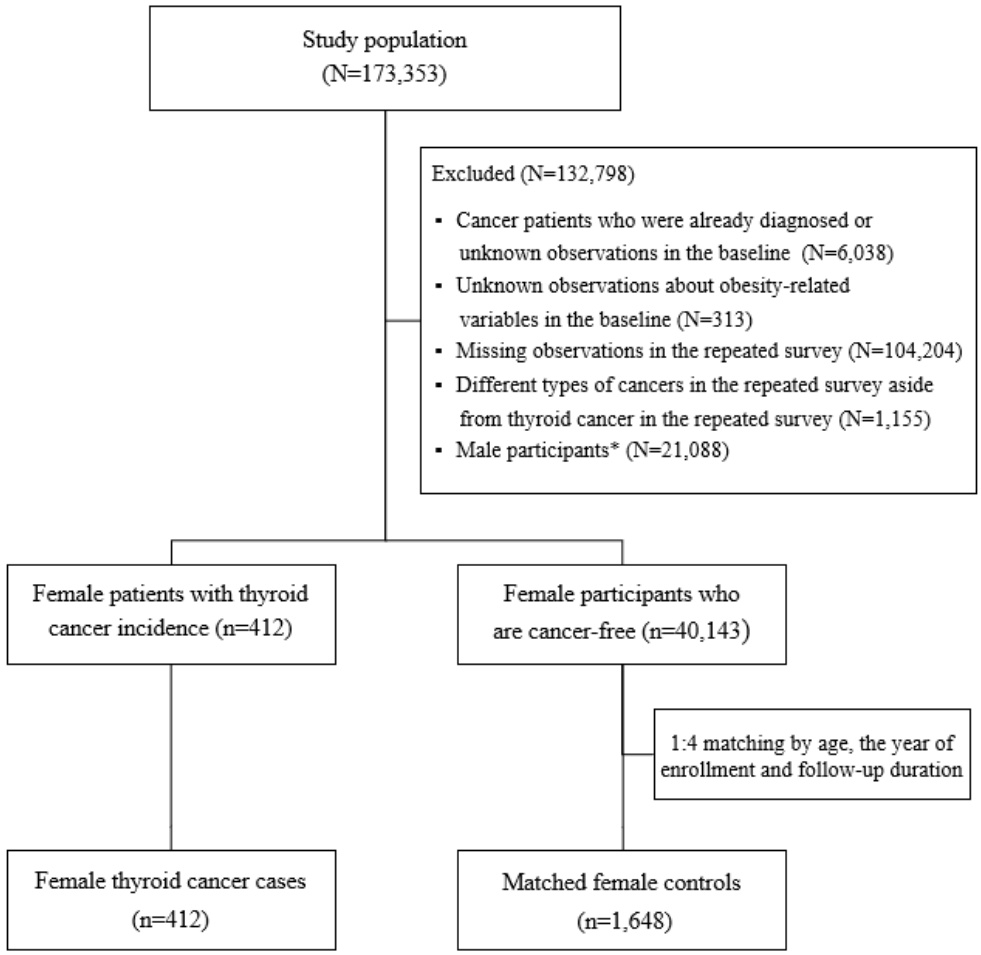
Study population

We prospectively conducted a study by utilizing data from the Health Examinee Study (HEXA), which is a part of the Korean Genome and Epidemiology Study (KoGES). The objective of KoGES is to examine the interactions between genetic and environmental elements with regard to the emergence of chronic and complex diseases in Korea (Kim and Han 2017). The study population of HEXA was composed of people aged 40–69 years who were recruited between 2004 and 2014 at 38 large health examination centers and training hospitals in eight regions of Korea. A total of 173,353 patients were recruited, and 65,639 completed the follow-up studies between 2012 and 2017.

To identify cancer cases, using a standardized questionnaire administered by skilled interviewers, participants were asked whether they had been diagnosis with cancer by a doctor. For those who finished the follow-up study (n=65,639), the incidence of thyroid cancer was determined using a follow-up questionnaire. To exclude cases of pre-existing cancer, individuals who had received a diagnosis for any type of cancer from a doctor during the baseline survey (n=6,038) were excluded. Moreover, participants with incomplete data on the variables that were essential to the calculation of obesity indices (height, weight, waist circumference, or hip circumference) were excluded (n=313). Furthermore, those who had cancers other than thyroid cancer during the follow-up survey (n=1,155) were excluded. Given the limited number of male participants with thyroid cancer, the final sample comprised 40,143 cancer-free female participants and 412 female patients with incident thyroid cancer.

According to the HEXA baseline study, self-reported thyroid cancer had a positive predictive value of 96.1% (Cho, Shin et al. 2017). Another prospective cohort study conducted in Korea demonstrated the accuracy of self-reported incident thyroid cancer as having sensitivity and specificity of 98.1% and 99.8%, respectively (Cho, Chang et al. 2018). Therefore, self-reported information on physician-diagnosed thyroid cancer is considered reliable. The HEXA study obtained informed consent from all participants for baseline and follow-up data collection, including interviews and physical examinations (Health Examinees Study 2015). This study was approved by the Institutional Review Board of Hanyang University College of Medicine (IRB No. HYUIRB-202205-025).

Figure 3-1. Flow chart of selection of the study participants.



* Excluded male participants because the number of male thyroid cancer cases was too small.

Nested case-control data set

A total of 412 females with thyroid cancer were identified. Control participants were selected randomly from among those who did not report any type of cancer in both the baseline and follow-up questionnaires. For every case, four controls were matched according to the birth year (exact match) and the enrollment year (±1 year). The follow-up period was determined by computing the difference between the enrollment and follow-up years. For matched controls, the follow-up

period was either equal to or exceeded that of each case with thyroid cancer. The final analysis included 412 females with thyroid cancer and 1,648 matched female controls.

Definition of variables

Throughout the health examinations, skilled nurses gathered anthropometric data, including measurements of height, weight, and waist circumference and hip circumference (Health Examinees Study 2015). Obesity indicators included body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), and waist-height ratio (WHTR). BMI categories included obese (≥25.0 kg/m^2), overweight (23.0-24.9 kg/m^2), and normal (<23.0 kg/m^2). Participants with a WC of 85 cm or more, WHR of 0.85 or more, and WHTR of 0.5 or more were classified as obese whereas those with WC less than 85, WHR less than 0.85, and WHTR less than 0.5 were considered normal (Lam, Koh et al. 2015, Ahn, Lee et al. 2020).

A standardized survey was administered by trained interviewers to obtain information on the participants' comorbidities as diagnosed by doctors (Health Examinees Study 2015), medical history of their immediate family, lifestyle factors, and reproductive factors. Lifestyle factors that were considered as covariates included alcohol consumption (never, former or current); smoking status (never, former or current); engaging in sweat-inducing exercise more than once a week (no, yes); and reproductive factors, including having a hysterectomy (no, yes), using oral contraceptives (never, former or current), and self-assessment of health status (good, normal, bad). The comorbidities that were examined as covariates were hypertension, diabetes, hyperlipidemia, osteoporosis, and intestinal polyps, which are linked to both obesity and thyroid cancer (Mack, Preston-Martin et al. 2002,

Tashiro, Akiyama et al. 2004, Navarro Silvera, Miller et al. 2005, Sullivan, Ghushchyan et al. 2008, Zhao, Jiang et al. 2008, Stansifer, Guynan et al. 2015). Furthermore, a family history of cancer, hypertension, and diabetes among first-degree relatives was considered a covariate (Xu, Li et al. 2012). Fasting blood glucose levels of blood samples obtained during health examinations were categorized as either less than 100 or more than or equal to 100 mg/dL (Hwang, Kang et al. 2016).

Statistical Analysis

Baseline survey characteristics for thyroid cancer cases and matched control groups were presented as proportions or means and compared using the chi-square or Fisher's exact test for categorical variables and the *t*-test for continuous variables. A conditional logistic regression model was used to examine the relationship between BMI, WC, WHR, WHTR, and thyroid cancer risk. Furthermore, multiple conditional logistic regression models were applied, after adjusting for factors such as drinking, smoking, sweating exercise, medical history (hypertension, diabetes, hyperlipidemia, osteoporosis, intestinal polyps), hysterectomy, oral contraceptive use, family history (cancer, hypertension, diabetes), fasting blood sugar, and subjective health assessment. The relationships of WC, WHR, WHTR, and BMI with thyroid cancer were analyzed using conditional logistic regression, after adjusting for the mentioned covariates and using normal obesity indices for both BMI and WC, WHR, and WHTR as the reference. Statistical significance was established with a two-sided $p<0.05$. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3.4. Results

Table 3-2 illustrates the key characteristics of recently diagnosed thyroid cancer cases and their corresponding control subjects. The thyroid cancer group comprised a greater proportion of individuals with a history of osteoporosis, intestinal polyps, and hysterectomy as compared to the matched control group (9.0% vs. 5.8%, 4.8% vs. 2.4%, and 15.5% vs. 10.2%, all $p<0.05$). The mean fasting blood sugar level was higher in patients with thyroid cancer than in their matched control counterparts (94.0 mg/dL vs. 91.0 mg/dL, $p<0.0039$). At the initial assessment, a worse self-evaluated health status was reported by individuals with incident thyroid cancer than by controls (22.1% vs. 16.4%). There was no significant difference in the remaining characteristics between the thyroid cancer cases and their matched controls.

Table 3-2. Baseline characteristics of patients with incident thyroid cancer and matched controls

Characteristic	Thyroid cancer cases [1]	Matched controls [1]	P-value
Sample size	418	1,648	
Age at cohort enrollment			
Mean (SD)	51.0 (±6.7)	51.0 (±6.7)	1.000
40–49	183 (44.4)	732 (44.4)	1.000
50–59	175 (42.5)	700 (42.5)	
≥ 60	54 (13.1)	216 (13.1)	
Alcohol drinking			
Never	272 (66.0)	1077 (65.4)	0.3970
Former or Current	135 (32.8)	561 (34.0)	
Unknown	5 (1.2)	10 (0.6)	
Smoking			
Never	397 (96.4)	1596 (96.8)	0.1358
Former or Current	9 (2.2)	43 (2.6)	
Unknown	6 (1.4)	9 (0.6)	
Sweating exercise once or more per			

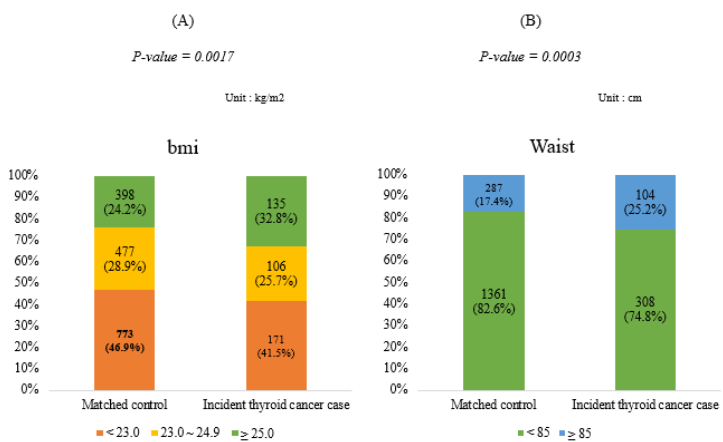
week			
No	170 (41.3)	750 (45.5)	0.2110
Yes	242 (58.7)	896 (54.4)	
Unknown	0 (0.0)	2 (0.1)	
Past medical history of hypertension			
No	348 (84.5)	1420 (86.2)	0.2616
Yes	63 (15.3)	227 (13.7)	
Unknown	1 (0.2)	1 (0.1)	
Past medical history of diabetes			
No	394 (95.6)	1586 (96.3)	0.6626
Yes	18 (4.4)	60 (3.6)	
Unknown	0 (0.0)	2 (0.1)	
Past medical history of hyperlipidemia			
No	379 (92.0)	1508 (91.5)	0.7507
Yes	33 (8.0)	140 (8.5)	
Past medical history of osteoporosis			
No	375 (91.0)	1553 (94.2)	0.0171
Yes	37 (9.0)	95 (5.8)	
Past medical history of polyp of intestine			
No	392 (95.2)	1608 (97.6)	0.0088
Yes	20 (4.8)	40 (2.4)	
Hysterectomy			
No	346 (84.0)	1474 (89.4)	0.0083
Yes	64 (15.5)	168 (10.2)	
Unknown	2 (0.5)	6 (0.4)	
Use oral contraceptive			
Never	324 (78.6)	1340 (81.3)	0.2267
Former or Current	82 (19.9)	296 (18.0)	
Unknown	6 (1.5)	12 (0.7)	
Family history of cancer			
No	267 (64.8)	1150 (69.8)	0.1208
Yes	143 (34.7)	487 (29.6)	
Unknown	2 (0.5)	11 (0.6)	
Family history of hypertension			
No	266 (64.6)	1105 (67.1)	0.5224
Yes	145 (35.2)	536 (32.5)	
Unknown	1 (0.2)	7 (0.4)	
Family history of diabetes			
No	313 (76.0)	1312 (79.6)	0.1560
Yes	97 (23.5)	322 (19.5)	
Unknown	2 (0.5)	14 (0.9)	
Fasting blood sugar			
Mean (SD)	94.0 (±20.6)	91.0 (±16.5)	0.0039
< 100 mg/dl	327 (79.4)	1370 (83.1)	0.0861

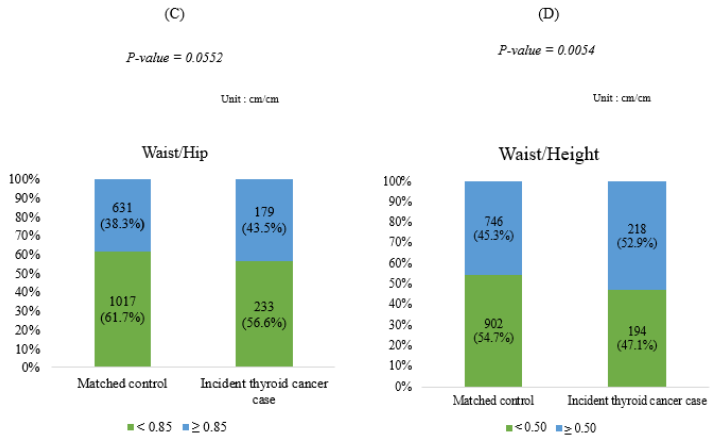
≥ 100 mg/dl	74 (18.0)	226 (13.7)	
Unknown	11 (2.6)	52 (3.2)	
Subjective health evaluation			
Good	127 (30.8)	578 (35.1)	0.0463
Normal	192 (46.6)	788 (47.8)	
Bad	91 (22.1)	271 (16.4)	
Unknown	2 (0.5)	11 (0.7)	

[1] Cases of thyroid cancer and their corresponding controls were precisely paired by sex, birth year, and enrollment year (±1 year). The monitoring period for the matched controls was established as equal to or longer than the duration for each thyroid cancer case. SD, standard deviation.

The proportions of obesity in terms of BMI, WC, WHR, and WHTR are shown in Fig. 3-2. The proportions of obese and overweight patients with BMI were 32.8% and 25.7% in thyroid cancer cases and 24.2% and 28.9% in matched controls, respectively (P-value = 0.0017). In group with thyroid cancer, the prevalence of obesity according to WC, WHR, and WHTR measurements was 25.2%, 43.5%, and 52.9%, respectively, whereas the corresponding proportions for matched controls were 17.4%, 38.3%, and 45.3%, respectively. Notably, a significantly increased prevalence of obesity based on WC and WHTR measurements was observed in the group with thyroid cancer.

Figure 3-2. Prevalence of obesity in baseline measurements [1]





[1] Figure A illustrates the prevalence of obesity based on BMI measurements whereas B, C, and D show the prevalence of obesity according to the WC, WHR, and WHTR measurements, respectively. BMI categories included obese (≥25.0 kg/m^2), overweight (23.0–24.9 kg/m^2), and normal (<23.0 kg/m^2). Participants were considered obese if they had a WC of 85 cm or more, a WHR of 0.85 or higher, or a WHTR of 0.5 or greater. Conversely, individuals with a WC less than 85 cm, WHR less than 0.85, and WHTR less than 0.5 were classified as having normal anthropometry. *P*-values were calculated using the chi-square test. The prevalence of obesity, as determined by BMI, WC, and WHTR measurements, was significantly greater in the group with thyroid cancer than in matched controls.

Table 3-3. Association between obesity indices and risk of thyroid cancer

Obesity index	Crude odds ratio (95% CI)	P-value	Adjusted odds ratio [1] (95% CI)	P-value
BMI				
≥ 25.0 Kg/m^2	1.46 (1.12-1.91)	0.0052	1.37 (1.03–1.81)	0.0300
23.0–24.9 Kg/m^2	0.96 (0.73-1.27)	0.7896	0.96 (0.72–1.28)	0.8000
< 23.0 Kg/m^2	ref (1)	-	ref (1)	-
Waist circumference				
≥ 85cm	1.65 (1.25-2.17)	0.0004	1.55 (1.16–2.07)	0.0035
< 85cm	ref (1)	-	ref (1)	-
Waist-Hip ratio				
≥ 0.85	1.25 (0.98-1.58)	0.0706	1.20 (0.93–1.54)	0.1529
< 0.85	ref (1)	-	ref (1)	-
Waist-Height ratio				
≥ 0.50	1.41 (1.11-1.78)	0.0045	1.37 (1.07–1.75)	0.0135
< 0.50	ref (1)	-	ref (1)	-

[1] This analysis considered various factors, after adjusting for the presence or absence of hypertension, diabetes, hyperlipidemia, osteoporosis, and intestinal polyps. Additionally, adjustments were made for family history of cancer, hypertension, and diabetes, as well as drinking and smoking habits, participation in intense exercise, hysterectomy status, and oral contraceptive use. Furthermore, fasting blood sugar levels and subjective health evaluations were considered. These adjustments were undertaken to provide a clearer understanding of the relationship between obesity indices and risk of thyroid cancer while controlling for potential confounding factors.

Table 3-3 presents the relationship between various obesity indices and the risk for thyroid cancer. Compared to the group with normal BMI (<23.0 kg/m2), the risk of thyroid cancer increased 1.37 times (95% CI, 1.03–1.81) in the obese BMI group (≥25.0 kg/m2), after accounting for other variables. Obesity, as defined by the WC (≥85.0 cm) and WHTR (≥0.5), was associated with an increased risk of thyroid cancer (OR [95% CI] 1.55 [1.16–2.07] and 1.37 [1.07–1.75], respectively). However, abdominal obesity, as measured by the WHR (≥0.85), was not significantly associated with the risk of thyroid cancer.

Table 3-4. Summary table of analysis for obesity indices and covariates

BMI (ref: <23.0 kg/m^2)	Waist circumference (ref: <85 cm)	Waist-hip ratio (ref: <0.85)	Waist-height ratio (ref: <0.50)
Obese (≥25.0 kg/m^2)	Obese (≥85 cm)	Obese (≥0.85)	Obese (≥ 0.5)
Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
1.37 (0.03–1.81)	1.55 (1.16–2.07)	1.20 (0.93–1.54)	1.37 (1.07–1.75)
P=0.0300	*P*=0.0035	*P*=0.1529	*P*=0.0135
Increased risk factors in covariates	Increased risk factors in covariates	Increased risk factors in covariates	Increased risk factors in covariates
Past medical history of hysterectomy, and intestinal polyps, and high fasting blood sugar (≥100 mg/dl) and subjective health evaluation	Past medical history of hysterectomy, intestinal polyps, and high fasting blood sugar (≥100 mg/dl) and subjective health evaluation	Past medical history of hysterectomy, intestinal polyps, and high fasting blood sugar (≥100 mg/dl) and subjective health evaluation	Past medical history of hysterectomy, intestinal polyps, and high fasting blood sugar (≥100 mg/dl) and subjective health evaluation

※ This table summarizes tables 3-5, 3-6, 3-7, and 3-8

Table 3-4 summarized four tables: tables 3-5, 3-6, 3-7, and 3-8. Regarding multiple conditional logistic regression results, the present study identified statistically significant covariates. Based on obesity indices as main variables, significant covariates such as past medical history of hysterectomy and intestinal polyps, high fasting blood sugar (≧100 mg/dl), and subjective health evaluations (cutoff point=P<0.05) were similar. This indicates that increased risk of thyroid cancer for different obesity indices is consistent, and the effects of covariates are similar in four obesity indices (BMI, WC, WHR, and waist-height ratio).

Table 3-5. Adjusted odds ratios between risk factors and incidence of thyroid cancer (body mass index)

Variable	Adjusted Odds ratio	95% CI	P-value
BMI			
<23.0	**ref (1)**		
23.0-24.9	**0.964**	**0.724-1.283**	**0.8**
>=25.0	**1.365**	**1.031-1.809**	**0.03**
Past medical history of hypertension			
No	ref (1)		
Yes	0.972	0.682-1.385	0.8755
Past medical history of diabetes			
No	ref (1)		
Yes	0.949	0.506-1.78	0.87
Past medical history of hyperlipidemia			
No	ref (1)		
Yes	0.771	0.497-1.193	0.2429
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.439	0.908-2.281	0.1209
Drinking			
Never	ref (1)		
Former or Current	0.988	0.771-1.266	0.923
Smoking			
Never	ref (1)		
Former or Current	0.777	0.365-1.655	0.5136
Intense exercise			
No	ref (1)		
Yes	1.223	0.964-1.551	0.0976
Familial cancer			
No	ref (1)		
Yes	1.196	0.935-1.529	0.1546
Familial hypertension			
No	ref (1)		
Yes	1.05	0.817-1.349	0.703

Familial diabetes			
No	ref (1)		
Yes	1.18	0.885-1.574	0.2583
Hysterectomy			
No	ref (1)	-	
Yes	1.614	1.158-2.252	0.0048
Oral contraceptive			
Never	ref (1)		
Former or Current	1.188	0.883-1.597	0.2545
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.253	1.243-4.083	0.0074
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.385	0.988-1.943	0.059
Subjective health evaluation			
Good	ref (1)		
Normal	1.121	0.859-1.462	0.3996
Bad	1.572	1.135-2.176	0.0065

Table 3-6. Adjusted odds ratios between risk factors and incidence of thyroid cancer (waist circumference)

Variable	Adjusted Odds ratio	95% CI	P-value
Waist circumference			
<85cm	**ref (1)**		
>=85cm	**1.548**	**1.155-2.074**	**0.0035**
Past medical history of hypertension			
No	ref (1)		
Yes	0.957	0.671-1.365	0.8082
Past medical history of diabetes			
No	ref (1)		
Yes	0.954	0.507-1.795	0.8846
Past medical history of hyperlipidemia			
No	ref (1)		
Yes	0.739	0.477-1.146	0.1765
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.444	0.911-2.288	0.1182
Drinking			
Never	ref (1)		
Former or Current	0.977	0.763-1.253	0.8558
Smoking			
Never	ref (1)		
Former or Current	0.773	0.363-1.647	0.5046
Intense exercise			
No	ref (1)		
Yes	1.228	0.967-1.559	0.0919
Familial cancer			
No	ref (1)		
Yes	1.191	0.932-1.522	0.1629
Familial hypertension			
No	ref (1)		
Yes	1.059	0.825-1.36	0.6513
Familial diabetes			

No	ref (1)		
Yes	1.2	0.899-1.601	0.2157
Hysterectomy			
No	ref (1)		
Yes	1.55	1.11-2.163	0.01
Oral contraceptive			
Never	ref (1)		
Former or Current	1.19	0.885-1.6	0.2505
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.181	1.204-3.95	0.0101
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.383	0.986-1.941	0.0603
Subjective health evaluation			
Good	ref (1)		
Normal	1.116	0.855-1.456	0.4181
Bad	1.594	1.151-2.208	0.005

Table 3-7. Adjusted odds ratios between risk factors and incidence of thyroid cancer (waist-height ratio)

Variable	Adjusted Odds ratio	95% CI	P-value
Waist-height ratio			
<0.5	**ref (1)**		
>=0.5	**1.366**	**1.066-1.75**	**0.0135**
Past medical history of hypertension			
No	ref (1)		
Yes	0.975	0.685-1.387	0.8874
Past medical history of diabetes			
No	ref (1)		
Yes	0.941	0.502-1.763	0.8489
Past medical history of hyperlipidemia			
No	ref (1)		
Yes	0.752	0.486-1.165	0.2019
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.432	0.903-2.272	0.1272
Drinking			
Never	ref (1)		
Former or Current	0.978	0.763-1.253	0.8588
Smoking			
Never	ref (1)		
Former or Current	0.797	0.374-1.699	0.5573
Intense exercise			
No	ref (1)		
Yes	1.237	0.973-1.571	0.0819
Familial cancer			
No	ref (1)		
Yes	1.205	0.943-1.54	0.1361
Familial hypertension			
No	ref (1)		
Yes	1.069	0.832-1.372	0.603
Familial diabetes			
No	ref (1)		

Yes	1.19	0.892-1.587	0.2364
Hysterectomy			
No	ref (1)	-	
Yes	1.611	1.156-2.245	0.0049
Oral contraceptive			
Never	ref (1)		
Former or Current	1.181	0.879-1.588	0.2696
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.268	1.253-4.105	0.0068
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.398	0.998-1.958	0.0514
Subjective health evaluation			
Good	ref (1)		
Normal	1.118	0.857-1.459	0.4122
Bad	1.579	1.14-2.187	0.006

Table 3-8. Adjusted odds ratios between risk factors and incidence of thyroid cancer (waist-hip ratio)

Variable	Adjusted Odds ratio	95% CI	P-value
Waist-hip ratio			
<0.85	**ref (1)**		
>=0.85	**1.2**	**0.934-1.542**	**0.1529**
Past medical history of hypertension			
No	ref (1)		
Yes	0.991	0.697-1.409	0.9598
Past medical history of diabetes			
No	ref (1)		
Yes	0.911	0.487-1.706	0.7716
Past medical history of hyperlipidemia			
Nio	ref (1)		
Yes	0.76	0.49-1.177	0.2189
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.424	0.9-2.255	0.1315
Drinking			
Never	ref (1)		
Former or Current	0.978	0.763-1.254	0.8626
Smoking			
Never	ref (1)		
Former or Current	0.788	0.37-1.678	0.5362
Intense exercise			
No	ref (1)		
Yes	1.211	0.954-1.536	0.1154
Familial cancer			
No	ref (1)		
Yes	1.191	0.931-1.523	0.1635
Familial hypertension			
No	ref (1)		
Yes	1.071	0.834-1.375	0.5908
Familial diabetes			
No	ref (1)		
Yes	1.197	0.899-1.595	0.2186

Hysterectomy			
No	ref (1)	-	
Yes	1.624	1.165-2.262	0.0042
Oral contraceptive			
Never	ref (1)		
Former or Current	1.187	0.884-1.595	0.255
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.23	1.233-4.035	0.008
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.426	1.019-1.996	0.0386
Subjective health evaluation			
Good	ref (1)		
Normal	1.115	0.855-1.454	0.4217
Bad	1.599	1.155-2.213	0.0046

Table 3-9 presents the relationship between the combination of BMI, other obesity indices, and the risk of thyroid cancer. Women who exhibited both an obese BMI level (≥25.0 kg/m^2) and other obesity indices (WC ≥ 85.0 cm, WHR ≥ 0.85, or WHTR ≥ 0.5) had an increased risk of thyroid cancer (OR [95% CI] 1.63 [1.14–2.31], 1.49 [1.05–2.12], and 1.42 [1.04–1.94], respectively) as compared with those who had normal levels of BMI and each respective obesity index. However, women with increased levels of only one obesity index did not display a significantly increased risk of thyroid cancer.

Table 3-9. Associations between abdominal obesity, BMI, and thyroid cancer risk (Combination of obesity indices)

Parameter	Crude odds ratio (95% CI)	P-value	Adjusted odds ratio [1] (95% CI)	P-value
BMI & waist circumference				
≥25.0 Kg/m^2 & ≥85 cm	1.79 (1.29–2.49)	0.0005	1.63 (1.14–2.31)	0.0070
23.0-24.9 Kg/m^2 & ≥85 cm	1.36 (0.76–2.42)	0.2989	1.39 (0.76–2.52)	0.2863
<23.0 Kg/m^2 & ≥85 cm	1.28 (0.51–3.23)	0.6046	1.36 (0.53–3.53)	0.5261
≥25.0 Kg/m^2 & <85 cm	1.20 (0.84–1.71)	0.3072	1.18 (0.82–1.70)	0.3719

23.0-24.9 Kg/m^2 & <85 cm	0.92 (0.69–1.24)	0.5927	0.93 (0.68–1.26)	0.6297
<23.0 Kg/m^2 & <85 cm	1		1	
BMI & waist-hip ratio				
≥25.0 Kg/m^2 & ≥0.85	1.60 (1.15–2.22)	0.0055	1.49 (1.05–2.12)	0.0266
23.0-24.9 Kg/m^2 & ≥0.85	1.07 (0.72–1.59)	0.7346	1.05 (0.70–1.57)	0.8140
<23.0 Kg/m^2 & ≥0.85	1.21 (0.82–1.81)	0.3392	1.23 (0.82–1.84)	0.3229
≥25.0 Kg/m^2 & <0.85	1.45 (0.98–2.16)	0.0633	1.37 (0.91–2.07)	0.1269
23.0-24.9 Kg/m^2 & <0.85	0.97 (0.68–1.39)	0.8716	0.99 (0.69–1.43)	0.9685
<23.0 Kg/m^2 & <0.85	1		1	
BMI & waist-height ratio				
≥25.0 Kg/m^2 & ≥0.5	1.51 (1.13-2.02)	0.0059	1.42 (1.04–1.94)	0.0267
23.0-24.9 Kg/m^2 & ≥0.5	1.20 (0.85–1.70)	0.2893	1.20 (0.85–1.72)	0.3023
<23.0 Kg/m^2 & ≥0.5	1.11 (0.71–1.74)	0.6577	1.10 (0.69–1.76)	0.6757
≥25.0 Kg/m^2 & <0.5	1.46 (0.74–2.87)	0.2712	1.30 (0.64–2.65)	0.4621
23.0-24.9 Kg/m^2 & <0.5	0.74 (0.50–1.12)	0.1524	0.75 (0.49–1.13)	0.1660
<23.0 Kg/m2 & <0.5	1		1	

[1] This analysis considered various factors, after adjusting for the presence or absence of hypertension, diabetes, hyperlipidemia, osteoporosis, and intestinal polyps. Additionally, adjustments were made for family history of cancer, hypertension, and diabetes, as well as drinking and smoking habits, participation in intense exercise, hysterectomy status, and oral contraceptive use. Furthermore, fasting blood sugar levels and subjective health evaluations were considered. These adjustments were undertaken to provide a clearer understanding of the relationship between obesity indices and thyroid cancer risk while controlling for potential confounding factors.

