Economic Burden of Cancers Attributable to Infection in Korea in 2014

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ABSTRACT

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Background: Infection is a major public health hazard for a variety of cancers. Because of the time lag involved, the number of cancer cases due to infection is of considerable concern. To date, no studies have examined the economic burden of cancers linked to infection in Korea. Therefore, current information on the economic cost of infection-related cancers is required.

Methods: The economic burden of cancers attributed to infection in Korea in 2014 is estimated using a prevalence approach. Cancer patients are defined as those having made medical claims using ICD-10 (International Classification of Disease) cancer codes, as recorded by the National Health Insurance Services. Then, we multiply the costs by the population-attributable fraction for each type of cancer. The study includes direct costs and indirect costs, where direct costs comprise the direct medical and non-medical costs of inpatients and outpatients. Then, indirect costs are estimated by identifying future income losses due to premature death, productivity loss during hospitalization and outpatient visits, and job loss.

Results: In 2014, there were 100,059 infection-related cancer patients, accounting for 10.7% of all Korean cancer cases for that year. The direct costs of cancers attributed to infection stood at nearly 739 billion KRW, while the indirect costs were much higher, at 2,804 billion KRW. The average expenditure of a typical patient was 35.4 million KRW in 2014. In the case of men, cancers due to the Hepatitis B virus and Helicobacter pylori (HP) had a far greater economic burden than other cancer types. In the case of women, the Human Papilloma virus and HP caused the most burdensome infection-associated cancers.

Conclusions: Effective policies such as prevention programs and early treatment of infectious disease must be implemented to reduce the burden of cancer.

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1. Introduction

1.1 Cancer incidence and mortality

By definition, cancer, which can be called as malignancy, is a term for diseases in which abnormal cells divide without control and can invade nearby tissues [1]. Cancer cells can also spread to other parts of the body through the blood and lymph system. According to the initial cancer site, there are several main types of cancer, namely carcinoma, sarcoma, leukemia, lymphoma/multiple myeloma and central nervous system cancers. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord.

According to WHO estimates for 2011, cancer now causes more deaths than all coronary heart disease or all stroke [2]. Overall, the number of new cancer cases and deaths stood at 14.1 and 8.2 million respectively in 2012 [3]. Furthermore, in that year, incidence rates in the 50 selected registries range from over 400 per 100,000 males and 300 per 100,000 females to less than 100 per 100,000 in both males and females [4]. Mortality rates, according to the above report, were less than

50 deaths per 100,000 in both genders. Cancer constitutes an enormous burden on society regardless of development levels of countries [5].

Alike other advanced nations, the burden of disease in Korea is characterized by an increasing importance of cancer [6]. Korea's convergence with other well-developed nations in cancer burden can be reflected in their fast-changing development of living standards, the age structure, health behavior and medical technology during the past four decades [7]. These transitions have been emphasized in the Second 10-Year Plan for Cancer Control in Korea during 2006-15, government policy consisting of four main programs i.e. primary prevention, early detection, diagnosis/treatment and palliative care. In 2014, 217,057 and 76,611 Koreans were newly diagnosed and died from cancer respectively. The Age-Standardized Rates (ASR) for cancer incidence and mortality in 2014 were 270.7 and 85.1 per 100,000 respectively [8]. The all-cancer incidence rate has increased significantly by 3.4% annually from 1999 to 2012, and started to decrease after 2012. However, overall cancer mortality has decreased 2.7% annually since 2002, while 5-year survival rates have improved remarkably from 1993-1995 to 2010-2014 in Korea. Korea had the third highest age-standardized incidence rates, at 253.8 on average, 286.5 in men, and 236.3 in women per 100,000 people [9]. It is forecasted that in 2015, the burden of cancers in Korea would possibly increase to 280,556 new cancer cases and 76,698 deaths in Korea [10].

1.2 Infection-related cancers

A considerable number of infectious agents have been classified as human carcinogens Group 1 by the International Agency for Research on Cancer, these

include Helicobacter pylori (HP), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human papillomavirus (HPV), Epstein-Barr virus (EBV), Clonorchis sinensis, Human immunodeficiency virus (HIV), and Kaposi sarcoma-associated herpes virus (KSHV) [11]. In 2008, approximately 2 million new cancer cases (16%) worldwide were attributable to infection [12]. A much higher proportion of cancer deaths was attributed to these infection in low- and middle-income countries than in high-income countries, with 9% of all cancer deaths attributed to infection in high-income countries and 20% in low- and middle-income regions [13]. In Korea, the fractions of all cancers attributable to infection were 25.1% and 16.8% for cancer incidence in men and women, and 25.8% and 22.7% of cancer mortality in men and women, respectively in 2007. Among infection-related cancers, HP was responsible for 56.5% of cases and 45.1% of deaths, followed by HBV (23.9% of cases and 37.5% of deaths) and HPV (11.3% of cases and 6% of deaths) and then by HCV (6% of cases and 9% of deaths). Over 97% of infection-related cancers were attributable to infection with HP, HBV, HCV and HPV [14]. These results were partly reflected in the recent infection condition in Korea.

Burden of disease is a definition that encompasses various aspects of the disease impact on the health outcomes in a country, specific regions, communities, and even individuals; these health outcomes are typically quantified using measures of mortality YLL (Years-life-lost) or morbidity YLD (Years Lived With Disability) or Costs of Illness (COI) [15]. To produce a direct comparison among alternative options, the measurement of costs is frequently described in monetary terms. Regarding COI studies, COI estimates continue to be produced despite of well-

known and well-documented shortcomings of the technique [16]. This can be explained by that fact that such COI evaluation is of value in indicating the burden of disease and in setting priorities in research, prevention and treatment. COI research acts as an essential tool of providing highly evidenced base for health priority setting and policy formulation as well as making accurate option of healthcare resource allocation with the sake of achieving policy efficiency, especially in countries with budget constraints, eventually achieving accurate knowledge. Indeed, it has been claimed that cost of illness studies are an essential component of the evaluation of alternative demands on scarce healthcare resources [16].

In Korea, COI studies have been used as a beneficial means of expressing the economic burden of disease. With an average annual growth rate of 8.9%, the health burden of cancers in economic terms in Korea increased from 11,424 to 20,858 million US$ during 2000-2010 [17]. In particular, in 2009, estimated total economic cost of cancer amounted to $17.3 billion at a 3% discount rate. Medical care accounted for 28.3% of total costs, followed by non-medical (17.2%), morbidity (24.2%) and mortality (30.3%) costs [18]. These results suggest a noticeable characteristic of the economic burden of cancer in Korea which relies on an increasing importance of chronic components. Also, given that the direct medical cost sharply increased over the last decade, much more efforts have to be put in constructing a sustainable healthcare system that provides better care while lowering the cost. In addition, a comprehensive cancer survivorship policy aimed at lower caregiving cost and higher rate of return to work has become more important

than previously considered [18]. This highlights the necessity of COI studies execution in terms of assisting policy makers with sufficient evidence on priority setting.

To date, in terms of cancer, there have been several COI studies emphasizing large burden of specific types of cancer e.g. breast cancer [19], liver cancer [20], colorectal cancer [21], as well as groups of cancers linked to risk factors, such as smoking-related cancers [22], metabolic syndrome-related cancers [23]. This combines with a considerable effect of infection on cancer since many infection-related cancers are preventable, particularly, those associated with HPV, HP, HIV-I, HBV, HCV, and liver flukes [24]. Consequently, the economic burden of cancers attributed to infection is of great concern and being conducted to stress the need of more contingent steps to be implemented in terms of infection prevention with two specific objectives:

1. To estimate the prevalence rates of infection-related cancers in Korea in 2014.
2. To determine the direct costs of infection-related cancers in Korea in 2014.
3. To identify the indirect costs of infection-related cancers in Korea in 2014.

2. Review literature

2.1 Infection and cancer

According to part B of Volume 100 of the IARC Monographs [25], EBV, HBV, HCV, KSHV, HIV-1, HPV-16, HTLV-1, HP, Clonorchis sinensis, Opisthorchis viverini, and Schistosoma haematobium are shown with sufficient evidence to be susceptible infectious causes of certain types of cancers. Furthermore, it has been newly proven that HCV and HP are probable causes of non-Hodgkin's lymphoma and low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma, while cholangiocarcinoma was evidenced to be attributed to Clonorchis sinensis [11]. In Korea, there were no exposure with Opisthorchis viverini and Schistosoma haematobium as well as negligible cases of adult T-cell leukemia and lymphoma linked to HTLV-1 were recorded [14]. Globally, in 2015, an estimated 257 million people were living with chronic HBV infection, and 71 million people with chronic HCV infection [26]. Chronic infection with these viruses is primarily known to cause hepatocellular carcinoma [27]. Furthermore, significant increases in the incidence and prevalence of liver cancer are expected as a result of the high endemic population of patients with chronic HBV infections in the Republic of Korea [28] . On the other hand, EBV is truly prolific, with prevalence of more than 90% in the adult human population [29]. This infectious agent has been identified for being linked with various types of cancer, including nasopharyngeal carcinoma which shows extremely high prevalence in Southeast Asia [30], and Burkitt's

lymphoma with a strikingly significant number of African children patients [31]. The lists of several cancers possibly caused by other agents are described as follows:

Table 1 List of infection-related cancers according to infectious agents

Group 1 agent	Cancers for which there is sufficient evidence in humans
Epstein-Barr virus (EBV)	Nasopharyngeal carcinoma, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma
Hepatitis B virus (HBV)	Hepatocellular carcinoma
Hepatitis C virus (HCV)	Hepatocellular carcinoma, non-Hodgkin lymphoma
Kaposi's sarcoma herpes virus (KSHV)	Kaposi's sarcoma, primary effusion lymphoma
Human immunodeficiency virus, type-1 (HIV-1)	Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma, cancer of the cervix, anus, conjunctiva
Human papillomavirus type 16 (HPV-16)	Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil
Helicobacter pylori	Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma
Clonorchis sinensis	Cholangiocarcinoma

2.2 Infection-related cancers' incidence and mortality

It is predicted that the number of total cancer deaths will increase from 7.1 million in 2002 to 11.5 million in 2020 [32]. HBV, HCV, HPV, and the gram-negative bacterium as well as HP have been responsible for causing more than 90% of global infection-related cancer cases [33] . 63% of stomach cancer deaths and 73% of liver cancer mortality were caused by HP and hepatitis viruses, whereas all cervical cancer deaths were contributed by infection with HPV [13] . These infectious agents account for a strikingly large burden of new cancer cases at partly national and global levels, especially in less developed countries. Ranging from 20% to 30% of newly diagnosed cancers were associated with infectious agents in low- and middle-income countries; by contrast, the proportion of incident cancers in the US and other highly industrialized populations fluctuated between 5% and less than 10% [34] , thus, stressing the substantial impact of infection on cancer incidence worldwide [13]. In terms of global population, the health burden of infection-associated cancers had been recorded in previous years, with 1.9 million cases being witnessed in 2002 [35]. The number of incident cancer cases associated with infectious agents then saw a steady growth to 2 million cases in 2008 [36] and 2.2 million in 2012 [37], making up more than 15% of all new cancer cases in both years. 23% and 7% fewer cases were estimated to have happened in less and highly developed regions of the world respectively in case there were accessible and appropriate treatments and preventive methods brought into effect [12]. Turning to Asia where long term controls of infectious agents were not highly applied yet, the burden of infection-related cancers were much more significant, with approximately

one quarter of all cancer cases and deaths in association with infection [38]. It is estimated that 19.6% of all new cancer cases and 22% of all deaths from cancer were resulted from infection in 13 Asian countries. There were no marked difference in the fractions of cancer incidence and deaths attributable to infection in both sexes, at around 20% of the total being recorded. In terms of individual countries 'populations, according to studies published from 1981 to 2005, the incidence of infection-attributable cancers ranged between 3.6% and 29.4% [39]. The contribution of infectious agents has recently been reported as less than 5% in Western populations [40-42]. Specifically, in France in 2015, of the 352,000 new cancer cases, 14,336 (4.1% of all new cancers) were attributable to infectious agents. The largest contributors were HPV and HP, accounting for 1.8 and 1.3% of all incident cancers respectively; this highlights a non-negligible infection-related health pressure in this country. On the other hand, slightly lower percentage of cancers caused by infection was seen in Australia, at 2.9% of all cancers associated with infectious agents annually [43], while in the UK in 2010, the figure was not noticeably different compared with that for Australia, at 2.5% and 3.7% of all cancers in men and women respectively. Furthermore, infectious agents are a major cause of cancer in the East Asian region [14]. In Japan, infectious agents were described as the second major risk factor of cancers [44] with nearly one fifth of all cancer incident cases and deaths attributed to infection. Moving on to the developing world which was highly susceptible to infection-attributable cancers, in China in 2013, the proportion of cancer deaths attributable to infection was over 99% for cervical and nasopharyngeal cancer, 78% for liver cancer, 50% for Hodgkin's

lymphoma, 40% for gastric cancer, and less than 14% for oral/oropharyngeal cancer and non-Hodgkin's lymphoma [45] whereas in Nigeria, the health burden infection-related cancer placed was much more significant, with 22% of incident cases in this population attributed to infections [46].

Out of 14 million new cancer cases worldwide in 2012, 2.2 million (15.4%) were estimated to be attributed to infection [36], of which two-thirds occurred in less developed countries. In 2012, the AFs of infection-related cancers were significantly lower in highly-developed countries, at less than 5% in the USA, Canada, Australia, New Zealand, and some countries in northern and Western Europe, but more than 40% in several countries in sub-Saharan Africa and in Mongolia.

Hepatitis B virus (HBV) infection gives rise to abundant human morbidity and mortality, mainly as a consequence of chronic infection [47]. It was identified that in 2010, globally, about 248 million individuals were HBsAg positive. HBsAg seroprevalence stood at 3.61% worldwide with the highest endemic countries of the African region (8.83%) and Western Pacific region (5.26%) [48]. In Korea, according to the Annual Report of KNHANNES 2016 [49], the seropositivity rate of HBsAg was 3.1% in people aged more than 10 and 3.8% in people aged higher than 30 in 2016. Furthermore, HBsAg seropositivity rate showed a slight decrease of 0.1%, from nearly 3.2% of people older than 10 in 1998 to around 3.1% in 2016 [50]. Hepatitis C virus (HCV) infection is paid increasing global attention due to its momentous effect on morbidity and mortality [51]. Whereas HBV predominates over HCV as a cause of liver cancer in low-HDI (Human Development Index) and

medium-HDI countries, cancer burden were similarly shared between HBV and HCV in high-HDI countries, and HCV predominates in countries with very high HDI [52] (Japan). In addition, there was huge gap in the prevalence of HCV in the general public between countries because of disparities in the presence and timing of mass episodes of iatrogenic transmission and, more recently, intravenous drug use [53]. From 2000 to 2015, taking into account 138 countries worldwide, global HCV prevalence is determined at 2.5% (177 million of HCV infected adults) [54]. Central Asia and Central Africa are the highest endemicity areas (>3.5%); East, South and Southeast Asia, West and East Africa, North Africa and Middle East, Southern and Tropical Latin America, Caribbean, Australasia, and Eastern Europe moderate prevalence (1.5-3.5%); whereas Southern Africa, North America, Andean and Central Latin America, Pacific Asia and Western and Central Europe have low prevalence (<1.5%). According to Annual Report of KNHANNES 2016 [49], the seropositivity rate of anti-HCV fluctuated around 0.7% in people more than 10 years old between 2012 and 2016 in Korea.

On the other hand, more than half of all infection-related cancers in women were contributed by HPV all over the world [36]. In low-HDI countries, it made up half of infection-attributable cancers in both sexes. Growing rates of cervical cancer were seen as a result of weakly constructed screening and not highly- accessed treatment of precancerous cervical lesions, together with high prevalence of HPV and HIV infections [55]. Overall, an estimated 610,000 (4.8%) of the 12.7 million new cancer cases occurring in 2008 could be attributable to HPV worldwide [56]. 70% of cervical cancer cases were caused by HPV 16 and 18 among the most

important high-risk subtype group [57]. Cervical cancer is the second most commonly occurring cancer in women worldwide [58]. It is predicted that by 2030, there will be around 10 to 14 million incident cervical cancer cases and 5 to 8 million women will die of the disease unless effective preventive programs are well-implemented, particularly in developing countries with considerable disease burden [59]. Turning to Korea, high-risk HPV infection is common among Korean women [60]. The prevalence of genital high-risk HPV was 12.6% among Korean women aged 20-59 years. Between 1995 and 2007, adjusted overall HPV prevalence was 23.9% in women with normal cytology and 95.8% in women with cervical cancer [61], primarily being caused by type 16 irrespective of cervical disease status in Korean women.

HP, HPV, HBV and HCV took the responsibility for causing 2 million new cancer cases worldwide in 2012, with HP sharing the largest contribution [36]. The highest prevalence of HP infection was seen in Central/South America and Asia, at least twice as high in countries with significant gastric cancer incidence (i.e. Korea, Japan) [62]. In Japan, HP infection rate had already declined to 27.5% in 2008, followed by a steady decline of prevalence until 2012 [63]. In Korea, one of the countries with highest gastric cancer burden [64, 65], the prevalence of infection decreased sharply from 1998 to 2005, reaching figures as low as those in settings with already low gastric cancer risk. In Korea, the prevalence decreased between 1998 and 2005, from 50% to 20% at 20 years and from 70% to 60% at 60 years; in 2011 the prevalence was similar to the observed in 2005.

At present, an estimate of more than 200 million people are on the verge of being infected by C.sinesis globally, of which over 15 million people are infected, and 1.5-2 million people experience symptoms or complications [66] .The largest burden was seen in China, with around 13 million people infected [67]. East Asia was one of the regions with high endemicity of Clonorchiasis, but other areas with frequent flux of immigrants may see this infection commonly occur. Due to the growth and movement of population and the rapid development of aqua culture, the fact of Clonorchiasis hindering the local economic development is increasingly notified [68]. In Korea, parasitic disease has been predominated by C.sinensis-related infection [69], with the egg positive rate at 5.1% in 2014 [70]. There was no meaningful decline of the average C.sinensis infection prevalence with regards to a national survey of intestinal parasitic infections (i.e. 2.6% in 1981 and 2.4% in 2004) [71]. One main reason for that was the recurred consumption of raw fish in those endemic areas, even after the interference of praziquantel use [72]. In addition, the prevalence remained considerable in 4 major rivers in southern areas in 2006, reaching 17.1% in Nakdong-gang, 11.2% in Seomijin-gang [73]. Ongoing control programs regarding health education promotion is crucially necessary in these commonly occurring areas of Clonorchiasis in Korea [74].

It was estimated that 5.5% of new cancer cases were attributed to EBV in 2012 [36]. Of the total of 842,674 deaths from 5 types of malignancies (Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, gastric carcinoma and post-transplant lymphoproliferative disease) in 2010, 142,979 were calculated to be EBV-attributed cases, representing 1.8% of all cancer deaths in 2010

worldwide [75]. Gastric carcinoma and nasopharyngeal carcinoma made up 92% of all EBV-associated cancer deaths. East Asia became one of the highest mortality areas in accordance with an analysis of EBV-attributed malignancies in 21 world regions. Consequently, it reflected that this region, covering China, Korea and Taiwan, has by far the highest prevalence of both gastric and nasopharyngeal carcinoma in the world.

The HIV epidemic pattern has changed over the last 30 years, from the first reported cases in the early 1980s, to a significant estimate of 3.7 million new infections in 1997, along with recently decreasing new infections and AIDS-related mortality throughout the 2000s [76]. The highest burden of HIV was recorded in Sub-Saharan Africa, particularly, southern Africa (70.8%). Asia has the second largest HIV burden following Africa. Alike the sub-Saharan Africa, Asia experienced a drop in the incidence of HIV, where China and India became the highest HIV burden contributors. In 2012, there were nearly 35.3 million people being infected by HIV [77]. A rise of around 4.3 million people was seen in the prevalence of HIV worldwide from 2002 to 2012, because people treated with antiretroviral therapy are living longer [78], while global incidence saw a steady decrease, falling from 3.3 million in 2002 to 2.3 million in 2012 [76]. Looking at Republic of Korea, although HIV prevalence is very low, the number of newly reported HIV cases increases sharply since 2000, from 219 to 868 in 2012. Korea experienced a rapid increase in incidence rates from 0.68% to 2.06% between 2001 and 2016, with a high of 1,062 notification of HIV infection cases in 2016 [79].

With regards to Kaposi's sarcoma herpes virus, an incredibly high percentage of KSHV-related cancers was seen in low-HDI countries (14%, compared with 2% worldwide) [36]. Kaposi's sarcoma predominantly affects individuals younger than 50 years and continues to be a growing concern among the general population in Africa, where KSHV is common and a major part of HIV-infected individuals cannot reach the treatments on time or get access to combined antiretroviral therapy [80]. These endemic areas consist of African and Mediterranean regions, where KSHV seroprevalence varies between 20% and 80% in the adult populations, whereas the figure for in the US and Northern Europe is much lower (<10%) [81]. Based on vast numbers of epidemiologic studies, it was strongly evidenced that there was a great diversity of seroprevalence of KSHV infection by geographical locations. It is differed by geographical characteristics and ethnicity [82]. In contrast with other herpes viruses which are ubiquitous in a wide range of populations, the prevalence of KSHV varies significantly by different geographic regions. KSHV has been generally widely studied in China and Japan. According to a systematic review, the pooled seroprevalence of KSHV in China mainland stood at approximately 11.3% for the general population [83], while in Japan, results from serological assays showed that the seroprevalence of KSHV was not significant, at 1.4% among the general populations [84]. The prevalence of KSHV in Korea stood at 8.63% [85]. A slight rise was seen in the prevalence of KSHV along with increasing age among subjects in highly endemic areas, such as Nigeria and Columbia, and it considerably declined with intensified improvement in the educational attainment in these areas.

2.3 Cost of illness studies

2.3.1 Burden of disease concepts

Evaluating the burden of disease is of perpetual interest to the general public, researchers and policy makers [86]. Such assessment are employed to demonstrate the general state of health of the population and to set public health goals, to compare health status, to identify the allocation of healthcare resources, and to measure the potential costs and benefits of public health interventions. First published in 1996, the Global Burden of Disease GBD concept, was a term used for the most comprehensive and consistent estimation of mortality and morbidity around the world [87], and WHO now develops GBD as a regular tool for regional and global level estimates of more than 135 causes of disease and injury [88]. A GBD study typically includes the quantification of premature mortality and disability burden as well as providing a summary measure of population health using the index DALY and estimating the years of life lost and years lived with disabilities. Therefore, according to a standardized approach, GBD analysis is conducted annually with the purpose of enhancing the capacity to make meaningful comparisons [89] as reliable; furthermore, comparable information about the main causes of disease and incidence in populations, and its changing pattern are critically important for priority setting in the health sector [90]. To date, there have been several studies conducted to demonstrate and highlight the global burden of disease [91-94]. The GBD construct of the burden of disease is health loss, not income or productivity loss [95].

2.3.2 Cost of illness concepts

Cost of illness (COI) studies existed for one of that reason with the aim of itemizing, valuing, and summing the costs of a particular problem in the idea of pressing its economic burden [96]. Costs are most commonly measured in monetary terms for a direct comparison among alternative options [15]. Cost of illness is defined as the combination of various aspects of the disease impact on the health outcomes in a country, specific regions, communities, and even individuals [15], and was the first economic evaluation technique used in the health field [97]. Although COI studies employ various approaches and many articles have methodological limitations [98], cost of illness estimates continue to be produced for two main reasons. Firstly, it has been claimed that cost of illness studies are an essential component of the evaluation of alternative demands on scarce healthcare resources [16]. Secondly, the economic costs of illness continue to play an important role in decision making regarding the allocation of resources in the health sector as they represent the monetary burden on society of illness and premature death [99]. In summary, estimating the cost burdens of illness in society is essential to governmental and private health policy decisions [100]. It is a descriptive study that can provide information to support political process as well as the management functions at different levels of the healthcare organizations [97]. In order to help with the important execution of these studies irrespective of different methods and calculation used, these COI studies have to follow well-accepted standards to guide policymakers, researchers, and the general public understand the real-life health burden of diseases in monetary terms [98]. These standards include the disclosure of

perspectives used in guiding the study, the inclusion (whenever possible) of all affected components of care, the identification of the components of care analyzed, the description of data sources, the assurance of reasonable number of cases included, the use of publicly available data sets, the identification of costs captured, and the description of the strategy for using primary and secondary diagnosis data [98].

2.3.3 Cost of illness methodology

The description of COI studies can be prevalence-based or incidence-based regarding the way in which the epidemiological data is used [101]. Costing methodologies has three components: identification, measurement, and valuation of relevant resources [102]. Moreover, the perspective of the study also affects the scope of resources to consider [103]. These perspectives may measure costs to a society, healthcare system, third-party payers, business sectors, the government, and the participants and their families [101]. With regard to the payer's perspective, the aim is to maximize value for money under the budget since only the payer's costs matter [103]. From the societal perspective, all costs incurred, including productivity costs, matter – maximizing efficient resource allocation within society [103]. The societal perspective provides the most comprehensive information of disease-related costs as it comprises of the overall picture of direct and indirect costs for all members involving in a given society [101].

The COI studies traditionally stratify costs into 3 categories: direct, indirect, and intangible costs [15]. Measuring the so called-intangible costs as well as making an objective evaluation on their impact requires thorough validation and is of high

difficulty; as a result, intangible costs are usually excluded in COI studies [104]. Here only the first two categories are paid attention in most health economic studies. Being incurred by the health system, society, family and individual patient, the direct costs consist of medical costs which is commonly cited in the oncology literature and non-medical costs [105]. While the former is described as costs incurred during diagnosis procedures, treatments, or rehabilitation stages etc., the latter is defined as medical expenditures spent on non-healthcare resources, for example, travel fees to visit hospital clinics or payment of caregivers during hospitalization. From a payer's perspective e.g. insurance company, the direct medical costs are most important. However, from a patient's perspective, it is the actual out-of-pocket expenses (direct non-medical costs) or expenses from indirect consequences of an illness (indirect costs) that matters [106]. By definition, the term indirect costs has come to be known as the expenses incurred from the cessation or reduction of work productivity as a result of the morbidity and mortality associated with a given disease [107]. The indirect costs resulting from illness morbidity include the amount of income lost by people due to reduced productivity during illness or disability endurance, or can be categorized as job loss. Mortality costs represent the present value of future earnings lost by those individuals who die prematurely, as well as worker replacement costs for the employer. Due to the complexity of collecting retrospective data of direct non-medical costs and indirect costs as well as the less well-established challenging methods of collecting them, particularly, for the treatment of patients with malignant diseases, various cancer studies did not accept to comprehensively measure these types of costs. These costs

become largely neglected in a lot of economic analyses, specifically, in studies done from a limited perspective, such as from the payer's or a particular healthcare organization's perspective, despite the fact that such costs visibly display a real burden to society. However, several studies have suggested that these latter costs represent a significant proportion of costs in certain settings and these costs are quite important from a societal perspective [19, 21, 23]. Cost estimates that exclude these other cost components will underestimate the cost of treatment, especially therapies that may rely heavily on the time of the patient, their caregivers, and other outpatient support [106].

3. Methods

Major cancers attributable to infection were selected according to IARC (International Agency of Research on Cancer) Monograph Evaluation Carcinogenic Risks to Humans 2012 [108] . These cancer types, with regards to ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th Revision) were composed of cancers of the oral cavity (C00-C09), oropharynx (C10), nasopharynx (C11), anus (C21), Kaposi's sarcoma (C46), vulva (C51), vagina (C52), uterine cervix (C53), penis (C60), Hodgkin's sarcoma (C81), Non-Hodgkin's lymphoma (C82-85, C96), noncardia gastric cancer (C161-C168), hepatocellular carcinoma (C220), cholangiocarcinoma (C221 + C240), Burkitt's lymphoma (C837), and MALT gastric lymphoma (C884). The list of infection causing agents included HP, HBV, HCV, HPV, Clonorchis sinensis, EBV, HIV and KSHV/HIV. This study used the population attributable fraction (PAF) based on a previous research article conducted in Korea [14] .