Table 3-10. Summary table of analysis for obesity indices and covariates

BMI and waist circumference	BMI and waist-hip ratio	BMI and waist-height ratio
Reference group: BMI <23.0 kg/m2 and WC <85 cm	Reference group: BMI <23.0 kg/m2 and WHR <0.85	Reference group: BMI <23.0 kg/m2 and WHTR <0.50
BMI ≥25.0 kg/m^2 & WC ≥85 cm	BMI ≥25.0 kg/m^2 & WHR ≥0.85	BMI ≥25.0 kg/m^2 & WHTR ≥0.50
Adjusted OR (95% CI) 1.63 (1.41–2.31)	Adjusted OR (95% CI) 1.49 (1.05–2.12)	Adjusted OR (95% CI) 1.42 (1.04–1.94)

P =0.0070	*P*=0.0266	*P*=0.0267
Increased risk factors in covariates Past medical history of hysterectomy and intestinal polyps and subjective health evaluation	Increased risk factors in covariates Past medical history of hysterectomy and intestinal polyps and subjective health evaluation	Increased risk factors in covariates Past medical history of hysterectomy and intestinal polyps and subjective health evaluation

※ This table summarizes tables 3-11, 3-12, and 3-13

Table 3-10 summarized three tables: 3-11, 3-12, and 3-13. Regarding multiple conditional logistic regression results with combined obesity indices, the present study identified statistically significant covariates. Based on the combined obesity indices as main variables, significant covariates such as past medical history of hysterectomy and intestinal polyps and subjective health evaluations (cutoff point: $P<0.05$) were similar. This means increased thyroid cancer risk by different combined obesity indices is consistent, and the effects of covariates are also similar in three combined obesity indices (BMI & WC, BMI & WHR, and BMI & waist-height ratio)

Table 3-11. Adjusted odds ratios between risk factors and incidence of thyroid cancer (combination BMI & waist circumference)

Variable	Adjusted Odds ratio	95% CI	P-value
BMI&WC			
<23.0 Kg/m^2 & <85 cm	**ref (1)**		
23.0-24.9 Kg/m^2 & <85 cm	**0.928**	**0.683-1.259**	**0.6297**
≥25.0 Kg/m^2 & <85 cm	**1.181**	**0.82-1.701**	**0.3719**
<23.0 Kg/m^2 & ≥85 cm	**1.361**	**0.525-3.525**	**0.5261**
23.0-24.9 Kg/m^2 & ≥85 cm	**1.385**	**0.761-2.519**	**0.2863**
≥25.0 Kg/m^2 & ≥85 cm	**1.625**	**1.142-2.312**	**0.007**
Past medical history of hypertension			
No	ref (1)		
Yes	0.95	0.665-1.357	0.7775
Past medical history of diabetes			
No	ref (1)		
Yes	0.964	0.512-1.813	0.9084
Past medical history of hyperlipidemia			
No	ref (1)		

Yes	0.744	0.48-1.156	0.1884
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.45	0.915-2.3	0.114
Drinking			
Never	ref (1)		
Former or Current	0.984	0.768-1.262	0.9014
Smoking			
Never	ref (1)		
Former or Current	0.772	0.362-1.645	0.5021
Intense exercise			
No	ref (1)		
Yes	1.236	0.973-1.569	0.0823
Familial cancer			
No	ref (1)		
Yes	1.188	0.929-1.519	0.1702
Familial hypertension			
No	ref (1)		
Yes	1.05	0.818-1.35	0.7
Familial diabetes			
No	ref (1)		
Yes	1.189	0.891-1.589	0.24
Hysterectomy			
No	ref (1)	-	
Yes	1.562	1.118-2.183	0.009
Oral contraceptive			
Never	ref (1)		
Former or Current	1.191	0.885-1.603	0.2483
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.196	1.211-3.98	0.0095
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.359	0.966-1.91	0.0779
Subjective health evaluation			
Good	ref (1)		
Normal	1.121	0.859-1.462	0.4017
Bad	1.577	1.138-2.186	0.0063

Table 3-12. Adjusted odds ratios between risk factors and incidence of thyroid cancer (combination BMI & waist-height ratio)

Variable	Adjusted Odds ratio	95% CI	P-value
BMI&WHTR			
<23.0 Kg/m2 & <0.5	**ref (1)**		
23.0-24.9 Kg/m^2 & <0.5	**0.746**	**0.493-1.129**	**0.166**
≥25.0 Kg/m^2 & <0.5	**1.304**	**0.643-2.645**	**0.4621**
<23.0 Kg/m^2 & ≥0.5	**1.104**	**0.693-1.759**	**0.6757**
23.0-24.9 Kg/m^2 & ≥0.5	**1.204**	**0.846-1.715**	**0.3023**
≥25.0 Kg/m^2 & ≥0.5	**1.421**	**1.041-1.939**	**0.0267**
Past medical history of hypertension			
No	ref (1)		
Yes	0.975	0.683-1.391	0.888
Past medical history of diabetes			
No	ref (1)		

Yes	0.953	0.508-1.787	0.8807
Past medical history of hyperlipidemia			
No	ref (1)		
Yes	0.76	0.49-1.178	0.2193
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.44	0.907-2.288	0.1222
Drinking			
Never	ref (1)		
Former or Current	0.981	0.765-1.259	0.8806
Smoking			
Never	ref (1)		
Former or Current	0.792	0.371-1.686	0.5447
Intense exercise			
No	ref (1)		
Yes	1.248	0.982-1.584	0.0698
Familial cancer			
No	ref (1)		
Yes	1.194	0.934-1.527	0.1569
Familial hypertension			
No	ref (1)		
Yes	1.057	0.822-1.359	0.666
Familial diabetes			
No	ref (1)		
Yes	1.169	0.876-1.56	0.2899
Hysterectomy			
No	ref (1)	-	
Yes	1.617	1.159-2.255	0.0047
Oral contraceptive			
Never	ref (1)		
Former or Current	1.174	0.873-1.58	0.2882
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.26	1.246-4.099	0.0073
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.366	0.974-1.917	0.0709
Subjective health evaluation			
Good	ref (1)		
Normal	1.124	0.861-1.467	0.3885
Bad	1.562	1.127-2.165	0.0075

Table 3-13. Adjusted odds ratios between risk factors and incidence of thyroid cancer (combination BMI & waist-hip ratio)

Variable	Adjusted Odds ratio	95% CI	P-value
BMI&WHR			
<23.0 Kg/m^2 & <0.85	**ref (1)**		
23.0-24.9 Kg/m^2 & <0.85	**0.993**	**0.689-1.43**	**0.9685**
≥25.0 Kg/m^2 & <0.85	**1.374**	**0.914-2.068**	**0.1269**
<23.0 Kg/m^2 & ≥0.85	**1.228**	**0.817-1.844**	**0.3229**
23.0-24.9 Kg/m^2 & ≥0.85	**1.05**	**0.701-1.572**	**0.814**
≥25.0 Kg/m^2 & ≥0.85	**1.491**	**1.047-2.123**	**0.0266**
Past medical history of hypertension			
No	ref (1)		

Yes	0.961	0.673-1.373	0.827
Past medical history of diabetes			
No	ref (1)		
Yes	0.939	0.501-1.761	0.8444
Past medical history of hyperlipidemia			
No	ref (1)		
Yes	0.762	0.491-1.183	0.2261
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.443	0.91-2.289	0.1192
Drinking			
Never	ref (1)		
Former or Current	0.99	0.772-1.269	0.9362
Smoking			
Never	ref (1)		
Former or Current	0.78	0.366-1.663	0.5205
Intense exercise			
No	ref (1)		
Yes	1.228	0.968-1.559	0.0912
Familial cancer			
No	ref (1)		
Yes	1.192	0.931-1.526	0.1633
Familial hypertension			
No	ref (1)		
Yes	1.051	0.818-1.351	0.6973
Familial diabetes			
No	ref (1)		
Yes	1.188	0.89-1.585	0.2429
Hysterectomy			
No	ref (1)	-	
Yes	1.613	1.156-2.251	0.0049
Oral contraceptive			
Never	ref (1)		
Former or Current	1.191	0.886-1.602	0.2473
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.246	1.24-4.069	0.0076
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.374	0.978-1.928	0.0667
Subjective health evaluation			
Good	ref (1)		
Normal	1.125	0.862-1.468	0.3853
Bad	1.572	1.134-2.179	0.0066

Obesity and overweight are associated with a higher risk of thyroid cancer (Shin, Jee et al. 2017, Son, Lee et al. 2018, Hoang, Song et al. 2021). Despite differences in obesity categories, the strength of the association and some variations in the dose-response pattern between men and women, the International Agency for Research on Cancer has conclusively confirmed the sufficiency of

evidence in support of the hypothesis that body fatness, as defined by the BMI category, increases the risk of thyroid cancer 1.1-fold for every increase of 5 BMI units (Lauby-Secretan, Scoccianti et al. 2016). In an Asian cohort consortium study, the connection between increased BMI and thyroid cancer risk was stronger in men than in women (Shin, Cho et al. 2022). Although the present study did not include men due to the small number of thyroid cancer cases among the participants, the association between BMI and thyroid cancer risk in women was consistent with findings from previous studies. There is a scarcity of epidemiological research that collects body measurements other than height and weight. Although BMI is a commonly used, practical obesity-related index, BMI does not reveal lean body mass or the distribution of central and peripheral body fat (Kitahara, McCullough et al. 2016).

Investigations of the associations between obesity indices other than BMI and thyroid cancer risk are limited and have produced inconsistent results for WC, WHR, or WHTR (Kabat, Kim et al. 2012, Kitahara, Platz et al. 2012, Rinaldi, Lise et al. 2012, Kitahara, McCullough et al. 2016). The European Prospective Investigation into Cancer and Nutrition Study, which included participants from 10 countries, revealed that increased WC and WHR were significantly associated with the thyroid cancer risk in females but not in males, whereas height and leg length were related to thyroid cancer in males (Rinaldi, Lise et al. 2012). In contrast, a study of postmenopausal women in the United States revealed that WC and WHR were not significantly associated with thyroid cancer risk whereas greater height was associated with the risk (Kabat, Kim et al. 2012). Another study that used the NIH-AARP Diet and Health Study demonstrated that a larger WC was significantly associated with an increased risk of thyroid cancer in both men and

women (Kitahara, Platz et al. 2012).

A recent pooled analysis of 22 prospective studies identified that not only BMI but also WC and height were associated with an increased risk of thyroid cancer with an HR of 1.03 per 5 cm increment of WC and 1.07 per 5 cm increment of height (Kitahara, McCullough et al. 2016). In Asia, although studies of obesity indices other than BMI and thyroid cancer risk are scarce, research related to thyroid nodules has shown a positive association between WC with the prevalence of thyroid nodules (Feng, Zhang et al. 2017). Of the available obesity indices, BMI, which provides information about total body fat, has been most frequently used to determine the obesity status in general populations. However, more recently, indices that reflect central obesity, such as WC, WHR, and WHTR, have been suggested to provide a more accurate indication of abdominal body fat when compared with BMI. Additionally, central obesity indices are said to be associated with disease risk to a greater extent than BMI (Huxley, Mendis et al. 2010, Liu, Tong et al. 2011, Zhou, Li et al. 2021, Ke, Wang et al. 2022). This study revealed a significant association between increased central obesity indices, such as WC or WHTR, and a higher risk of thyroid cancer in women from East Asia, where a thyroid cancer epidemic has emerged.

3.5. Conclusion and Discussion

This research revealed that obesity indices, such as BMI, WC, and WHTR, were linked to an increased risk of thyroid cancer in Korean women. On combining obesity indices such as WC, WHR, and WHTR with BMI categories, a significantly increased risk of thyroid cancer was detected for women with both an

obese-level BMI and other obesity indices as compared to women with normal BMI and other obesity indices.

Only a few studies have assessed the association between obesity indices and the risk of thyroid cancer. A study showed that people who had both abnormally obese levels of BMI and WC were much more vulnerable to thyroid cancer than that of the reference group with normal BMI and WC (Kitahara, Platz et al. 2012). Our findings indicate that only the combined variables of both obese-level BMI and abdominal obesity (WC, WHR, and WHTR) were significantly associated with the incidence of thyroid cancer. When only one of the indices was classified as obese, either with BMI or an abdominal obesity index, the combinations did not yield significant results. These outcomes provide further evidence in support of the role of both total and central adiposity throughout an individual's life in the risk of thyroid cancer.

The primary limitation of this study was the low participation rate in both the baseline and follow-up surveys, which could have conferred selection bias due to the loss to follow-up. However, when comparing baseline characteristics between women who did or did not participate in the follow-up survey, no significant differences were found, which suggests minimal impact from selection bias.

Additionally, incident thyroid cancer cases were identified using a questionnaire during follow-up (Health Examinees Study 2015). Although the high accuracy of self-reported cancer history in the HEXA study (Cho, Shin et al. 2017), and another previous research (Cho, Chang et al. 2018) has been demonstrated the validity of self-reported information, some comorbidity information might be biased. However, considering the high accuracy of medical histories obtained via self-reported questionnaires (Leggett, Khadaroo et al. 2016), the information

regarding comorbidities in this study, which was measured by trained interviewers, would be accurate.

This study could not account for thyroid cancer subtypes or other markers due to the lack of specific information. However, a previous pooled analysis indicated that excess body fat was linked to an increased risk for most major thyroid cancer types (Kitahara, McCullough et al. 2016).

Possible confounding factors or major risk factors for thyroid cancer, such as ionizing radiation exposure or iodine intake, were not measured and could not be adjusted. In addition, information about the covariates was obtained based on self-reports in the survey, and the accuracy of the information was limited. Despite these limitations, to the best of our knowledge, this study is the first to investigate the association between a combination of obesity indexes and thyroid cancer risk, suggesting that a combination of general obesity in terms of BMI and abdominal obesity could elevate risk.

Thyroid cancer is the most prevalent cancer in Korea, and its incidence has been increasing in many countries, with a resultant significant disease burden. Given this situation, it is crucial to consider strategies to modify the risk factors to mitigate the current thyroid cancer epidemic. The simultaneous increase in obesity prevalence and thyroid cancer incidence, along with evidence from epidemiological studies, raises questions about the role of obesity or other risk factors in the pathogenesis of thyroid cancer. Future studies should focus on identifying potential causes of the thyroid cancer epidemic by ascertaining various risk factors.

Appendix of chapter 3

Table 3-14. Crude odds ratios between each risk factor and incidence of thyroid cancer

Variable	Crude odds ratio	95% CI	P-value
BMI			
<23.0	ref (1)		
23.0-24.9	0.963	0.728-1.272	0.7896
>=25.0	1.462	1.12-1.907	0.0052
Waist circumference			
<85cm	ref (1)		
>=85cm	1.648	1.252-2.169	0.0004
Waist-hip ratio			
<0.85	ref (1)		
>=0.85	1.246	0.982-1.58	0.0706
Waist-height ratio			
<0.5	ref (1)		
>=0.5	1.408	1.112-1.784	0.0045
Past medical history of hypertension			
No	ref (1)		
Yes	1.195	0.865-1.651	0.2789
Past medical history of diabetes			
No	ref (1)		
Yes	1.325	0.757-2.319	0.3242
Past medical history of hyperlipidemia			
No	ref (1)		
Yes	0.962	0.638-1.451	0.8545
Past medical history of osteoporosis			
No	ref (1)		
Yes	1.507	0.977-2.325	0.0638
Drinking			
Never	ref (1)		
Former or Current	0.996	0.785-1.265	0.975
Smoking			
Never	ref (1)		
Former or Current	0.865	0.412-1.818	0.7023
Intense exercise			
No	ref (1)		
Yes	1.187	0.945-1.493	0.1409
Familial cancer			
No	ref (1)		
Yes	1.225	0.965-1.555	0.0949
Familial hypertension			
No	ref (1)		
Yes	1.125	0.891-1.422	0.3222
Familial diabetes			
No	ref (1)		
Yes	1.215	0.926-1.594	0.1591
Hysterectomy			

No	ref (1)	-	
Yes	1.655	1.2-2.282	0.0021
Oral contraceptive			
Never	ref (1)		
Former or Current	1.224	0.921-1.627	0.1634
Past medical history of polyp of the intestine			
No	ref (1)		
Yes	2.21	1.246-3.918	0.0067
Fasting blood sugar			
<100mg/dl	ref (1)		
>=100mg/dl	1.447	1.064-1.969	0.0186
Subjective health evaluation			
Good	ref (1)		
Normal	1.106	0.855-1.43	0.445
Bad	1.62	1.189-2.206	0.0022

Table 3-15. Crude odds ratios between combined obesity indices and incidence of thyroid cancer

Variable	Adjusted odds ratio	95% CI	P-value
BMI & waist circumference			
<23.0 Kg/m2 & <85 cm	ref (1)		
23.0-24.9 Kg/m2 & <85 cm	0.922	0.685-1.242	0.5927
≥25.0 Kg/m2 & <85 cm	1.202	0.844-1.712	0.3072
<23.0 Kg/m2 & ≥85 cm	1.277	0.506-3.226	0.6046
23.0-24.9 Kg/m2 & ≥85 cm	1.358	0.763-2.417	0.2989
≥25.0 Kg/m2 & ≥85 cm	1.789	1.288-2.486	0.0005
BMI & waist-hip ratio			
<23.0 Kg/m2 & <0.85	ref (1)		
23.0-24.9 Kg/m2 & <0.85	0.971	0.68-1.387	0.8716
≥25.0 Kg/m2 & <0.85	1.453	0.98-2.156	0.0633
<23.0 Kg/m2 & ≥0.85	1.214	0.816-1.806	0.3392
23.0-24.9 Kg/m2 & ≥0.85	1.07	0.722-1.586	0.7346
≥25.0 Kg/m2 & & ≥0.85	1.595	1.147-2.217	0.0055
BMI & waist-height ratio			
<23.0 Kg/m2 & <0.5	ref (1)		
23.0-24.9 Kg/m^2 & <0.5	0.744	0.496-1.116	0.1524
≥25.0 Kg/m^2 & <0.5	1.46	0.744-2.868	0.2712
<23.0 Kg/m^2 & ≥0.5	1.108	0.705-1.742	0.6577
23.0-24.9 Kg/m^2 & ≥0.5	1.204	0.854-1.698	0.2893
≥25.0 Kg/m^2 & ≥0.5	1.51	1.126-2.024	0.0059

Chapter 4. The economic burden incurred by cancer in HIV-infected people[⑤]

4.1. Study Background

The burden of cancer has quickly grown worldwide due to factors such as early detection, an aging population, increased prevalence of risk factors, and medical technological advances. In 2020, it was estimated that there were 19.3 million new cancer cases and 10 million cancer-related deaths, which contributed to cancer as the first or second leading cause of death in 112 out of 183 countries, and the third or fourth leading cause in 23 countries (Sung, Ferlay et al. 2021). The total global economic burden of cancer from 2020 to 2050 was estimated as US dollars ($) 25.2 trillion, which is comparable to a tax of 0.55% on gross domestic product per year worldwide (Chen, Cao et al. 2023). Although direct comparison of this cost is difficult due to different methods or different years for cost estimation, this value has been considerably increased compared to that in 2010, which was estimated as $290 billion, including $154 billion of medical cost, $67 billion of non-medical cost, and $69 billion of income loss in 2020 (Bloom, Cafiero et al. 2012).

The socioeconomic burden of disease can be categorized as direct expenses (medical, transportation, and nursing expenses) and indirect expenses (future income losses from early death and productivity losses owing to treatment). (NHIS 2017, Kim, Lee et al. 2020).

According to a report by the Korean NHIS, as of 2015, the socioeconomic

[⑤]This chapter is based on material that was originally presented in the "Economic burden of cancer for the first five years after cancer diagnosis in patients with HIV in Korea", which was published in *The Journal of Cancer Prevention* in 2023.

cost of diseases was KRW 148.25 trillion, approximately 9.5% of the annual gross domestic product (GDP). This is approximately 1.8 times higher than the cost in 2006 (KRW 82.46 trillion). As of 2015, cancer medical expenses amounted to KRW 6.40 trillion, accounting for approximately 33.5% of the total medical expenses of KRW 19.47 trillion caused by top 10 causes of death (cancer, heart disease, cerebrovascular disease, pneumonia, suicide, etc.). Medical expenses account for approximately 88.7% of the KRW 7.22 trillion in direct expenses (NHIS 2017).

Previous studies on cancer burden have mostly focused on the total population. However, some groups of people are more vulnerable to cancer. Understanding the economic burden of cancer in this population would help policymakers to establish targeted health policies for specific groups and effectively decrease cancer-related morbidity. These groups include people with human immunodeficiency virus (HIV) infection who are at a higher risk of cancer, particularly infection-related cancer, due to immunosuppression as a consequence of HIV infection (Yarchoan and Uldrick 2018). Expensive antiretroviral therapy against HIV is a global issue for HIV control policy (Bingham, Shrestha et al. 2021) and poses a barrier to treatment access and adherence (McCann, Horn et al. 2020, Tran, Saleem et al. 2021). Thus, people with HIV and poor adherence may be more vulnerable not only to HIV-related complications but also to cancer. Estimating the economic burden of cancer in this vulnerable population can facilitate the management of cancer in individuals with HIV. Despite several studies on HIV treatment costs (Nakagawa, Miners et al. 2015, McCann, Horn et al. 2020, Tran, Saleem et al. 2021), to the best of our knowledge, there have been no studies worldwide estimating the burden on healthcare system related to cancer treatment of patients

with HIV. This study aimed to estimate the medical costs of cancer during the first 5 years after diagnosis and the last 6 months of life for patients with HIV infection in Korea to provide essential data on the economic burden associated with cancer in this high-risk population.

4.2. Literature Review

4.2.1. Cancer Burden and Related Issues in Korea

Cancer medical expenses in Korea more than doubled to KRW 9.9 trillion in 2020, compared with KRW 4.2 trillion in 2010. For newly diagnosed patients with cancer, the average medical expenses per person increased significantly from KRW 8.4 million in 2010 to KRW 13.7 million in 2020. Despite cancer medical expenses accounting for 11.8% of the total medical expenditure of the health insurance system as of 2020, ongoing research on cancer medical expenses per cancer patient from the time of cancer diagnosis is disorganized and diverse; thus, confirming objective analysis results is challenging (Han 2022).

In a previous study (Han 2022), from 2007 to 2014, data of 16,774 patients with cancer in the sample database of the NHIS were analyzed. The average annual medical cost per patient was the highest for the first year after the diagnosis of cancer in all five cancers (gastric, colon, liver, lung, and thyroid cancers and leukemia); however, cost for each cancer type significantly differed. A comparison of the five cancer types revealed that stomach cancer had the highest annual medical cost per patient in the first year of diagnosis, approximately KRW 45 million. Colorectal, liver, and lung cancers were between KRW 10 million and KRW 15 million. Leukemia was between KRW 5 million and KRW 10 million.

The cancer with the lowest medical cost was thyroid cancer, approximately KRW 3 million. Except for leukemia, the average annual medical cost per person for all cancers in the second year of diagnosis sharply declined compared with the first year of diagnosis and exhibited minimal change until the third to fifth years. However, leukemia significantly declined in the second year of diagnosis compared with the first year of diagnosis and continued to decline until the third and fourth years; however, in the fifth year of diagnosis, the average annual medical cost per person increased to that slightly below the third year of diagnosis.

(Yoo 2019) estimated the average annual medical cost per person for cancer using data from the Korea Health Panel Survey in 2012. Cancer medical expenses included patients' co-payment, insurers' payments, and non-reimbursement. According to an analysis of a total of 308 newly diagnosed patients with cancer (119 men and 189 women), the average medical cost per person was ₩129,093,729 as of 2012, estimated at ₩158,100,612 for men and ₩110,482,075 for women. However, this study did not estimate the average annual medical cost per person for each type of cancer; hence, a direct comparison with the results of (Han 2022)'s study was not possible.

(Shin, Kim et al. 2012) estimated the average annual medical cost of cancer per person for five years from the time of cancer diagnosis for six most common cancers (stomach, breast, liver, lung, colon, and thyroid cancers) using data from the Korea Central Cancer Registry (2006–2010). The final study 28,509 participants were those selected by random sampling of 30% of patients with cancer registered in the Korea Central Cancer Registry. The pattern of the highest cancer medical expenses in the first year of diagnosis and a significant decrease in medical expenses in the second year compared with the first year of diagnosis was

common in all cancers; however, the first year medical expenses per person for breast cancer was estimated to be $10,053, whereas that for thyroid cancer was estimated to be $2,978. In all six carcinomas analyzed in this study, the second year medical cost of diagnosis declined to 24–35% of that in the first year of diagnosis and maintained a moderate decline. Moreover, (Shin, Kim et al. 2012) compared the average medical expenses for five years from the time of diagnosis per patient according to the SEER stages. SEER stages describe the extent of disease spread from the organ where it occurred. It is divided into localized, regional, and distant stages. For colorectal (localized $10,866 vs. regional $21,560 vs. distant $27,374), breast (localized $14,775 vs. regional $22,649 vs. distant $35,557), and thyroid cancers (localized $4,936 vs. regional $6,260 vs. distant $11,409), medical costs in regional stage or distant stages were 2–2.5 times higher than those in the localized stage.

(Park, An et al. 2020) calculated the average annual medical expenses per patient with non-Hodgkin's lymphoma using the 2002–2015 Health Insurance Corporation Health Examination database. The study participants were patients diagnosed with non-Hodgkin's lymphoma between 2004 and 2010. According to estimates of 521 patients (331 men and 190 women), the second year annual mean medical cost per person declined >50% compared with the annual mean medical cost per person in the first year of diagnosis. The annual mean medical cost per person from the second year exhibited a moderate decline until the fifth year (first year: ₩16,241,853, second year: ₩7,266,744, third year: ₩5,711,032, fourth year: ₩4,430,109, and fifth year: ₩3,450,786).

4.2.2. Cancer Burden and Related Issues Worldwide

(Laudicella, Walsh et al. 2016) estimated medical expenses for patients diagnosed with cancer between 2001 and 2010 among adults aged >18 years in the UK from 3 years before diagnosis to up to 9 years after diagnosis. A total of three data sources (National Cancer Data Repository (NCDR), Hospital Episode Statistics (HES), and National Schedules of Reference Costs (NSRC)) were used to analyze colon (n = 275,985), breast (n = 359,771), lung (n = 283,940), and prostate (n = 286,426) cancers. Comparison of the annual mean medical cost per person in the first year of cancer diagnosis by classifying it into those aged 18–64 years and ≥65 years for each type of cancer revealed the following estimates: colorectal (£17,241 vs. £14,776), breast (£11,109 vs. £7,788), prostate (£5,171 vs. £4,699), and lung (£12,083 vs. £9,061) cancers. The annual mean medical cost per person in the first year differed by stage at the time of cancer diagnosis, especially in patients aged 18–64 years with colon cancer, the annual mean medical cost per person in the first year was £4,276 higher in stages 3–4 than stages 1–2. In all cancers, except prostate cancer, the annual mean medical cost per person in the second year declined to approximately 28.6–47.4% compared with the first year and subsequently maintained a moderate decline as it moved away from the time of diagnosis. However, in the case of patients with prostate cancer aged ≥65 years, the annual mean medical cost per person increased again in the 7th year from the time of diagnosis.

(McGarvey, Gitlin et al. 2022) used Optum's De-identified Clinformatics Data Mart Insurance Claims database in the US to estimate the difference in medical expenses according to the time of cancer diagnosis for each type of cancer

in patients diagnosed with cancer in 2016–2020. The annual mean medical cost per patient from the time of cancer diagnosis is the sum of the average monthly medical expenses per patient for 1–12 months from the time of diagnosis. By observing medical expenses for 4 years from the time of diagnosis, the average cumulative medical expenses per patient were additionally estimated. A total of 20,422 individuals were diagnosed with breast, colon, cervical, lung, prostate, and ovarian cancers. In the first year of diagnosis according to stage at the time of diagnosis, the annual mean medical cost per person estimates were as follows: breast (stage 1: $82,931 vs. stage 4: $249,187), cervical (stage 1: $60,443 vs. stage 4: $215,871), colon (stage 1: $110,882 vs. stage 4: $255,666), lung (stage 1: $161,115 vs. stage 4: $418,590), ovarian (stage 1: $63,474 vs. stage 4: $217,214), and prostate (stage 1: $60,530 vs. stage 4: $147,182) cancers. Additionally, the average medical expenses per patient for 4 years from the time of diagnosis were as follows: breast (stage 1: $169,479 vs. stage 4: $805,817), cervical (stage 1: $131,308 vs. stage 4: $439,502), colon (stage 1: $232,346 vs. stage 4: $614,783), lung (stage 1: $391,926 vs. stage 4: $1,037,868), ovarian (stage 1: $124,694 vs. stage 4: $580,636), and prostate (stage 1: $131,943 vs. stage 4: $441,273) cancers. (McGarvey, Gitlin et al. 2022) emphasized the need for early cancer diagnosis because a higher stage at the time of diagnosis confirmed a higher average medical cost burden per person for all cancers.

(Banegas, Yabroff et al. 2018) used the SEER-Medicare data in the US to observe medical expenses from January 1, 2000 to December 31, 2008 for 45,522 patients diagnosed with cancer between January 1, 1988 and December 31, 2007 for four common cancers (breast, colon, lung, and prostate cancers). Medical expenses in the first year of diagnosis for each carcinoma displayed a noticeable

difference depending on the severity of cancer at the time of cancer diagnosis. Based on the baseline age of 65 years, the annual mean medical cost per cancer patient in the first year of diagnosis <65 years estimates were as follows: lung (stage 1: $50,700 vs. stage 4: $97,400), breast (stage 1: $33,800 vs. stage 4: $92,500), colon (stage 1: $34,100 vs. stage 4: $85,300), and prostate (stage 1: $18,000 vs. stage: $42,400) cancers. Estimates of age ≥65 years were as follows: lung (stage 1: $44,000 vs. stage 4: $71,200), breast (stage 1: $30,000 vs. stage 4: $51,400), colon (stage 1: $35,500 vs. stage 4: $74,500), and prostate (stage 1: $17,400 vs. stage 4: $24,500) cancers.

(Kutikova, Bowman et al. 2006) observed change over time in the cost of medical care for patients with non-Hodgkin's lymphoma from the beginning of diagnosis in the US using the MarketScan medical and drug claims database. The study participants were patients who were diagnosed with non-Hodgkin's lymphoma from 2000 to 2001. The average monthly medical cost per patient for the initial stage of treatment after being diagnosed with aggressive non-Hodgkin's lymphoma (n = 356) was estimated to be $10,970. The average monthly medical expenses per patient during the 12-month care period before death or during hospice care were confirmed to be approximately $9,836. In addition, it was found that higher medical expenses were spent when the treatment process failed after the diagnosis of aggressive non-Hodgkin's lymphoma.