Table 2 Population attributable fraction (PAF, %) of infection-related cancers with 95% CI [14]

Agents	Cancer sites	Men	Women
Helicobacter pylori	Noncardia gastric	80.3 (66.7-88.5)	78.7 (64.5-87.5)
	MALT gastric lymphoma	81.5 (45.4-94.0)	80.0 (43.0-93.4)
HBV	Hepatocellular carcinoma	68.1 (65.8-70.3)	69.9 (60.2-78.0)
	Cholangiocarcinoma	12.8 (4.3-24.6)	10.3 (3.4-20.3)
HCV	Hepatocellular carcinoma	15.2 (3.1-43.2)	18.8 (4.0-49.6)
	Cholangiocarcinoma	1.4 (0.7-2.4)	1.8 (0.8-3.0)
	Non-Hodgkin's lymphoma	2.5 (1.8-3.3)	3.2 (2.3-4.2)

HPV	Uterine cervix		100
	Vulva		40
	Vagina		40
	Penis	40	
	Oral cavity	3	3
	Oropharynx	12	12
	Anus	90	90
Clonorchis sinensis	Cholangiocarcinoma	11.9 (4.3-24.5)	5.5 (1.9-12.3)
EBV	Nasopharynx	90	90
	Hodgkin's lymphoma	46	46
	Burkitt's lymphoma	25	25
HIV	Anus	0.07	0.06
	Uterine cervix		0.24
	Hodgkin's lymphoma	0.21	0.16
	Non-Hodgkin's lymphoma	1.08	1.58
KSHV/HIV	Kaposi's sarcoma	100	100

The total economic costs of cancers due to infection were measured by multiplying the costs of each cancer site by their respective PAFs as described in the following formula:

Infection-attributable cost = Total costs per cancer site x PAF

The economic burden of cancers due to infection was evaluated using a prevalence-based approach targeting existing and newly diagnosed patients. Numerous studies have selected National Health Insurance Service (NHIS) as the primary dataset for cost analysis of specific diseases in Korea [19-21], as NHIS provides universally mandatory insurance programs in this country [109] . In this study, medical claims data provided by 2014 NHIS was employed and the data

costs with special code-V193 of infection-attributable cancers were computed. The study population was patients who visited medical institutions for the treatment of infection-related cancers or had been hospitalized and had primary diagnosis of these cancer types. Due to the time-lag characteristic in cancers attributable to infection, the participants of interest consisted of only those aged 20 years and above [12].

Total economic burden of infection-related cancers included direct costs, indirect costs, and intangible costs [110]. Intangible costs, however, are difficult to quantify and converted to monetary terms as it is defined as costs associated with pain, suffering, or bereavement. Direct costs are costs required during the period of medical treatment, composed of direct medical and non-medical care costs. While the former component is considered as costs incurred with hospitalization, outpatient visits, and prescribed pharmaceuticals, the latter element is related to transportation costs used for inpatient/outpatient travels and caregivers' cost. Indirect costs, as productivity loss due to premature death and absences following hospitalization and outpatient visits to clinics, are estimated in accordance with human capital approach.

To obtain direct medical care costs, medical claims records from 2014 NHIS were used targeting existing and newly diagnosed patients of infection-attributable cancers. However, one limitation of this database is that it does not provide information about the non-covered medical services employed by such cancer patients, such as food expenses or fees for specialized treatments/diagnosis and costs incurred by poor or non-insured patients; as a result, the non-covered costs

were calculated using the non-coverage rate given by previous study, at 19.9% [111]. As for direct non-medical care costs, the quantification was accomplished by acquiring transportation costs of inpatient and outpatient visits and total payments of caregivers. The one-way transportation fees per inpatient and outpatient visit were obtained by analyzing raw data from 2014 Korea Health Panel Survey (KHPS), at 15,000 KRW and 4,000 KRW respectively; it then was used together with the frequency of visits in order to achieve transportation costs. Based on 2014 KHPS, the overall daily wage of caregivers was estimated to be 63,000 KRW along with the utilization rate of 67% among inpatients only. Caregivers' costs were broken down into costs incurred during inpatient and outpatient care. For inpatient care costs, it was assumed that each inpatient was accompanied by a guardian for the entire day; thus the cost was calculated by including the daily caregiver payment, days of hospitalized admission, and nursing utilization rate. Moreover, for the outpatient study population aged 65 and above, costs paid by outpatients were determined by multiplying the days that patients visited outpatient clinics by one third of the caregivers' wage per day.

Formula:

$$DC=\sum_i \sum_j \sum_y \{(1+\propto) IP_{ijy} + (1+\propto) OP_{ijy}\} \times PAF_{iy} + \sum_i \sum_j \sum_y \{(IV_{ijy} \times TIV \times 2) + (OV_{ijy} \times TOV \times 2)\} \times PAF_{iy} + \sum_i \sum_j \sum_y \left\{(IV_{ijy} \times CGR \times C) + \left(\frac{1}{3} \times OV'_{ijy} \times CGR\right)\right\} \times PAF_{iy}$$

DC = direct costs; j = age; i = gender; y = cancer type

IP = total treatment amount of inpatients of i and j in NHIS data

OP = total treatment amount of outpatients of i and j in NHIS data

α = the proportion between non-coverage and coverage rate (in this study, α = 19.9/80.1)

IV = number of days of inpatient visits

OV = number of days of outpatient visits

TIV = cost per one-way trip to hospitals among inpatients

TOV = cost per one-way trip to hospitals among outpatients

CGR = caregivers' average wage per day

C = utilization rate

OV' = number of days of outpatient visits among those aged 65 and above

PAF = population attributable fraction

In this study, indirect costs consisted of future lost income, productivity loss during inpatient/outpatient visits and job loss. In order to identify future income loss, human capital approach was taken into account, considering the present values of future earnings that each prematurely deceased person might have gained from the year of their deaths until the average life expectancy during their lifetime. In particular, human capital approach was made under the assumption that future incomes acts as a substitute of future productivity though not representing precisely in several cases [15]. Productivity loss due to premature death was classified as lost potential future incomes being converted into present values using data from Cause of Death Statistics [112], employment rate, annual average wage by sex and age according to Korea Ministry of Employment and Labor (2014) [113] with a discount rate of 3% per year.

Formula:

$$\text{FIL} = \sum_i \sum_j \sum_t \sum_{k=1}^{n} \left\{ D_{ijt} \times DPAF_{iy} \times \left(\frac{YW_{ij(t+k)} \times E_{ij(t+k)}}{(1+r)^k} \right) \right\}$$

FIL = future income loss

i = sex; j = age; t = age at death

y = cancer type

k = 1, 2,…., n (n is the difference between age of death and life expectancy of the age cohort)

D = number of deaths

DPAF = death population attributable fractions

YW = yearly wage by i and j

E = employment rates by i and j

r = discount rate

To calculate loss of productivity due to visits to medical institutions and hospitalization, the total numbers of outpatient visits and inpatient days of admission were collected through NHIC claims data, which were then combined with age and sex-specific Employment Rate and per month salaries.

Formula:

$$\text{PL} = \sum_i \sum_j \sum_y \left\{ \left(IV_{ijy} + \frac{1}{2} OV_{ijy} \right) \times PAF_{iy} \times E_{ij} \times DW_{ij} \right\}$$

PL = productivity loss

i = sex; j = age; y = cancer type

IV = number of inpatient visits

OV = number of outpatient visits

E = employment rates

DW = daily wage

PAF = population attributable fraction

Job loss was defined by addressing the number of pre-existing and newly diagnosed infection-attributable cancer cases along with the overall job loss rate in Korea, at 47% [114]. These figures were used together with employment rate and daily average wage by age and gender to determine the costs incurred due to unemployment after cancer diagnosis.

Formula:

$$\text{JL} = \sum_i \sum_j \sum \left(N_{ijy} \times YW_{ij} \times E_{ij} \times L \times PAF_{iy} \right)$$

JL = job loss

N = number of prevalent cancer cases

i = sex; j = age; y = cancer type

YW = yearly wage

E = employment rates

L = job loss rate

PAF = population attributable fraction

Sensitivity analysis was performed for the productivity loss following premature death with 0% and 5% annual discount rates. Furthermore, sensitivity analysis was stratified by non-insured healthcare costs and the upper and lower bound of 95% confidence interval (CI) of PAF. All the analysis included was conducted using SAS and Excel 2013.

Table 3 Types of costs, description, and sources of data

Type of costs		Description	Data sources
Direct costs	Direct medical costs	Medical care covered by NHIS	NHIS claims data (2014)
		Medical care not covered by NHIS	Survey on the Benefit Coverage Rate of NHIS (2014) [111]
	Direct non-medical costs		
	Transportation costs	One-way cost per visit	Korea Health Panel Survey (2014)
		Frequency of inpatient/outpatient visits	NHIS claims data (2014)
	Caregivers' costs	Days of inpatient admission	NHIS claims data (2014)
		Frequency of over-65-year-old outpatients	NHIS claims data (2014)
		Caregivers' daily wage and utilization rate	Korea Health Panel Survey (2014)
Indirect costs	Future income loss	Number of cancer specific deaths	Cause of death statistics, Korea (2014)
		Employment rates	Ministry of Employment and Labor, Korea (2014)

		Average annual wage	Ministry of Employment and Labor, Korea (2014)
		Life expectancy	Life tables, Statistics Korea (2014)
	Productivity loss	Frequency of inpatient/outpatient visits	NHIS claims data (2014)
		Employment rates	Ministry of Employment and Labor, Korea (2014)
		Average daily wage	Ministry of Employment and Labor, Korea (2014)
	Job loss	Number of cancer cases	NHIS claims data (2014)
		Job loss average rate	Park J.H. et al. (2008) [114]
		Employment rates	Ministry of Employment and Labor, Korea (2014)
		Average daily wage	Ministry of Employment and Labor, Korea (2014)

4. Results

4.1 Prevalence

In 2014, there were approximately 100,059 infection-related cancer patients in Korea, accounting for nearly 10.7% of all cancer cases in that year, of which no remarkable difference in the figures for males and females was recorded with a relatively equal share of less and more than 50,000 patients for each sex. Overall, the largest numbers of prevalent cancers attributed to infection were seen in people in the mid-50s to 60s; the same pattern was seen in men whereas in women, infection-attributable cancers were more common among the age group of 70-74 in addition to those in fifties. According to infectious agents, HP represents the highest factor for causing nearly 35% of all infection-related cancers, followed by HBV and HPV irrespective of gender. In particular, HPV became the most frequent infection-related cancer causing agent, with around 45% of all these cases attributed to this factor in women, while in men, HCV stood out to be highest.

Table 4 Prevalence rates of infection-related cancers by infectious agents and sex in Korea, 2014 (Unit: per 100,000 people)

Men	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**
Prevalence	117	124	28	3	4	8	0	1	286
Women	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**
Prevalence	55	35	10	90	1	3	1	0 (0.17)	196
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**
Prevalence	85	79	19	48	2	6	1	0 (0.43)	240

As clearly illustrated from table 4, the prevalence rate of cancers due to infection in Korea stood at approximately 240 per 100,000. It is also noticeable that HP and HBV were the most common infectious agents causing cancers in both sexes and that men always showed a much higher prevalence rates compared with women.

Table 5 Number of prevalent cases of infection-related cancers applying PAF by sex and infectious agents in Korea, 2014

Men	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	9	8	7	4	0 (0.119)	64	2	1	94	0.16
25-29	29	16	8	3	0 (0.238)	46	2	2	105	0.18
30-34	108	90	27	5	1	67	3	1	303	0.52
35-39	262	251	65	13	2	83	4	2	683	1.18
40-44	720	760	182	17	8	125	6	4	1,822	3.14
45-49	1,358	1,695	393	30	19	162	7	8	3,672	6.34
50-54	2,546	3,459	790	67	42	248	10	7	7,169	12.37
55-59	3,494	4,807	1,091	79	83	243	13	5	9,815	**16.93**
60-64	3,608	4,219	953	94	104	200	11	12	9,202	**15.88**
65-69	3,790	3,678	830	87	132	168	11	13	8,708	**15.03**
70-74	3,601	3,071	691	93	156	122	11	30	7,776	13.42
75-59	2,627	2,039	456	77	142	73	8	26	5,447	9.40
80+	1,503	1,158	256	66	109	32	5	32	3,161	5.45
Total	23,656	25,250	5,749	635	800	1,633	93	143	**57,959**	100.00
%	**40.81**	**43.57**	**9.92**	1.10	1.38	2.82	0.16	0.25	100.00	
Women	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	17	7	5	20	0 (0.055)	39	2	0	89	0.21

25-29	55	11	7	217	0 (0.110)	33	3	0	328	0.78
30-34	153	37	18	978	0 (0.440)	42	6	0	1,234	2.93
35-39	289	81	30	1,476	1	43	8	1	1,928	4.58
40-44	672	143	51	2,174	2	64	11	0	3,116	7.40
45-49	883	300	96	2,659	4	67	14	1	4,024	9.56
50-54	1,207	614	186	2,717	10	77	18	4	4,833	**11.48**
55-59	1,444	982	291	2,466	17	91	20	8	5,319	**12.63**
60-64	1,266	1,094	313	1,861	22	51	16	2	4,625	10.99
65-69	1,407	1,205	343	1,512	33	48	16	4	4,567	10.85
70-74	1,729	1,280	362	1,420	44	52	16	4	4,906	**11.65**
75-59	1,459	1,060	297	1,023	48	37	12	4	3,940	9.36
80+	1,223	791	218	857	56	28	9	9	3,190	7.58
Total	11,803	7,606	2,217	19,379	236	672	151	37	**42,100**	100.00
%	**28.04**	**18.07**	5.27	**46.03**	0.56	1.60	0.36	0.09	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	26	15	12	23	0 (0.174)	102	4	1	184	0.18
25-29	85	27	15	220	0 (0.348)	79	5	2	433	0.43
30-34	260	127	45	983	1	110	9	1	1,537	1.54
35-39	551	332	95	1,489	3	126	12	3	2,612	2.61

40-44	1,392	903	233	2,191	9	189	17	4	4,938	4.93
45-49	2,240	1,994	489	2,689	24	229	22	9	7,695	7.69
50-54	3,754	4,073	976	2,785	52	324	28	11	12,002	12.00
55-59	4,938	5,789	1,382	2,545	99	335	33	13	15,134	**15.13**
60-64	4,875	5,313	1,267	1,955	127	251	26	14	13,827	**13.82**
65-69	5,197	4,883	1,173	1,599	165	215	27	17	13,276	**13.27**
70-74	5,330	4,351	1,053	1,514	200	174	26	34	12,682	12.67
75-59	4,086	3,099	753	1,099	189	109	20	30	9,387	9.38
80+	2,725	1,949	474	922	165	61	14	41	6,352	6.35
Total	35,459	32,856	7,966	20,015	1,036	2,304	244	180	**100,059**	100.00
%	**35.44**	**32.84**	7.96	**20.00**	1.04	2.30	0.24	0.18	100.00	

4.2 Direct medical costs

In Korea, the total spending paid by both the insurer and infection-related cancer inpatients and outpatients themselves during cancer diagnosis/treatment/rehabilitation stood at approximately 669 billion KRW, of which nearly two thirds were contributed by male expenditures. Regardless of gender, HBV, HP and HPV were responsible for around 80% of direct medical costs, and the figures were seen highest in the ages of 50-64. Looking in more detail, the pattern of increasing costs in people aged between 50 and 64 was again noticed in males, while in females, rather than the age group of 60-64, patients aged from 65 to 69 were shown to have experienced cancers associated infection quite frequently. In men, nearly half of medical expenditure used for diagnosing/treating infection-related cancers relied on HBV. By contrast, in women, more than 40% of direct medical costs were spent on cancers linked to HPV, followed by HBV (27%) and HP (19%). Furthermore, with regards to Table 5 and 6 providing information about costs among inpatients and outpatients, it can be clearly seen that expenditure of inpatient care (478 billion KRW) was almost more considerable than outpatient care spending (191 billion KRW) by infection types.

Table 6 Direct medical costs of inpatients of infection-related cancers (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	20,475,028	73,756,914	65,109,489	4,184,381	2,332,556	246,679,558	21,802,173	1,155,855	435,495,953	0.14
25-29	124,915,820	245,621,295	95,404,470	5,863,016	0	166,713,376	17,956,182	36,736,667	693,210,826	0.22
30-34	435,574,176	980,234,443	277,143,124	23,828,472	4,806,536	293,816,878	26,170,521	718,277	2,042,292,428	0.64
35-39	928,755,370	2,381,683,888	598,215,647	67,133,264	49,846,303	444,751,087	31,767,919	1,263,196	4,503,416,672	1.42
40-44	2,211,063,000	6,540,824,897	1,552,140,599	46,389,335	105,422,280	547,585,898	46,116,341	0	11,049,542,349	3.49
45-49	4,267,848,848	14,616,324,175	3,405,390,221	224,404,869	219,831,018	840,870,244	74,417,101	24,320,587	23,673,407,062	7.47
50-54	7,581,886,319	29,854,106,879	6,801,466,672	319,346,204	563,153,559	1,393,961,095	90,129,567	29,929,863	46,633,980,157	**14.72**
55-59	10,223,337,112	37,273,188,147	8,462,293,751	386,137,564	965,216,244	1,176,477,420	113,880,657	0	58,600,530,895	**18.50**
60-64	9,717,881,272	29,690,657,874	6,740,469,106	471,993,614	1,225,601,610	942,767,474	114,817,078	18,565,106	48,922,753,135	**15.45**
65-69	10,098,656,036	24,590,759,693	5,537,862,044	395,960,635	1,508,758,970	673,043,900	101,488,790	29,127,628	42,935,657,697	13.56
70-74	10,420,564,393	19,053,711,086	4,265,273,354	430,039,454	1,713,497,771	782,493,990	97,004,241	31,586,192	36,794,170,482	11.62
75-79	7,667,349,191	12,473,615,219	2,796,013,804	364,283,528	1,408,268,573	376,582,652	80,257,480	18,197,066	25,184,567,513	7.95
80&above	4,987,470,817	7,007,855,075	1,539,449,708	257,535,275	1,068,941,460	251,954,628	46,109,818	82,627,016	15,241,943,799	4.81
Total	68,685,777,384	184,782,339,583	42,136,231,990	2,997,099,611	8,835,676,880	8,137,698,200	861,917,868	274,227,453	**316,710,968,968**	100
%	**21.69**	**58.34**	**13.30**	0.95	2.79	2.57	0.27	0.09	100	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	49,067,208	83,285,107	51,142,338	48,268,803	34,608	211,762,381	14,945,480	0	458,505,925	0.28
25-29	150,857,326	150,538,901	71,880,293	715,166,432	1,184,166	83,746,471	17,470,280	0	1,190,843,869	0.74
30-34	631,245,797	398,511,873	161,391,192	2,537,357,933	6,491,577	167,659,541	33,744,650	0	3,936,402,563	2.44
35-39	957,090,611	844,958,034	292,182,480	4,473,225,068	5,058,783	148,214,591	43,283,899	0	6,764,013,465	4.19
40-44	2,425,842,628	1,043,365,294	375,866,104	6,654,031,861	16,681,561	454,416,396	64,427,965	0	11,034,631,808	6.83
45-49	2,389,052,930	2,028,051,634	668,656,800	7,677,875,540	49,687,577	215,732,825	83,330,526	0	13,112,387,832	8.12
50-54	3,543,098,327	5,019,750,655	1,504,668,877	9,169,408,013	123,005,658	426,858,763	108,641,240	10,645,156	19,906,076,689	**12.32**

55-59	3,233,578,866	6,803,943,753	2,031,511,732	7,977,510,976	223,082,931	401,924,989	137,718,116	4,502,484	20,813,773,848	**12.89**
60-64	2,812,531,172	6,710,465,603	1,938,735,014	5,694,617,276	287,729,800	205,603,346	104,265,205	10,986,816	17,764,934,231	11.00
65-69	3,145,449,880	7,762,011,121	2,224,811,246	4,385,274,979	387,517,196	207,063,541	111,427,117	728,926	18,224,284,005	**11.28**
70-74	3,723,029,352	6,676,425,458	1,899,998,715	3,387,490,665	511,447,074	193,873,168	103,762,376	13,253,895	16,509,280,702	10.22
75-79	3,766,366,181	6,676,425,458	1,899,998,715	3,387,490,665	511,447,074	193,873,168	103,762,376	13,253,895	16,552,617,531	10.25
80&above	4,207,872,956	4,917,150,583	1,354,841,922	3,955,256,634	535,679,573	151,428,955	71,027,422	64,619,326	15,257,877,369	9.45
Total	31,035,083,234	49,114,883,472	14,475,685,426	60,062,974,846	2,659,047,577	3,062,158,133	997,806,650	117,990,499	**161,525,629,838**	100.00
%	**19.21**	**30.41**	8.96	**37.18**	1.65	1.90	0.62	0.07	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	69,542,236	157,042,021	116,251,826	52,453,184	2,367,164	458,441,939	36,747,652	1,155,855	894,001,877	0.19
25-29	275,773,146	396,160,195	167,284,763	721,029,447	1,184,166	250,459,847	35,426,463	36,736,667	1,884,054,695	0.39
30-34	1,066,819,973	1,378,746,315	438,534,316	2,561,186,405	11,298,113	461,476,419	59,915,172	718,277	5,978,694,991	1.25
35-39	1,885,845,981	3,226,641,922	890,398,127	4,540,358,332	54,905,085	592,965,677	75,051,817	1,263,196	11,267,430,138	2.36
40-44	4,636,905,627	7,584,190,190	1,928,006,702	6,700,421,196	122,103,841	1,002,002,295	110,544,306	0	22,084,174,157	4.62
45-49	6,656,901,779	16,644,375,808	4,074,047,022	7,902,280,409	269,518,594	1,056,603,069	157,747,626	24,320,587	36,785,794,895	7.69
50-54	11,124,984,647	34,873,857,534	8,306,135,549	9,488,754,216	686,159,217	1,820,819,858	198,770,806	40,575,019	66,540,056,846	**13.91**
55-59	13,456,915,979	44,077,131,900	10,493,805,483	8,363,648,540	1,188,299,175	1,578,402,409	251,598,773	4,502,484	79,414,304,742	**16.61**
60-64	12,530,412,444	36,401,123,477	8,679,204,120	6,166,610,889	1,513,331,410	1,148,370,820	219,082,282	29,551,923	66,687,687,366	**13.94**
65-69	13,244,105,916	32,352,770,814	7,762,673,290	4,781,235,614	1,896,276,165	880,107,442	212,915,907	29,856,554	61,159,941,702	12.79
70-74	14,143,593,746	25,730,136,543	6,165,272,069	3,817,530,119	2,224,944,845	976,367,158	200,766,617	44,840,087	53,303,451,184	11.15
75-79	11,433,715,372	19,150,040,677	4,696,012,519	3,751,774,194	1,919,715,647	570,455,819	184,019,856	31,450,961	41,737,185,045	8.73
80&above	9,195,343,773	11,925,005,657	2,894,291,630	4,212,791,910	1,604,621,034	403,383,583	117,137,240	147,246,342	30,499,821,168	6.38
Total	99,720,860,619	233,897,223,054	56,611,917,416	63,060,074,456	11,494,724,457	11,199,856,333	1,859,724,518	392,217,953	**478,236,598,806**	100.00
%	**20.85**	**48.91**	11.84	**13.19**	2.40	2.34	0.39	0.08	100.00	

Table 7 Direct medical costs of outpatients of infection-related cancers (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	18,958,773	7,217,984	13,731,634	7,580,794	106,164	183,192,954	5,741,490	284,220	236,814,013	0.21
25-29	52,325,889	43,038,254	20,337,881	4,288,716	206,871	145,538,846	5,075,502	3,081,860	273,893,820	0.24
30-34	181,714,932	203,687,664	67,201,705	7,303,124	2,363,411	347,165,786	9,904,599	418,839	819,760,061	0.72
35-39	385,234,347	618,819,969	163,930,444	42,058,978	6,863,492	456,235,827	11,897,015	3,415,156	1,688,455,228	1.48
40-44	996,152,843	1,829,474,083	444,062,560	45,904,054	23,619,500	593,868,847	17,045,332	9,862,335	3,959,989,553	3.47
45-49	2,014,246,694	4,514,651,211	1,054,062,539	127,420,659	49,194,331	904,686,085	23,071,581	9,025,156	8,696,358,257	7.61
50-54	3,379,309,677	10,213,552,370	2,335,891,037	216,545,369	113,899,996	1,042,495,275	30,873,478	37,598,727	17,370,165,927	**15.20**
55-59	4,486,109,369	13,357,133,288	3,038,402,894	250,221,123	241,448,837	1,076,644,215	38,070,152	10,522,971	22,498,552,849	**19.69**
60-64	4,509,678,354	10,813,196,969	2,454,923,847	282,328,070	268,705,491	797,883,396	32,554,509	23,204,782	19,182,475,417	**16.79**
65-69	4,676,220,748	8,272,388,035	1,883,873,973	279,817,626	304,772,992	667,744,465	32,682,981	17,209,863	16,134,710,683	14.12
70-74	4,444,970,403	5,873,964,470	1,351,348,690	192,831,181	283,785,048	444,906,093	32,735,702	41,964,095	12,666,505,681	11.08
75-79	2,815,987,830	3,263,678,184	751,231,974	186,324,811	192,252,793	248,181,985	20,277,415	52,292,709	7,530,227,700	6.59
80&above	1,226,853,017	1,339,199,756	308,173,397	113,176,375	87,889,156	78,904,987	8,762,830	50,554,020	3,213,513,538	2.81
Total	29,187,762,875	60,350,002,235	13,887,172,574	1,755,800,882	1,575,108,082	6,987,448,761	268,692,587	259,434,732	**114,271,422,729**	100.00
%	**25.54**	**52.81**	**12.15**	1.54	1.38	6.11	0.24	0.23	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	21,016,683	11,458,735	10,935,239	42,694,573	705,244	140,592,497	4,496,287	39,988	231,939,244	0.30
25-29	68,720,339	16,230,600	15,968,496	423,018,648	191,679	129,978,072	7,081,044	0	661,188,879	0.87
30-34	260,734,853	87,366,708	46,078,031	1,815,123,018	1,852,412	124,367,914	15,866,000	0	2,351,388,936	3.08
35-39	374,534,578	168,148,392	68,504,688	2,878,856,265	3,345,836	140,284,522	18,745,812	21,973	3,652,442,066	4.79
40-44	1,053,305,434	316,469,090	117,271,328	4,369,562,739	3,766,890	300,330,433	26,664,751	72,197	6,187,442,863	8.11
45-49	1,149,380,347	742,799,617	238,857,147	5,222,276,516	8,906,142	286,520,493	32,338,027	968,040	7,682,046,328	10.07
50-54	1,583,231,744	1,574,291,594	474,836,040	6,180,398,634	26,700,385	269,392,887	42,139,769	965,169	10,151,956,221	**13.31**

55-59	1,875,548,711	2,503,816,402	743,895,693	5,351,953,327	47,772,810	350,304,203	51,441,983	5,533,333	10,930,266,463	**14.33**
60-64	1,514,928,111	2,690,529,339	775,160,552	3,796,229,385	54,756,323	163,208,349	38,913,751	2,918,489	9,036,644,300	**11.85**
65-69	1,665,154,098	2,776,226,074	798,881,554	3,268,355,997	72,835,956	159,742,741	39,388,780	5,057,428	8,785,642,630	11.52
70-74	1,890,533,801	2,267,206,059	657,922,908	2,893,565,388	71,832,576	123,456,235	36,435,701	2,563,795	7,943,516,463	10.42
75-79	1,468,682,515	1,517,073,639	441,216,622	1,866,561,935	59,878,516	69,660,168	25,727,434	2,091,598	5,450,892,428	7.15
80&above	831,071,478	691,346,734	203,892,949	1,342,446,766	34,453,272	78,953,849	14,861,491	5,921,486	3,202,948,024	4.20
Total	13,756,842,692	15,362,962,983	4,593,421,248	39,451,043,191	386,998,042	2,336,792,364	354,100,830	26,153,496	**76,268,314,845**	100.00
%	**18.04**	**20.14**	6.02	**51.73**	0.51	3.06	0.46	0.03	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	39,975,456	18,676,719	24,666,873	50,275,368	811,408	323,785,451	10,237,777	324,207	468,753,258	0.25
25-29	121,046,228	59,268,854	36,306,377	427,307,364	398,551	275,516,919	12,156,546	3,081,860	935,082,699	0.49
30-34	442,449,785	291,054,373	113,279,736	1,822,426,142	4,215,824	471,533,700	25,770,599	418,839	3,171,148,997	1.66
35-39	759,768,926	786,968,360	232,435,132	2,920,915,243	10,209,328	596,520,350	30,642,827	3,437,129	5,340,897,295	2.80
40-44	2,049,458,276	2,145,943,173	561,333,888	4,415,466,794	27,386,391	894,199,279	43,710,083	9,934,532	10,147,432,416	5.33
45-49	3,163,627,041	5,257,450,828	1,292,919,686	5,349,697,176	58,100,473	1,191,206,578	55,409,608	9,993,196	16,378,404,586	8.60
50-54	4,962,541,422	11,787,843,964	2,810,727,077	6,396,944,002	140,600,381	1,311,888,162	73,013,246	38,563,895	27,522,122,148	**14.44**
55-59	6,361,658,080	15,860,949,690	3,782,298,587	5,602,174,450	289,221,647	1,426,948,418	89,512,135	16,056,305	33,428,819,312	**17.54**
60-64	6,024,606,464	13,503,726,308	3,230,084,400	4,078,557,455	323,461,814	961,091,744	71,468,261	26,123,271	28,219,119,717	**14.81**
65-69	6,341,374,846	11,048,614,109	2,682,755,528	3,548,173,623	377,608,948	827,487,207	72,071,761	22,267,291	24,920,353,313	13.08
70-74	6,335,504,203	8,141,170,529	2,009,271,597	3,086,396,569	355,617,624	568,362,328	69,171,403	44,527,890	20,610,022,143	10.82
75-79	4,284,670,345	4,780,751,823	1,192,448,596	2,052,886,746	252,131,309	317,842,153	46,004,850	54,384,307	12,981,120,128	6.81
80&above	2,057,924,495	2,030,546,490	512,066,346	1,455,623,142	122,342,427	157,858,836	23,624,321	56,475,506	6,416,461,562	3.37
Total	42,944,605,566	75,712,965,219	18,480,593,822	41,206,844,073	1,962,106,124	9,324,241,126	622,793,417	285,588,227	**190,539,737,574**	100.00
%	**22.54**	**39.74**	9.70	**21.63**	1.03	4.89	0.33	0.15	100.00	