In Taiwan, (Huang, Chen et al. 2020) analyzed the 3-year medical expenses per patient from the time of cancer diagnosis for 10 most expensive cancers (leukemia, oral cancer, lung cancer, etc.) using the Taiwan National Health Insurance Research Database (NHIRD). The study participants were 545,221 patients diagnosed with cancer between 2007 and 2014. Leukemia ($28,464), non-

Hodgkin's lymphoma ($18,050), and esophageal ($19,816), oral ($19,644), and lung ($18,410) cancers have a high average medical expenses per patient for 3 years from the time of diagnosis. Conversely, the cancer with the lowest medical cost was liver cancer ($10,759).

A U-shape pattern was observed in three clinical stages of cancer care: the initial phase, the first 6–12 months following diagnosis; the terminal phase, the final 12 months before death; and the continuing phase, the period between the initial and terminal phases. Consequently, previous studies have calculated the cost of cancer care throughout these phases (Laudicella, Walsh et al. 2016, Goldsbury, Yap et al. 2018, Mariotto, Enewold et al. 2020). Regarding end-of-life cancer care, various cutoff timepoints have been examined, such as 3, 6, or 12 months before death (Langton, Reeve et al. 2016, Laudicella, Walsh et al. 2016, Goldsbury, Yap et al. 2018, Park and Song 2018, Leng, Jing et al. 2019, Mariotto, Enewold et al. 2020, Han, Kim et al. 2022, Luta, Diernberger et al. 2022). The initial and terminal phases displayed a higher burden of medical expenses than the continuing phase, illustrating a general U-shaped pattern (Laudicella, Walsh et al. 2016, Goldsbury, Yap et al. 2018).

Medical spending in the US doubled from USD 1.9 trillion in 2010 to USD 3.8 trillion in 2019 (McCullough, Speer et al. 2020). Among these, cancer-related medical expenses were estimated to have exceeded USD 200 billion (Martin, Hartman et al. 2021). Based on medical information data before 2011, (Chow, Bradley et al. 2022) concluded that the US was generally better at cancer management than other developed countries, even if it spent more on cancer management than other European countries. However, as of 2020, the US has the highest medical expenditure per cancer patient among other high-income countries,

and whether the survival rate of cancer patients is better than that in other countries remains unclear. (Chow, Bradley et al. 2022) compared the mortality rate and medical expenses of patients with cancer in the US and 22 high-income countries and demonstrated that in the US the age-standardized cancer mortality rate per 100,000 was 86.2. Six countries had a lower age-standardized cancer mortality rate per 100,000 than the US (Japan: 81.5, Iceland: 84.0, Finland: 84.2, Austria: 85.8, Australia: 83.3, and South Korea: 75.5). However, the other 15 countries had a higher age-standardized cancer mortality rate per 100,000 than the US, for example, 93.5 in Canada, 100.5 in the UK, and 107.9 in France. According to this study, South Korea had the lowest age-standardized mortality rate per 100,000 among 22 developed countries. Regarding the proportion of cancer medical expenses in total health care expenditures in each country, the US had a lower proportion at 5.33%, as of 2015, than the median proportion 6.0% in 22 countries. Regarding annual medical expenditure, the lowest proportion of cancer expenses was 3.70% in Sweden in 2018. However, the year for calculating the proportion of cancer medical expenses was different for each country. The study estimated age-standardized cancer mortality rate using the GLOBCAN database and identified the health care expenditure budget using OECD data. World Bank data was used for the population size estimates of each country (Chow, Bradley et al. 2022).

Table 4-1. The Summary of Literature Review

Reference	Details	Data source
Han.2022 (Korea)	► First year average medical expenses per patient • Stomach cancer: ₩45 million • Colorectal cancer, liver cancer, or lung cancer: ₩10–15 million • Leukemia: ₩5–10 million	National Health Insurance Service database; 2007–2014; sample size = 16,774

Park, An et al. 2020 (Korea)	► First year average medical expenses per patient • Non-Hodgkin's lymphoma: ₩16,241,853. (Second year: ₩7,266,744, third year: ₩5,711,032, fourth year: ₩4,430,109, and fifth year: ₩3,450,786)	Health Insurance Corporation Health Examination database; 2002–2015; sample size = 521 (331 men and 190 women)
Yoo. 2019 (Korea)	► First year average medical expenses per patient * Included non-payment medical services • All types of cancer: ₩129,093,729 • All types of cancer (man): ₩158,100,612 • All types of cancer (woman): ₩110,482,075	The Korea Health Panel Survey in 2012; sample size = 308 (119 men, 189 women)
Shin, Kim et al. 2012 (Korea)	► First year average medical expenses per patient • Colon cancer: $10,053 • Lung cancer: $12,896 • Liver cancer: $9,956 • Colorectal cancer: $11,024 • Thyroid cancer: $2,978 ► Five-year average medical expenses per patient *In colorectal (localized $10,866 vs. regional $21,560 vs. distant $27,374), breast (localized $14,775 vs. regional $22,649 vs. distant $35,557), and thyroid (localized $4,936 vs. regional $6,260 vs. distant $11,409) cancers, medical expenses in regional or distant stages were 2–2.5 times higher than that in the localized stage.	The Korea Central Cancer Registry; 2006–2010; sample size = 28,509 (US$ 1 = ₩1100)
Huang, Chen et al. 2020 (Taiwan)	► Three-year average medical expenses per patient • Leukemia: $28,464 • Non-Hodgkin's lymphoma: $18,050 • Lung cancer: $18,410 • Gastric cancer: $11,883 • Colorectal cancer: $11,998 • Liver cancer: $10,759	The Taiwan National Health Insurance Research database; 2007–2014; sample size=545,221 * Unit: US dollar (USD)
Banegas, Yabroff et al. 2018 (US)	► First year average medical expenses per patient • Lung cancer Age 18–64 years (stage 1: $50,700 vs. stage 4: $97,400) Age ≥65 years (stage 1: $44,000 vs. stage 4: $71,200) • Breast cancer	SEER-Medicare data; 2000–2008; sample size = 45,522

	Age 18–64 years (stage 1: $33,800 vs. stage 4: $92,500) Age ≥65 years (stage 1: $30,000 vs. stage 4: $51,400) • Colon cancer Age 18–64 years (stage 1: $34,100 vs. stage 4: $85,300) Age ≥65 years (stage 1: $35,500 vs. stage 4: $74,500) • Prostate cancer Age 18–64 years (stage 1: $18,000 vs. stage: $42,400) Age ≥65 years (stage 1: $17,400 vs. stage 4: $24,500)	
Laudicella, Walsh et al. 2016 (England)	► First year average medical expenses per patient • Colorectal cancer Age 18–64 years (stages 1–2: £14,911 vs. stages 3–4: £19,187) Age ≥65 years (stages 1–2: £14,196 vs. stages 3–4: £15,411) • Breast cancer Age 18–64 years (stages 1–2: £10,746 vs. stages 3–4: £13,315) Age ≥65 years (stages 1–2: £7,597 vs. stages 3–4: £8,804) • Prostate cancer Age 18–64 years (£5,171), ≥65 years (£4,699) • Lung cancer Age 18–64 years (£12,083), ≥65 years (£9,061) *No classification about the stage in lung and prostate cancer	National Cancer Data Repository (NCDR), Hospital Episode Statistics (HES), and National Schedules of Reference Costs (NSRC); 2001–2010; sample size = 922,182
Kutikova, Bowman et al. 2006 (US)	►Monthly average medical expenses per patient • Non-Hodgkin lymphoma - Monthly average medical expenses per patient in the initial phase: $10,970 - Monthly average medical expenses per patient before death or during hospice care: $9,836	The MarketScan medical and drug claims database; 2000–2001; sample size = 356

(Vodicka, Chung et al. 2019) interviewed 54 patients and 23 medical staff at two medical centers in Kenya from July to October 2014 and suggested that integrating cervical cancer and HIV treatments can ease the economic burden on the medical system and individual patients. This study additionally estimated

medical expenses for the treatment of cervical cancer in people with HIV in Kenya and estimated that medical expense for treating one patient with cervical cancer was approximately $1,345–$6,514.

4.3. Materials and Methods

This study utilized the Korea National Health Insurance Service-National Health Information Database (NHIS-NHID), which is a mandatory and universal claims database containing information of approximately 97% of the Korean population. The NHIS-NHID comprised information of socioeconomic characteristics, healthcare service usage, health screening, medical expenses for all healthcare services and prescription drugs reimbursed by the NHIS, and death.

The researchers identified patients with incident HIV infection between 2004 and 2020, based on the International Classification of Disease-10th revision (ICD-10) codes (B20–B24) and the cost-sharing system code (V103) for HIV infection. The cost-sharing system in Korea is associated with a reduction in out-of-pocket medical expenses for diseases with high financial burden, such as HIV infection, cancer, and rare diseases; thus, the cost-sharing system code is valid for defining diseases. To focus on incident HIV cases, patients who had received HIV-related medical services between 2002 and 2003 were excluded from the study. To calculate cancer-related medical cost per year after diagnosis, we selected HIV-infected people who were newly diagnosed with cancer. To improve the accuracy of cancer diagnosis, cost-sharing system codes (V193, V194, or V027) for cancer, in combination with the primary diagnosis of cancer based on the ICD-10 codes (C00–C99), were applied. We excluded patients who were diagnosed with cancer

before HIV diagnosis by excluding those who received medical services for cancer before HIV diagnosis.

Of the 16,671 patients who were newly diagnosed with HIV between 2004 and 2020, the study identified 757 patients who were subsequently diagnosed with cancer after their HIV diagnosis The newly diagnosed cancer cases included AIDS-defining and non-AIDS-defining cancers. AIDS-defining cancers included Kaposi's sarcoma (C46), non-Hodgkin's lymphoma (C82–C86, C96), and cervical cancer (C53) (Park, Ahn et al. 2022). The remaining cancer types were considered as non-AIDS-defining cancers.

Medical Costs

In this research, only direct medical costs were taken into account as "costs" whereas indirect costs and expenses for non-covered healthcare services by the NHIS were not considered. To distinguish cancer-related costs from those of HIV or other diseases, all NHIS claims for inpatient, outpatient, and prescription with a cost-sharing system code for cancer (V193, V194, or V027) were defined as cancer-related costs. In the NHIS-NHID, expenses consist of patients' co-payments and insurers' payments. The total medical cost for cancer was determined by adding the patients' co-payments and insurance payments.

The total 5-year cancer-related cost from 2006 to 2020 was calculated from the date of cancer diagnosis, and the cost was adjusted for annual variation with a discount rate of 3% each year to standardize all expenses to the currency value in 2020. Subsequently, the monthly average medical cost of cancer from the first month to 60th month was calculated. The individual average total cancer-related medical cost for each year was calculated using the following equation.

$$E_t = \sum_{j=1}^{12} P_{tj} C_{tj}$$

Notation,

E_t = individual average medical cost related to cancer during each year after cancer diagnosis

P_{tj} = survival rate at month *j* during each year *t*

C_{tj} = personal average expense of cancer patient at month *j* during each year *t*

t = each year after cancer diagnosis (*t* = 1, 2, ···, 5)

j = month of each year (*j* = 1, 2, ···, 12)

To adjust annual currency value, (Kang, Yun et al. 2019) used fee-for-service (FFS), (Park, An et al. 2020) applied the consumer price index (CPI, health), and (Jung and Ko 2009) utilized a discount rate of 3%. According to a previous study (Kim, Yoo et al. 2019), the annual rate of increase for FFS varies depending on the type of medical institutions such as hospitals, dental clinics, and oriental medicine clinics. During 2011–2018, the FFS of each medical institution exhibited an increase in rate of 1.0–3.5%. The CPI, health recorded a rate of 0.4–2.2% between 2006 and 2020, excluding a negative 0.1% rate in 2018. For comparing FFS and CPI, health, the author deemed that application of an annual discount rate of 3% on average was reasonable.

The individual average monthly medical cost of cancer for 60 months was calculated using the survival rate and monthly expenses from 2006 to 2020, which were adjusted to the discount rate. Monthly survival rates were estimated using non-parametric Kaplan-Meier estimates for censored data, and then monthly

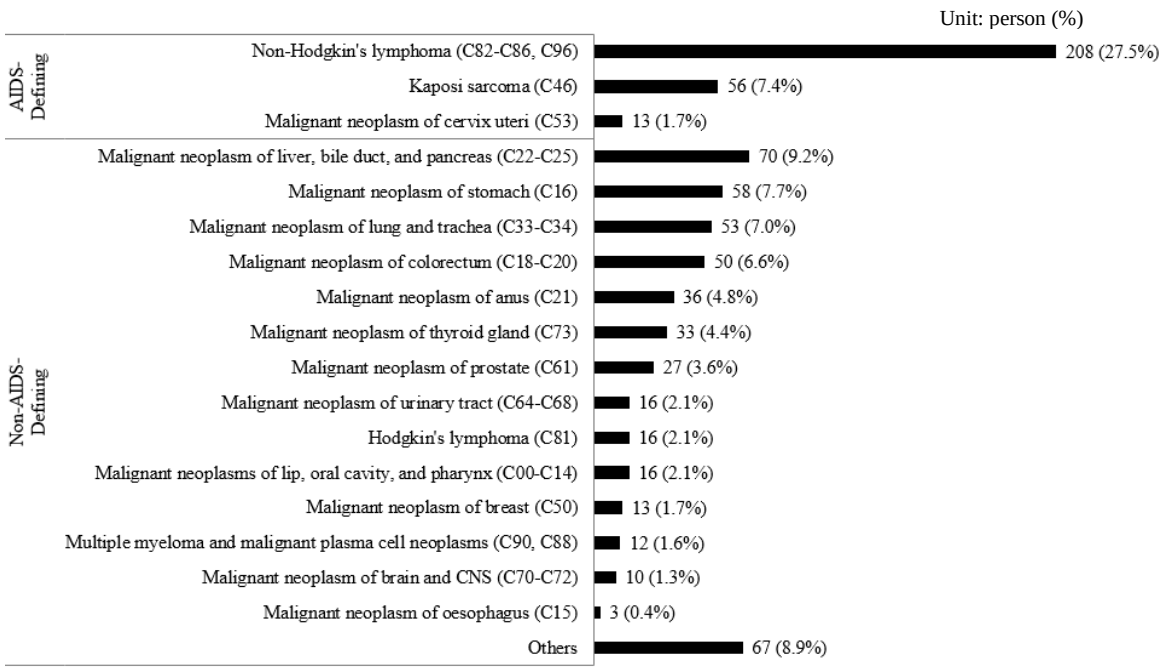
survival rates were multiplied by monthly expenses for cancer treatment. The Kaplan–Meier method does not need to divide the period into specific intervals, based on non-parametric statistics, without assuming the distribution of the study population (Lang, Lines et al. 2009). Considering that a significant part of cancer-related medical costs is incurred within one year of cancer diagnosis, individual average medical cost during the first year of cancer diagnosis was presented as monthly expenses from the first to 12th month of cancer diagnosis. The cost estimation was categorized for the AIDS-defining cancers and non-AIDS-defining cancers, which were further subdivided based on the number of cases of each cancer, including Kaposi's sarcoma; non-Hodgkin's lymphoma; and malignant neoplasms of colorectum; malignant neoplasms of liver, bile duct, pancreas; and malignant neoplasms of stomach. Despite relatively large number of malignant neoplasms of the lung and trachea, their cost was not presented separately because no patient could survive for up to 60 months. Other types of cancer were not sub-categorized because of small number of cases.

To estimate cancer-related medical costs as a total social burden and its trend, the total cancer-related medical cost during the first year of cancer diagnosis by each month was calculated by the summation of the costs associated with all individuals, stratified by the following year ranges: 2006–2008, 2009–2011, 2012–2014, 2015–2017, and 2018–2020. Furthermore, for patients who were diagnosed with cancer after the HIV diagnosis and subsequently died, the individual average total medical cost (not limited to cancer-related medical costs) for the 6 months before death was presented. The estimated medical costs in period t were converted into US dollars according to the average 2020 exchange rate (USD 1$ = 1180 Korean won).

The study was approved by the Institutional Review Board of Hanyang University, Korea (approval no: HYUIRB-202111-005). We received permission to analyze NHIS-NHID using pseudonymized information. This study complied with the regulations of the Reporting of Observational Studies in Epidemiology for cohort studies.

4.4. Results

Figure 4-1. Type of incident cancer in patients with human immunodeficiency virus (HIV) in Korea



Of the 757 patients newly diagnosed with cancer after HIV diagnosis (Figure 4-1), AIDS-defining cancer, including 208 non-Hodgkin's lymphoma, 56 Kaposi sarcoma, and 13 cervical cancers, accounted for 36.6% (N=277). Non-AIDS-defining cancers, which accounted for 63.4% of cancer developed in HIV patients included 70 cases of hepatobiliary and pancreatic cancer (9.2%), 58 stomach cancer (7.7%), 53 lung and tracheal cancer (7.0%), and 50 colorectal cancer (6.6%).

Figure 4-2. Mean annual medical cost due to cancer per patient in the first 5 years following cancer diagnosis in patients with human immunodeficiency virus

Fig 4-2-A

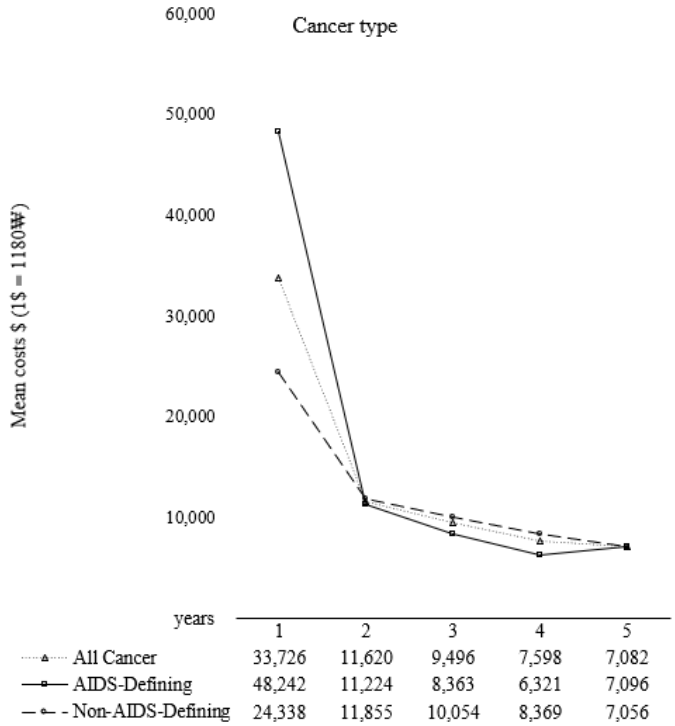
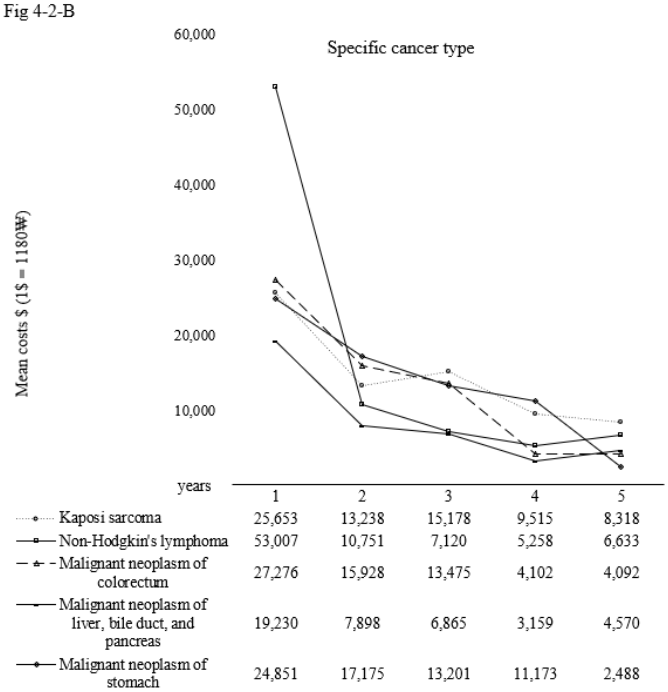


Fig 4-2-B



The mean annual medical cost due to cancer per patient in the first five years following cancer diagnosis for all cancers, AIDS-defining cancers, and non-AIDS-defining cancers, are presented in Figure 4-2.

In all three groups, medical costs were the highest in the first year of cancer diagnosis and decreased significantly in the second year. Compared with cancer costs in the first year, the mean medical cost due to cancer in the second year decreased by 65.5% ($33,725→$11,620) for all cancers, 76.7% ($48,242→$11,224) for AIDS-defining cancers, and 51.3% ($24,338→$11,855) for non-AIDS-defining cancers. Although the cost decreased over the years following cancer diagnosis, the decrease after the second year was less significant. In the first year, the mean annual medical cost was approximately two-fold higher for AIDS-defining cancers than that for non-AIDS-defining cancers; however, there was no significant difference in the mean annual medical cost from the second to fifth year between the two groups (Figure 4-2-A).

Similarly, the mean annual medical cost per patient stratified by the cancer type was the highest in the first year and largely decreased in the second year. In the first year, non-Hodgkin's lymphoma showed a significantly higher mean annual medical cost ($53,007) than that of other cancer types (less than $30,000). In the second year, the mean annual medical cost of non-Hodgkin's lymphoma ($10,751) decreased by 79.7% compared to that in the first year and was lower than that of other types of cancers (Figure 4-2-B).

Figure 4-3. Mean monthly medical cost due to cancer per patient in the first 12 months following cancer diagnosis in patients with human immunodeficiency virus infection

Fig 4-3-A

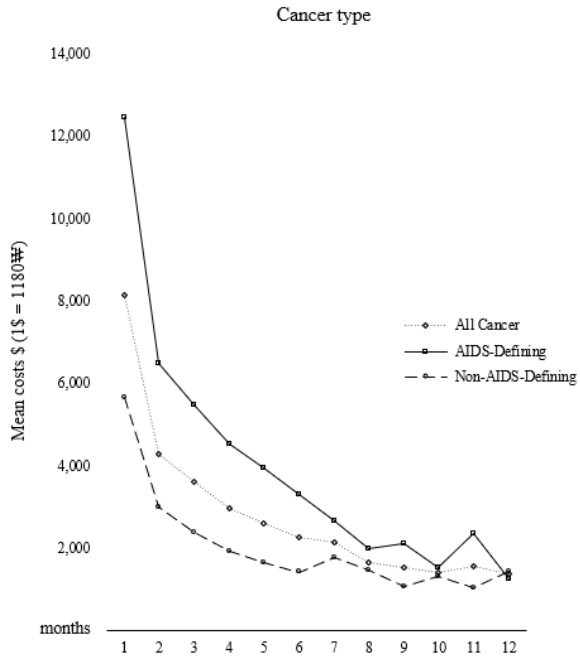


Fig 4-3-B

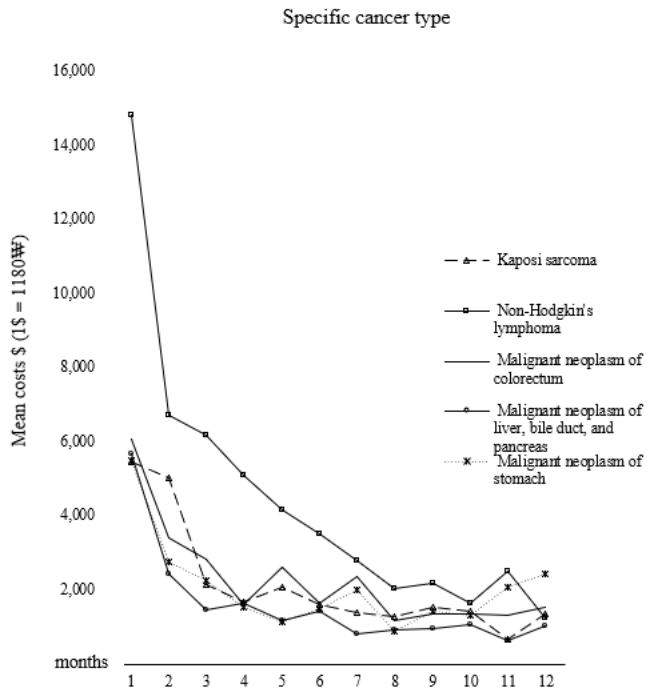


Figure 4-3 shows the mean monthly medical costs of cancer per patient during the first 12 months of cancer diagnosis. The AIDS-defining cancer group showed a mean monthly medical cost of $12,461 in the first month, which was 2.2-times higher than that of the non-AIDS-defining cancer group ($5,679). The mean monthly medical cost for AIDS-defining cancers and non-AIDS-defining cancers in the second month decreased by 47–48% compared to that in the first month. When analyzed by the cancer type, all cancer types showed the highest mean medical cost for the first month after diagnosis, followed by a significant decrease in the second month. The mean monthly medical cost of non-Hodgkin's lymphoma was the highest in almost each of the first 12 months among all cancer types, which was $14,833 and $6,729 in the first and second months after diagnosis, respectively.

Figure 4-4. Total monthly medical cost due to cancer in the first 12 months following cancer diagnosis in patients with human immunodeficiency virus infection

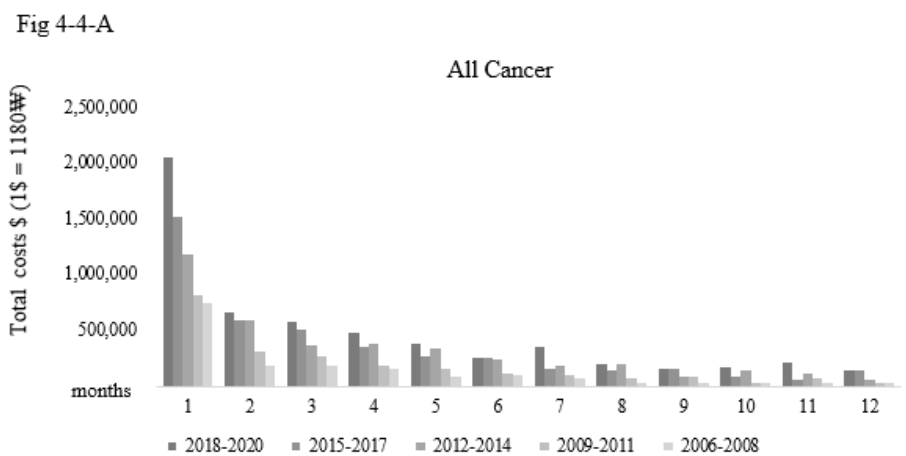


Fig 4-4-B

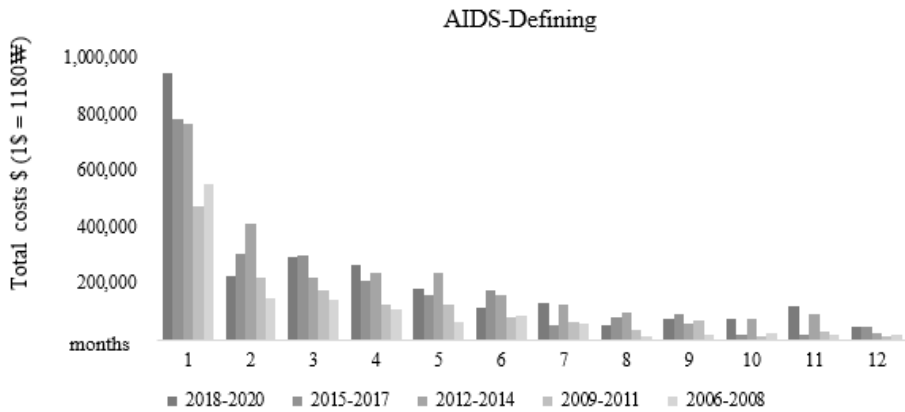
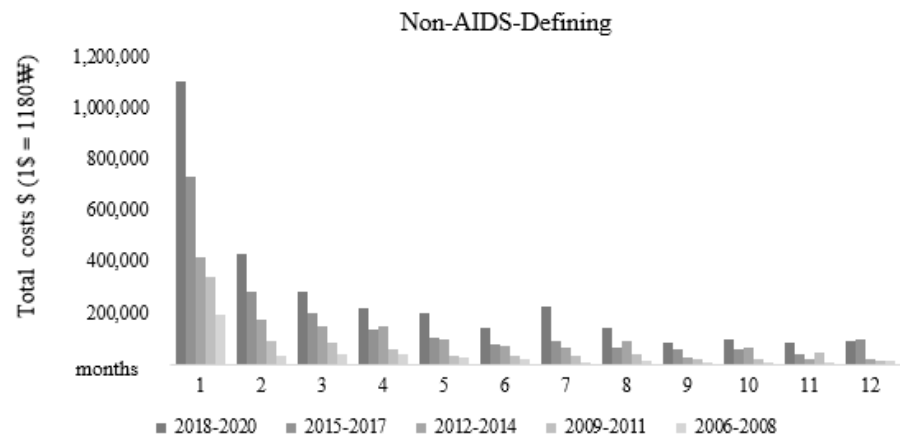


Fig 4-4-C



The total medical cost due to cancer for the first year of cancer diagnosis in patients with HIV infection was $17,799,522 in 2006–2020. The total medical costs due to cancer per month for the first year of cancer diagnosis in patients with HIV infection in the year 2006–2008, 2009–2011, 2012–2014, 2015–2017, and 2018–2020 are shown in Figure 4-4. For the non-AIDS-defining cancer group, the total monthly medical cost during the first 12 months was higher in recent years (2018–2020) and decreased in the remote year groups, despite standardization using the discount rate. However, for the AIDS-defining cancer group, there was no consistent pattern in the total monthly medical cost according to the year of

diagnosis, except in the first month, in which the highest cost was shown in recent years.