Table 8 Direct medical costs due to infection-related cancers (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	39,433,801	80,974,898	78,841,123	11,765,175	2,438,720	429,872,512	27,543,662	1,440,075	672,309,966	0.16
25-29	177,241,709	288,659,548	115,742,351	10,151,732	206,871	312,252,223	23,031,685	39,818,527	967,104,646	0.22
30-34	617,289,109	1,183,922,107	344,344,829	31,131,596	7,169,948	640,982,664	36,075,121	1,137,116	2,862,052,489	0.66
35-39	1,313,989,717	3,000,503,856	762,146,091	109,192,242	56,709,795	900,986,914	43,664,934	4,678,352	6,191,871,901	1.44
40-44	3,207,215,842	8,370,298,980	1,996,203,159	92,293,389	129,041,780	1,141,454,745	63,161,673	9,862,335	15,009,531,902	3.48
45-49	6,282,095,542	19,130,975,386	4,459,452,761	351,825,528	269,025,349	1,745,556,329	97,488,682	33,345,743	32,369,765,320	7.51
50-54	10,961,195,996	40,067,659,249	9,137,357,709	535,891,572	677,053,554	2,436,456,370	121,003,044	67,528,589	64,004,146,084	**14.85**
55-59	14,709,446,481	50,630,321,435	11,500,696,645	636,358,687	1,206,665,081	2,253,121,635	151,950,809	10,522,971	81,099,083,744	**18.82**
60-64	14,227,559,626	40,503,854,843	9,195,392,954	754,321,684	1,494,307,102	1,740,650,869	147,371,587	41,769,888	68,105,228,552	**15.80**
65-69	14,774,876,784	32,863,147,728	7,421,736,017	675,778,261	1,813,531,961	1,340,788,366	134,171,772	46,337,491	59,070,368,380	13.71
70-74	14,865,534,796	24,927,675,555	5,616,622,044	622,870,634	1,997,282,819	1,227,400,083	129,739,943	73,550,287	49,460,676,162	11.48
75-79	10,483,337,021	15,737,293,403	3,547,245,777	550,608,340	1,600,521,366	624,764,636	100,534,896	70,489,775	32,714,795,214	7.59
80&above	6,214,323,834	8,347,054,831	1,847,623,105	370,711,651	1,156,830,616	330,859,615	54,872,649	133,181,036	18,455,457,336	4.28
Total	97,873,540,259	245,132,341,818	56,023,404,564	4,752,900,493	10,410,784,962	15,125,146,961	1,130,610,455	533,662,185	**430,982,391,697**	100.00
%	**22.71**	**56.88**	**13.00**	1.10	2.42	3.51	0.26	0.12	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	70,083,890	94,743,842	62,077,576	90,963,376	739,852	352,354,878	19,441,767	39,988	690,445,169	0.29
25-29	219,577,665	166,769,501	87,848,789	1,138,185,080	1,375,845	213,724,543	24,551,324	0	1,852,032,748	0.78
30-34	891,980,650	485,878,581	207,469,223	4,352,480,951	8,343,990	292,027,455	49,610,650	0	6,287,791,499	2.64
35-39	1,331,625,189	1,013,106,426	360,687,168	7,352,081,333	8,404,619	288,499,113	62,029,711	21,973	10,416,455,532	4.38
40-44	3,479,148,062	1,359,834,384	493,137,431	11,023,594,600	20,448,451	754,746,829	91,092,716	72,197	17,222,074,671	7.24
45-49	3,538,433,277	2,770,851,250	907,513,947	12,900,152,057	58,593,719	502,253,318	115,668,552	968,040	20,794,434,161	8.74
50-54	5,126,330,072	6,594,042,249	1,979,504,917	15,349,806,646	149,706,044	696,251,649	150,781,008	11,610,325	30,058,032,910	**12.64**

55-59	5,109,127,577	9,307,760,155	2,775,407,425	13,329,464,302	270,855,742	752,229,192	189,160,099	10,035,818	31,744,040,311	**13.35**
60-64	4,327,459,282	9,400,994,942	2,713,895,566	9,490,846,660	342,486,123	368,811,695	143,178,956	13,905,306	26,801,578,530	11.27
65-69	4,810,603,978	10,538,237,195	3,023,692,800	7,653,630,976	460,353,152	366,806,283	150,815,896	5,786,355	27,009,926,635	**11.36**
70-74	5,613,563,153	8,943,631,517	2,557,921,623	6,281,056,054	583,279,650	317,329,402	140,198,077	15,817,690	24,452,797,165	10.28
75-79	5,235,048,696	8,193,499,097	2,341,215,337	5,254,052,600	571,325,589	263,533,336	129,489,810	15,345,493	22,003,509,959	9.25
80&above	5,038,944,433	5,608,497,316	1,558,734,871	5,297,703,401	570,132,845	230,382,803	85,888,913	70,540,811	18,460,825,394	7.76
Total	44,791,925,926	64,477,846,455	19,069,106,674	99,514,018,036	3,046,045,620	5,398,950,498	1,351,907,480	144,143,995	**237,793,944,683**	100.00
%	**18.84**	**27.12**	8.02	**41.85**	1.28	2.27	0.57	0.06	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	109,517,691	175,718,740	140,918,699	102,728,552	3,178,572	782,227,390	46,985,429	1,480,062	1,362,755,135	0.20
25-29	396,819,375	455,429,050	203,591,140	1,148,336,811	1,582,717	525,976,766	47,583,009	39,818,527	2,819,137,394	0.42
30-34	1,509,269,759	1,669,800,688	551,814,051	4,383,612,547	15,513,937	933,010,119	85,685,771	1,137,116	9,149,843,988	1.37
35-39	2,645,614,906	4,013,610,282	1,122,833,259	7,461,273,575	65,114,413	1,189,486,027	105,694,645	4,700,325	16,608,327,433	2.48
40-44	6,686,363,904	9,730,133,364	2,489,340,590	11,115,887,989	149,490,231	1,896,201,574	154,254,389	9,934,532	32,231,606,573	4.82
45-49	9,820,528,819	21,901,826,636	5,366,966,708	13,251,977,585	327,619,067	2,247,809,648	213,157,235	34,313,783	53,164,199,480	7.95
50-54	16,087,526,068	46,661,701,498	11,116,862,626	15,885,698,219	826,759,598	3,132,708,019	271,784,053	79,138,914	94,062,178,994	**14.06**
55-59	19,818,574,059	59,938,081,590	14,276,104,070	13,965,822,990	1,477,520,823	3,005,350,827	341,110,908	20,558,789	112,843,124,055	**16.87**
60-64	18,555,018,908	49,904,849,785	11,909,288,520	10,245,168,344	1,836,793,224	2,109,462,564	290,550,543	55,675,194	94,906,807,083	**14.19**
65-69	19,585,480,762	43,401,384,923	10,445,428,818	8,329,409,237	2,273,885,113	1,707,594,649	284,987,668	52,123,845	86,080,295,015	12.87
70-74	20,479,097,949	33,871,307,072	8,174,543,667	6,903,926,688	2,580,562,469	1,544,729,486	269,938,020	89,367,978	73,913,473,327	11.05
75-79	15,718,385,717	23,930,792,500	5,888,461,114	5,804,660,940	2,171,846,955	888,297,972	230,024,706	85,835,268	54,718,305,173	8.18
80&above	11,253,268,268	13,955,552,147	3,406,357,976	5,668,415,051	1,726,963,461	561,242,418	140,761,561	203,721,848	36,916,282,730	5.52
Total	142,665,466,185	309,610,188,273	75,092,511,238	104,266,918,529	13,456,830,581	20,524,097,459	2,482,517,935	677,806,180	**668,776,336,380**	100.00
%	**21.33**	**46.30**	11.23	**15.59**	2.01	3.07	0.37	0.10	100.00	

4.3 Transportation costs

The total expenditure that inpatients/outpatients of infection-related cancers spent during hospital/outpatient clinics stood at around 7.6 billion KRW in 2014, of which the top three highest contributors were HBV (39.18%), HP (24.16%) and HPV (21.30%). In men, the largest proportion of transportation expenses were seen in people aged from 55 to 69, whereas an older group of women (79-74) was recorded as one with huge spending on diagnosis/treatment visits, at around 10.85%. While HBV, HP and HCV consecutively share largest burden of transportation costs in men, HPV took the lead in women (nearly 50%), followed by HBV and HP.

Table 9 Transportation costs due to infection-related cancers (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	657,268	845,944	658,114	215,040	21,658	5,740,700	220,521	34,000	8,393,245	0.19
25-29	2,320,872	1,420,238	714,766	152,580	4,760	4,015,640	183,812	146,000	8,958,668	0.20
30-34	6,491,948	9,214,700	2,768,476	373,000	131,138	8,127,520	328,201	114,000	27,548,983	0.61
35-39	17,463,024	26,025,518	6,636,932	1,376,540	452,438	12,640,760	392,281	78,000	65,065,493	1.45
40-44	38,522,914	73,971,352	17,648,126	1,296,480	1,533,196	15,236,640	587,394	144,000	148,940,102	3.31
45-49	76,413,568	165,377,176	38,241,404	4,687,560	3,203,956	24,060,700	762,390	382,000	313,128,754	6.96
50-54	137,889,456	324,753,206	73,947,818	7,801,780	7,703,108	31,233,420	1,060,979	772,000	585,161,767	13.00
55-59	186,832,630	443,483,212	100,327,700	8,537,960	13,844,698	29,301,580	1,332,955	260,000	783,920,735	**17.41**
60-64	180,242,948	388,503,016	87,554,022	10,084,880	16,178,050	24,229,480	1,237,514	1,048,000	709,077,910	**15.75**
65-69	192,672,120	335,552,178	75,434,218	9,427,960	18,859,596	19,949,600	1,245,481	1,196,000	654,337,153	**14.54**
70-74	184,893,828	281,935,834	63,443,568	8,863,580	18,948,370	15,986,860	1,242,465	1,976,000	577,290,505	12.82
75-79	134,218,182	185,611,316	41,666,200	7,577,200	14,845,964	8,447,380	899,905	1,694,000	394,960,147	8.77
80&above	79,416,074	101,071,006	22,434,734	4,972,240	10,586,716	3,416,600	510,858	2,228,000	224,636,228	4.99
Total	1,238,034,832	2,337,764,696	531,476,078	65,366,800	106,313,648	202,386,880	10,004,755	10,072,000	**4,501,419,689**	100.00
%	**27.50**	**51.93**	**11.81**	1.45	2.36	4.50	0.22	0.22	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,036,402	874,572	557,716	1,418,740	10,890	4,340,600	176,895	8,000	8,423,815	0.27
25-29	3,438,194	1,029,510	714,300	17,262,840	34,650	3,285,320	267,943	0	26,032,757	0.83
30-34	12,312,432	4,494,562	1,901,180	71,013,700	118,690	4,060,640	529,890	0	94,431,094	3.01
35-39	19,910,280	7,062,198	2,769,804	112,102,640	141,570	4,068,360	712,452	4,000	146,771,304	4.68
40-44	44,309,724	12,233,116	4,438,484	165,250,300	241,450	7,970,960	985,418	20,000	235,449,452	7.51
45-49	49,411,712	25,614,964	8,431,168	203,450,180	699,160	8,195,380	1,302,747	68,000	297,173,311	9.48
50-54	67,934,526	54,311,978	16,589,824	242,041,280	1,759,340	8,486,000	1,699,488	312,000	393,134,436	**12.55**

55-59	72,766,374	82,046,628	24,529,824	216,307,300	3,026,760	9,076,180	1,980,589	330,000	410,063,655	**13.09**
60-64	59,142,050	93,416,136	26,751,708	146,257,580	3,561,030	5,714,320	1,452,412	258,000	336,553,236	10.74
65-69	63,824,364	103,618,128	29,593,720	122,859,420	4,682,700	4,841,900	1,535,830	270,000	331,226,062	10.57
70-74	77,097,476	108,105,728	30,893,276	110,657,420	5,423,990	5,925,080	1,618,287	214,000	339,935,257	**10.85**
75-79	70,283,662	92,366,030	26,072,476	79,673,360	5,416,730	3,804,980	1,257,240	136,000	279,010,478	8.90
80&above	65,138,634	68,512,498	18,916,612	72,606,720	5,737,270	2,826,440	898,900	646,000	235,283,074	7.51
Total	606,605,830	653,686,048	192,160,092	1,560,901,480	30,854,230	72,596,160	14,418,092	2,266,000	**3,133,487,932**	100.00
%	**19.36**	**20.86**	6.13	**49.81**	0.98	2.32	0.46	0.07	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,693,670	1,720,516	1,215,830	1,633,780	32,548	10,081,300	397,416	42,000	16,817,060	0.22
25-29	5,759,066	2,449,748	1,429,066	17,415,420	39,410	7,300,960	451,755	146,000	34,991,425	0.46
30-34	18,804,380	13,709,262	4,669,656	71,386,700	249,828	12,188,160	858,091	114,000	121,980,077	1.60
35-39	37,373,304	33,087,716	9,406,736	113,479,180	594,008	16,709,120	1,104,733	82,000	211,836,797	2.77
40-44	82,832,638	86,204,468	22,086,610	166,546,780	1,774,646	23,207,600	1,572,812	164,000	384,389,554	5.03
45-49	125,825,280	190,992,140	46,672,572	208,137,740	3,903,116	32,256,080	2,065,137	450,000	610,302,065	7.99
50-54	205,823,982	379,065,184	90,537,642	249,843,060	9,462,448	39,719,420	2,760,467	1,084,000	978,296,203	12.81
55-59	259,599,004	525,529,840	124,857,524	224,845,260	16,871,458	38,377,760	3,313,544	590,000	1,193,984,390	**15.64**
60-64	239,384,998	481,919,152	114,305,730	156,342,460	19,739,080	29,943,800	2,689,926	1,306,000	1,045,631,146	**13.70**
65-69	256,496,484	439,170,306	105,027,938	132,287,380	23,542,296	24,791,500	2,781,312	1,466,000	985,563,216	**12.91**
70-74	261,991,304	390,041,562	94,336,844	119,521,000	24,372,360	21,911,940	2,860,752	2,190,000	917,225,762	12.01
75-79	204,501,844	277,977,346	67,738,676	87,250,560	20,262,694	12,252,360	2,157,144	1,830,000	673,970,624	8.83
80&above	144,554,708	169,583,504	41,351,346	77,578,960	16,323,986	6,243,040	1,409,758	2,874,000	459,919,302	6.02
Total	1,844,640,662	2,991,450,744	723,636,170	1,626,268,280	137,167,878	274,983,040	24,422,848	12,338,000	**7,634,907,622**	100.00
%	**24.16**	**39.18**	9.48	**21.30**	1.80	3.60	0.32	0.16	100.00	

4.4 Caregivers' cost

In 2014, more than 60 billion KRW were expended for nursing in both inpatients and outpatients due to infection-attributed cancers. The payment for employing caregiver services was understandably higher among in aged people, particularly highest in the age group of 65-59, followed by those aged 70-74 and 55-59. Men saw a similar trend of the most prevalent age groups associated with guardians during outpatient visits or hospitalizations, while in women, people aged 70 and above were shown to spend significantly more on paying caregivers. The total caregivers' payment in men stood at nearly 38 billion KRW, of which more than half were contributed by patients of cancers due to HBV in addition to HP and HCV as the second and third highest. On the other hand, the expenditure for caregivers' usage in women was slightly lower than in men, at around 25 billion KRW; HPV remained as the infectious agent leading to the largest burden of caregivers' costs in female infection-related cancers.