Figure 4-5. Mean medical cost including the cost of cancer treatment and other treatments per patient in the last 6 months of life in patients with human immunodeficiency virus infection who were subsequently diagnosed with cancer

Fig 4-5-A

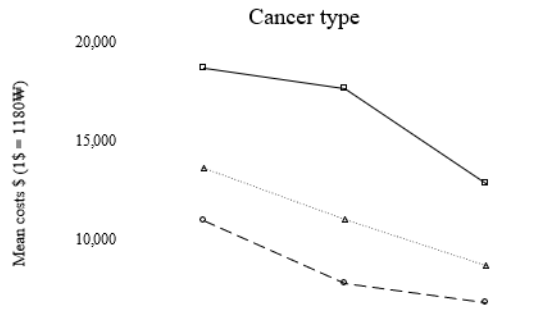


Fig 4-5-B

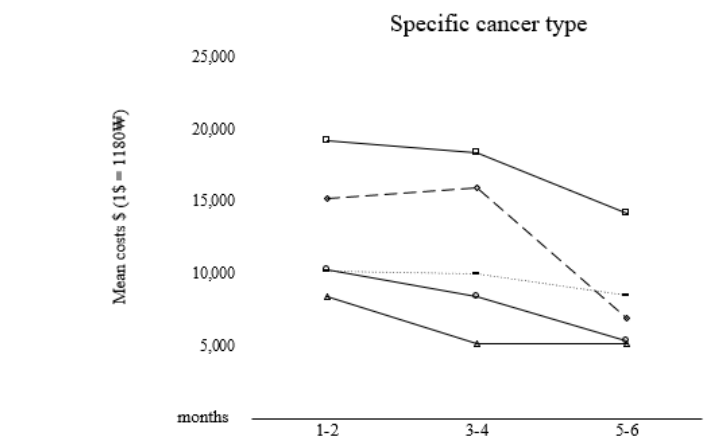


Figure 4-5 shows the mean medical cost (for every two months) for all healthcare services, including the cost of cancer treatment and other treatments for each cancer patients with HIV infection in the final six months before death. The mean medical costs increased closer to the time of death in the AIDS-defining, non-AIDS-defining, and specific cancer types. Compared to the non-AIDS-defining cancer group, the AIDS-defining cancer group showed a 69.1% ($18,670 vs. $ 11,043), 124.3% ($17,658 vs. $7,873), and 87.1% ($12,911 vs. 6,901) increase in mean medical costs in the last 1–2 months, 3–4 months, and 5–6 months before death, respectively. Comparison among groups according to the cancer type showed a higher medical cost burden in all final months of life in the non-Hodgkin's lymphoma than that in the other cancer groups.

Although the timing and data of previous studies are different from the present study, the average annual medical cost per person after cancer diagnosis for people with HIV has been confirmed to be much higher than that for the general population.

(Park, An et al. 2020) calculated the average annual medical expenses per patient with non-Hodgkin's lymphoma using the 2002–2015 Health Insurance Corporation Health Examination database. The study participants were patients diagnosed with non-Hodgkin's lymphoma between 2004 and 2010. According to estimates for 521 patients with non-Hodgkin's lymphoma, after declining to >50% in the second year compared to the first year, the average annual medical expenses per patient maintained a moderate decline until the fifth year (first year: ₩16,241,853, second year: ₩7,266,744, third year: ₩5,711,032, fourth year: ₩4,430,109, and fifth year: ₩ 3,450,786).

Regarding non-Hodgkin's lymphoma-related costs, the present study found

that over time, the average annual medical cost per person decreases. However, after the diagnosis of non-Hodgkin's lymphoma in people with HIV, the average annual medical cost per person was higher than that reported in previous studies (first year: $53,007, second year: $10,751, third year: $7,120, fourth year: $5,258, and fifth year: $6,633; $1 = ₩1180).

Furthermore, (Shin, Kim et al. 2012) estimated the average annual medical cost of cancer per person for five years from the time of diagnosis for six most common cancers (stomach, liver, lung, colon, breast, and thyroid cancers) using data from the Korea Central Cancer Registry (2006–2010). The pattern of the highest cancer medical expenses in the first year of diagnosis and a significant decrease in medical expenses in the second year compared with the first year of diagnosis was common for all six cancers. The average annual medical expenses per person after cancer diagnosis in this study was estimated as below(converted from won into US dollars ($1 = ₩1100):

Stomach (first year: $7,715, second year: $2,018, third year: $1,291, and fourth year: $998), liver (first year: $9,956, second year: $3,466, third year: $2,504, and fourth year: $1,986), and colorectal (first year: $11,024, second year: $2,615, third year: $1,818, and fourth year: $1,320) cancers

Although the criteria for detailed carcinomas in our study and previous studies were not similar, the average annual expenses of cancer per person for people with HIV is higher than that for the general population. The present study estimated the individuals' average annual medical expenses for each type of cancer as below (converted from won into US dollars ($1 = ₩1100): *Malignant neoplasms of the stomach (first year: $24,851, second year: $17,175, third year: $13,201, and fourth year: $11,173), liver, bile duct, and pancreas (first year: $19,230, second*

year: $7,898, third year: $6,865, and fourth year: $3,159), and colorectum (first year: $27,276, second year: $15,928, third year: $13,475, and fourth year: $4,102)

The initial and terminal phases generally had a higher burden of cancer-related medical costs than that of the progressive phase, displaying an overall U-shaped pattern. Previous studies usually defined the initial phase of cancer as the 6–12-month period after cancer diagnosis. However, the present study confirmed that the first 30 days after cancer diagnosis needed approximately 25% of medical expenses for the first year. Regarding health policy implications, the author determined that excessive spending in the first 30 days would be much more burdensome for health care systems and patients than spending at a constant level per month for 6–12 months after cancer diagnosis.

(Choi, Golinkoff et al. 2023) found that 104 (58.1%) of 180 people with HIV earned less than the minimum wage. In the present study, the average out-of-pocket medical expenses per patient in the first month after cancer diagnosis was identified as approximately $917 ($1 = ₩1180) for non-Hodgkin's lymphoma. This is approximately 6% of the average first month medical expenses per patient; however, this can burdensome for people with incomes below the minimum wage. A cost-sharing system may help patients with HIV and cancer financially. However, society should remember that the economic status of people with HIV is low.

4.5. Conclusion and Discussion

In the present study, based on nationwide insurance claim data, we estimated the annual direct medical cost due to cancer in the first five years following cancer diagnosis, monthly medical cost due to cancer in the first 12 months of cancer

diagnosis, and total medical cost in the last six months of life in all cancers, AIDS-defining cancers, non-AIDS-defining cancers, and specific cancer groups in patients with HIV infection, one of the most vulnerable populations to cancer. To the best of our knowledge, this study is the first to estimate cancer-related medical costs as an important chronic disease in HIV-infected people at the personal and social levels.

The main findings of this study can be summarized as follows: first, we identified that the mean annual medical cost due to cancer in HIV-infected people was higher in AIDS-defining cancers ($48,242) than that in non-AIDS-defining cancers ($24,338), particularly in non-Hodgkin's lymphoma ($53,007) for the first year of cancer diagnosis; from the second year, the mean annual medical cost due to cancer was significantly reduced and differences in the mean annual medical cost of cancer were not observed according to the cancer type. Second, the highest medical cost for the first year of cancer diagnosis was incurred during the first month of cancer diagnosis. Third, total medical cost, which was affected by both mean medical cost and number of cancer cases, was higher for non-AIDS-defining cancers, reflecting higher incidence rate of non-AIDS-defining cancers, considering their lower mean medical costs. Fourth, the mean monthly total medical cost per HIV-infected person who died after cancer diagnosis increased closer to the time of death.

Our findings showed a comparable pattern of expenses in medical costs due to cancer for AIDS-defining cancer, non-AIDS-defining cancer, and each cancer type in patients who developed cancer after HIV diagnosis. None of the previous studies estimated cancer cost by month; our study revealed that the mean monthly cost of cancer per patient was the highest in the first month of cancer diagnosis and then

decreased by approximately 45–60% in the second month. The percentage of medical costs due to cancer in the first month of the first year of cancer diagnosis was 24.2% for all cancers, 25.8% for AIDS-defining cancers, and 23.3% for non-AIDS-defining cancers. The results suggest that medical support for cancer in HIV-infected people should be focused during the earlier period of cancer diagnosis.

The high medical costs of cancer during the initial phase in recent years might be attributable to expensive anticancer therapies (Meropol and Schulman 2007, Yabroff, Warren et al. 2007, Kimman, Jan et al. 2012). In another aspect, recent increase in the total medical cost of cancer in terms of social burden can be attributed not only to the increased cost but also to the increasing number of cancer patients infected with HIV. A previous study suggested an increased cancer burden in HIV-infected patients, and predicted that the burden of non-AIDS defining cancers would increase whereas that of AIDS-defining cancers would decrease due to aging and improved HIV therapies (Shiels, Islam et al. 2018). In this study, the number of HIV patients with cancer was 235 in 2018–2020, 177 in 2015–2017, 152 in 2012–2014, 108 in 2009–2011, and 85 in 2006–2008. The increased total medical cost due to non-AIDS-defining cancers in recent years would reflect this.

Previous studies on the general population reported increased medical costs in the final months of the life of patients (Park and Song 2018, Leng, Jing et al. 2019, Han, Kim et al. 2022, Luta, Diernberger et al. 2022). In Korea, cost-sharing systems to reduce out-of-pocket medical expenses for cancer are available for five years after cancer diagnosis; hence, there are difficulties in estimating the medical cost of cancer after five years of diagnosis. Thus, although we evaluated the burden of medical costs in the last six months of life, we could not distinguish the cost of cancer treatment from the total medical cost; thus, the cost included all health care

services, in addition to cancer treatment. Our results showed that the mean total medical cost per patient in the last two months of life was similar to that in the initial phase. When the total medical cost per patient in the last six months of life was assessed in 2-month increments, the total medical cost was the highest in the last two months of life and tended to decrease in months that were farther from the time of death.

There are several limitations of our study that must be considered while interpreting its findings. First, cost considered in this study did not include the cost of non-benefited healthcare services and prescription drugs that were not covered by the NHIS. Despite expanding health insurance coverage for cancer treatment, approximately 29.0% of healthcare services in cancer patients in 2006 were not covered by the NHIS, and 11.0% of these services are still not covered by the NHIS. Thus, medical cost estimated using the NHIS may underestimate the actual medical cost of each patient. In addition, considering the coverage rate of cancer treatment in previous years was lower than that in recent years, medical cost of cancer in previous years may be underestimated to a greater extent than that in recent years. Second, HIV-infected people are generally diagnosed with cancer at an advanced stage due to a lower uptake of screening or limited medical access for primary or secondary prevention (Shiels, Goedert et al. 2010, Park, Ahn et al. 2022) than the general population. Patients with advanced cancer at diagnosis have higher medical costs than those with early stage cancer (Lao, Mondal et al. 2022, McGarvey, Gitlin et al. 2022, Reddy, Broder et al. 2022). Because the NHIS-NHID data did not include information on cancer stage, we could not consider stage-specific cancer costs and their comparison with estimated cost in the general population. Third, previous studies have defined the initial phase as the period

spanning 6–12 months after cancer diagnosis and reported that the cancer-related medical expenses are high in the initial phase and then decreases over time (Goldsbury, Yap et al. 2018, Mariotto, Enewold et al. 2020). In contrast to previous studies, our research focused on analyzing the monthly average medical expenses per patient spent monthly from the time of cancer diagnosis. Our findings revealed that approximately 25% of the average medical expenses per patient within the first year after cancer diagnosis were spent in the first month. However, we were unable to determine the details of the medical expenses. Further investigations are warranted to elucidate the types of medical services that are associated with high medical expenses in the first month after cancer diagnosis. Fourth, this study considered medical costs of cancer from the NHIS for a long period (2006–2020). The quality of information reported to the NHIS varies over time according to changes in insurance policies. For example, the proportion of cancer cost-sharing by the NHIS decreased from 30% to 10% in 2005 and from 10% to 5% in 2009 (Cho, Park et al. 2021). Thus, we showed the cost of adding patients' co-payments and insurers' payments to avoid the impact of changes in the cost-sharing system. However, other changes, such as reporting policies, are not reflected. Fifth, several studies have provided separate estimations of the direct and indirect medical costs of cancer in assessing the burden of cancer and reported high economic burden of indirect medical costs, including production loss, cost of care, and transportation expenses (Huang, Chen et al. 2020, Iragorri, de Oliveira et al. 2021, Mohammadpour, Soleimanpour et al. 2022). In this study, we focused on changes in medical costs from the date of cancer diagnosis and did not consider indirect medical costs of cancer. Further studies considering both direct and indirect economic burden of cancer in HIV-infected people, including premature death

followed by productivity loss, are warranted. However, the estimated medical cost of cancer in this study may be a simple and adequate index to understand the economic burden of cancer in patients with HIV who are at a high risk for cancer.

The burden of medical costs in patients with HIV estimated in the present study may be an important index for establishing healthcare policies for HIV patients in whom cancer-related burden is expected to increase (Shiels, Islam et al. 2018). Further studies to estimate future cancer burden in people infected with HIV, including projections of cancer incidence, mortality, and cancer-related costs, including both direct and indirect costs, are warranted.

Appendix of chapter 4

Table 4-2. Annual cancer incidence cases in patients with human immunodeficiency virus (HIV) in Korea

	All cancer [1]		AIDS-Defining		Non-AIDS-Defining	
	Incidence cases	Column percent	Incidence cases	Column percent	Incidence cases	Column percent
Total	757	100.0	277	100.0	480	100.0
2006	25	3.3	11	4.0	14	2.9
2007	30	4.0	21	7.6	9	1.9
2008	30	4.0	16	5.8	14	2.9
2009	27	3.6	9	3.2	18	3.8
2010	35	4.6	16	5.8	19	4.0
2011	46	6.1	19	6.9	27	5.6
2012	44	5.8	21	7.6	23	4.8
2013	50	6.6	22	7.9	28	5.8
2014	58	7.7	20	7.2	38	7.9
2015	47	6.2	20	7.2	27	5.6
2016	68	9.0	21	7.6	47	9.8
2017	62	8.2	17	6.1	45	9.4
2018	77	10.2	26	9.4	51	10.6
2019	73	9.6	17	6.1	56	11.7
2020	85	11.2	21	7.6	64	13.3

[1] All cancer (patients) includes those who were diagnosed with AIDS-defining or non-AIDS-defining cancer.

Table 4-3. The mean monthly medical cost of cancer per patient in the first 12 months of cancer diagnosis in patients with HIV

Table 4-3-A. Cancer type

Unit: US dollar (1$ = 1180₩)

Month	All Cancer [1]	AIDS-Defining	Non-AIDS-Defining
1	8,158	12,461	5,679
2	4,314	6,490	3,017
3	3,623	5,492	2,399
4	2,996	4,534	1,953
5	2,623	3,949	1,677
6	2,265	3,320	1,436
7	2,149	2,677	1,780
8	1,668	1,998	1,473
9	1,550	2,136	1,076
10	1,429	1,554	1,325
11	1,560	2,358	1,062
12	1,390	1,273	1,463

[1] All cancer (patients) includes those who were diagnosed with AIDS-defining or non-AIDS-defining cancer.

Table 4-3-B. Specific cancer type

Unit: US dollar (1$ = 1180₩)

Month	Kaposi sarcoma	Non-Hodgkin's lymphoma	Malignant neoplasm of colorectum	Malignant neoplasm of liver, bile duct, and pancreas	Malignant neoplasm of stomach
1	5,451	14,833	6,084	5,674	5,494
2	5,041	6,729	3,399	2,420	2,767
3	2,141	6,191	2,832	1,457	2,263
4	1,688	5,115	1,601	1,654	1,541
5	2,080	4,177	2,599	1,184	1,136
6	1,616	3,516	1,638	1,420	1,503
7	1,393	2,789	2,370	810	2,002
8	1,276	2,055	1,175	920	869
9	1,522	2,183	1,371	963	1,418
10	1,429	1,637	1,347	1,053	1,315
11	678	2,519	1,314	636	2,093
12	1,340	1,263	1,545	1,038	2,451

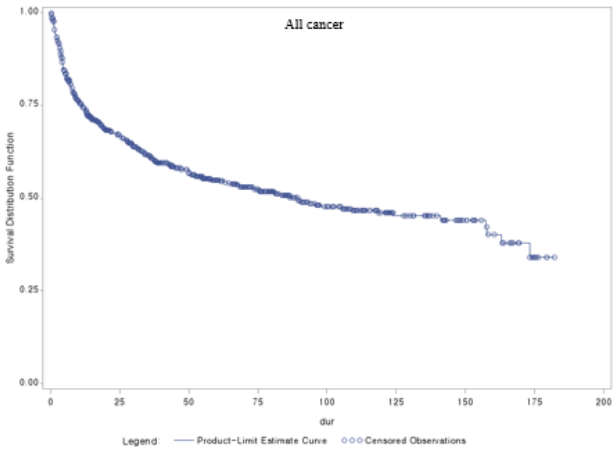
Table 4-4. The total monthly medical cost of cancer in the first 12 months following cancer diagnosis in patients with HIV

Unit: US dollar (1$ = 1180₩)

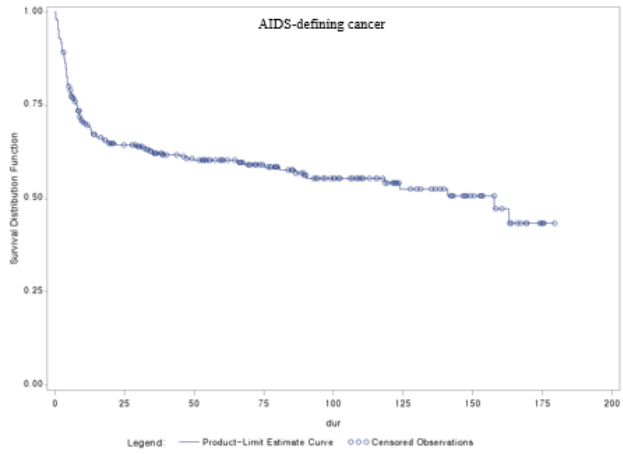
Type	Month	2018-2020	2015-2017	2012-2014	2009-2011	2006-2008
All cancer [1]	1	2,055,725	1,522,329	1,187,021	823,837	755,074
	2	665,491	592,179	591,629	315,477	184,465
	3	586,476	506,642	371,206	263,111	185,060
	4	486,380	350,811	388,554	187,718	154,045
	5	385,277	268,303	337,781	163,448	93,143
	6	259,301	252,407	235,705	121,460	107,097
	7	358,955	151,644	191,409	96,234	68,463
	8	197,849	144,030	193,734	75,056	29,371
	9	162,834	154,382	87,050	89,681	29,374
	10	176,154	82,390	142,221	36,957	34,987
	11	211,513	63,757	118,348	78,862	27,743
	12	139,131	143,280	51,810	30,409	34,743
AIDS-Defining	1	949,613	786,872	769,098	478,012	557,761
	2	230,758	305,999	415,426	220,672	147,242
	3	298,147	302,469	223,084	177,296	144,547
	4	266,402	212,287	239,314	126,963	110,527
	5	180,888	163,359	238,518	127,764	67,019
	6	116,258	175,246	161,573	83,305	87,349
	7	131,605	55,744	126,496	62,879	61,112
	8	53,876	79,803	101,812	35,938	14,061
	9	76,706	93,110	58,049	69,603	20,247
	10	79,322	21,845	74,477	15,169	25,587
	11	122,402	22,014	94,382	32,938	18,006
	12	46,945	46,761	27,912	13,501	21,220
Non-AIDS-Defining	1	1,106,112	735,457	417,922	345,825	197,313
	2	434,733	286,181	176,203	94,805	37,223
	3	288,330	204,173	148,122	85,815	40,513
	4	219,978	138,524	149,240	60,756	43,518
	5	204,389	104,944	99,262	35,684	26,123
	6	143,043	77,161	74,133	38,155	19,748
	7	227,350	95,900	64,913	33,356	7,351
	8	143,973	64,227	91,922	39,118	15,310
	9	86,128	61,272	29,001	20,078	9,127
	10	96,832	60,545	67,743	21,788	9,400
	11	89,111	41,742	23,966	45,924	9,737
	12	92,185	96,518	23,898	16,908	13,523

[1] All cancer (patients) includes those who were diagnosed with AIDS-defining or non-AIDS-defining cancer.

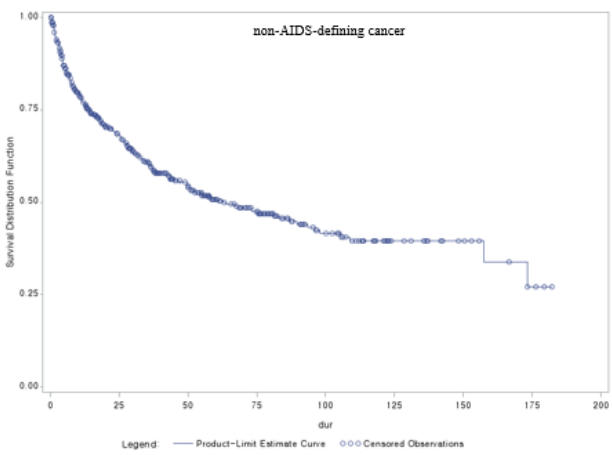
Figure 4-6. The survival rates after diagnosis of cancer in HIV-infected people



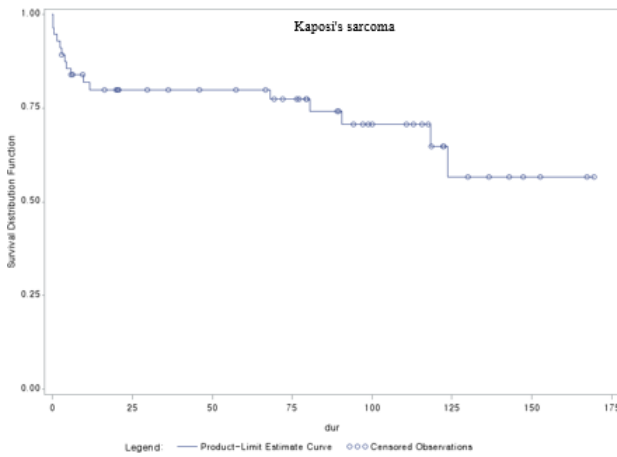
Unit: x-axis=months



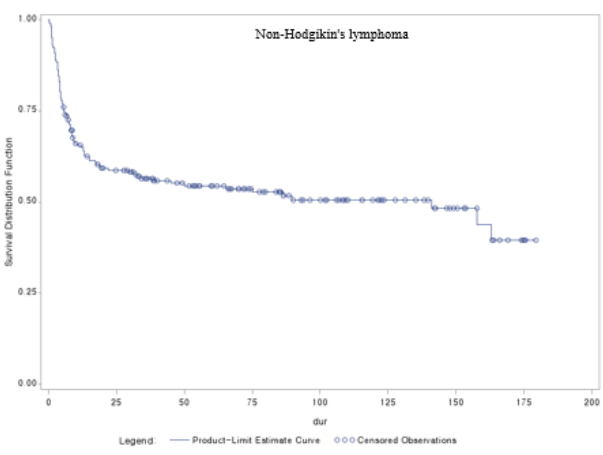
Unit: x-axis=months



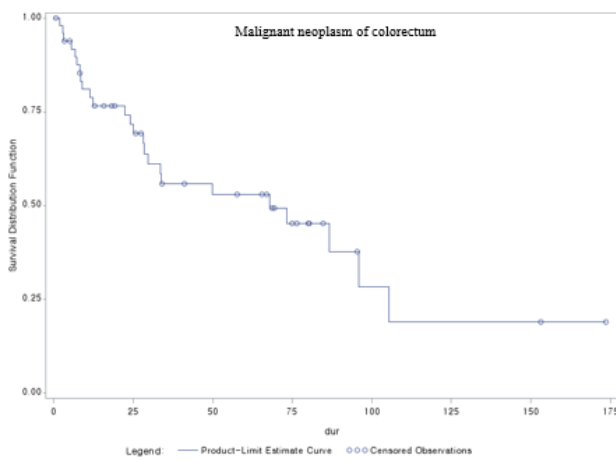
Unit: x-axis=months



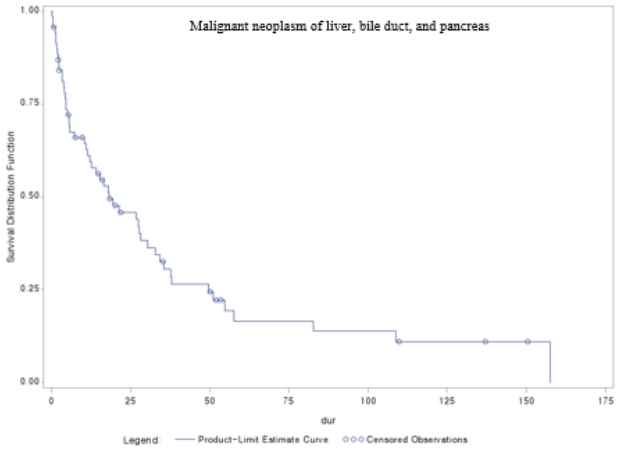
Unit: x-axis=months



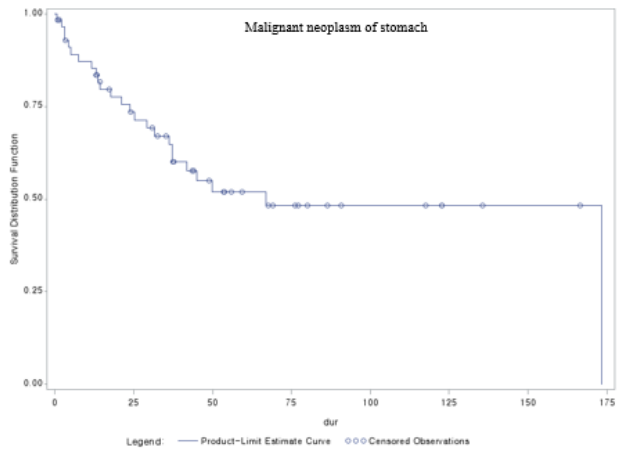
Unit: x-axis=months



Unit: x-axis=months



Unit: x-axis=months



Unit: x-axis=months

Chapter 5. The value of a statistical life of HIV

5.1. Study Background

In Korea, health care sector spending is significantly increasing owing to advanced medical technology, population aging, and chronic diseases (Sang, Bae et al. 2013). According to the Korean government's notification, the Ministry of Health and Welfare's budget for 2023 is KRW 109.2 trillion, an increase of 12% from the previous year. Consequently, many studies are being conducted on the effect of diseases on society and economy through various methodologies such as COI and the VSL to estimate the burden of diseases.

The present study focuses on HIV from economic and epidemiological perspectives. The development of effective HIV treatment has significantly increased the life expectancy of people with HIV; however, the risk of chronic diseases, especially cancer, has increased as well. In the previous chapter, the present study determined the preventable risk factors of cancer to reduce the incidence of cancer in people with HIV, as well as the amount of medical expenses spent on average per person for people with HIV and cancer.

There are increasing concerns regarding the costs associated with the long-term handling of the HIV infection. These expenses include obtaining medical care, HIV medications, and addressing comorbid conditions (Ritchwood, Bishu et al. 2017). A prior study utilizing the cost of illness method examined the medical costs for individuals with HIV in Korea. Based on the findings, the average yearly medical expenditure per person was 9,966,415 won in 2013 (Kwon, Bang et al. 2015). As the increasing pattern of annual new infections in Korea has persisted for over 30 years, it may have exacerbated the economic burden on the Korean society

in terms of not only medical expenses but also economic productivity losses due to HIV.

Estimates of the cost of illness are good indicators of the socioeconomic burden associated with a particular disease; however, they cannot capture the loss of a country's welfare due to disease. Therefore, the present study aims to estimate the amount of money society is willing to pay to reduce the mortality rate of HIV, often referred to as the VSL. In addition, from 2004 to 2020, the annual medical expenses of people with HIV were estimated, which could be a comparative index for the VSL.

Additionally, the VSL and COI are explained to clarify the interpretation of the analysis results.

The VSL is based on the following question: how much is the society willing to pay to avoid the death of an unspecified person. It is not an evaluation of the value of an individual's life, rather a value derived from the amount of payment for a small change in the probability of death or a value given ex-ante. It is an estimate of the amount society is willing to pay to reduce mortality rates without knowing the decedent, a methodology that determines the amount society is willing to pay to reduce the risk of probabilistic death before the event occurs. From a post-mortem perspective, people at high risk of death probably spend all their money to survive (Iii, Herriges et al. 2003).

Conversely, COI is a methodology from a post-ante perspective. COI is an analytical method for patients with certain diseases. It includes the amount of medical expenses Korea spends to treat people with HIV, and the amount of future income a person has lost from death if he or she has died due to HIV.

5.2. Literature Review

5.1.1. Cost of illness⑥

COI can be broadly divided into direct cost (medical expenses, nursing expenses, and transportation expenses) and indirect cost (future income loss from early death and the time loss from inpatient or outpatient treatment [income earned if a person worked during the treatment period] etc.).

(Kwon, Bang et al. 2015) analyzed the detailed medical expenses for 6,781 people with HIV as of 2013 in Korea using data from the Korea Health Insurance Review and Assessment Service. The average age of the study participants was 43 years, and 89.1% were men. With 244 new HIV infections in 2000, 900 in 2008, and 1,114 in 2013, this study aimed to identify the cost of HIV treatment in the Korean medical system and determine the recipient of the largest portion of the cost. The results revealed that the annual mean medical expenses incurred by one person with HIV in Korea in 2013 was ₩8,966,415, 83.4% of which were drug costs, and ART accounted for 94% of the drug costs.

(Treskova, Kuhlmann et al. 2016) analyzed the average annual medical expenses per person for 1,154 people with HIV receiving HIV treatment during 2009–2012 at eight medical institutions in Germany. The results revealed that the annual mean medical cost per patient was €22,231, and that ART accounted for 83.8% of the total medical cost.

In the UK alone in 2013, a total of 6,000 new HIV infections were identified, approximately 50% of which or 3,250 cases were confirmed to be men who had

⑥ Cost of illness is the methodology with the post-ante perspectives. Cost of illness is an analytical methodology for patients with certain diseases.

sex with men. (Nakagawa, Miners et al. 2015) estimated the lifetime immune status and the distribution of HIV treatment costs for the aforementioned men with HIV for the age of 30 years as of 2013. This estimate included the assumption that HIV treatment had no shortage of resources and that the standard cost of health care remained the same. The cost of treating a single 30-year-old person up to an average life expectancy of 71.5 years (45.0–81.5) for MSM was estimated to be £360,800. If 3.5% discount rate was applied, the estimated cost was £185,200. ART accounted for approximately 68% of total medical expenses. In addition, simulations have estimated that the cost of lifelong HIV treatment in 2013 would be more than £1 billion if 3,000 new HIV infection occurred in 30-year-old men who had sex with men (Nakagawa, Miners et al. 2015).

(Bingham, Shrestha et al. 2021) used US National HIV Behavioral Surveillance (NHBS) data (2006-2015) to estimate the average amount spent on lifelong medical expenses, from diagnosis to treatment of a single person with HIV in the US. The average medical cost across a person's life (from diagnosis to death) with HIV was estimated to be $490,045 with an applied discount rate of 3% and $1,079,999 without a discount. Lifetime medical expenses for one person included inpatient and outpatient treatment, preventive therapy for related diseases, and tests for other infection.