Table 10 Caregivers' costs due to infection-related cancers (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	6,476,407	7,377,506	5,190,057	559,283	311,425	26,753,964	1,615,499	126,630	48,410,771	0.13
25-29	11,492,306	11,383,024	5,371,940	726,856	0	16,713,050	1,259,880	1,561,770	48,508,825	0.13
30-34	40,441,865	87,396,902	23,809,226	3,300,822	492,253	42,754,509	1,962,710	126,630	200,284,918	0.54
35-39	121,502,287	196,248,979	48,164,607	5,676,401	5,324,369	71,940,191	2,212,484	84,420	451,153,738	1.21
40-44	249,300,195	648,449,690	150,291,364	5,628,704	15,732,005	73,941,368	3,345,636	0	1,146,688,962	3.08
45-49	484,975,678	1,427,142,598	327,467,248	39,748,735	27,882,617	102,854,795	5,452,962	4,052,160	2,419,576,794	6.50
50-54	874,130,604	2,598,800,433	586,730,354	53,141,124	69,101,273	217,008,786	6,666,453	5,824,980	4,411,404,008	11.86
55-59	1,177,284,766	3,339,926,948	750,008,216	66,724,724	117,412,391	161,332,952	8,285,456	0	5,620,975,453	**15.11**
60-64	1,057,329,982	2,727,269,523	611,530,291	67,069,157	143,160,238	139,851,860	8,905,673	2,405,970	4,757,522,695	12.79
65-69	1,648,348,903	3,063,178,804	684,435,368	89,673,408	206,219,904	146,385,992	11,329,994	14,564,760	5,864,137,133	**15.77**
70-74	1,673,446,139	2,639,111,893	586,868,671	104,984,237	225,276,353	145,678,052	11,152,758	14,266,770	5,400,784,874	**14.52**
75-79	1,310,398,984	1,925,556,622	427,698,828	78,790,360	196,191,192	83,149,809	9,583,138	11,525,010	4,042,893,943	10.87
80&above	996,063,301	1,199,626,807	260,355,837	62,509,427	173,601,632	62,662,072	6,031,288	23,495,640	2,784,346,003	7.49
Total	9,651,191,418	19,871,469,730	4,467,922,008	578,533,238	1,180,705,654	1,291,027,399	77,803,930	78,034,740	**37,196,688,117**	100.00
%	**25.95**	**53.42**	**12.01**	1.56	3.17	3.47	0.21	0.21	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	4,796,196	6,567,454	3,831,317	6,452,221	9,286	16,913,547	1,082,383	0	39,652,403	0.16
25-29	21,001,163	8,973,466	4,558,680	86,032,422	143,936	10,925,636	1,293,466	0	132,928,770	0.52
30-34	74,569,832	36,858,490	13,728,971	331,198,232	712,716	19,441,504	2,769,668	0	479,279,413	1.88
35-39	135,154,310	58,862,816	20,296,510	570,147,776	898,440	23,307,940	3,657,868	0	812,325,659	3.19
40-44	301,488,133	96,103,855	32,972,848	914,531,990	2,035,999	53,043,197	5,867,629	0	1,406,043,651	5.53
45-49	289,020,987	229,088,021	72,576,043	1,211,542,233	7,600,755	28,835,762	8,941,446	0	1,847,605,247	7.26

50-54	450,413,075	459,680,618	136,466,112	1,433,360,849	16,083,698	62,227,670	11,108,456	3,630,060	2,572,970,539	10.11
55-59	450,105,533	645,079,264	189,336,079	1,281,063,792	28,162,723	63,966,722	13,209,535	717,570	2,671,641,217	10.50
60-64	350,609,007	653,398,517	184,395,989	909,189,471	33,896,952	32,088,886	9,305,709	1,857,240	2,174,741,771	8.55
65-69	530,454,727	994,611,787	282,958,425	1,025,664,507	54,847,901	39,927,445	14,701,995	1,471,050	2,944,637,836	11.58
70-74	729,689,820	1,113,083,134	317,062,246	1,012,896,219	66,477,157	75,681,722	16,815,234	2,001,720	3,333,707,251	**13.11**
75-79	692,178,386	1,145,696,206	320,419,699	944,069,809	84,901,948	54,876,041	15,613,493	2,340,660	3,260,096,242	**12.82**
80&above	953,609,193	1,076,637,651	294,108,819	1,271,666,687	103,571,356	37,564,157	13,885,863	11,201,610	3,762,245,336	**14.79**
Total	4,983,090,362	6,524,641,278	1,872,711,738	10,997,816,208	399,342,867	518,800,229	118,252,745	23,219,910	**25,437,875,336**	100.00
%	**19.59**	**25.65**	7.36	**43.23**	1.57	2.04	0.46	0.09	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	11,272,603	13,944,960	9,021,374	7,011,503	320,712	43,667,511	2,697,882	126,630	88,063,175	0.14
25-29	32,493,469	20,356,490	9,930,620	86,759,278	143,936	27,638,686	2,553,346	1,561,770	181,437,596	0.29
30-34	115,011,698	124,255,392	37,538,197	334,499,054	1,204,969	62,196,013	4,732,378	126,630	679,564,331	1.08
35-39	256,656,596	255,111,795	68,461,117	575,824,177	6,222,809	95,248,131	5,870,352	84,420	1,263,479,397	2.02
40-44	550,788,328	744,553,544	183,264,212	920,160,694	17,768,004	126,984,564	9,213,265	0	2,552,732,612	4.08
45-49	773,996,666	1,656,230,619	400,043,291	1,251,290,968	35,483,372	131,690,557	14,394,408	4,052,160	4,267,182,041	6.81
50-54	1,324,543,680	3,058,481,052	723,196,466	1,486,501,972	85,184,972	279,236,456	17,774,910	9,455,040	6,984,374,547	11.15
55-59	1,627,390,299	3,985,006,212	939,344,295	1,347,788,516	145,575,114	225,299,674	21,494,991	717,570	8,292,616,670	**13.24**
60-64	1,407,938,990	3,380,668,040	795,926,280	976,258,628	177,057,190	171,940,747	18,211,382	4,263,210	6,932,264,466	11.07
65-69	2,178,803,630	4,057,790,591	967,393,793	1,115,337,915	261,067,805	186,313,436	26,031,988	16,035,810	8,808,774,969	**14.06**
70-74	2,403,135,959	3,752,195,027	903,930,917	1,117,880,457	291,753,510	221,359,774	27,967,992	16,268,490	8,734,492,125	**13.95**
75-79	2,002,577,371	3,071,252,828	748,118,527	1,022,860,169	281,093,140	138,025,850	25,196,631	13,865,670	7,302,990,186	11.66
80&above	1,949,672,494	2,276,264,458	554,464,656	1,334,176,114	277,172,988	100,226,230	19,917,150	34,697,250	6,546,591,339	10.45
Total	14,634,281,781	26,396,111,008	6,340,633,746	11,576,349,446	1,580,048,521	1,809,827,628	196,056,675	101,254,650	**62,634,563,454**	100.00
%	**23.36**	**42.14**	10.12	**18.48**	2.52	2.89	0.31	0.16	100.00	

4.5 Future income loss

The future earnings lost due to premature death in Korean infection-related cancer patients were estimated at a high of nearly 1,800 billion KRW in 2014. It is also noticeable that the loss of income resulting from deaths happening before the life expectancy according to different age cohorts was considerably much higher in men as nearly 7.3 times as that in women. Overall, HBV, HP and HCV were recorded as the top three infectious agents causing significant future income loss. This pattern was also witnessed in men; however, in women, HPV took the leading responsibility of premature cancer deaths due to infection, followed closely by HP and HBV. The highest amount of potential earnings lost due to premature death in patients with cancers linked to infection was seen in those aged in their forties, particularly, aged from 40 to 54.

Table 11 Future income loss due to infection-related cancers (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	702,600,126	111,996,035	187,243,371	0	104,121,314	402,485,751	77,434,759	0	1,585,881,356	0.10
25-29	5,978,516,042	2,020,448,058	507,205,984	27,919,595	110,747,729	837,587,864	30,153,163	0	9,512,578,436	0.60
30-34	14,056,095,545	22,194,756,360	5,088,275,264	55,277,298	219,266,615	2,948,122,550	79,322,922	0	44,641,116,554	2.79
35-39	19,172,156,737	55,130,609,396	12,392,321,378	673,634,755	507,357,821	1,159,675,021	66,254,963	0	89,102,010,069	5.57
40-44	38,896,983,775	120,897,121,634	27,165,063,974	1,218,328,863	2,270,788,856	3,838,469,851	203,299,455	0	194,490,056,408	12.17
45-49	58,719,229,235	203,537,462,258	45,716,830,410	1,122,782,646	2,946,296,820	3,408,652,956	282,653,334	0	315,733,907,659	**19.75**
50-54	91,639,013,338	257,671,983,592	57,241,398,417	1,177,246,288	5,813,354,288	8,529,029,229	194,766,189	0	422,266,791,340	**26.42**
55-59	62,462,203,590	186,977,235,210	41,548,094,458	1,645,022,349	5,257,491,427	4,082,005,457	199,776,214	0	302,171,828,704	**18.90**
60-64	30,928,112,809	75,641,753,752	16,733,240,658	499,787,152	3,191,989,227	1,787,082,958	105,115,784	0	128,887,082,340	8.06
65-69	16,161,859,167	31,822,499,731	6,990,074,433	270,360,648	1,912,501,187	892,690,808	52,835,480	100,133,574	58,202,955,028	3.64
70-74	7,522,539,080	13,913,133,368	3,056,161,330	102,437,521	1,046,939,978	345,192,045	34,333,880	0	26,020,737,201	1.63
75-79	1,934,536,613	2,838,433,377	625,055,837	49,870,660	248,949,220	47,517,788	9,569,540	5,114,940	5,759,047,975	0.36
Total	348,173,846,058	972,757,432,771	217,250,965,514	6,842,667,775	23,629,804,482	28,278,512,275	1,335,515,682	105,248,513	**1,598,373,993,070**	100.00
%	**21.78**	**60.86**	**13.59**	0.43	1.48	1.77	0.08	0.01	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	952,136,880	1,127,562,353	316,169,129	12,098,309	0	185,507,397	7,017,019	0	2,600,491,087	1.18
25-29	908,980,449	269,113,653	97,019,514	2,321,538,377	0	354,198,227	18,941,905	0	3,969,792,124	1.81
30-34	7,052,258,590	2,409,113,847	681,031,325	6,589,736,303	0	310,186,332	32,052,588	0	17,074,378,985	7.77
35-39	11,536,404,418	2,934,135,169	816,699,532	13,207,796,464	115,175,575	406,853,979	55,703,096	0	29,072,768,233	13.22
40-44	16,656,423,741	3,152,518,958	983,900,921	20,546,745,341	121,818,648	999,159,014	127,183,591	0	42,587,750,214	**19.37**
45-49	13,217,421,036	7,838,641,650	2,177,711,471	13,109,188,590	215,531,855	261,250,733	83,973,450	0	36,903,718,786	**16.79**

50-54	10,395,353,878	9,625,542,920	2,622,746,463	15,031,655,291	406,832,147	807,059,875	87,653,835	0	38,976,844,410	**17.73**
55-59	6,624,283,343	8,759,456,548	2,417,760,045	7,434,044,185	346,083,073	295,825,436	78,107,722	0	25,955,560,351	11.81
60-64	2,463,442,863	4,994,283,411	1,362,851,731	2,981,981,082	226,640,072	188,206,353	36,317,883	0	12,253,723,395	5.57
65-69	1,227,404,896	2,514,269,527	683,299,581	1,106,990,809	166,194,834	48,250,113	20,495,738	0	5,766,905,498	2.62
70-74	950,510,198	1,392,989,514	381,470,558	695,061,833	80,531,561	44,489,464	12,006,524	6,257,309	3,563,316,960	1.62
75-79	342,709,829	427,121,094	115,669,248	181,294,219	28,935,146	9,793,663	3,335,790	1,486,140	1,110,345,128	0.51
Total	72,327,330,119	45,444,748,645	12,656,329,519	83,218,130,802	1,707,742,910	3,910,780,587	562,789,140	7,743,449	**219,835,595,170**	100.00
%	**32.90**	**20.67**	5.76	**37.85**	0.78	1.78	0.26	0.00	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,654,737,006	1,239,558,388	503,412,500	12,098,309	104,121,314	587,993,148	84,451,778	0	4,186,372,443	0.23
25-29	6,887,496,491	2,289,561,711	604,225,499	2,349,457,972	110,747,729	1,191,786,091	49,095,068	0	13,482,370,561	0.74
30-34	21,108,354,135	24,603,870,207	5,769,306,589	6,645,013,601	219,266,615	3,258,308,882	111,375,510	0	61,715,495,539	3.39
35-39	30,708,561,154	58,064,744,565	13,209,020,910	13,881,431,218	622,533,397	1,566,529,000	121,958,059	0	118,174,778,303	6.50
40-44	55,553,407,516	124,049,640,592	28,148,964,894	21,765,074,203	2,392,607,504	4,837,628,865	330,483,046	0	237,077,806,621	13.04
45-49	71,936,650,272	211,376,103,908	47,894,541,881	14,231,971,236	3,161,828,675	3,669,903,689	366,626,784	0	352,637,626,444	**19.39**
50-54	102,034,367,216	267,297,526,512	59,864,144,880	16,208,901,579	6,220,186,435	9,336,089,104	282,420,024	0	461,243,635,750	**25.37**
55-59	69,086,486,933	195,736,691,757	43,965,854,503	9,079,066,534	5,603,574,499	4,377,830,893	277,883,936	0	328,127,389,055	**18.05**
60-64	33,391,555,672	80,636,037,163	18,096,092,389	3,481,768,234	3,418,629,298	1,975,289,311	141,433,667	0	141,140,805,734	7.76
65-69	17,389,264,062	34,336,769,258	7,673,374,014	1,377,351,458	2,078,696,021	940,940,921	73,331,218	100,133,574	63,969,860,526	3.52
70-74	8,473,049,277	15,306,122,882	3,437,631,888	797,499,355	1,127,471,539	389,681,508	46,340,404	6,257,309	29,584,054,162	1.63
75-79	2,277,246,442	3,265,554,471	740,725,085	231,164,879	277,884,366	57,311,451	12,905,330	6,601,080	6,869,393,103	0.38
Total	420,501,176,177	############	229,907,295,032	90,060,798,576	25,337,547,392	32,189,292,863	1,898,304,823	112,991,962	**1,818,209,588,240**	100.00
%	**23.13**	**56.00**	**12.64**	4.95	1.39	1.77	0.10	0.01	100.00	

4.6 Productivity loss

An estimate of approximately 137 billion KRW was lost during hospitalization or visits to outpatient clinics in Korean cancer patients associated with infection. Nearly 80% of the total loss of productivity was contributed by male patients, at around 110 billion KRW, whereas the potential earnings lost throughout cancer diagnosis/treatment in women were much lower, at only nearly 27 billion KRW. Since productivity loss is measured as the income lost due to outpatient/inpatient visits, it was not surprising to see a markedly high proportion of cancer patients in their mid-working ages falling into this category. Overall, almost a quarter of the total productivity loss was seen in infection-related cancer patients aged between 55 and 59, followed by the two next younger age groups (45-49 and 50-54). With regards to particular causes, HBV, HP and HPV were responsible for the highest amount of earning lost due to outpatient admission and hospitalization irrespective of gender. Specifically, these three agents remained as the top three causes with significant loss of productivity in men, whereas in women, it was HPV that contributed to the largest part of income lost during time of cancer diagnosis/treatment, making up more than 50% of the total.

Table 12 Loss of productivity due to absence from work (Unit: KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	6,738,189	6,638,062	5,223,937	927,924	265,449	33,501,592	1,716,920	118,293	55,130,366	0.05
25-29	35,238,239	31,120,088	14,959,929	2,675,037	53,268	61,155,658	3,615,534	3,939,144	152,756,898	0.14
30-34	204,172,630	362,162,819	101,765,082	14,283,588	2,503,777	232,814,335	9,554,179	2,000,295	929,256,704	0.84
35-39	693,435,544	1,097,329,871	272,280,296	40,309,407	26,336,640	457,089,537	13,532,050	1,473,600	2,601,786,944	2.36
40-44	1,737,761,182	4,020,404,892	939,289,736	51,433,472	91,953,672	576,589,466	23,693,135	3,829,032	7,444,954,587	6.77
45-49	3,553,047,647	9,244,052,589	2,125,415,575	266,329,682	172,069,444	895,601,477	36,769,602	25,863,983	16,319,149,998	**14.83**
50-54	5,896,910,504	16,048,137,198	3,632,722,760	352,178,212	394,033,044	1,457,622,459	43,621,331	38,712,576	27,863,938,082	**25.32**
55-59	6,439,449,206	17,056,726,563	3,838,252,411	359,091,832	562,450,659	960,320,430	43,883,025	5,365,555	29,265,539,681	**26.60**
60-64	3,616,460,271	8,525,297,289	1,914,549,938	225,648,827	404,586,137	484,892,294	26,846,286	15,633,468	15,213,914,509	13.83
65-69	1,794,828,924	3,334,441,470	745,053,919	97,649,498	224,383,902	159,463,128	12,331,567	15,854,650	6,384,007,057	5.80
70-74	835,789,503	1,317,693,057	293,025,736	52,405,554	112,428,418	72,750,484	5,568,241	7,135,950	2,696,796,942	2.45
75-79	359,898,981	528,687,348	117,432,174	21,640,547	53,844,840	22,835,808	2,630,768	3,172,235	1,110,142,702	1.01
Total	25,173,730,818	61,572,691,245	13,999,971,491	1,484,573,580	2,044,909,249	5,414,636,668	223,762,640	123,098,780	**110,037,374,471**	100.00
%	**22.88**	**55.96**	**12.72**	1.35	1.86	4.92	0.20	0.11	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	7,941,463	8,509,827	5,150,218	11,418,014	60,392	29,953,263	1,532,609	43,921	64,609,707	0.24
25-29	58,227,330	21,809,211	11,995,185	260,260,159	346,495	39,933,222	3,758,180	0	396,329,781	1.45
30-34	196,935,152	88,666,332	34,596,407	1,024,638,016	1,797,429	59,809,868	8,013,806	0	1,414,457,011	5.19
35-39	352,581,748	144,510,373	51,404,279	1,722,275,941	2,436,012	66,603,598	10,559,865	41,010	2,350,412,825	8.63
40-44	802,297,529	244,303,623	84,725,823	2,717,406,346	4,978,291	149,591,170	16,298,244	205,808	4,019,806,833	14.75
45-49	763,743,941	520,882,005	166,464,064	3,252,951,107	15,793,743	103,814,452	22,074,623	654,296	4,846,378,231	**17.79**
50-54	865,835,816	808,938,187	241,293,451	2,920,689,041	26,455,269	117,627,321	20,870,954	5,998,662	5,007,708,700	**18.38**

55-59	843,457,054	1,078,101,616	317,732,281	2,399,286,963	43,011,182	117,320,757	22,986,177	2,535,703	4,824,431,733	**17.71**
60-64	427,166,171	724,009,767	205,233,619	1,097,513,835	32,890,636	39,993,871	10,565,591	1,999,981	2,539,373,471	9.32
65-69	184,430,931	345,629,414	98,328,473	356,612,847	19,050,620	13,882,099	5,108,556	512,747	1,023,555,687	3.76
70-74	112,638,602	171,751,023	48,923,123	156,370,914	10,253,221	11,675,850	2,594,298	309,034	514,516,066	1.89
75-79	51,757,361	85,619,364	23,945,518	70,572,716	6,342,683	4,100,718	1,166,739	174,933	243,680,031	0.89
Total	4,667,013,099	4,242,730,742	1,289,792,439	15,989,995,898	163,415,974	754,306,189	125,529,642	12,476,094	**27,245,260,076**	100.00
%	**17.13**	**15.57**	4.73	**58.69**	0.60	2.77	0.46	0.05	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	14,679,652	15,147,890	10,374,155	12,345,938	325,841	63,454,854	3,249,529	162,214	119,740,073	0.09
25-29	93,465,570	52,929,299	26,955,113	262,935,196	399,763	101,088,880	7,373,715	3,939,144	549,086,679	0.40
30-34	401,107,781	450,829,151	136,361,489	1,038,921,604	4,301,206	292,624,203	17,567,985	2,000,295	2,343,713,715	1.71
35-39	1,046,017,292	1,241,840,244	323,684,574	1,762,585,348	28,772,652	523,693,135	24,091,916	1,514,610	4,952,199,770	3.61
40-44	2,540,058,711	4,264,708,515	1,024,015,559	2,768,839,818	96,931,963	726,180,635	39,991,379	4,034,840	11,464,761,419	8.35
45-49	4,316,791,587	9,764,934,594	2,291,879,639	3,519,280,789	187,863,187	999,415,929	58,844,225	26,518,279	21,165,528,230	**15.42**
50-54	6,762,746,320	16,857,075,384	3,874,016,210	3,272,867,253	420,488,313	1,575,249,780	64,492,285	44,711,238	32,871,646,782	**23.94**
55-59	7,282,906,260	18,134,828,179	4,155,984,692	2,758,378,795	605,461,841	1,077,641,187	66,869,202	7,901,258	34,089,971,414	**24.83**
60-64	4,043,626,442	9,249,307,056	2,119,783,557	1,323,162,661	437,476,773	524,886,165	37,411,877	17,633,449	17,753,287,980	12.93
65-69	1,979,259,855	3,680,070,884	843,382,392	454,262,344	243,434,522	173,345,227	17,440,124	16,367,396	7,407,562,744	5.40
70-74	948,428,105	1,489,444,080	341,948,859	208,776,468	122,681,640	84,426,334	8,162,539	7,444,984	3,211,313,008	2.34
75-79	411,656,342	614,306,712	141,377,693	92,213,263	60,187,523	26,936,526	3,797,507	3,347,168	1,353,822,733	0.99
Total	29,840,743,917	65,815,421,987	15,289,763,931	17,474,569,478	2,208,325,223	6,168,942,856	349,292,282	135,574,874	**137,282,634,548**	100.00
%	**21.74**	**47.94**	11.14	**12.73**	1.61	4.49	0.25	0.10	100.00	

4.7 Indirect costs due to job loss

In this study, we assume that the average job loss rate in Korea in 2014 was 47% given by a previous study [114]. It is estimated that the total income lost due to unemployment followed cancers attributed to infection stood at around 849 billion KRW, of which men shared most of the economic burden, at almost 78%, compared to only nearly 22% in women. Regardless of gender, HBV was responsible for the largest amount of money that might have been earned due to job loss during cancer diagnosis/treatment, accounting for around 39% of the total, followed by HP (34%) and HPV (14%). Men saw the similar pattern of the top three infectious agents with highest burden as a result of unemployment, but HPV being replaced by HCV. By contrast, alike other cost categories described above, in women, the largest proportion of income lost due to unemployment went to HPV, at nearly 58%, while the second and third highest percentages were related to HP and HBV. In terms of ages that were associated with most lost potential earnings, patients aged between 45 and 59 were more likely to be influenced by cancers attributed to infection.

Table 13 Job loss costs due to infection-related cancers (Unit KRW, %)

Male	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	33,468,240	28,596,448	26,032,939	13,812,170	446,644	239,123,202	9,195,603	3,753,307	354,428,552	0.05
25-29	296,943,552	162,508,402	78,850,110	27,256,576	2,429,612	468,363,937	19,987,135	20,416,911	1,076,756,236	0.16
30-34	1,812,764,207	1,515,956,870	459,045,886	78,792,461	15,993,694	1,130,478,615	55,438,644	16,800,098	5,085,270,475	0.77
35-39	5,446,101,282	5,213,513,901	1,344,064,148	272,448,239	51,854,391	1,725,989,685	83,116,426	41,500,113	14,178,588,184	2.15
40-44	17,165,762,307	18,127,859,260	4,340,155,931	412,330,672	184,463,722	2,973,359,643	139,818,016	95,391,711	43,439,141,263	6.58
45-49	33,475,968,644	41,791,653,552	9,686,125,799	740,765,531	478,316,545	3,993,821,085	182,932,590	197,274,442	90,546,858,188	13.71
50-54	58,016,828,995	78,803,435,024	17,990,537,961	1,530,334,991	967,890,746	5,643,580,180	229,497,848	159,481,092	163,341,586,838	**24.73**
55-59	63,944,190,227	87,965,952,772	19,969,887,959	1,450,627,319	1,513,487,226	4,451,982,012	228,863,132	91,499,137	179,616,489,784	**27.20**
60-64	38,174,641,889	44,632,791,089	10,087,275,654	995,210,184	1,105,363,564	2,118,431,883	114,521,641	126,953,569	97,355,189,472	**14.74**
65-69	18,187,497,315	17,648,470,652	3,982,142,137	419,859,358	632,749,983	805,310,308	52,748,041	62,386,234	41,791,164,028	6.33
70-74	7,899,227,679	6,737,456,091	1,515,556,065	204,956,060	343,017,867	268,156,147	23,517,408	65,810,573	17,057,697,890	2.58
75-79	3,157,880,657	2,450,527,362	548,327,269	92,362,509	170,216,747	87,302,043	9,722,224	31,252,280	6,547,591,091	0.99
Total	247,611,274,996	305,078,721,423	70,028,001,858	6,238,756,071	5,466,230,740	23,905,898,739	1,149,358,707	912,519,468	**660,390,762,001**	100.00
%	**37.49**	**46.20**	**10.60**	0.94	0.83	3.62	0.17	0.14	100.00	
Female	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	82,501,205	35,021,907	26,119,539	96,627,481	271,564	190,884,947	9,022,844	0	440,449,486	0.23
25-29	505,341,422	103,770,509	67,965,583	1,981,296,970	1,002,173	302,929,711	25,402,365	0	2,987,708,733	1.59
30-34	1,355,805,733	330,333,629	155,835,858	8,690,497,294	3,910,115	376,881,771	55,009,987	0	10,968,274,386	5.82
35-39	2,558,461,452	714,382,561	268,158,137	13,078,777,899	7,796,325	377,501,593	69,934,806	8,859,460	17,083,872,232	9.07
40-44	6,000,477,907	1,275,146,765	452,754,037	19,410,697,416	14,244,007	573,957,591	102,029,959	0	27,829,307,683	14.77
45-49	7,554,604,845	2,564,509,781	822,317,311	22,755,509,325	37,189,757	572,953,357	122,482,261	8,559,208	34,438,125,844	**18.28**
50-54	7,947,414,869	4,042,945,214	1,225,820,720	17,888,532,847	62,997,295	503,715,049	115,882,109	26,331,158	31,813,639,260	**16.88**
55-59	8,806,593,389	5,990,115,750	1,772,206,415	15,041,058,016	102,320,330	558,049,895	123,413,872	48,796,581	32,442,554,248	**17.22**