Table 5-1. The Summary of Literature Review for Cost of illness of HIV

Reference	Details	Notes
Bingham, Shrestha et al. 2021 U. S	The average medical cost across the life of a person with HIV (diagnosis to death) was estimated to be $490,045, with an applied discount rate of 3%, and $1,079,999, without a discount	U.S. National HIV Behavioral Surveillance (NHBS) data for 2006–2015

Nakagawa, Miners et al. 2015 U. K	The cost of treating one 30-year-old person up to an average life expectancy of 71.5 years (45.0–81.5) for men who have sex with men (MSMs) was estimated to be £360,800. If a 3.5% discount rate was applied, the estimated cost was £185,200. Antiretroviral therapy (ART) accounted for approximately 68% of total medical expenses	Computer simulation for MSMs
Kwon, Bang et al. 2015 Korea	Annual mean medical expenses incurred by one person with HIV in Korea in 2013 was ₩8,966,415, 83.4% of which were drug expenses. Antiretroviral therapy (ART) accounted for 94% of the drug costs.	The Korea Health Insurance Review and Assessment Service data in 2013
Treskova, Kuhlmann et al. 2016 Germany	The annual mean medical cost per patient is €22,231, and antiretroviral therapy (ART) accounts for 83.8% of the total medical cost	Eight medical institutions' database in Germany; 2009–2012

5.2.2. Revealed Preference vs. Stated Preference

The VSL can be estimated using the stated preference or the revealed preference method. Determining the better method from among the two for estimating the VSL remains a challenge. Stated preference surveys the willingness to pay for goods that cannot be traded in the market (non-market goods) for samples representative of the population group. For the survey, sufficient explanation of an objective and background (scenario) is needed to investigate without bias the amount people are willing to pay. When conducting a survey on stated preference, respondents should not be encouraged to answer in a socially desirable direction. Moreover, the source and basis of reference data to form a study scenario should be transparently and clearly disclosed. Revealed preference is a method of estimating the amount of money people are willing to pay to avoid mortality or certain risks using the information on the optional behavior that people employ to maximize utility. In this case, sufficient information on the incidence

and the mortality of diseases is needed, and a quantitative estimate of the amount people are willing to spend is needed to reduce the corresponding mortality rate using this information. Therefore, the researcher must review the study's purpose and the level of information that can be confirmed to determine the appropriate methodology (Ahn, Bae et al. 2016, Kim 2016).

5.2.3. Willingness to Pay (Not Stated Preference)

Several studies asked people with HIV or high-risk groups to mention the amount of money they are willing to pay for HIV self-test kits, prevention drugs, or HIV. These studies (Nunn, Brinkley-Rubinstein et al. 2017, Mbachu, Okoli et al. 2018, Morgan, Ferlatte et al. 2018) were significant in determining whether the risk group of HIV or people with HIV were willing to pay for preventive measures or treatments.

However, the aforementioned studies and studies on the VSL need to be differentiated. A previous study (Ahn, Bae et al. 2016) is used to elucidate the VSL. Furthermore, the studies of (Nunn, Brinkley-Rubinstein et al. 2017, Mbachu, Okoli et al. 2018, Morgan, Ferlatte et al. 2018) are reviewed herein.

According to (Hamlyn, Hickling et al. 2012), approximately 50% of newly diagnosed persons with HIV in the US are those who have been infected by people who were unaware of their HIV status; hence, HIV testing is an important part of HIV/AIDS prevention and treatment. (Nunn, Brinkley-Rubinstein et al. 2017) surveyed 1,535 people (December 2012– January 2014) in Philadelphia in the US, where HIV prevalence is high, on their willingness to pay a certain amount of money to buy HIV self-tests. Downtown Philadelphia, where the study was conducted, is an area mainly inhabited by African Americans with an HIV

prevalence of 3%. Among 1,535 participants, 1,362 (89.7%) were African Americans and 1,198 (78.0%) were single. Approximately 90% of the 1,535 respondents said they were willing to use an HIV self-test, while 55% said they were willing to buy an HIV self-test kit; however, only 23% said they were willing to buy an HIV self-test kit priced ≥$40. The survey presented a total of six options (None, $0–10, $11–20, $21–30, $31–40, and ≥$40) and defined that if a person was willing to pay >$40, they would be willing to pay $40 for a HIV self-test kit. In this study (Nunn, Brinkley-Rubinstein et al. 2017), the 1,535 respondents were categorized into low-risk groups, people with concurrent sexual partners, drug users, and people having condom-free sex with multiple sexual partners. Compared with the low-risk group, people with concurrent sexual partners and those who use drugs were more willing to use HIV self-test kits; however, no significant differences were observed in the cost they were willing to pay. In conclusion, only 23% of participants said they were willing to pay a market price of $40 to buy an HIV self-test kit (Nunn, Brinkley-Rubinstein et al. 2017).

(Morgan, Ferlatte et al. 2018) surveyed 7,176 people who belonged to the high-risk HIV group (gays, men having sex with men, and bisexuals) in Canada on whether they are willing to take pre-exposure prophylaxis（PrEP) and the amount they are willing to pay if taking PrEP. PrEP is medication to prevent HIV infection. According to US Centers for Disease Control and Prevention (CDC), PrEP can reduce the probability of HIV infection via sexual relationships and injection drugs by 99% and 74%, respectively. In Canada, PrEP received approval from Health Canada in early 2016, and Canada includes PrEP distribution as an HIV prevention strategy for men, gays, and bisexuals (Stahlman, Lyons et al. 2017). In this context, (Morgan, Ferlatte et al. 2018) surveyed high-risk groups who were not infected

with HIV in Canada on whether they were willing to take PrEP and the amount they were willing to pay if choosing PrEP. This study collected information via an online app in 2015, just before Health Canada approved PrEP distribution. The results of the analysis revealed that 54.7% (n = 3,923) of the 7,176 survey participants had awareness of PrEP and 47.4% (n = 3,399) said they were interested in PrEP. Among the participants who were interested in PrEP (n = 3,399), 947 (27.9%) said they were willing to pay for it and take it. Awareness of PrEP was different depending on the region where the survey participants lived, and it was relatively high among participants living in the city. Factors affecting the willingness to pay for PrEP were annual income and education levels. People with an annual income with ≥$40,000 were more likely to pay to take PrEP than those with an annual income of ≤$20,000, and regarding education, those with a college education or higher were more likely to pay than those with a high school diploma or lower. The procedure to determine the amount people were willing to pay to take PrEP was as follows: first, the respondents were asked to check if they were interested in PrEP, and if interested, move on to the question of the maximum amount they could pay to take PrEP, and second, regarding the amount they were willing to pay for PrEP/month, they were provided a choice of up to $1,200, starting from <$100. According to the analysis, approximately 72.1% (n = 2,452) of the 3,399 respondents who said they were interested in PrEP said they would take it only if health insurance was applied. Among the remaining 27.9% (n = 947), most chose <$100/month. This study highlighted the problem that access to PrEP varies depending on income and education levels, and that costs covered only through private insurance can lead to health inequality (Morgan, Ferlatte et al. 2018).

In 2014, (Mbachu, Okoli et al. 2018) conducted a survey among 125 people with HIV/AIDS aged ≥18 years who are receiving free ART⑦ benefits at Nigerian public hospitals and asked whether they or their families intended to pay a monthly fee to receive ART. This determined whether HIV treatment provided free of charge by the national hospital is valuable and whether it was important to people with HIV. The results revealed that approximately one-third of the 125 participants were willing to pay a monthly fee of $15.26–$15.31. Respondents were more willing to pay if they were currently engaged in economic activities, had a high social status, and were younger. The gender proportion was 50% (Mbachu, Okoli et al. 2018).

Table 5-2. The Summary of Literature Review for WTP not VSL

Reference	Participants	Details
Morgan, Ferlatte et al. 2018 Canada WTP Not VSL	7,176 people who belong to the high-risk HIV group (gays, men having sex with men, and bisexuals) in Canada. * N=7176	**Question:** **Are you interested in PrEP⑧ (pre-exposure prophylaxis)? If you are interested in PrEP, how much money are you willing to pay for PrEP?** Among the 7,176 participants, 3,399 (47.4%) responded that they were interested in PrEP; subsequently, the research teams asked these participants about their intention to pay for

⑦ Antiretroviral therapy (ART) is HIV treatment with regimen to suppress the virus in the body. People living with HIV should take HIV medicine right after the diagnosis of HIV. Antiretroviral therapy (ART) cannot perfectly cure HIV but through treatments, HIV infected people have a longer lifespan and healthy lives. The purpose of antiretroviral therapy (ART) is to reduce the amount of the virus in the body and people with the status of undetectable virus have no risk to transmit HIV to others according to National Institutes of Health (NIH).

⑧ Antiretroviral therapy (ART) is HIV treatment with regimen to suppress the virus in the body. People living with HIV should take HIV medicine right after the diagnosis of HIV. Antiretroviral therapy (ART) cannot perfectly cure HIV but through treatments, HIV infected people have a longer lifespan and healthy lives. The purpose of antiretroviral therapy (ART) is to reduce the amount of the virus in the body and people with the status of undetectable virus have no risk to transmit HIV to others according to National Institutes of Health (NIH).

		PrEP. Approximately 72.1% (n=2,452) of these respondents answered they would take PrEP only if health insurance was applied. Of the remaining 27.9% (n=947), most chose < $100/month
Nunn, Brinkley-Rubinstein et al. 2017 U. S WTP Not VSL	1,535 people in Philadelphia, US * N=1535 (Respondents were categorized into low-risk groups, those with concurrent sexual partners, drug users, and those having condomless sex with multiple sexual partners)	**Question:** **How much would you be willing to pay for a HIV self-test kit?** Only 23% of participants said they were willing to pay a market price of $40 to buy an HIV self-test kit, 77% answered none or <$40. *Downtown Philadelphia, where the study was conducted, is an area mainly inhabited by African Americans with an HIV prevalence of 3%
Mbachu, Okoli et al. 2018 Nigeria WTP Not VSL	125 survey participants (people with HIV/AIDS) in Nigeria *N=125 (Considered age, economic activities, and social statuses)	**Question:** **How much are you willing to pay per month for HIV treatment?** Approximately one-third of the 125 survey participants were willing to pay $15.26–15.31/month. Respondents were found to be more willing to pay if they were currently engaged in economic activities, if they had high social status, and if they were younger.

5.2.4. Willingness to Pay by Stated Preference to Estimate the VSL

Although the study of (Ahn, Bae et al. 2016) is not for HIV, from the author's perspective, it is a good example of the stated preference methodology to understand the VSL. This study conducted a face-to-face survey among 1,000 adults aged 20– 64 years to identify the amount of money they are willing to pay to reduce mortality from air pollution by 0.01% from 0.04% to 0.03%. Prior to conducting this face-to-face survey, this study simplified the terminology of the

questionnaire through focus group interviews. Moreover, (Ahn, Bae et al. 2016) conducted a preliminary survey among 208 people and set an appropriate amount of money that participants can choose as the willingness to pay to reduce mortality. The options for participants to choose were ₩10,000, ₩15,000, ₩30,000, ₩50,000, and ₩80,000. The willingness to pay to reduce the mortality from air pollution by 0.01% was estimated to be an annual average of ₩10,141 per person for 10 years. Based on this, the VSL of environmental pollution (calculation formula = 10,141*10/0.0001) was estimated as ₩1,014,130,000. After a discount rate of 5.5% was applied, the VSL for environmental pollution was ₩806,455,977. Identifying the amount money for people to pay to avoid the death of one unspecified person in society is important when estimating the VSL. The probability of death to be reduced is presented; however, the questionnaire should be conducted in uncertain situations (i.e., no one knows who will die).

5.2.5. Willingness to Pay by Revealed Preference to Estimate the VSL

(Soares and Philipson 2005) estimated the VSL for HIV/AIDS using the revealed preference methodology in sub-Saharan Africa. In 2000, the death toll of people with HIV/AIDS in sub-Saharan Africa was estimated to be approximately 2.2 million, and the HIV/AIDS mortality rate was 0.38%. In this context, (Soares and Philipson 2005) calculated the VSL to identify the economic welfare loss caused by HIV/AIDS in sub-Saharan Africa. The methodology of the VSL begins with the following question: how much does the ssssociety intend to pay to reduce the difference in mortality between the general population and people with HIV. This study estimated the amount of money people were willing to pay at each

individual level to lower the mortality rate of HIV/AIDS, and subsequently, multiplied this estimated individual willingness to pay by the number of people in the age group to calculate the VSL. However, detailed information on the status of HIV/AIDS incidence and prevalence provided by each sub-Saharan country was insufficient. Therefore, (Soares and Philipson 2005) used the World Health Organization (WHO) life table to identify the population size and death toll as of 2000. The number of HIV/AIDS-related deaths was confirmed by UNAIDS's Joint United Nations program on HIV/AIDS. The number of deaths by age group could not be identified because of data restrictions; hence, the age-specific number of deaths at that time in sub-Saharan Africa was estimated under the assumption that the age-specific death distribution is the same as the age-specific population distribution. Sub-Saharan Africa's GDP per capita for each country was used as an income variable. The social welfare loss caused by HIV/AIDS in 34 countries in sub-Saharan Africa as estimated by (Soares and Philipson 2005) was $800 billion, comparable to the total annual GDP of the sub-Saharan region. In the case of Botswana and Zimbabwe, 1.5% of people with HIV/AIDS were confirmed to be dead annually. The term individual willingness to pay means the average amount that one person intends to pay to reduce the mortality from HIV/AIDS based on the GDP per capita. The individual willingness to pay at the age of 18 years was approximately $1,867, which was 129% of the GDP per capita in the region. The individual willingness to pay from age 5–30 years exhibited an increasing trend and subsequently decreased after the age of 30 years. The pattern of willingness to pay by age group had an inverted U-shape (Soares and Philipson 2005).

(Fimpel and Stolpe 2010) estimated the VSL of HIV in Eastern Europe considering the level of human capital investment and risk aversion propensity in

each age group. This study used information such as HIV prevalence and mortality for 25 Eastern European countries between 1995 and 2004. (Fimpel and Stolpe 2010) benchmarked the revealed preference model from (Soares and Philipson 2005). The coefficients of income, education, HIV-prevalence, HIV-incidence, HIV-mortality, and HIV-treatment accessibility were estimated for each country. The research question (the VSL for HIV) was as follows: how much money you are willing to pay ("how much you are willing to give up") to extend your life by lowering the mortality from HIV. This referred to the amount society wanted to pay to reduce the difference in the 7-year survival rate between people with HIV and people without HIV in each age group. Mortality rates of people with HIV were confirmed from the 2004 EuroHIV (HIV Surveillance Report for Europe). The 7-year survival rate indicators were used from the time of HIV diagnosis by distinguishing between groups receiving and not receiving HIV treatment. However, accurate information on the distribution of HIV treatments in each Eastern European country was difficult to confirm; hence, the WHO's data on the accessibility of HIV treatments in each country between 2003 and 2005 was used. (Fimpel and Stolpe 2010) classified the level of healthcare systems in 25 Eastern European countries into grades 1–6. The distribution rates of HIV treatment were assumed to be >80% in first-class countries and ≤10% in sixth-class countries. Information on each country's income used GDP per capita; however, it was adjusted by age group in consideration of the level of human capital investment. This study assumed that in Eastern Europe in the early 2000s, on average, an individual's human capital level was the highest at the age of 35 years with adequate academic and work experiences, which gradually decreased. This is based on the idea that up to the age of 35 years, people go through the process of

acquiring and learning new information, and subsequently, this knowledge becomes outdated. The VSL in 25 Eastern European countries was estimated as approximately $841 billion, which was approximately 10% of the total GDP per year between 1995 and 2001. The HIV mortality rate in Eastern Europe at that time was 0.15%, which is the number of people with HIV who died divided by the number of Eastern European population size. Even the death of person with HIV by suicide or from an accident was not excluded. The VSL by age group was the highest among those aged 25–45 years. However, this did not suggest that Eastern Europeans between the ages of 25 and 45 years considered life to be more dignified. In addition, young adults tend to behave in a less risk-averse manner than others; therefore, the amount young adults are willing to pay to reduce the mortality rate can be lower than that of the middle-aged adults. For example, regarding individual willingness to pay to reduce the mortality rate for HIV, Russia's VSL was approximately $30,000 (age: 35 years) and $15,000–$20,000 (age: 25 years). In the author's perspective, (Fimpel and Stolpe 2010) assumed that productivity of older adults is lower than that of middle-aged adults; the old generation's risk aversion propensity is unclear. The VSL is intricately linked with income, health status, and risk aversion propensity of each age group; hence, affirming that the VSL is high in a specific age group for only one reason may be prove difficult.

5.3. Materials and Methods

Revealed preference approach to estimate VSL for HIV

The present study used the revealed preference method. Regarding the stated preference method for the survey, an objective and sufficient background

(scenario) explanation is needed to identify the amount of money people are willing to pay to decrease the mortality rate. When conducting a survey on stated preference, respondents should not be encouraged to answer in a socially desirable or purposed direction. Although it may be technically possible to design a suitable survey to estimate the VSL for HIV, social stigmatization of people with HIV poses a challenge.

Issue of stigma for people with HIV

Since the development of effective HIV treatments, the immunity of people with HIV has improved, and their life expectancy has increased. However, HIV infection is uncurable, and people with HIV experience emotional issues such as social atrophy, frustration, depression, and anxiety. Notably, HIV stigma can lead to social discrimination. People with HIV may have difficulties in familial relationships. Families residing with people with HIV experience anxiety and fear as well. Korea is implementing programs for people with HIV such as protection of personal information, support for long-term care and treatment for mental health issues, and expansion of the scope of medical expenses; however, social adaptation remains a challenge for people with HIV-(Rhee, Kim et al. 2018). Previous studies have reported that most people in Korea regard people with HIV as homosexuals or those leading sexually promiscuous lives and tend to stigmatize and discriminate them. Furthermore, the general population tends to disregard people with HIV (Sohn and Park 2012, Yang 2021).

In this context, the author deemed that the revealed preference approach is a more suitable research method for this study because of the possibility of accurately estimating detailed epidemiological indicators of the survival rate and

HIV treatment distribution rate of people with HIV using the Korean NHIS database. If the public has already negatively stereotyped people with HIV, an unbiased and accurate survey cannot be easily conducted.

Theory of the value of a statistical life by revealed preference

Assuming that personal preferences play a significant role in the shift of economic welfare, the value of a statistical life related to a specific accident or illness can be determined by the amount of money someone is willing to pay to decrease the mortality rate, or the compensation one may accept to relinquish it (Freeman III, Herriges et al. 2014). The value of a statistical life is not merely a calculation of an individual's contribution to the gross domestic product (GDP), but an empirical analysis method that measures the intrinsic value of life (Fimpel and Stolpe 2010).

In this present study, the Philipson and Soares's approach (Soares and Philipson 2005) was adopted to estimate the monetary value of welfare loss due to HIV. The hypothetical question is how much money society is willing to pay to decrease HIV mortality until it aligns with the general population's age-dependent mortality rate.

The survival rate between ages *a* and *t* is represented by $S(t,a)$. θ serves as the exogenous variable, such as HIV, which leads to varying survival rates for those living with HIV. We can express $S_\theta(t,a) = \partial S(t,a;\theta)/\partial\theta$ as the difference in survival rates between individuals with HIV and the general population. The objective of our study was to identify the monetary value connected to $S_\theta(t,a)$. MWP_a represents the marginal value that an individual at

age a is willing to substitute the income to reduce mortality due to HIV.

$$MWP_a = \int_a^{\infty} e^{-\rho(t-a)} \left(\frac{c(t)}{\varepsilon(c(t))} + y(t) - c(t)\right) S_\theta(t,a)dt$$

Equation 1

Notation,

$a = the\ specific\ current\ age$

$t = the\ specific\ future\ age\ as\ time\ passes$

$S_\theta(t,a) = S(t,a) - S_{HIV}(t,a)$

$S(t,a) = the\ cumulative\ survival\ rate\ age\ from\ a\ to\ t\ in\ general\ population$

$S_{HIV}(t,a) = the\ cumulative\ survival\ rate\ age\ from\ a\ to\ t\ in\ people\ living\ with\ HIV$

$S_{HIV}(t,a) = \eta(a)\{\psi(a)S_{treat}(t,a) + (1 - \psi(a))S_{non\_treat}(t,a)\} + (1 - \eta(a))S(t,a)$

$\eta(a) = the\ age\ dependdant\ HIV\ incidence\ rate$

$\psi(a) = the\ age\ dependdant\ probabitity\ of\ getting\ access\ of\ HIV\ treatment$

$y(t) = income\ at\ give\ time\ t$

$c(t) = consumption\ at\ give\ time\ t$

$\rho = dicount\ rate$

In this present study, age-specific population size was utilized as the weighting parameter to estimate welfare loss. We used the terms, social-level willingness to pay to reduce HIV mortality, the value of a statistical life (VSL) for HIV, and welfare loss due to HIV in our society interchangeably, as they share the same meaning. In the results section, the cost of illness (COI) is presented as an

index comparable to the VSL; however, these methods have distinct research targets. The scope of the COI analysis is limited to people living with HIV while that of VSL should be based on the entire population, considering the potential risk of the illness to the whole society.

MWP_a is the marginal value that an individual at age *a* is willing to substitute the income for to reduce mortality due to HIV. $P(a)$ is the age-specific population size as the weight to estimate social marginal willingness to pay.

$$MWP_{social} = MWP_a * P(a)$$

Equation 2

Empirical Analysis and Data Source

$$\varepsilon(c(t)) = \frac{(\frac{\partial u(c)}{u(c)})}{(\frac{\partial c(t)}{c(t)})} = the\ consumption\ elasticity\ of\ utility\ function$$

$$u(c) = \frac{c^{1-\frac{1}{\gamma}}}{1-1/\gamma} + \delta$$

$$\gamma = the\ elasticity\ of\ substitution\ in\ consumption$$

$$\delta = the\ value\ to\ generalize\ utility\ of\ the\ death\ to\ zero$$

We followed the approach of (Soares and Philipson 2005, Fimpel and Stolpe 2010) using parameter values calibrated based on data from the U.S, as explained by (Murphy and Topel 2003). (Murphy and Topel 2003) confirmed that ε (the consumption elasticity of the utility function) is 0.346 from an early influential

study by (Viscusi 1993). Using 0.346 as ε, (Browning, Hansen et al. 1999) arrived at a conclusion regarding γ (the elasticity of substitution in consumption) from a meta-analysis, suggesting a value slightly above 1. Subsequently, (Soares and Philipson 2005) set γ at 1.25 and established -16.16 as the value for δ (the value to generalize the utility of death to zero).

Several assumptions were made in the present study. First, the VSL for HIV was only based on the survival rate; thus, both pain and morbidity were not considered. Second, the endpoint of life was set at the life expectancy for 2019, which is 83.7 years old. Third, the income variable, denoted by $c(t)$, was not time-dependent, and thus remained constant during the calibration of VSL.

To estimate the cumulative survival rate from age *a* to *t* in people living with HIV, denoted by $S_{HIV}(t,a)$, the Korea National Health Insurance Service (NHIS) database, which includes all 16,671 incidence cases in Korea from 2004 to 2020, was employed. To compare the survival rate between the general population and people with HIV, we determined the 10-year cumulative survival rate from the specific age, represented by *a*. The age specific access rate to HIV treatment was identified using the NHIS database. If an individual with HIV received HIV treatment for over 30 days, they were considered to have access to medical care. In contrast, individuals that did not receive HIV treatment or received HIV treatment for less than 30 days were considered to not have access to care. The Kaplan-Meier function was employed to estimate the survival rate of people living with HIV based on two groups (more than 30 days of HIV treatment vs None or less than 30 days of HIV treatment).

Regarding the age-specific incidence rate of HIV, the parameter, $\eta(a)$, was

derived using the 2019 Annual Report on Notified HIV/AIDS in Korea. The general population's age-specific cumulative survival rate from *a* to *t*, represented by $S(t,a)$, was calibrated using life tables from 2004 to 2020 released by Statistics Korea. As a weight parameter to estimate the VSL for HIV, the 2019 mid-year population size was used. The 2019 median income data were also employed as the annual income. To account for the future currency value, a 3% discount rate was applied.

How to derive the equation of an individual's marginal willingness to pay

The revealed preference method is based on (Soares and Philipson 2005). To explain details of the equation, this present study showed how to derive the model of individual marginal willingness to pay.

$$V(a) = \int_a^{\infty} e^{-\rho(t-a)} S(t,a) u\big(c(t)\big) dt$$

$$where \int_a^{\infty} e^{-\rho(t-a)} S(t,a) y(t) dt = \int_a^{\infty} e^{-\rho(t-a)} S(t,a) c(t) dt$$

Equation3

$$\mathcal{L} = \int_a^{\infty} e^{-\rho(t-a)} S(t,a) u(c(t)) dt + \lambda \{ \int_a^{\infty} e^{-\rho(t-a)} S(t,a)(y(t) - c(t)) dt \}$$

First order condition,

$$\frac{\partial L}{\partial c(t)} = e^{-\rho(t-a)} S(t,a) u'\big(c(t)\big) - \lambda_a e^{-\rho(t-a)} S(t,a) = 0$$

$$e^{-\rho(t-a)}S(t,a)u'\big(c(t)\big) = \lambda_a e^{-\rho(t-a)}S(t,a)$$

$$u'\big(c(t)\big) = \lambda_a$$

$$Defined\ as\ MWP_a = \frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a}$$

$$\frac{\partial V(a)}{\partial \theta} = \int_a^{\infty} e^{-\rho(t-a)}S_\theta(t,a)u\big(c(t)\big)dt + \lambda_a\{\int_a^{\infty} e^{-\rho(t-a)}S_\theta(t,a)(y(t)-c(t))dt\}$$

$$\frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a} = \frac{(\int_a^{\infty} e^{-\rho(t-a)}S_\theta(t,a)u\big(c(t)\big)dt)}{\lambda_a} + \int_a^{\infty} e^{-\rho(t-a)}S_\theta(t,a)\big(y(t)-c(t)\big)dt$$

$$\frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a} = \int_a^{\infty} e^{-\rho(t-a)}(\frac{u(c(t))}{\lambda_a} + y(t) + c(t))S_\theta(t,a)dt$$

$$\frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a} = \int_a^{\infty} e^{-\rho(t-a)}(\frac{u(c(t))}{u'(c(t))} + y(t) + c(t))S_\theta(t,a)dt$$

$$\frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a} = \int_a^{\infty} e^{-\rho(t-a)}(\frac{\frac{u(c(t))}{1}}{\frac{\partial u(c(t)}{\partial c(t)}} + y(t) + c(t))S_\theta(t,a)dt$$

$$\frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a} = \int_a^{\infty} e^{-\rho(t-a)}(\frac{u\big(c(t)\big)\partial c(t)}{\partial u(c(t))} + y(t) + c(t))S_\theta(t,a)dt)$$

$$Defined\ as\ \varepsilon(c(t)) = \frac{(\frac{\partial u(c)}{u(c)})}{(\frac{\partial c(t)}{c(t)})} = \frac{\partial u(c)c(t)}{u(c)\partial c(t)}$$

$$\frac{1}{\varepsilon(c(t))} = \frac{u(c)\partial c(t)}{\partial u(c)c(t)}$$

$$\frac{\partial V(a)}{\partial \theta}\frac{1}{\lambda_a} = \int_a^{\infty} e^{-\rho(t-a)}(\frac{c(t)}{\varepsilon(c(t))} + y(t) + c(t))\,S_\theta(t,a)dt$$

$$\therefore\ MWP_a = \int_a^{\infty} e^{-\rho(t-a)}(\frac{c(t)}{\varepsilon\big(c(t)\big)} + y(t) - c(t))\,S_\theta(t,a)dt$$

5.4. Results

Figure 5-1. Annual medical expenses for HIV treatment from 2004 to 2020

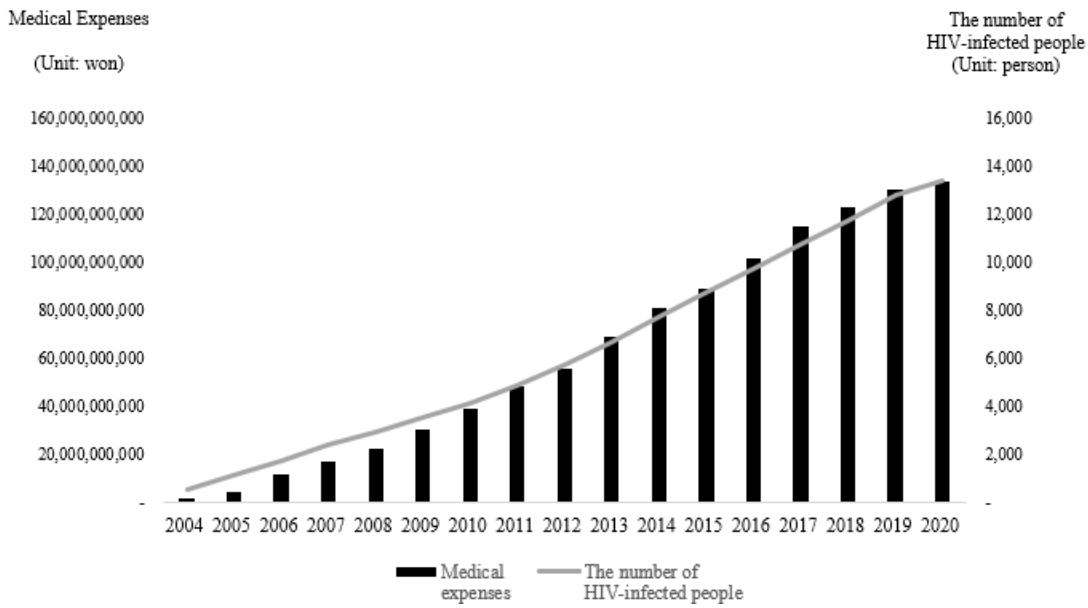


Figure 5-1 displays the annual medical expenses for HIV treatment from 2004 to 2020, as defined by the cost-sharing code (V103) in the Korea National Health Insurance Service (NHIS) database. The annual expenses for HIV treatment were found to exhibit an upward trend, which explains the worsening of the economic burden of HIV over time. Improved accessibility to antiretroviral therapy (ART) for people living with HIV has increased the survival rates after HIV infection; however, the annual incidence of HIV in Korea continues to increase, leading to a cumulative burden on the healthcare system. Moreover, we found no significant change in the age distribution of medical expenses. In 2020, the proportion of individuals in their 20s and 30s remained high, accounting for 50% of the total expenses. A higher proportion of young individuals with longer lifespans among HIV-infected people could place a greater burden on our society.

Table 5-3. The mean annual medical expenses Per person to treat HIV

Unit: won

Year	Total Medical Expenses	The number of People with HIV	The mean annual medical expenses Per person
2004	1,468,948,520	533	2,756,001
2005	4,678,903,220	1,149	4,072,152
2006	11,782,943,070	1,762	6,687,255
2007	17,177,220,630	2,373	7,238,610
2008	22,601,604,970	2,945	7,674,569
2009	30,549,536,330	3,547	8,612,782
2010	38,884,880,390	4,140	9,392,483
2011	47,967,915,750	4,864	9,861,825
2012	55,684,596,200	5,716	9,741,882
2013	68,816,638,260	6,657	10,337,485
2014	81,075,150,880	7,721	10,500,602
2015	88,868,814,550	8,713	10,199,566
2016	101,793,351,940	9,743	10,447,845
2017	115,079,190,400	10,738	10,717,004
2018	122,861,365,130	11,710	10,492,004
2019	130,201,366,700	12,777	10,190,292
2020	133,667,130,070	13,403	9,972,926

Table 5-3 presents the average annual medical expenses per person with HIV. This represents only the cost of treating HIV. From 2013 to 2020, the average annual medical expense for HIV treatment per person is approximately ₩10,000,000.

Table 5-4 presents the probability of obtaining a prescription for HIV treatment for >30 days among people with HIV. As the age at diagnosis increases, the chances of accessing treatment for >30 days decreases, with a probability of 91% and 83% for those aged 20–24 and 60–64 years, respectively. Duration of HIV treatment >30 days) was classified based on the medical advice that at least 30 days are needed to suppress the viral load.

Table 5-4. Probability of gaining access to treatment for over 30 days with an ART prescription by HIV-infected people

Unit: person

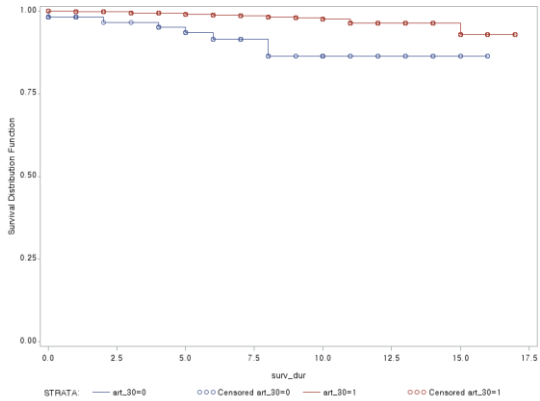
Age group	Yes	No	Total	Rate
20 - 24	1623	155	1778	0.912823
25 - 29	2287	277	2564	0.891966
30 - 34	1967	254	2221	0.885637
35 - 39	1811	189	2000	0.905500
40 - 44	1729	183	1912	0.904289
45 - 49	1428	164	1592	0.896985
50 - 54	1213	191	1404	0.863960
55 - 59	867	174	1041	0.832853
60 - 64	536	132	668	0.802395

In Table 5-5 the age-wise HIV incidence rate in 2019 was calculated by dividing the age-wise number of new HIV infections by the age-wise modified population size (age-wise modified population size in 2019 = age-wise population size in 2019 - the age-wise number of people with HIV in 2018). Owing to concerns that the 2020 Annual Report on the Notified HIV/AIDS in Korea may not accurately represent the true number of HIV infections during the COVID-19 pandemic, the 2019 HIV incidence rate was instead used. The 25–29 age group had a higher incidence rate than all the other age groups.

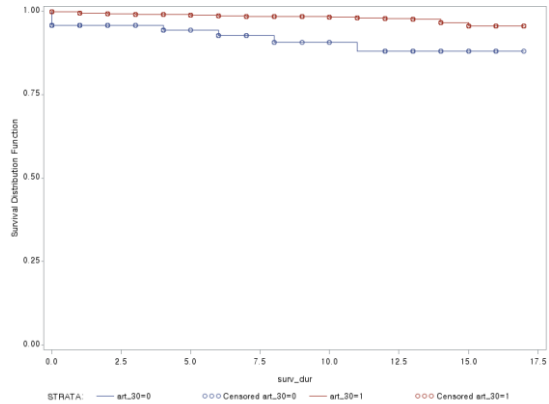
Table 5-6 presents the age-specific 10-year survival rates for people with HIV, depending on whether they received HIV treatment for >30 days. The disparity in the 10-year survival rate for individuals (those receiving HIV treatment for >30 days vs. those that do not receive treatment or receive treatment for <30 days) was found to increase when the age at HIV diagnosis is older. Ages 25–29 and 60–64 exhibited a difference of 7.7% and 20.0%, respectively, depending on whether HIV treatment was received. The survival rate change pattern in Table 5-6 can be confirmed via Figure 5-2.

Figure 5-2. Survival rate of HIV infected people depending on HIV treatment access[1] and age group[2]

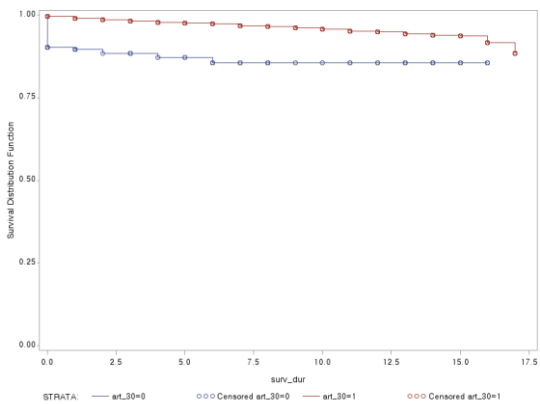
20-24 years old



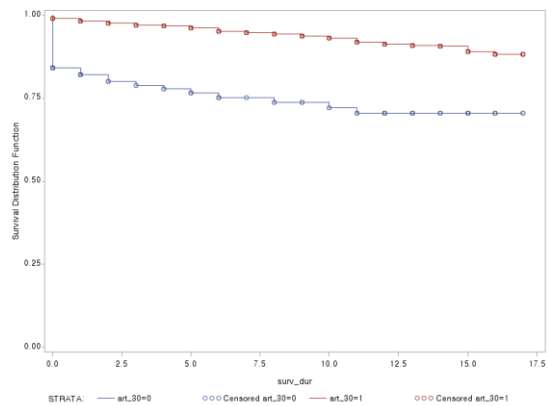
25-29 years old



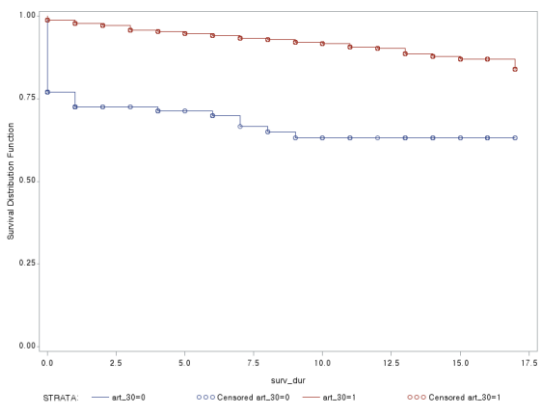
30-34 years old



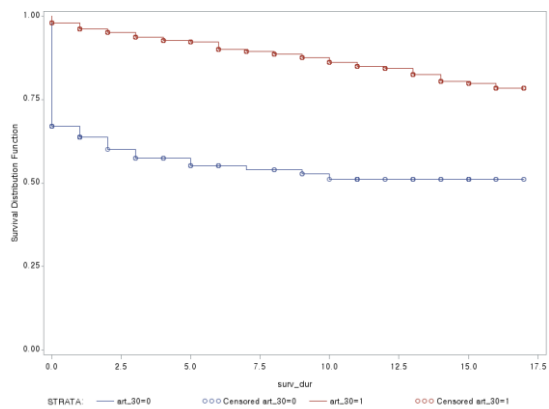
35-39 years old



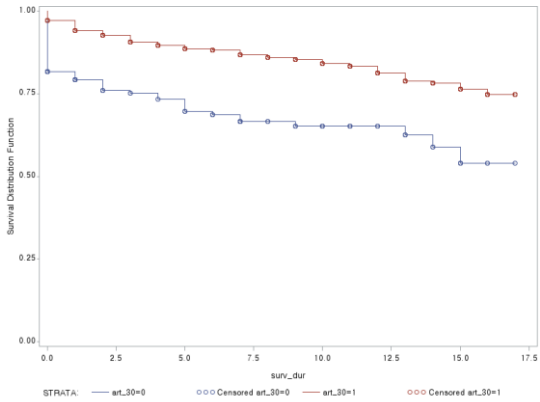
40-44 years old



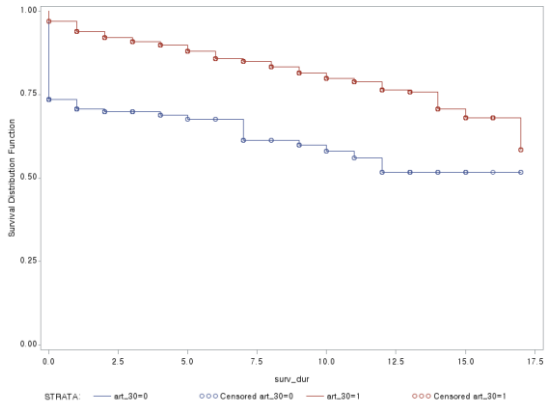
45-49 years old



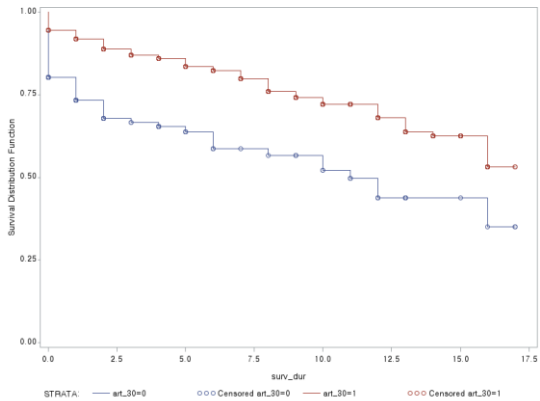
50-54 years old



55-59 years old



60-64 years old



[1] More than 30 days of HIV treatment (red line) vs. none or less than 30 days of HIV treatment (blue line)
[2] Age is based on time of HIV diagnosis

Table 5-5. Age-specific HIV incidence rate in 2019

Age group	Rate
20-24	0.00004234727
25-29	0.00008631378
30-34	0.00007016557
35-39	0.00003031121
40-44	0.00002671548
45-49	0.00002211239
50-54	0.00001503301
55-59	0.00001526295
60-64	0.00001194265

Table 5-6. 10-year survival rate of HIV-infected people according to gaining access to HIV treatment for more than 30 days with an ART prescription

Age	HIV-infected people	
	Over 30 days	None or below 30 days
20-24	0.8637	0.9764
25-29	0.9059	0.9825
30-34	0.8559	0.9573
35-39	0.7214	0.9304
40-44	0.6312	0.9163
45-49	0.5123	0.8614
50-54	0.6522	0.8405
55-59	0.5803	0.799
60-64	0.5212	0.7212

Table 5-7. Difference in the 10-year survival rates between individuals with HIV[1] and the general population

Age	General population	HIV-infected people	Difference
20-24	0.9949553685	0.9949541667	0.0000012018
25-29	0.9934852182	0.9934835558	0.0000016625
30-34	0.9908456382	0.9908424708	0.0000031674
35-39	0.9859867153	0.9859844317	0.0000022836
40-44	0.9782631950	0.9782608106	0.0000023844
45-49	0.9677157341	0.9677125880	0.0000031461
50-54	0.9536032602	0.9536011748	0.0000020854
55-59	0.9315460792	0.9315434982	0.0000025810
60-64	0.8916059252	0.8916034181	0.0000025071

[1] Survival rates for people with HIV estimated using the Korea National Health Insurance Service (NHIS) database

Table 5-7 shows the difference in 10-year survival rates between individuals with HIV and the general population, denoted by $S_\theta(t,a)$. This coefficient is key to estimating the VSL of HIV. $S_\theta(t,a)$ depends on accessibility to HIV treatment and HIV incidence rate. In this study, no statistical assumption was made regarding parameter $S_\theta(t,a)$. In table 5-7, the age-wise 10-year survival rate of the general

population was estimated using the life table. The life table, obtainable from the Korean Statistical Information Service, is based on age-adjusted rates per 100,000 people, which presents the survival rate of the 1-year-old unit by standardizing the population in Korea annually. When calculating the cumulative 10-year survival rate for those aged 20 years, the number of survivors aged 30 years is divided by the number of survivors aged 20 years (based on a standardized population of 100,000).

Table 5-8 displays the annual income and population size for each age group. The age-specific population size was utilized as a weight parameter to calibrate the social marginal willingness to pay to reduce the mortality rate of HIV in our society (social MWP).

Table 5-8. Annual income and population size

Unit: won

Age group	Annual median income	Population size
20-24	21,480,000	3,353,801
25-29	28,440,000	3,430,877
30-34	34,200,000	3,151,167
35-39	38,040,000	3,960,321
40-44	38,040,000	3,857,129
45-49	33,600,000	4,478,730
50-54	30,000,000	4,258,855
55-59	26,400,000	4,259,892
60-64	22,080,000	3,601,453

Source: Korean Statistical Information Service

Korea has consistently increased its budget for providing medical care to people living with HIV from 2004 to 2020, with a significant amount (i.e., 133,667,130,070 won) spent in 2020. This substantial economic burden can be associated with not only the high cost of HIV treatment but also the increasing

trend of new HIV cases each year and the extended life expectancy resulting from medical care for HIV. In 2019, of the 1,222 new cases of HIV in Korea, 469 (38.4%) were among individuals younger than 30 years. The economic burden can become increasingly heavier with time if the same pattern of HIV new cases persists. In this context, the VSL for HIV was estimated based on five-year age intervals, ranging from 20-24 to 60-64, to identify the welfare loss due to the higher mortality rate of individuals with HIV relative to that of the general population. To enhance accuracy, the VSL for HIV was estimated using the revealed preference methodology, with epidemiological indices, such as HIV incidence, survival rate, and treatment accessibility, all differentiated by age groups, considered.

Table 5-9. Individual and social marginal willingness to pay to reduce the mortality rate due to HIV

Unit: won

Age group	MWP individual	MWP social
20 - 24	2,096	7,030,606,574
25 - 29	3,724	12,775,748,814
30 - 34	8,223	25,912,515,765
35 - 39	6,307	24,978,306,913
40 - 44	6,237	24,057,569,285
45 - 49	6,797	30,443,568,105
50 - 54	3,699	15,751,562,607
55 - 59	3,618	15,411,303,412
60 - 64	2,552	9,189,910,454

Based on the study findings, age-specific survival rates vary depending on whether individuals receive HIV treatment for more than 30 days. For individuals in their 20s, the survival rates did not dramatically decrease even if they did not receive treatment for more than 30 days. However, for individuals older than 40,

HIV treatment was identified to be more crucial for reducing the mortality rate. Fortunately, the rates of accessing HIV treatment with a prescription for more than 30 days were consistently high in the 20-49 age cohort. However, for people living with HIV who were older than 50 years at the time of diagnosis, the rates were lower: 86% for individuals between 50 and 54, 83% for the 55-59 age group, and 80% for people aged 60-64.

Figure 5-3. The value of a statistical life of HIV in Korea (Social MWP)

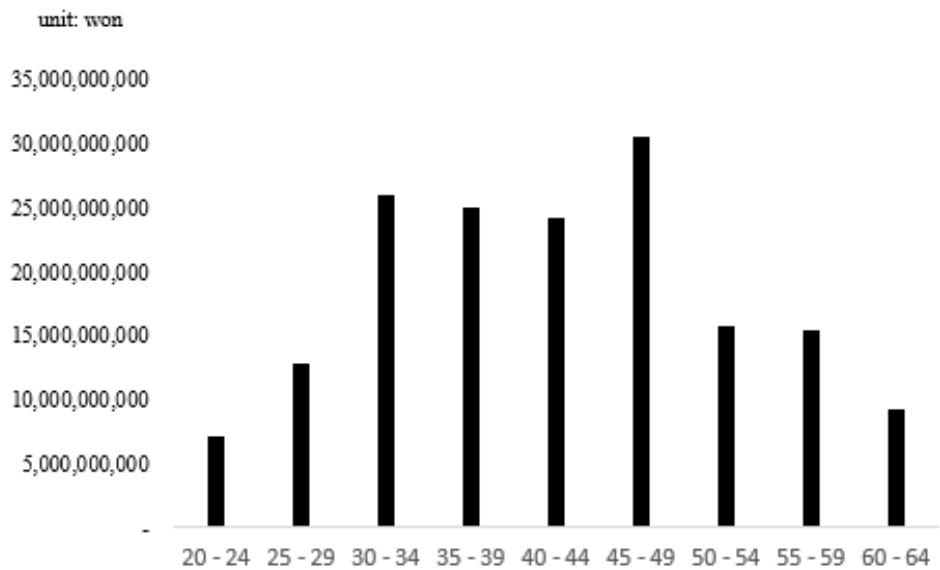


Figure 5-3 displays an inverted U-shaped curve for age-specific social willingness to pay to reduce the mortality rate for HIV, which aligns with findings of previous studies (Johannesson, Johansson et al. 1997, Kip Viscusi and Aldy 2007, Aldy and Viscusi 2008, O'Brien 2018, Viscusi 2020). The 30-49 age group had a higher income than the other age groups. If a specific age group invests more in developing human capital, they will experience greater welfare gains from a reduced risk of HIV mortality (Fimpel and Stolpe 2010). Thus, throughout

extended life expectancy, people aged 30 to 49 with a high level of human capital have a higher value than those younger than 30 or older than 49 (Table 5-9). Additionally, as the 45 to 49 age group has a larger population size than any other group and age-specific population sizes were employed as weight parameters, the welfare gain for ages 45 to 49 holds the highest value.

The present study estimated the value of a statistical life (VSL) for HIV in Korea. Table 5-10 summarizes the estimated VSL for HIV. However, the populations examined in the three studies differed significantly in terms of HIV mortality rates, accessibility of HIV treatment, health care systems, population size, and GDP per capita. Additionally, the statistical assumptions utilized in the three studies also varied. Therefore, it is challenging to directly compare the specific VSL estimate from this study with the results of another study.

The results for the VSL demonstrate considerable variation across each study. (Lindhjem, Navrud et al. 2011) conducted a compilation of 76 previous studies that estimated the VSL in relation to health, the environment, or traffic using the stated prevalence method. Within the environmental category, the average estimated VSL was $8,963,795, with a minimum value of $24,427 and a maximum value of $197,000,000. Concerning health-related studies, the average estimated VSL was $3,996,563, with a minimum value of $4,450 and a maximum value of $75,400,000. For traffic-related studies, the average estimated VSL was $6,861,777, with a minimum value of $21,086 and a maximum value of $112,000,000. These findings indicate substantial variation in the VSL estimates across previous studies, which can be attributed to factors such as the level of mortality risk reduction, the nature of the risk, the population size, and the characteristics of the methodology.

Table 5-10. The comparison of the results with previous studies

	Present study	Fimpel and Stolpe 2010	Soares and Philipson 2005
Region	Korea	Eastern Europe 25 countries	sub-Saharan Africa 34 countries
VSL (% of GDP)	$150.5 million (0.009% of the Korea GDP, 1$=1100won)	$841 billion (10.2% of the whole regions' GDP)	$800 billion (Approximately 100% of the entire regions' GDP)
HIV gross mortality rate [1]	0.0003% [2]	0.15%	0.38%
HIV treatment distribution rate	91% (20–24 years) 89% (25–29 years) 89% (20–34 years) 91% (35–39 years) 90% (40–44 years) 90% (45–49 years) 86% (50–54 years) 83% (55–59 years) 80% (60–64 years)	Average 44% Classified the level of healthcare systems in 25 Eastern European countries into grades 1–6. The distribution rate of HIV treatment was assumed to be >80% and ≤10% in the first-class and sixth-class countries, respectively.	Not included
Age range	20–64 years	20–65 years	0–49 years
Income data	Age-specific median income	GDP per capita (Adjusted for human capital level according to age group)	GDP per capita

[1] All deaths among people with HIV are included (suicide or accident was not excluded). In Korea, HIV mortality rate excluding deaths due to suicide and accidents can be calculated. However, in the table, this study used the same criteria with previous studies to compare HIV gross mortality rates.

[2] Between 2006 and 2018, 1669 people with HIV died (Park, Choi et al. 2022); this was divided by pooling the annual population in this period.

5.5. Conclusion and Discussion

To provide valuable information for policymakers in the medical field, an understanding of not only medical science and micro-economics, but also epidemiology is required (Kim 2009). As a result, epidemiological indices, such as survival rate and incidence rate for HIV, were estimated in the present study using the National Health Insurance Service (NHIS) database in Korea. We used a pseudonymized NHIS database, which includes all HIV incidence cases from 2004 to 2020. These data are not randomly sampled but consist of comprehensive claims data, including medical administration information (Ryu 2017), such as medical expenses, diagnosis, prescription, treatment, and death. The use of epidemiological data, such as the NHIS, can help gain a better understanding of the progression of a disease (Fairchild, Tasseff et al. 2018). The strength of the present study lies in the use of the VSL approach, combined with realistic epidemiological indices based on a large dataset (NHIS).

Previous studies have estimated the VSL for HIV in developing countries, such as those in sub-Saharan Africa and Eastern Europe. Due to low rates of access to HIV treatment and high mortality rates among people living with HIV, the VSL for HIV was significantly high in these regions. In Eastern European countries, the VSL for HIV was 10% of the annual regional GDP from 1995 to 2001 (Fimpel and Stolpe 2010) and in specific sub-Saharan African countries, it ranged from 50% to 200% of the annual GDP (Soares and Philipson 2005).

Korea also had an increasing pattern of HIV cases from 2004 to 2019 based on the NHIS database. In this context, estimating the VSL for HIV in a country with a high level of GDP, such as Korea, can be valuable for policymakers.

Despite its strengths, the present study had a few limitations. First, we could not include individuals younger than 20 and older than 65 years in estimating the VSL for HIV. In previous studies related to children's health policies, the VSL method was applied to the 5-9 and 10-14 age groups to reduce mortality risk with safety gear (Jenkins, Owens et al. 2001). Another study measured job risks for elderly individuals and estimated their VSL (Viscusi and Aldy 2007). However, our study focused on the economically active population, specifically ages 20-64. Notably, the VSL curve of this study had an inverted U-shape with peak at ages 45-49. Therefore, although we did not include individuals younger than 20 and older than 64, the overall estimation would not be significantly underestimated. Besides the 20-64 age range, the income data were not accurate based on 5-year intervals. As a result, we did not extend our analysis beyond the economically active population. Second, people living with HIV have varying characteristics, such as region, race, gender, and immigrant status. Thus, understanding the heterogeneity of the study population is important from an economic aspect and for risk management (Viscusi 2010). Even though the characteristics of heterogeneity could not be considered in this study, we stratified the age group with a 5-year interval, which is a significant factor used to estimate VSL in previous studies (Evans and Smith 2006, Aldy and Viscusi 2008, Fimpel and Stolpe 2010, O'Brien 2018, Herrera-Araujo and Rochaix 2020). Third, we assumed individual consumption is constant and time independent. If time-dependent employment rates and the amount of consumption could be considered, the estimate of the VSL would be more valid. However, to mitigate the effect of the constant amount of consumption, we applied the discount rate of consumption for future consumption.

In this study, we used economic methods and epidemiological data to

calculate the VSL for HIV. Korea has experienced a growing trend of new HIV diagnoses based on the NHIS database since 2004, leading to an increased economic burden with the extended lifespan of individuals with HIV. Our study highlights the VSL and the cost of illness for HIV as indicators of welfare loss and economic impact within our society, which can be useful to policy makers. Nonetheless, additional research with a dynamic methodology, which accounts for time-dependent variations in consumption and considers HIV-related morbidity conditions, is necessary. This approach will facilitate the monitoring of disease progression and enable a deeper understanding of the virus.

Chapter 6. Conclusion

The research was centered on individuals living with HIV, given their increased risk for cancer. While previous investigations in Korea have shown an elevated cancer risk among HIV-positive individuals compared to the general population (Park, Ahn et al. 2022), specific risk factors within this group remain largely undefined. Notably, in Korea, no study has yet been conducted to pinpoint cancer risk factors among those living with HIV.

It's widely accepted that lifestyle modifications can play a significant role in cancer management (Kim, Yeom et al. 2014), and so this study sought to identify modifiable cancer risk factors for people living with HIV. Among these risk factors, obesity, physical activity levels, dietary habits, and smoking come into consideration (Anand, Kunnumakkara et al. 2008). As per the Korea Health Panel survey, both smoking and drinking rates among adults in 2018 were less than in 2010 (Park 2021). However, obesity continues to be a global health concern, with its prevalence increasing more than threefold since 1975 (Congdon and Amugsi 2022). Previous research anticipates a steady growth in the rate of obesity by 2030 (Finkelstein, Khavjou et al. 2012). Given this backdrop, the current study selected obesity as the primary lifestyle-related risk factor for cancer.

The rising concerns surrounding obesity and cancer among individuals living with HIV/AIDS cannot be overstated. Previously, severe HIV infection was often termed a ‘wasting disease’ due to the accompanying weight and muscle loss. However, the narrative has shifted with the introduction of HAART (Highly Active Antiretroviral Therapy), which suppresses viral replication, reduces metabolic demand, and often leads to weight gain. Post-HAART, the prevalence of obesity

among those living with HIV/AIDS has risen, especially among those who were underweight when they initiated the therapy (Yuh, Tate et al. 2015, Kanters, Renaud et al. 2022). Consequently, recent updates to the treatment protocols for HIV and AIDS have broadened their scope to incorporate the management of both obesity and cancer (Ryom, De Miguel et al. 2022).

In Korea, the incidence of non-AIDS-related cancer among HIV/AIDS patients has been on the rise. This study's outcomes highlight the association of obesity, a significant issue in HIV care, with an increased risk for non-AIDS-defining cancers, but not for AIDS-defining ones. The evaluation of cancer risk associated with obesity in Korean adults living with HIV showed an increased likelihood for non-AIDS-defining cancers. However, the correlation between obesity and AIDS-defining cancers was found to be statistically insignificant.

Hence, evaluating and managing obesity during the course of HIV infection is of clinical significance, especially for the prevention of chronic illnesses such as cancer. More comprehensive prospective studies, featuring a larger pool of incident cancer cases, data on weight or BMI fluctuations over the disease's duration, relevant clinical information, and confounding factors, are necessary to fully comprehend the actual connection between obesity and cancer risk.

Moreover, this study explored the risk factors for thyroid cancer in Korean women over 40 years old, a demographic deemed high-risk. Although most types of cancer present statistically significant elevated risks for HIV-positive individuals compared to the general population, thyroid cancer seems to pose a greater risk for the general populace. The high incidence of thyroid cancer among the general population could be linked to overdiagnosis issues, suggesting that those living with HIV, who may have restricted access to healthcare services, could exhibit

lower risk factors for thyroid cancer. Even though overdiagnosis is a concern for both breast and prostate cancers, the risk connected with these cancers is higher for the HIV-positive population compared to the general population (Park, Ahn et al. 2022). This makes it difficult to attribute the trend in thyroid cancer solely to overdiagnosis. Thus, the study also incorporated an examination of the risk factors for thyroid cancer in Korean women aged 40 and above, categorized as a high-risk group.

This investigation found a connection between obesity markers such as body mass index (BMI), waist circumference (WC), and waist-height ratio (WHTR), and a heightened risk of thyroid cancer in Korean women. By combining obesity indices like waist circumference (WC), waist-hip ratio (WHR), and waist-height ratio (WHTR) with body mass index (BMI) categories, a notably increased risk of thyroid cancer was identified in women exhibiting both an obesity-level BMI and other obesity indices, compared to women with normal BMI and other obesity indicators. This represents the first research to consider the combination of overall (BMI) and abdominal (WC, WHR, and WHTR) obesity as a risk factor for thyroid cancer.

Thyroid cancer is the most prevalent cancer in Korea, and its incidence is increasing in numerous countries, resulting in a substantial disease burden. Given this situation, it's crucial to develop strategies to alter risk factors to mitigate the current thyroid cancer epidemic. The simultaneous upsurge in obesity prevalence and thyroid cancer incidence, supported by epidemiological studies, raises queries about the potential role of obesity and other risk factors in the onset of thyroid cancer. Future studies should focus on identifying potential catalysts for the thyroid cancer epidemic by examining a range of risk factors.

Individuals living with HIV are at a higher risk for cancer compared to the general population (Park, Ahn et al. 2022). However, globally, no studies have been undertaken to measure the strain on the healthcare system due to cancer treatment in HIV patients. The objective of this study was to calculate the healthcare expenses associated with cancer in the first five years post-diagnosis and the final six months of life for individuals living with HIV in Korea. This would provide crucial information about the economic impact linked to cancer in this at-risk group.

The principal conclusions from this section are as follows: Firstly, it was discovered that the average yearly medical costs associated with cancer were higher for AIDS-defining cancers compared to non-AIDS-defining cancers. This was particularly evident in the case of non-Hodgkin's lymphoma during the first-year post-diagnosis. However, the average yearly medical expenses related to cancer significantly reduced from the second year onwards, with no noticeable difference based on the cancer type. Secondly, the largest medical expenses in the first year after a cancer diagnosis were typically incurred in the month immediately following the diagnosis. Thirdly, total medical costs, influenced by both average medical expenses and the number of cancer instances, were higher for non-AIDS-defining cancers as compared to AIDS-defining cancers. This implies a higher occurrence rate for these cancers despite their lower average medical costs. Finally, the average monthly total medical expenses for each HIV-positive individual who died after a cancer diagnosis tended to increase as they approached the time of death.

The estimated medical cost burden for patients with HIV, as assessed in this study, could provide a critical reference point for crafting healthcare policies aimed

at this demographic, particularly given the anticipated rise in their cancer-related burden (Shiels, Islam et al. 2018). There is a need for additional research to precisely forecast the future cancer burden among individuals living with HIV. This includes estimations of cancer incidence, death rates, and associated costs, covering both direct and indirect expenditures.

Ultimately, this study calculates the value of a statistical life for HIV, an amount that society is willing to invest in reducing HIV mortality rates (Soares and Philipson 2005, Fimpel and Stolpe 2010). The application of the value of a statistical life method is key to comprehending the socioeconomic consequences of HIV in our community. Simply focusing on the medical or opportunity costs associated with HIV doesn't fully capture its overall impact. Consequently, this study emphasizes the significance of the value of a statistical life for HIV as an indicator of welfare loss and economic impact within our society. This can provide valuable insight to policymakers when allocating limited medical budgets.

According to the findings of the study, survival rates that are age-specific differ based on whether individuals undergo HIV treatment for more than 30 days. For those in their 20s, survival rates did not substantially decrease even without treatment for more than 30 days. However, for those aged over 40, HIV treatment was deemed essential for reducing mortality rates. Encouragingly, rates of accessing HIV treatment with a prescription for over 30 days remained consistently high in the 20-49 age bracket. Yet, for HIV-positive individuals who were over 50 years old at the time of diagnosis, these rates were lower: 86% for those aged between 50 and 54, 83% for the 55-59 age group, and 80% for individuals aged 60-64.

If a particular age group invests more in human capital development, they will

reap greater welfare benefits from a reduced risk of HIV mortality (Fimpel and Stolpe 2010). Hence, people aged between 30 to 49 with a high level of human capital have a higher value over their extended life expectancy than those younger than 30 or older than 49. Furthermore, as the 45 to 49 age group has a larger population size than any other group and age-specific population sizes were used as weight parameters, the welfare gain for ages 45 to 49 has the highest value.

Despite the global decrease in new HIV cases due to the broadening scope of HIV treatment, there has been an upward trend since 2010 in countries with high GDP, including the United States, Brazil, and Spain (Govender, Hashim et al. 2021). Korea also exhibited a rising pattern of HIV cases from 2004 to 2019, according to the NHIS database. In this scenario, calculating the VSL for HIV in a high-GDP country like Korea can provide valuable insights for policymakers. However, further research employing a dynamic method that takes into account time-dependent changes in consumption and HIV-related morbidity conditions is required. This strategy will aid in tracking disease progression and promoting a more comprehensive understanding of the virus.

In conclusion, this study presents three novel findings. Firstly, it identifies obesity as a lifestyle-related risk factor for cancer in individuals with HIV (non-AIDS-defining cancer) and Korean women over the age of 40 (thyroid cancer). Secondly, it provides first-of-its-kind data on the financial burden associated with cancer treatment during the first five years post-diagnosis and the final six months of life for HIV-infected patients in Korea. Thirdly, the study underscores the importance of the value of a statistical life for HIV as a measure of welfare loss and societal economic impact. This research is hoped to provide valuable insights for medical professionals managing and preventing cancer risk groups, as well as

policymakers in charge of budget allocation in healthcare.

Bibliography

Ahn, H. S., H. J. Kim and H. G. Welch (2014). "Korea's thyroid-cancer "epidemic"--screening and overdiagnosis." N Engl J Med 371(19): 1765-1767.

Ahn, S. E., H. J. Bae, S. Y. Gwak, Y. H. Im, M. H. Kim and S. Y. Oh (2016). " Assessment of Human Health Effects of Air-Pollution Using Cohort DB and Estimation of Associated Economic Costs in Korea (II)" Korea Environment Institute.

Ahn, Y., H. Lee and Y. S. Cho (2020). "Identification of Genetic Variants for Female Obesity and Evaluation of the Causal Role of Genetically Defined Obesity in Polycystic Ovarian Syndrome." Diabetes Metab Syndr Obes 13: 4311-4322.

Alavanja, M. C. and M. R. Bonner (2012). "Occupational pesticide exposures and cancer risk: a review." J Toxicol Environ Health B Crit Rev 15(4): 238-263.

Aldy, J. E. and W. K. Viscusi (2008). "Adjusting the Value of a Statistical Life for Age and Cohort Effects." The Review of Economics and Statistics 90(3): 573-581.

Alizadeh, D., E. Katsanis and N. Larmonier (2013). "The multifaceted role of Th17 lymphocytes and their associated cytokines in cancer." Clin Dev Immunol 2013: 957878.

Altavilla, G., A. Caputo, M. Lanfredi, C. Piola, G. Barbanti-Brodano and A. Corallini (2000). "Enhancement of chemical hepatocarcinogenesis by the HIV-1 tat gene." Am J Pathol 157(4): 1081-1089.

Altavilla, G., A. Caputo, C. Trabanelli, E. Brocca Cofano, S. Sabbioni, M. A. Menegatti, G. Barbanti-Brodano and A. Corallini (2004). "Prevalence of liver tumours in HIV-1 tat-transgenic mice treated with urethane." Eur J Cancer 40(2): 275-283.

An, S.-Y., S. Y. Kim, D. J. Oh, C. Min, S. Sim and H. G. Choi (2020). "Obesity is positively related and tobacco smoking and alcohol consumption are negatively related to an increased risk of thyroid cancer." Scientific Reports 10(1): 19279.

Anand, P., A. B. Kunnumakkara, C. Sundaram, K. B. Harikumar, S. T. Tharakan, O. S. Lai, B. Sung and B. B. Aggarwal (2008). "Cancer is a preventable disease that requires major lifestyle changes." Pharm Res 25(9): 2097-2116.

Bailin, S. S., C. L. Gabriel, C. N. Wanjalla and J. R. Koethe (2020). "Obesity and Weight Gain in Persons with HIV." Curr HIV/AIDS Rep 17(2): 138-150.

Banegas, M. P., K. R. Yabroff, M. C. O'Keeffe-Rosetti, D. P. Ritzwoller, P. A. Fishman, R. G. Salloum, J. E. Lafata and M. C. Hornbrook (2018). "Medical Care Costs Associated With Cancer in Integrated Delivery Systems." J Natl Compr Canc Netw 16(4): 402-410.

Bingham, A., R. K. Shrestha, N. Khurana, E. U. Jacobson and P. G. Farnham (2021). "Estimated Lifetime HIV-Related Medical Costs in the United States." Sex Transm Dis 48(4): 299-304.

Blask, D. E. (2009). "Melatonin, sleep disturbance and cancer risk." Sleep Medicine Reviews 13(4): 257-264.

Bloom, D. E., E. Cafiero, E. Jané-Llopis, S. Abrahams-Gessel, L. R. Bloom, S. Fathima, A. B. Feigl, T. Gaziano, A. Hamandi and M. Mowafi (2012). The global economic burden of noncommunicable diseases, Program on the Global Demography of Aging.

Bogović Crnčić, T., M. Ilić Tomaš, N. Girotto and S. Grbac Ivanković (2020). "Risk Factors for Thyroid Cancer: What Do We Know So Far?" Acta Clin Croat 59(Suppl 1): 66-72.

Brodt, H. R., B. S. Kamps, P. Gute, B. Knupp, S. Staszewski and E. B. Helm (1997). "Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy." Aids 11(14): 1731-1738.

Browning, M., L. P. Hansen and J. J. Heckman (1999). Chapter 8 Micro data and general equilibrium models. Handbook of Macroeconomics, Elsevier. 1: 543-633.

Burki, T. (2021). "European Commission classifies obesity as a chronic disease." Lancet Diabetes Endocrinol 9(7): 418.

Celentano, D. D., M. Szklo and L. Gordis (2018). Gordis Epidemiology. Philadelphia, Elsevier.

Chang, H. H. (2022). "Weight Gain and Metabolic Syndrome in Human Immunodeficiency Virus Patients." Infect Chemother 54(2): 220-235.

Chen, S., Z. Cao, K. Prettner, M. Kuhn, J. Yang, L. Jiao, Z. Wang, W. Li, P. Geldsetzer, T. Bärnighausen, D. E. Bloom and C. Wang (2023). "Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050." JAMA Oncology 9(4): 465-472.

Cheng, S. H., F. Y. Chu, Y. S. Lin and Y. M. Hsueh (2012). "Influence of age and CD4+ T cell counts on the prevalence of genital human papillomavirus infection among HIV-seropositive men who have sex with men in Taiwan." J Med Virol 84(12): 1876-1883.

Cho, A., Y. Chang, J. Ahn, H. Shin and S. Ryu (2018). "Cigarette smoking and thyroid cancer risk: a cohort study." British Journal of Cancer 119(5): 638-645.

Cho, D.-Y., J. Park and D.-S. Kim (2021). "The impact of expanding health insurance coverage for anti-cancer drugs on cancer survival in Korea." 10(13): 4555-4563.

Cho, S., A. Shin, D. Song, J. K. Park, Y. Kim, J.-Y. Choi, D. Kang and J.-K. Lee (2017). "Validity of self-reported cancer history in the health examinees (HEXA) study: A comparison of self-report and cancer registry records." Cancer Epidemiology 50: 16-21.

Choi, J. Y. (2020). "The HIV Care Cascade in Korea: Status of UNAIDS 90-90-90 Targets." J Korean Med Sci 35(6): e55.

Choi, S. K., J. Golinkoff, W. Y. Lin, L. Hightow-Weidman, K. Muessig and J. Bauermeister (2023). "Current and Future Perspectives of HIV Prevention Research Among Young Sexual Minority Men in South Korea." Archives of Sexual Behavior 52(2): 721-732.

Chow, R. D., E. H. Bradley and C. P. Gross (2022). "Comparison of Cancer-Related Spending and Mortality Rates in the US vs 21 High-Income Countries." JAMA Health Forum 3(5): e221229.

Congdon, P. and D. Amugsi (2022). "Editorial: The obesity epidemic: Causes, context, prevention." Frontiers in Public Health 10.

Corallini, A., R. Sampaolesi, L. Possati, M. Merlin, P. Bagnarelli, C. Piola, M. Fabris, M. A. Menegatti, S. Talevi, D. Gibellini, R. Rocchetti, A. Caputo and G. Barbanti-Brodano (2002). "Inhibition of HIV-1 Tat activity correlates with down-regulation of bcl-2 and results in reduction of angiogenesis and oncogenicity." Virology 299(1): 1-7.

Cowie, C. C., K. F. Rust, E. S. Ford, M. S. Eberhardt, D. D. Byrd-Holt, C. Li, D. E. Williams, E. W. Gregg, K. E. Bainbridge, S. H. Saydah and L. S. Geiss (2009). "Full Accounting of Diabetes and Pre-Diabetes in the U.S. Population in 1988–1994 and 2005–2006." Diabetes Care 32(2): 287-294.

Crepaz, N., K. L. Hess, D. W. Purcell and H. I. Hall (2019). "Estimating national rates of HIV infection among MSM, persons who inject drugs, and heterosexuals in the United States." AIDS 33(4).

De Simone, V., F. Pallone, G. Monteleone and C. Stolfi (2013). "Role of T(H)17 cytokines in the control of colorectal cancer." Oncoimmunology 2(12): e26617.

Deeken, J. F., A. Tjen-A-Looi, M. A. Rudek, C. Okuliar, M. Young, R. F. Little and B. J. Dezube (2012). "The Rising Challenge of Non–AIDS-Defining Cancers in HIV-Infected Patients." Clinical Infectious Diseases 55(9): 1228-1235.

Dekkers, O. and R. Groenwold (2020). "When observational studies can give wrong answers: The potential of immortal time bias." European Journal of Endocrinology 184.

Evans, M. F. and V. K. Smith (2006). "Do we really understand the age–VSL relationship?" Resource and Energy Economics 28(3): 242-261.

Fairchild, G., B. Tasseff, H. Khalsa, N. Generous, A. R. Daughton, N. Velappan, R. Priedhorsky and A. Deshpande (2018). "Epidemiological Data Challenges: Planning for a More Robust Future Through Data Standards." Frontiers in Public Health 6.

Fang, X., J. Wei, X. He, J. Lian, D. Han, P. An, T. Zhou, S. Liu, F. Wang and J. Min (2018). "Quantitative association between body mass index and the risk of cancer: A global Meta-analysis of prospective cohort studies." Int J Cancer 143(7): 1595-1603.

Feng, S., Z. Zhang, S. Xu, X. Mao, Y. Feng, Y. Zhu and C. Liu (2017). "The Prevalence of Thyroid Nodules and Their Association with Metabolic Syndrome Risk Factors in a Moderate Iodine Intake Area." Metab Syndr Relat Disord 15(2): 93-97.

Fimpel, J. and M. Stolpe (2010). "The welfare costs of HIV/AIDS in eastern Europe: an empirical assessment using the economic value-of-life approach." Eur J Health Econ 11(3): 305-322.

Finkelstein, E. A., O. A. Khavjou, H. Thompson, J. G. Trogdon, L. Pan, B. Sherry and W. Dietz (2012). "Obesity and severe obesity forecasts through 2030." Am J Prev Med 42(6): 563-570.

Franzetti, M., E. Ricci and P. Bonfanti (2019). "The Pattern of Non-AIDS-defining

Cancers in the HIV Population: Epidemiology, Risk Factors and Prognosis. A Review." Curr HIV Res 17(1): 1-12.

Freeman III, A. M., J. A. Herriges and C. L. Kling (2014). The measurement of environmental and resource values: theory and methods, Routledge.

Gallant, J., P. Y. Hsue, S. Shreay and N. Meyer (2017). "Comorbidities Among US Patients With Prevalent HIV Infection—A Trend Analysis." The Journal of Infectious Diseases 216(12): 1525-1533.

Gilbert, C. A. and J. M. Slingerland (2013). "Cytokines, Obesity, and Cancer: New Insights on Mechanisms Linking Obesity to Cancer Risk and Progression." Annual Review of Medicine 64(1): 45-57.

Goldsbury, D. E., S. Yap, M. F. Weber, L. Veerman, N. Rankin, E. Banks, K. Canfell and D. L. O'Connell (2018). "Health services costs for cancer care in Australia: Estimates from the 45 and Up Study." PLoS One 13(7): e0201552.

Govender, R. D., M. J. Hashim, M. A. Khan, H. Mustafa and G. Khan (2021). "Global Epidemiology of HIV/AIDS: A Resurgence in North America and Europe." J Epidemiol Glob Health 11(3): 296-301.

Grundy, S. M. (2016). "Metabolic syndrome update." Trends in Cardiovascular Medicine 26(4): 364-373.

Guiot, H., C. Muñoz-Massó, D. Medina Laabes, A. Ortiz, V. Colon-Lopez and M. Tirado Gomez (2018). "Is obesity a risk for anal neoplasia in a group of HIV-infected Hispanics from Puerto Rico?" Papillomavirus Research 5: S5.

Hamlyn, E., S. Hickling, K. Porter, J. Frater, R. Phillips, M. Robinson, N. E. Mackie, S. Kaye, M. McClure and S. Fidler (2012). "Increased levels of CD4 T-cell activation in individuals with CXCR4 using viruses in primary HIV-1 infection." Aids 26(7): 887-890.

Han, K.-T., W. Kim and S. Kim (2022). "Disparities in healthcare expenditures according to economic status in cancer patients undergoing end-of-life care." BMC Cancer 22(1): 303.

Han, K. T. (2022). The study of cancer patients' healthcare institution utilization, the burden of medical cost, and current fact-finding. Korea Institute for Health and Social Affairs.

Health Examinees Study, G. (2015). "The Health Examinees (HEXA) study: rationale, study design and baseline characteristics." Asian Pac J Cancer Prev 16(4): 1591-1597.

Heath, K., J. Levi and A. Hill (2021). "The Joint United Nations Programme on HIV/AIDS 95–95–95 targets: worldwide clinical and cost benefits of generic manufacture." AIDS 35(Supplement 2).

Hernández-Ramírez, R. U., M. S. Shiels, R. Dubrow and E. A. Engels (2017). "Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study." The Lancet HIV 4(11): e495-e504.

Herrera-Araujo, D. and L. Rochaix (2020). "Does the Value per Statistical Life vary with age or baseline health? Evidence from a compensating wage study in France." Journal of

Environmental Economics and Management 103: 102338.

Hoang, T., D. Song, J. Lee, E. K. Lee, Y. Hwangbo and J. Kim (2021). "Association among Body Mass Index, Genetic Variants of FTO, and Thyroid Cancer Risk: A Hospital-Based Case-Control Study of the Cancer Screenee Cohort in Korea." Cancer Res Treat 53(3): 857-873.

Huang, S. Y., H. M. Chen, K. H. Liao, B. S. Ko and F. Y. Hsiao (2020). "Economic burden of cancers in Taiwan: a direct and indirect cost estimate for 2007-2017." BMJ Open 10(10): e036341.

Huxley, R., S. Mendis, E. Zheleznyakov, S. Reddy and J. Chan (2010). "Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature." Eur J Clin Nutr 64(1): 16-22.

Hwang, H. (2016). "Health Literacy, Cancer Knowledge, and Cancer Preventive Behaviors among Rural Older Adults." Asian Oncol Nurs 16(4): 234-241.

Hwang, S.-H., J.-M. Kang, J.-H. Seo, K.-d. Han and Y.-H. Joo (2016). "Gender Difference in the Epidemiological Association between Metabolic Syndrome and Olfactory Dysfunction: The Korea National Health and Nutrition Examination Survey." PLOS ONE 11(2): e0148813.

Hyppönen, E., A. Mulugeta, A. Zhou and V. K. Santhanakrishnan (2019). "A data-driven approach for studying the role of body mass in multiple diseases: a phenome-wide registry-based case-control study in the UK Biobank." Lancet Digit Health 1(3): e116-e126.

Iii, M., J. Herriges and C. Kling (2003). The Measurement of Environmental and Resource Values: Theory and Methods.

Ip, B., N. A. Cilfone, A. C. Belkina, J. DeFuria, M. Jagannathan-Bogdan, M. Zhu, R. Kuchibhatla, M. E. McDonnell, Q. Xiao, T. B. Kepler, C. M. Apovian, D. A. Lauffenburger and B. S. Nikolajczyk (2016). "Th17 cytokines differentiate obesity from obesity-associated type 2 diabetes and promote TNFα production." Obesity (Silver Spring) 24(1): 102-112.

Iragorri, N., C. de Oliveira, N. Fitzgerald and B. Essue (2021). "The Indirect Cost Burden of Cancer Care in Canada: A Systematic Literature Review." Applied Health Economics and Health Policy 19(3): 325-341.

Jahagirdar, D., M. K. Walters, A. Novotney, E. D. et al (2021). "Global, regional, and national sex-specific burden and control of the HIV epidemic, 1990–2019, for 204 countries and territories: the Global Burden of Diseases Study 2019." The Lancet HIV 8(10): e633-e651.

Jenkins, R. R., N. Owens and L. B. Wiggins (2001). "VALUING REDUCED RISKS TO CHILDREN: THE CASE OF BICYCLE SAFETY HELMETS." Contemporary Economic Policy 19(4): 397-408.

Jin, Z.-Y., X. Liu, Y.-Y. Ding, Z.-F. Zhang and N. He (2017). "Cancer risk factors among people living with HIV/AIDS in China: a systematic review and meta-analysis." Scientific Reports 7(1): 4890.

Johannesson, M., P.-O. Johansson and K.-G. LÖFgren (1997). "On the Value of Changes in Life Expectancy: Blips Versus Parametric Changes." Journal of Risk and Uncertainty 15(3):

221-239.

Jung, Y. H. and S. J. Ko (2009). Studies on the lifetime medical expenditure.1, Korea Institute for Health and Social Affairs.

Kabat, G. C., M. Y. Kim, C. A. Thomson, J. Luo, J. Wactawski-Wende and T. E. Rohan (2012). "Anthropometric factors and physical activity and risk of thyroid cancer in postmenopausal women." Cancer Causes Control 23(3): 421-430.

Kang, H. W., S. J. Yun, J. I. Chung, H. Choi, J. H. Kim, H. S. Yu, Y. S. Ha, I. C. Cho, H. J. Kim, H. C. Chung, J. S. Koh, W. J. Kim, J. H. Park, J. Y. Lee and S. Y. Kim (2019). "National practice patterns and direct medical costs for prostate cancer in Korea across a 10 year period: a nationwide population-based study using a national health insurance database." BMC Health Serv Res 19(1): 408.

Kang, M. J., Y. J. Won, J. J. Lee, K. W. Jung, H. J. Kim, H. J. Kong, J. S. Im and H. G. Seo (2022). "Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2019." Cancer Res Treat 54(2): 330-344.

Kanters, S., F. Renaud, A. Rangaraj, K. Zhang, E. Limbrick-Oldfield, M. Hughes, N. Ford and M. Vitoria (2022). "Evidence synthesis evaluating body weight gain among people treating HIV with antiretroviral therapy - a systematic literature review and network meta-analysis." EClinicalMedicine 48: 101412.

KDCA. (2021). "Korea Centers for Disease Control and Prevention." from https://www.kdca.go.kr/contents.es?mid=a20301070601.

Ke, J. F., J. W. Wang, J. X. Lu, Z. H. Zhang, Y. Liu and L. X. Li (2022). "Waist-to-height ratio has a stronger association with cardiovascular risks than waist circumference, waist-hip ratio and body mass index in type 2 diabetes." Diabetes Res Clin Pract 183: 109151.

Kim, C. (2009). "Health Economics and Outcomes Research." Korean Journal of Family Medicine 30(8): 577-587.

Kim, E. J. and S. H. Kim (2021). "Structural Equation Modeling Analysis on Health Literacy and Cancer Prevention Behaviors among Medically-Underserved, Low-Income Populations." Journal of the Korean Academy of Fundamentals of Nursing 28(1): 83-95.

Kim, I. O., G. J. Yeom and S. H. Shin (2014). "Factors Affecting on Cancer Prevention Behaviors in Adult Women" Korean Journal of Adult Nursing 26(4): 455-465.

Kim, J. M., J. Y. Choi, W. Y. Jeong, H. Seong, S. W. Kim, W. J. Kim, H. J. Choi, M. J. Kim, J. H. Woo, Y. J. Kim, B. Y. Choi, Y. S. Choi, M. K. Kee and K. S. Kim (2018). "Mode of Human Immunodeficiency Virus Transmission in Korea: The Korea HIV/AIDS Cohort Study." Korean J Med 93(4): 379-386.

Kim, K., S. Choi and S. M. Park (2018). "Association of High Body Mass Index and Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Virus Infection: A Korean Population-Based Cohort Study." JAMA Oncol 4(5): 737-739.

Kim, Y. (2016). "Estimating the Value of Life: Method and limitations." Korea Review of

Applied Economics 18(3): 105-124.

Kim, Y. and B. G. Han (2017). "Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium." Int J Epidemiol 46(2): e20.

Kim, Y. A., Y. R. Lee, J. Park, I. H. Oh, H. Kim, S. J. Yoon and K. Park (2020). "Socioeconomic Burden of Cancer in Korea from 2011 to 2015." Cancer Res Treat 52(3): 896-906.

Kimman, M., S. Jan, D. Kingston, H. Monaghan, E. Sokha, H. Thabrany, B. Bounxouei, N. Bhoo-Pathy, M. Khin, G. Cristal-Luna, T. Khuhaprema, N. C. Hung and M. Woodward (2012). "Socioeconomic impact of cancer in member countries of the Association of Southeast Asian Nations (ASEAN): the ACTION study protocol." Asian Pac J Cancer Prev 13(2): 421-425.

Kip Viscusi, W. and J. E. Aldy (2007). "Labor market estimates of the senior discount for the value of statistical life." Journal of Environmental Economics and Management 53(3): 377-392.

Kitahara, C. M., M. L. McCullough, S. Franceschi, S. Rinaldi, A. Wolk, G. Neta, H. Olov Adami, K. Anderson, G. Andreotti, L. E. Beane Freeman, L. Bernstein, J. E. Buring, F. Clavel-Chapelon, L. A. De Roo, Y. T. Gao, J. M. Gaziano, G. G. Giles, N. Håkansson, P. L. Horn-Ross, V. A. Kirsh, M. S. Linet, R. J. MacInnis, N. Orsini, Y. Park, A. V. Patel, M. P. Purdue, E. Riboli, K. Robien, T. Rohan, D. P. Sandler, C. Schairer, A. B. Schneider, H. D. Sesso, X. O. Shu, P. N. Singh, P. A. van den Brandt, E. Ward, E. Weiderpass, E. White, Y. B. Xiang, A. Zeleniuch-Jacquotte, W. Zheng, P. Hartge and A. Berrington de González (2016). "Anthropometric Factors and Thyroid Cancer Risk by Histological Subtype: Pooled Analysis of 22 Prospective Studies." Thyroid 26(2): 306-318.

Kitahara, C. M., E. A. Platz, Y. Park, A. R. Hollenbeck, A. Schatzkin and A. Berrington de González (2012). "Body fat distribution, weight change during adulthood, and thyroid cancer risk in the NIH-AARP Diet and Health Study." Int J Cancer 130(6): 1411-1419.

Korea Institute for Health and Social Affairs (KIHASA). Accessed: April 27, 2023. https://repository.kihasa.re.kr/handle/201002/38120

Korean Statistical Information Service (KOSIS). Life table. Accessed: May 1, 2023. https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1B42&conn_path=I2

Korea Health Promotion Institute (KHPI). Accessed: May 27, 2023. https://www.khepi.or.kr/kps/rsrhBusnRept/view?menuId=MENU00894&rsrh_idx=1087

Kumar, S. and K. Samaras (2018). "The Impact of Weight Gain During HIV Treatment on Risk of Pre-diabetes, Diabetes Mellitus, Cardiovascular Disease, and Mortality." Front Endocrinol (Lausanne) 9: 705.

Kutikova, L., L. Bowman, S. Chang, S. R. Long, M. Arning and W. H. Crown (2006). "Medical costs associated with non-Hodgkin's lymphoma in the United States during the first two years of treatment." Leuk Lymphoma 47(8): 1535-1544.

Kwon, S. M., J. H. Bang, K. Y. Kim and Y. M. Cho (2015). "Utilization of health care

services among people with HIV infection." Korea Disease Control and Prevention Agency.

Kyrgiou, M., I. Kalliala, G. Markozannes, M. J. Gunter, E. Paraskevaidis, H. Gabra, P. Martin-Hirsch and K. K. Tsilidis (2017). "Adiposity and cancer at major anatomical sites: umbrella review of the literature." Bmj 356: j477.

La Vecchia, C., S. H. Giordano, G. N. Hortobagyi and B. Chabner (2011). "Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle." The oncologist 16(6): 726-729.

Lam, B. C., G. C. Koh, C. Chen, M. T. Wong and S. J. Fallows (2015). "Comparison of Body Mass Index (BMI), Body Adiposity Index (BAI), Waist Circumference (WC), Waist-To-Hip Ratio (WHR) and Waist-To-Height Ratio (WHtR) as predictors of cardiovascular disease risk factors in an adult population in Singapore." PLoS One 10(4): e0122985.

Lang, K., L. M. Lines, D. W. Lee, J. R. Korn, C. C. Earle and J. Menzin (2009). "Lifetime and treatment-phase costs associated with colorectal cancer: evidence from SEER-Medicare data." Clin Gastroenterol Hepatol 7(2): 198-204.

Langton, J. M., R. Reeve, P. Srasuebkul, M. Haas, R. Viney, D. Currow and S. A. Pearson (2016). "Health service use and costs in the last 6 months of life in elderly decedents with a history of cancer: a comprehensive analysis from a health payer perspective." Br J Cancer 114(11): 1293-1302.

Lao, C., M. Mondal, M. Kuper-Hommel, I. Campbell and R. Lawrenson (2022). "Differences in Breast Cancer Costs by Cancer Stage and Biomarker Subtype in New Zealand." PharmacoEconomics - Open 6(4): 539-548.

Larsson, S. C. and S. Burgess (2021). "Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies." BMC Medicine 19(1): 320.

Lauby-Secretan, B., C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini and K. Straif (2016). "Body Fatness and Cancer--Viewpoint of the IARC Working Group." N Engl J Med 375(8): 794-798.

Laudicella, M., B. Walsh, E. Burns and P. C. Smith (2016). "Cost of care for cancer patients in England: evidence from population-based patient-level data." British Journal of Cancer 114(11): 1286-1292.

Lee, J. H., Y. J. Chai and K. H. Yi (2021). "Effect of Cigarette Smoking on Thyroid Cancer: Meta-Analysis." Endocrinol Metab (Seoul) 36(3): 590-598.

Leggett, L. E., R. G. Khadaroo, J. Holroyd-Leduc, D. L. Lorenzetti, H. Hanson, A. Wagg, R. Padwal and F. Clement (2016). "Measuring Resource Utilization: A Systematic Review of Validated Self-Reported Questionnaires." Medicine (Baltimore) 95(10): e2759.

Leng, A., J. Jing, S. Nicholas and J. Wang (2019). "Catastrophic health expenditure of cancer patients at the end-of-life: a retrospective observational study in China." BMC Palliat Care 18(1): 43.

Lewis, D. E., J. Lysaght and H. Wu (2019). "Editorial: T Cell Alterations in Adipose Tissue During Obesity, HIV, and Cancer." Front Immunol 10: 1190.

Li, L., Y. Gan, W. Li, C. Wu and Z. Lu (2016). "Overweight, obesity and the risk of gallbladder and extrahepatic bile duct cancers: A meta-analysis of observational studies." Obesity (Silver Spring) 24(8): 1786-1802.

Lindhjem, H., S. Navrud, N. A. Braathen and V. Biausque (2011). "Valuing mortality risk reductions from environmental, transport, and health policies: a global meta-analysis of stated preference studies." Risk Anal 31(9): 1381-1407.

Liu, Y., L. Su and H. Xiao (2017). "Review of Factors Related to the Thyroid Cancer Epidemic." Int J Endocrinol 2017: 5308635.

Liu, Y., G. Tong, W. Tong, L. Lu and X. Qin (2011). "Can body mass index, waist circumference, waist-hip ratio and waist-height ratio predict the presence of multiple metabolic risk factors in Chinese subjects?" BMC Public Health 11: 35.

Luta, X., K. Diernberger, J. Bowden, J. Droney, P. Hall and J. Marti (2022). "Intensity of care in cancer patients in the last year of life: a retrospective data linkage study." Br J Cancer 127(4): 712-719.

Ma, Y., Y. Yang, F. Wang, P. Zhang, C. Shi, Y. Zou and H. Qin (2013). "Obesity and risk of colorectal cancer: a systematic review of prospective studies." PLoS One 8(1): e53916.

Mack, W. J., S. Preston-Martin, L. Bernstein and D. Qian (2002). "Lifestyle and other risk factors for thyroid cancer in Los Angeles County females." Ann Epidemiol 12(6): 395-401.

Mariotto, A. B., L. Enewold, J. Zhao, C. A. Zeruto and K. R. Yabroff (2020). "Medical Care Costs Associated with Cancer Survivorship in the United States." Cancer Epidemiol Biomarkers Prev 29(7): 1304-1312.

Martin, A. B., M. Hartman, D. Lassman and A. Catlin (2021). "National Health Care Spending In 2019: Steady Growth For The Fourth Consecutive Year." Health Aff (Millwood) 40(1): 14-24.

Martínez-Sanz, J., S. Serrano-Villar, M. J. Vivancos, R. Rubio and S. Moreno (2022). "Management of Comorbidities in Treated HIV Infection: A Long Way to Go: HIV, comorbidities and aging." International Journal of Antimicrobial Agents 59(1): 106493.

Mbachu, C., C. Okoli, O. Onwujekwe and F. Enabulele (2018). "Willingness to pay for antiretroviral drugs among HIV and AIDS clients in south-east Nigeria." Health Expect 21(1): 270-278.

McCann, N. C., T. H. Horn, E. P. Hyle and R. P. Walensky (2020). "HIV Antiretroviral Therapy Costs in the United States, 2012-2018." JAMA Intern Med 180(4): 601-603.

McCullough, J. M., M. Speer, S. Magnan, J. E. Fielding, D. Kindig and S. M. Teutsch (2020). "Reduction in US Health Care Spending Required to Meet the Institute of Medicine's 2030 Target." Am J Public Health 110(12): 1735-1740.

McGarvey, N., M. Gitlin, E. Fadli and K. C. Chung (2022). "Increased healthcare costs by

later stage cancer diagnosis." BMC Health Services Research 22(1): 1155.

Ministry of Health and Welfare. News & Welfare Services. Accessed: February 1, 2023. https://www.mohw.go.kr/react/al/sal0301ls.jsp?PAR_MENU_ID=04&MENU_ID=0403

Meropol, N. J. and K. A. Schulman (2007). "Cost of cancer care: issues and implications." J Clin Oncol 25(2): 180-186.

Mohammadpour, S., S. Soleimanpour, J. Javan-Noughabi, N. A. Gallehzan, A. Aboutorabi, R. Jahangiri, R. Bagherzadeh, J. F. Gorman and A. Nemati (2022). "A systemmatic literature review on indirect costs of women with breast cancer." Cost Effectiveness and Resource Allocation 20(1): 68.

Morgan, J., O. Ferlatte, T. Salway, J. Wilton and M. Hull (2018). "Awareness of, interest in, and willingness to pay for HIV pre-exposure prophylaxis among Canadian gay, bisexual, and other men who have sex with men." Canadian Journal of Public Health 109(5): 791-799.

Murphy, K. M. and R. H. Topel (2003). Chapter Two. The Economic Value of Medical Research. Measuring the Gains from Medical Research. M. M. Kevin and H. T. Robert. Chicago, University of Chicago Press: 41-73.

Myung, S.-K., C. W. Lee, J. Lee, J. Kim and H. S. Kim (2017). "Risk Factors for Thyroid Cancer: A Hospital-Based Case-Control Study in Korean Adults." Cancer Res Treat 49(1): 70-78.

Myung, S. K., C. W. Lee, J. Lee, J. Kim and H. S. Kim (2017). "Risk Factors for Thyroid Cancer: A Hospital-Based Case-Control Study in Korean Adults." Cancer Res Treat 49(1): 70-78.

Nakagawa, F., A. Miners, C. J. Smith, R. Simmons, R. K. Lodwick, V. Cambiano, J. D. Lundgren, V. Delpech and A. N. Phillips (2015). "Projected Lifetime Healthcare Costs Associated with HIV Infection." PLOS ONE 10(4): e0125018.

Nam, G. E. (2022). "Current status and epidemiology of adult obesity in Korea." J Korean Med Assoc 65(7): 394-399.

Nanditha, N. G. A., J. Zhu, L. Wang, J. Kopec, R. S. Hogg, J. S. G. Montaner and V. D. Lima (2022). "Disability-adjusted life years associated with chronic comorbidities among people living with and without HIV: Estimating health burden in British Columbia, Canada." PLOS Glob Public Health 2(10): e0001138.

Nansseu, J. R., J. J. Bigna, A. D. Kaze and J. J. Noubiap (2018). "Incidence and Risk Factors for Prediabetes and Diabetes Mellitus Among HIV-infected Adults on Antiretroviral Therapy: A Systematic Review and Meta-analysis." Epidemiology 29(3): 431-441.

Navarro Silvera, S. A., A. B. Miller and T. E. Rohan (2005). "Risk factors for thyroid cancer: a prospective cohort study." Int J Cancer 116(3): 433-438.

National Health Insurance Service (NHIS). Accessed: May 17, 2023. http://lib.nhis.or.kr/search/detail/CATXAZ000000037282

Nicholson, B. D., W. Hamilton, J. O'Sullivan, P. Aveyard and F. R. Hobbs (2018).

"Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis." Br J Gen Pract 68(670): e311-e322.

Nkwonta, C. A., J. Zhang, S. Chen, S. Weissman, B. Olatosi and X. Li (2023). "Prevalence and trend of AIDS-defining cancers and non-AIDS-defining cancers and their association with antiretroviral therapy among people living with HIV in South Carolina: a population-based cohort study." AIDS Care 35(5): 753-763.

Nunn, A., L. Brinkley-Rubinstein, J. Rose, K. Mayer, T. Stopka, C. Towey, J. Harvey, K. Santamaria, K. Sabatino, S. Trooskin and P. A. Chan (2017). "Latent class analysis of acceptability and willingness to pay for self-HIV testing in a United States urban neighbourhood with high rates of HIV infection." Journal of the International AIDS Society 20(1): 21290.

O'Brien, J. (2018). "Age, autos, and the value of a statistical life." Journal of Risk and Uncertainty 57.

Okoye, A. A. and L. J. Picker (2013). "CD4(+) T-cell depletion in HIV infection: mechanisms of immunological failure." Immunol Rev 254(1): 54-64.

Ory, M. G., L. A. Anderson, D. B. Friedman, J. C. Pulczinski, N. Eugene and W. A. Satariano (2014). "Cancer Prevention Among Adults Aged 45–64 Years: Setting the Stage." American Journal of Preventive Medicine 46(3, Supplement 1): S1-S6.

Ott, J. J., A. Ullrich, M. Mascarenhas and G. A. Stevens (2011). "Global cancer incidence and mortality caused by behavior and infection." J Public Health (Oxf) 33(2): 223-233.

Park, B., K. H. Ahn, Y. Choi, J. H. Kim, H. Seong, Y. J. Kim, J. Y. Choi, J. Y. Song, E. Lee, Y. H. Jun, Y. K. Yoon, W. S. Choi, M. Lee, J. Seong and S. W. Kim (2022). "Cancer Incidence Among Adults With HIV in a Population-Based Cohort in Korea." JAMA Netw Open 5(8): e2224897.

Park, B., Y. Choi, J. H. Kim, H. Seong, Y. J. Kim, M. Lee, J. Seong, S. W. Kim, J. Y. Song, H. J. Choi, D. W. Park, H. Y. Kim, J. Y. Choi, S. I. Kim and B. Y. Choi (2022). "Mortality and Causes of Death among Individuals Diagnosed with Human Immunodeficiency Virus in Korea, 2004-2018: An Analysis of a Nationwide Population-Based Claims Database." Int J Environ Res Public Health 19(18).

Park, H. Y., S. N. An, S. M. Jeon and K. J. W. (2020). "Disease Burden of Non-Hodgkin Lymphoma." The Pharmaceutical Society Of Korea 64(5): 369-376.

Park, L. S., R. U. Hernández-Ramírez, M. J. Silverberg, K. Crothers and R. Dubrow (2016). "Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis." Aids 30(2): 273-291.

Park, M. and I. Song (2018). "Medical care costs of cancer in the last year of life using national health insurance data in Korea." PLOS ONE 13(6): e0197891.

Prasad, S., B. Sung and B. B. Aggarwal (2012). "Age-associated chronic diseases require age-old medicine: role of chronic inflammation." Prev Med 54 Suppl(Suppl): S29-37.

Preziosi, G., J. A. Oben and G. Fusai (2014). "Obesity and pancreatic cancer." Surg Oncol

23(2): 61-71.

Quiros-Roldan, E., M. Magoni, E. Raffetti, F. Donato, C. Scarcella, G. Paraninfo and F. Castelli (2016). "The burden of chronic diseases and cost-of-care in subjects with HIV infection in a Health District of Northern Italy over a 12-year period compared to that of the general population." BMC Public Health 16(1): 1146.

Ray, M., R. Logan, J. A. Sterne, S. Hernández-Díaz, J. M. Robins, C. Sabin, L. Bansi, A. van Sighem, F. de Wolf, D. Costagliola, E. Lanoy, H. C. Bucher, V. von Wyl, A. Esteve, J. Casbona, J. del Amo, S. Moreno, A. Justice, J. Goulet, S. Lodi, A. Phillips, R. Seng, L. Meyer, S. Pérez-Hoyos, P. García de Olalla and M. A. Hernán (2010). "The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals." Aids 24(1): 123-137.

Reddy, S. R., M. S. Broder, E. Chang, C. Paydar, K. C. Chung and A. R. Kansal (2022). "Cost of cancer management by stage at diagnosis among Medicare beneficiaries." Current Medical Research and Opinion 38(8): 1285-1294.

Rhee, y. s., h. n. Kim and h. j. Kim (2018). "A Systematic Review Of The Psychosocial Aspects Of People Living With HIV/AIDS(PLWHA)." Korean Journal of Social Welfare 70(2): 223-245.

Rinaldi, S., M. Lise, F. Clavel-Chapelon, M.-C. Boutron-Ruault, G. Guillas, K. Overvad, A. Tjønneland, J. Halkjær, A. Lukanova, R. Kaaks, M. M. Bergmann, H. Boeing, A. Trichopoulou, D. Zylis, E. Valanou, D. Palli, C. Agnoli, R. Tumino, S. Polidoro, A. Mattiello, H. Bas Bueno-de-Mesquita, P. H. Peeters, E. Weiderpass, E. Lund, G. Skeie, L. Rodríguez, N. Travier, M.-J. Sánchez, P. Amiano, J.-M. Huerta, E. Ardanaz, T. Rasmuson, G. Hallmans, M. Almquist, J. Manjer, K. K. Tsilidis, N. E. Allen, K.-T. Khaw, N. Wareham, G. Byrnes, I. Romieu, E. Riboli and S. Franceschi (2012). "Body size and risk of differentiated thyroid carcinomas: Findings from the EPIC study." International Journal of Cancer 131(6): E1004-E1014.

Ritchwood, T. D., K. G. Bishu and L. E. Egede (2017). "Trends in healthcare expenditure among people living with HIV/AIDS in the United States: evidence from 10 Years of nationally representative data." International Journal for Equity in Health 16(1): 188.

Ryom, L., R. De Miguel, A. G. Cotter, D. Podlekareva, C. Beguelin, H. Waalewijn, J. R. Arribas, P. W. G. Mallon, C. Marzolini, O. Kirk, A. Bamford, A. Rauch, J. M. Molina, J. D. Kowalska, G. Guaraldi, A. Winston, C. Boesecke, P. Cinque, S. Welch, S. Collins, G. M. N. Behrens and t. E. G. Board (2022). "Major revision version 11.0 of the European AIDS Clinical Society Guidelines 2021." HIV Medicine 23(8): 849-858.

Ryu, D.-R. (2017). "Introduction to the Medical Research Using National Health Insurance Claims Database." emj 40(2): 66-70.

Sang, J. S., E. Y. Bae, J. Y. Park, H. J. Song, Y. H. Kim, Y. J. Jung and T. J. Lee (2013). " Review for Cost estimation for Cost of illness and Economic Evaluation in Korea" The Korean Journal of Health Economics and Policy 19(1): 77-92.

Sharma, A., D. R. Hoover, Q. Shi, D. Gustafson, M. W. Plankey, R. C. Hershow, P. C. Tien, E. T. Golub and K. Anastos (2015). "Relationship between Body Mass Index and Mortality in HIV-Infected HAART Users in the Women's Interagency HIV Study." PLoS One 10(12): e0143740.

Shiels, M. S., J. J. Goedert, R. D. Moore, E. A. Platz and E. A. Engels (2010). "Reduced risk of prostate cancer in U.S. Men with AIDS." Cancer Epidemiol Biomarkers Prev 19(11): 2910-2915.

Shiels, M. S., J. Y. Islam, P. S. Rosenberg, H. I. Hall, E. Jacobson and E. A. Engels (2018). "Projected Cancer Incidence Rates and Burden of Incident Cancer Cases in HIV-Infected Adults in the United States Through 2030." Ann Intern Med 168(12): 866-873.

Shin, A., S. Cho, D. Jang, S. K. Abe, E. Saito, M. S. Rahman, M. R. Islam, N. Sawada, X. O. Shu, W. P. Koh, A. Sadakane, I. Tsuji, Y. Sugawara, H. Ito, C. Nagata, S. K. Park, J. M. Yuan, J. Kim, S. Tsugane, H. Cai, W. Wen, K. Ozasa, S. Matsuyama, S. Kanemura, I. Oze, K. Wada, R. Wang, K. Y. Yoo, J. D. Potter, H. Ahsan, P. Boffetta, K. S. Chia, K. Matsuo, Y. L. Qiao, N. Rothman, W. Zheng, M. Inoue and D. Kang (2022). "Body Mass Index and Thyroid Cancer Risk: A Pooled Analysis of Half a Million Men and Women in the Asia Cohort Consortium." Thyroid 32(3): 306-314.

Shin, A., S. Park, H. R. Shin, E. H. Park, S. K. Park, J. K. Oh, M. K. Lim, B. Y. Choi, M. Boniol and P. Boffetta (2011). "Population attributable fraction of infection-related cancers in Korea." Ann Oncol 22(6): 1435-1442.

Shin, H. Y., Y. H. Jee and E. R. Cho (2017). "Body mass index and incidence of thyroid cancer in Korea: the Korean Cancer Prevention Study-II." J Cancer Res Clin Oncol 143(1): 143-149.

Shin, J. Y., S. Y. Kim, K. S. Lee, S. I. Lee, Y. Ko, Y. S. Choi, H. G. Seo, J. H. Lee and J. H. Park (2012). "Costs during the first five years following cancer diagnosis in Korea." Asian Pac J Cancer Prev 13(8): 3767-3772.

Siddiqui, J., S. K. Samuel, B. Hayward, K. A. Wirka, K. L. Deering, Q. Harshaw, A. Phillips and M. Harbour (2022). "HIV-associated wasting prevalence in the era of modern antiretroviral therapy." Aids 36(1): 127-135.

Sidibé, M., L. Loures and B. Samb (2016). "The UNAIDS 90-90-90 target: a clear choice for ending AIDS and for sustainable health and development." J Int AIDS Soc 19(1): 21133.

Simmons, R. D., B. C. Ciancio, M. M. Kall, B. D. Rice and V. C. Delpech (2013). "Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer." HIV Med 14(10): 596-604.

Soares, R. and T. Philipson (2005). "The Economic Cost of AIDS in Sub-Saharan Africa: A Reassessment." Health and Economic Growth: Findings and Policy Implications, MIT Press.

Sohn, A. and S. Park (2012). "HIV/AIDS Knowledge, Stigmatizing Attitudes, and Related Behaviors and Factors that Affect Stigmatizing Attitudes against HIV/AIDS among Korean

Adolescents." Osong public health and research perspectives 3: 24-30.

Sohn, W., H. W. Lee, S. Lee, J. H. Lim, M. W. Lee, C. H. Park and S. K. Yoon (2021). "Obesity and the risk of primary liver cancer: A systematic review and meta-analysis." Clin Mol Hepatol 27(1): 157-174.

Son, H., H. Lee, K. Kang and I. Lee (2018). "The risk of thyroid cancer and obesity: A nationwide population-based study using the Korea National Health Insurance Corporation cohort database." Surg Oncol 27(2): 166-171.

Stahlman, S., C. Lyons, P. S. Sullivan, K. H. Mayer, S. Hosein, C. Beyrer and S. D. Baral (2017). "HIV incidence among gay men and other men who have sex with men in 2020: where is the epidemic heading?" Sex Health 14(1): 5-17.

Stansifer, K. J., J. F. Guynan, B. M. Wachal and R. B. Smith (2015). "Modifiable risk factors and thyroid cancer." Otolaryngol Head Neck Surg 152(3): 432-437.

Stone, T. W., M. McPherson and L. Gail Darlington (2018). "Obesity and Cancer: Existing and New Hypotheses for a Causal Connection." EBioMedicine 30: 14-28.

Su, P., F. Tao, J. Hao, K. Huang and P. Zhu (2010). "[Mental health and risk behavior of married adult HIV/AIDS subjects derived from paid blood donation in the rural of Anhui Province]." Wei sheng yan jiu = Journal of hygiene research 39: 739-732, 746.

Sullivan, P. W., V. H. Ghushchyan and R. Ben-Joseph (2008). "The impact of obesity on diabetes, hyperlipidemia and hypertension in the United States." Qual Life Res 17(8): 1063-1071.

Sung, H., J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal and F. Bray (2021)."Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71(3): 209-249.

Tashiro, M., T. Akiyama, I. Yoshikawa, K. Kume and M. Otsuki (2004). "Obesity as a risk factor for colorectal polyps in Japanese patients." Gut 53(1): 156.

Tate, T., A. L. Willig, J. H. Willig, J. L. Raper, L. Moneyham, M. C. Kempf, M. S. Saag and M. J. Mugavero (2012). "HIV infection and obesity: where did all the wasting go?" Antivir Ther 17(7): 1281-1289.

Tran, H., K. Saleem, M. Lim, E. P. F. Chow, C. K. Fairley, F. Terris-Prestholt and J. J. Ong (2021). "Global estimates for the lifetime cost of managing HIV." Aids 35(8): 1273-1281.

Treskova, M., A. Kuhlmann, J. Bogner, M. Hower, H. Heiken, H. J. Stellbrink, J. Mahlich, J. M. Schulenburg and M. Stoll (2016). "Analysis of contemporary HIV/AIDS health care costs in Germany: Driving factors and distribution across antiretroviral therapy lines." Medicine (Baltimore) 95(26): e3961.

Trinchieri, G. (2012). "Cancer and Inflammation: An Old Intuition with Rapidly Evolving New Concepts." Annual Review of Immunology 30(1): 677-706.

Viscusi, W. and J. Aldy (2007). "Labor Market Estimates of the Senior Discount for the Value of Statistical Life." Journal of Environmental Economics and Management 53: 377-392.

Viscusi, W. K. (1993). "The Value of Risks to Life and Health." Journal of Economic Literature 31(4): 1912-1946.

Viscusi, W. K. (2010). "The heterogeneity of the value of statistical life: Introduction and overview." Journal of Risk and Uncertainty 40(1): 1-13.

Viscusi, W. K. (2020). "Wellbeing measures of mortality risks: life-cycle contradictions and ordinal index challenges." Behavioural Public Policy 4(2): 245-253.

Vodicka, E. L., M. H. Chung, M. R. Zimmermann, R. J. Kosgei, F. Lee, N. R. Mugo, T. C. Okech, S. R. Sakr, A. Stergachis, L. P. Garrison, Jr. and J. B. Babigumira (2019). "Estimating the costs of HIV clinic integrated versus non-integrated treatment of pre-cancerous cervical lesions and costs of cervical cancer treatment in Kenya." PLoS One 14(6): e0217331.

White, M. C., D. M. Holman, J. E. Boehm, L. A. Peipins, M. Grossman and S. J. Henley (2014). "Age and cancer risk: a potentially modifiable relationship." Am J Prev Med 46(3 Suppl 1): S7-15.

Wolin, K. Y., K. Carson and G. A. Colditz (2010). "Obesity and Cancer." The Oncologist 15(6): 556-565.

World Health Organization. Regional Office for the Western Pacific. (2000). The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia. https://apps.who.int/iris/handle/10665/206936.

Wu, S.-B., Y.-C. Huang, Y.-F. Huang and J.-C. Huang (2022). "Estimating HIV incidence, prevalence, and percent of undiagnosed infections in Taiwan using CD4 data." Journal of the Formosan Medical Association 121(2): 482-489.

Xu, L., G. Li, Q. Wei, A. K. El-Naggar and E. M. Sturgis (2012). "Family history of cancer and risk of sporadic differentiated thyroid carcinoma." Cancer 118(5): 1228-1235.

Yabroff, K. R., J. L. Warren and M. L. Brown (2007). "Costs of cancer care in the USA: a descriptive review." Nat Clin Pract Oncol 4(11): 643-656.

Yang, H. Y., M. R. Beymer and S. C. Suen (2019). "Chronic Disease Onset Among People Living with HIV and AIDS in a Large Private Insurance Claims Dataset." Sci Rep 9(1): 18514.

Yang, K. a. (2021). "Factors affecting stigma communication towards people living with HIV/AIDS." The Journal of Korean Academic Society of Nursing Education 27(2): 163-174.

Yang, Y. S., B. D. Han, K. Han, J. H. Jung and J. W. Son (2022). "Obesity Fact Sheet in Korea, 2021: Trends in Obesity Prevalence and Obesity-Related Comorbidity Incidence Stratified by Age from 2009 to 2019." J Obes Metab Syndr 31(2): 169-177.

Yarchoan, R. and T. S. Uldrick (2018). "HIV-Associated Cancers and Related Diseases." N Engl J Med 378(11): 1029-1041.

Yim, S. Y. and J. H. Kim (2019). "The epidemiology of hepatitis B virus infection in Korea." Korean J Intern Med 34(5): 945-953.

Yoo, I. S. (2019). The Study on the annual average direct cost incidence per cancer patient. The journal of Convergence on Culture Technology 5(4): 137-145.

Yuh, B., J. Tate, A. A. Butt, K. Crothers, M. Freiberg, D. Leaf, M. Logeais, D. Rimland, M. C. Rodriguez-Barradas, C. Ruser and A. C. Justice (2015). "Weight change after antiretroviral therapy and mortality." Clin Infect Dis 60(12): 1852-1859.

Zhao, L. J., H. Jiang, C. J. Papasian, D. Maulik, B. Drees, J. Hamilton and H. W. Deng (2008). "Correlation of obesity and osteoporosis: effect of fat mass on the determination of osteoporosis." J Bone Miner Res 23(1): 17-29.

Zhivin, S., D. Laurier, S. Caër-Lorho, A. Acker and I. Guseva Canu (2013). "Impact of chemical exposure on cancer mortality in a French cohort of uranium processing workers." American Journal of Industrial Medicine 56(11): 1262-1271.

Zhou, Z., K. Li, X. Li, R. Luan and R. Zhou (2021). "Independent and joint associations of body mass index, waist circumference, waist-height ratio and their changes with risks of hyperuricemia in middle-aged and older Chinese individuals: a population-based nationwide cohort study." Nutr Metab (Lond) 18(1): 62.

국문 초록

암과 인간면역결핍바이러스로 인한 사회경제적 부담 및 예방 가능한 질병 위험요인

장 윤 영

농경제사회학부 지역정보학전공
서울대학교 대학원

흔히 HIV라 불리는 인간면역결핍바이러스는 체내 면역 세포(CD4 양성 T-림프구)를 파괴하여 HIV 감염자의 면역력을 저하시킨다. HIV(human immunodeficiency virus) 감염으로 면역력이 저하된 상태에서는 각종 감염성 질환에 취약해진다. 시의 적절한 치료받지 않은 HIV 감염자들에게는 세 가지 질병 단계가 있다. 첫 번째 단계는 높은 바이러스 부하 즉, 감염자의 혈액에 존재하는 바이러스의 양이 많은 상태로 독감과 비슷한 증상을 보인다. 두 번째 단계는 만성 HIV 감염 상태로 무증상 잠복기이기만 바이러스 복제는 계속 이루어진다. 이 단계는 10여년 동안 지속될 수 있으나, 바이러스 복제가 빨리 진행되어 훨씬 짧을 수도 있다. 세 번째 단계는 후천성면역결핍증후군(AIDS) 상태이다. 이 단계에 이른 사람들은 바이러스 부하가 상당하고, 다른 심각한 질병에 취약하며, 치료받지 않으면 기대수명이 약 3년으로 줄어든다.

1990년부터 2019년까지 HIV 관련 전세계 통계를 보면, 1997년에 신규 HIV 감염자가 330만명으로 가장 많았고, 7년 뒤 2004년에 가장 많은 사망자 180만명을 기록하였다. 2019년에는 전 세계적으로 약 3,680만 명의 HIV

유병자가 살아가고 있고, 약 69만 명이 HIV 관련 질병으로 사망하였으며, 170만 명이 HIV에 새롭게 감염된 것으로 확인되었다.

전세계적인 추세와는 반대로, 1986년 이후 한국의 HIV 신규 감염자 수는 증가하고 있는데 특히 젊은 층에서 추세가 뚜렷하다. 2019년에는 1,222명의 HIV 신규 감염자가 발생하였고, HIV 유병자는 13,857명인 것으로 확인되었다. 이는 한국의 우수한 의료 시스템, 높은 교육 수준, 예방과 관리를 위한 민관의 노력을 고려할 때 예외적인 결과이다.

한편, 항레트로바이러스 요법(HAART)이라는 새로운 치료법의 발전으로 HIV 감염자의 기대수명이 늘어나면서 장기적인 치료로 인한 재정 부담이 가중되고 있다. 이 비용에는 HIV/AIDS 및 동반상병 의료비 등이 포함된다.

이 연구는 HIV 감염자를 주대상으로 한다. 최근 들어 HIV 감염자의 암 및 비만에 대한 우려의 목소리가 더욱 커지고 있다. HIV 감염자의 암 발생 위험이 일반 인구에 비해 높다는 것이 선행연구에서 확인되었지만, 구체적인 위험 요소들은 대체로 확실하지 않다. 특히 HIV 감염자의 암 위험 요인을 정확하게 파악하기 위한 연구는 아직 한국에서 수행되지 않았다.

예전에는 HIV 감염이 심각해지면 '소모성 질환(Wasting disease)'으로 불릴 정도로, 체중 감소 및 근육 손실이 주요 증상으로 나타났다. 그러나 바이러스 복제를 억제하고 대사수요를 감소시키는 HAART가 도입되면서, 대사수요 감소가 체중 증가로 이어져 HIV 감염자의 비만 유병률이 증가하였다. 이는 특히 치료 시작 시 저체중이었던 감염자 집단에서 두드러지게 나타났다. 최근에는 HIV/AIDS 관리 지침에 비만과 암에 대한 부분이 새롭게 추가되었다.

한국에서는 HIV/AIDS 환자에게서 AIDS 비정의암 발생이 늘어나고 있는데, 이 연구에서는 결과적으로 AIDS 비정의암 위험이 증가하는 것과 비만 사이의 연관성을 확인하였다. 따라서 HIV 감염 상태인 경우, 비만 수준을

평가하고 관리하는 것은 특히 암과 같은 만성 질환의 예방을 위해 임상적으로 중요한 것으로 사료된다.

더불어, 이 연구는 갑상선암 위험군으로 여겨지는 40세 이상 한국 여성의 갑상선암 위험요인을 탐색하였다. HIV 감염자가 대부분의 암 유형에서 일반인구에 비해 암 발생 위험이 더 높은 것으로 확인되었지만, 갑상선암에서는 반대로 일반인구에서의 암 발생 위험이 HIV 감염자보다 높았다.

연구 결과, 한국 여성의 체질량지수(BMI), 허리둘레(WC), 허리/키 비율(WHTR) 등 비만 지표와 높은 갑상선암 위험도 사이에 연관성이 있는 것으로 나타났다. 허리둘레(WC), 허리/엉덩이 비율(WHR), 허리/키 비율(WHTR)과 같은 복부 비만 지표를 전신 비만 지표인 체질량지수(BMI)와 함께 고려하였을 때, 정상 수준의 BMI 및 정상 수준의 복부 비만 지표를 가진 여성에 비해 비만 수준의 BMI 및 복부 비만 지표를 가진 여성에게서 갑상선암 위험이 현저히 증가한 것으로 확인되었다.

HIV 감염자가 일반 인구에 비해 암 발생 위험이 높은 것으로 알려져 있음에도 불구하고, HIV 감염자의 암 치료로 인한 의료시스템의 재정적 부담을 추정한 국내외 연구는 찾아보기 어렵다. 이 연구는 한국 HIV 감염자의 암 진단 후 첫 5년 기간, 그리고 사망 전 마지막 6개월 기간의 의료비를 추정하였다. 이는 HIV 감염자에서의 암과 관련된 경제적 부담에 대한 중요한 정보를 제공할 것으로 보인다.

이 주제의 주요 연구 결과는 다음과 같다. 암 관련 연간 평균 의료비는 AIDS 정의암이 AIDS 비정의암에 비해 높은 것으로 나타났다. 일반적으로, 암 진단 후 첫 1년 동안 특히 첫 1개월에 가장 많은 의료비가 지출되었다. 1인당 평균 의료비 및 암 발생 건수에 영향을 받는 총 의료비는 AIDS 정의암에 비해 AIDS 비정의암에서 더 높았다. 마지막으로, 암 진단 후 사망한 HIV 감염자의

1인당 월 평균 총 의료비는 사망시점에 가까워질수록 증가하는 경향을 보였다.

최종적으로, 이 연구는 우리 사회가 HIV 사망률을 줄이기 위해 지불하고자 하는 금액 즉, 통계적 생명가치를 추정하였다. 통계적 생명가치 방법을 적용하는 것은 한국 사회에서 HIV의 사회경제적 영향을 이해하는 데에 중요한 역할을 한다. 단순히 HIV와 관련된 의료비나 기회비용에 초점을 맞추는 것만으로는 HIV의 전반적인 영향을 충분히 파악할 수 없다. 따라서 이 연구는 한국 사회의 후생적 손실과 경제적 영향의 지표로서 통계적 생명가치에 대한 추정이 필요함을 강조하였다.

만약 특정 연령층이 인적 자본 개발에 더 많은 투자를 한다면, 그들은 HIV 사망률 감소로부터 더 큰 후생적 이익을 얻을 것이다. 따라서 인적자본 수준이 높은 30~49세는 30세 이하 또는 49세 이상 연령층에 비해 기대수명 연장에 따른 기대 이익이 높은 것으로 나타났다. 한편 45~49세 연령층의 후생적 이익이 가장 높은 것으로 나타났는데, 이는 가중치로 사용한 연령별 인구규모가 45~49세 구간에서 가장 크기 때문이다.

결론적으로 이 연구는 세 가지 새로운 사실을 제시한다. 첫째, 비만을 HIV 감염자(AIDS 비정의암) 및 40세 이상 한국 여성(갑상선암)의 위험요인으로 파악하였다. 둘째, 국내 HIV 감염자의 암 진단 후 첫 5년과 사망 전 마지막 6개월 동안의 재정적 부담에 대한 최초의 자료를 제공한다. 셋째, 사회경제적 영향과 후생적 손실의 측정 척도로서 HIV에 대한 통계적 생명가치의 중요성을 강조한다. 이 연구는 의사결정을 담당하는 의료정책 입안자뿐 만 아니라 암 위험군을 관리하고 예방하는 의료전문가들에게 참고 지표가 될 수 있기를 기대한다.

Keyword: 인간면역결핍바이러스 (HIV), 후천성면역결핍증후군 (AIDS), AIDS 정의암, AIDS 비정의암, 질병피해비용 (COI), 지불의사금액 (WTP), 통계적 생명가치 (VSL)

Student Number: 2020-39228