60-64	4,964,492,321	4,288,847,944	1,227,452,830	7,296,353,968	86,463,255	198,840,004	61,020,202	7,840,694	18,131,311,219	9.62
65-69	2,280,984,739	1,954,118,157	555,923,825	2,451,134,600	53,499,108	77,135,987	25,226,289	6,484,740	7,404,507,445	3.93
70-74	1,240,073,431	917,997,862	259,446,576	1,018,913,678	31,285,804	37,400,936	11,222,289	2,869,270	3,519,209,846	1.87
75-79	509,599,873	370,343,458	103,769,146	357,146,267	16,692,064	12,824,199	4,301,415	1,396,972	1,376,073,394	0.73
Total	43,806,351,185	22,587,533,537	6,937,769,977	110,066,545,761	417,671,799	3,783,075,039	724,948,397	111,138,082	**188,435,033,776**	100.00
%	**23.25**	**11.99**	3.68	**58.41**	0.22	2.01	0.38	0.06	100.00	
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	115,969,445	63,618,355	52,152,477	110,439,651	718,208	430,008,148	18,218,447	3,753,307	794,878,038	0.09
25-29	802,284,974	266,278,911	146,815,693	2,008,553,546	3,431,786	771,293,648	45,389,499	20,416,911	4,064,464,968	0.48
30-34	3,168,569,940	1,846,290,499	614,881,744	8,769,289,755	19,903,809	1,507,360,386	110,448,631	16,800,098	16,053,544,861	1.89
35-39	8,004,562,733	5,927,896,462	1,612,222,285	13,351,226,138	59,650,716	2,103,491,277	153,051,231	50,359,573	31,262,460,415	3.68
40-44	23,166,240,214	19,403,006,025	4,792,909,969	19,823,028,088	198,707,729	3,547,317,235	241,847,975	95,391,711	71,268,448,946	8.40
45-49	41,030,573,489	44,356,163,333	10,508,443,110	23,496,274,856	515,506,302	4,566,774,442	305,414,851	205,833,650	124,984,984,033	**14.72**
50-54	65,964,243,864	82,846,380,238	19,216,358,681	19,418,867,838	1,030,888,041	6,147,295,229	345,379,957	185,812,250	195,155,226,097	**22.99**
55-59	72,750,783,616	93,956,068,522	21,742,094,374	16,491,685,335	1,615,807,556	5,010,031,908	352,277,003	140,295,718	212,059,044,033	**24.98**
60-64	43,139,134,210	48,921,639,033	11,314,728,484	8,291,564,152	1,191,826,819	2,317,271,887	175,541,843	134,794,263	115,486,500,691	13.61
65-69	20,468,482,054	19,602,588,808	4,538,065,962	2,870,993,958	686,249,092	882,446,295	77,974,330	68,870,975	49,195,671,473	5.80
70-74	9,139,301,110	7,655,453,953	1,775,002,641	1,223,869,738	374,303,671	305,557,082	34,739,697	68,679,843	20,576,907,736	2.42
75-79	3,667,480,530	2,820,870,820	652,096,415	449,508,775	186,908,811	100,126,242	14,023,639	32,649,252	7,923,664,485	0.93
Total	291,417,626,180	327,666,254,959	76,965,771,835	116,305,301,831	5,883,902,538	27,688,973,778	1,874,307,104	1,023,657,550	**848,825,795,777**	100.00
%	**34.33**	**38.60**	9.07	**13.70**	0.69	3.26	0.22	0.12	100.00	

4.8 Overall costs

The total costs of cancers attributed to infection in Korea in 2014 reached a high of nearly 3,543 billion KRW. In comparison, men endured a much significantly higher burden of infection-related cancer costs than women as high as around 4 times. Furthermore, there was a clearly noticeable difference in the impact of infectious agents in both genders. In men, more than half of the costs were attributed to HBV (56.55%), followed by HP (25.68%) and HCV (12.75%), while the biggest burden of infection-related cancers in economic terms in women was contributed by HPV (45.78%) along with the other two factors HP (24.39%) and HBV (20.51%). Overall, HBV was responsible for a significantly huge economic burden of cancers attributable to infection, at 49.41%, while the second and third top agents were HP and HCV, at 25.43% and 11.41% respectively. People aged between 45 and 59 were the most susceptible groups to be influenced by cancers linked to infection.

Table 14 Overall costs of infection-related cancers (Unit: KRW, %)

Male	**H,pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	789,374,031	236,428,893	303,189,541	27,279,592	107,605,210	1,137,477,721	117,726,964	5,472,305	2,724,554,257	0.10
25-29	6,501,752,721	2,515,539,359	722,845,080	68,882,377	113,442,240	1,700,088,371	78,231,209	65,882,352	11,766,663,709	0.41
30-34	16,737,255,304	25,353,409,758	6,020,008,763	183,158,765	245,557,424	5,003,280,193	182,681,778	20,178,139	53,745,530,123	1.89
35-39	26,764,648,590	64,664,231,520	14,825,613,451	1,102,637,584	648,035,454	4,328,322,108	209,173,138	47,814,485	112,590,476,330	3.96
40-44	61,295,546,216	152,138,105,808	34,608,652,290	1,781,311,580	2,693,513,230	8,619,051,712	433,905,310	109,227,078	261,679,313,223	9.21
45-49	102,591,730,314	275,296,663,559	62,353,533,198	2,526,139,682	3,896,794,731	10,170,547,342	606,059,560	260,918,328	457,702,386,714	**16.11**
50-54	167,525,968,893	395,514,768,702	88,662,695,019	3,656,593,967	7,929,136,014	18,314,930,443	596,615,843	272,319,237	682,473,028,119	**24.02**
55-59	148,919,406,901	346,413,646,140	77,707,267,390	4,166,362,870	8,671,351,482	11,938,064,066	634,091,591	107,647,663	598,557,838,101	**21.06**
60-64	88,184,347,525	172,419,469,512	38,629,543,516	2,552,121,884	6,355,584,318	6,295,139,345	403,998,484	187,810,895	315,028,015,478	11.09
65-69	52,760,083,212	89,067,290,563	19,898,876,093	1,562,749,133	4,808,246,534	3,364,588,201	264,662,335	240,472,708	171,966,968,779	6.05
70-74	32,981,431,024	49,817,005,798	11,131,677,414	1,096,517,586	3,743,893,805	2,075,163,670	205,554,695	162,739,580	101,213,983,574	3.56
75-79	17,380,270,439	23,666,109,428	5,307,426,085	800,849,616	2,284,569,329	874,017,464	132,940,471	123,248,240	50,569,431,072	1.78
80&above	7,289,803,209	9,647,752,644	2,130,413,676	438,193,318	1,341,018,964	396,938,287	61,414,795	158,904,676	21,464,439,567	0.76
Total	729,721,618,381	1,606,750,421,684	362,301,741,514	19,962,797,954	42,838,748,735	74,217,608,922	3,927,056,171	1,762,635,686	**2,841,482,629,044**	100.00
%	**25.68**	**56.55**	**12.75**	0.70	1.51	2.61	0.14	0.06	100.00	
Female	**H,pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,118,496,036	1,273,279,956	413,905,495	218,978,140	1,091,985	779,954,631	38,273,516	91,909	3,844,071,667	0.55
25-29	1,716,566,224	571,465,849	270,102,051	5,804,575,847	2,903,100	924,996,659	74,215,184	0	9,364,824,914	1.33
30-34	9,583,862,389	3,355,345,441	1,094,562,964	21,059,564,496	14,882,940	1,062,407,571	147,986,589	0	36,318,612,389	5.17
35-39	15,934,137,396	4,872,059,543	1,520,015,429	36,043,182,052	134,852,540	1,166,834,583	202,597,798	8,926,443	59,882,605,785	8.53
40-44	27,284,145,095	6,140,140,701	2,051,929,544	54,778,225,993	163,766,847	2,538,468,760	343,457,558	298,005	93,300,432,504	13.29
45-49	25,412,635,799	13,949,587,672	4,155,014,004	53,432,793,492	335,408,989	1,477,303,002	354,443,079	10,249,544	99,127,435,580	**14.12**
50-54	24,853,282,236	21,585,461,166	6,222,421,487	52,866,085,953	663,833,793	2,195,367,565	387,995,851	47,882,204	108,822,330,255	**15.50**

55-59	21,906,333,270	25,862,559,961	7,496,972,068	39,701,224,559	793,459,809	1,796,468,183	428,857,994	62,415,671	98,048,291,514	**13.97**
60-64	12,592,311,695	20,154,950,717	5,720,581,443	21,922,142,596	725,938,067	833,655,130	261,840,754	25,861,221	62,237,281,622	8.87
65-69	9,097,703,635	16,450,484,208	4,673,796,824	12,716,893,159	758,628,315	550,843,827	217,884,305	14,524,891	44,480,759,164	6.34
70-74	8,723,572,680	12,647,558,777	3,595,717,402	9,274,956,119	777,251,383	492,502,454	184,454,708	27,469,023	35,723,482,546	5.09
75-79	6,901,577,807	10,314,645,249	2,931,091,425	6,886,808,971	713,614,161	348,932,937	155,164,486	20,880,197	28,272,715,233	4.03
80&above	6,057,692,260	6,753,647,465	1,871,760,302	6,641,976,807	679,441,471	270,773,401	100,673,676	82,388,421	22,458,353,804	3.20
Total	171,182,316,521	143,931,186,704	42,017,870,439	321,347,408,184	5,765,073,399	14,438,508,702	2,897,845,497	300,987,529	**701,881,196,975**	100.00
%	**24.39**	**20.51**	5.99	**45.78**	0.82	2.06	0.41	0.04	100.00	
Overall	**H,pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,907,870,067	1,509,708,849	717,095,036	246,257,732	108,697,195	1,917,432,352	156,000,480	5,564,214	6,568,625,924	0.19
25-29	8,218,318,945	3,087,005,208	992,947,131	5,873,458,224	116,345,340	2,625,085,030	152,446,393	65,882,352	21,131,488,623	0.60
30-34	26,321,117,693	28,708,755,199	7,114,571,726	21,242,723,261	260,440,364	6,065,687,763	330,668,367	20,178,139	90,064,142,512	2.54
35-39	42,698,785,986	69,536,291,063	16,345,628,880	37,145,819,636	782,887,995	5,495,156,691	411,770,935	56,740,928	172,473,082,114	4.87
40-44	88,579,691,311	158,278,246,509	36,660,581,834	56,559,537,573	2,857,280,078	11,157,520,472	777,362,867	109,525,084	354,979,745,727	10.02
45-49	128,004,366,113	289,246,251,230	66,508,547,202	55,958,933,174	4,232,203,719	11,647,850,344	960,502,639	271,167,871	556,829,822,293	**15.71**
50-54	192,379,251,129	417,100,229,869	94,885,116,506	56,522,679,920	8,592,969,807	20,510,298,008	984,611,694	320,201,441	791,295,358,374	**22.33**
55-59	170,825,740,171	372,276,206,100	85,204,239,457	43,867,587,429	9,464,811,291	13,734,532,249	1,062,949,584	170,063,334	696,606,129,616	**19.66**
60-64	100,776,659,220	192,574,420,229	44,350,124,960	24,474,264,480	7,081,522,385	7,128,794,474	665,839,237	213,672,115	377,265,297,100	10.65
65-69	61,857,786,847	105,517,774,770	24,572,672,917	14,279,642,292	5,566,874,849	3,915,432,027	482,546,640	254,997,600	216,447,727,943	6.11
70-74	41,705,003,704	62,464,564,576	14,727,394,816	10,371,473,705	4,521,145,188	2,567,666,124	390,009,403	190,208,602	136,937,466,120	3.86
75-79	24,281,848,246	33,980,754,677	8,238,517,510	7,687,658,586	2,998,183,490	1,222,950,401	288,104,957	144,128,437	78,842,146,304	2.23
80&above	13,347,495,469	16,401,400,109	4,002,173,978	7,080,170,126	2,020,460,435	667,711,688	162,088,471	241,293,097	43,922,793,370	1.24
Total	900,903,934,902	1,750,681,608,388	404,319,611,953	341,310,206,138	48,603,822,134	88,656,117,623	6,824,901,668	2,063,623,215	**3,543,363,826,019**	100.00
%	**25.43**	**49.41**	**11.41**	9.63	1.37	2.50	0.19	0.06	100.00	

4.9 Sensitivity analysis

4.9.1 Sensitivity analysis by discount rates

We estimated the changes of future income loss by applying two different discount rates, 0% and 5%. An increase of nearly 12% was seen in the total costs of infection-related cancers regarding the discount rate of 0%, with an estimate of approximately 4,028 billion KRW being spent, whereas the costs experienced a slight decline of 6%, at around 3,318 billion KRW in Korea, 2014.

Table 15 Sensitivity analysis of infection-related cancers' costs by discount rates (Unit: KRW, %)

Discount rate 0%										
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	3,247,619,371	2,436,390,784	1,119,759,575	255,099,372	204,121,295	2,421,870,440	232,095,294	5,564,214	9,922,520,345	0.25
25-29	13,042,797,779	4,694,317,555	1,414,335,470	7,303,442,857	195,488,332	3,438,774,829	185,499,313	65,882,352	30,340,538,486	0.75
30-34	37,968,453,732	42,575,637,892	10,360,375,642	24,690,718,855	385,094,563	7,902,532,427	392,382,111	20,178,139	124,295,373,360	3.09
35-39	56,437,956,521	95,921,583,246	22,344,745,434	43,184,208,276	1,063,970,377	6,199,944,251	466,122,564	56,740,928	225,675,271,597	5.60
40-44	108,679,913,378	203,332,780,860	46,882,868,810	64,364,041,459	3,725,962,677	12,910,130,519	896,796,324	109,525,084	440,902,019,110	10.95
45-49	148,823,305,660	350,210,959,161	80,324,909,743	60,148,488,185	5,144,794,922	12,707,160,758	1,066,718,793	271,167,871	658,697,505,093	**16.35**
50-54	215,637,182,819	477,879,745,701	108,501,288,420	60,330,491,627	10,008,894,245	22,637,167,773	1,049,484,908	320,201,441	896,364,456,935	**22.25**
55-59	183,324,836,234	407,722,658,439	93,164,604,080	45,487,964,087	10,479,254,314	14,526,986,715	1,113,050,124	170,063,334	755,989,417,327	**18.77**
60-64	105,867,545,124	204,878,301,840	47,108,766,207	24,976,294,779	7,602,997,777	7,429,498,669	687,128,695	213,672,115	398,764,205,206	9.90
65-69	64,100,185,486	109,945,031,217	25,561,279,615	14,450,853,841	5,834,805,585	4,036,884,400	491,905,795	267,954,941	224,688,900,880	5.58
70-74	42,431,496,496	63,778,455,886	15,022,162,402	10,437,012,261	4,618,031,905	2,601,074,406	393,950,773	190,719,059	139,472,903,188	3.46
75-79	24,281,848,246	33,980,754,677	8,238,517,510	7,687,658,586	2,998,183,490	1,222,950,401	288,104,957	144,128,437	78,842,146,304	1.96
80&above	13,347,495,469	16,401,400,109	4,002,173,978	7,080,170,126	2,020,460,435	667,711,688	162,088,471	241,293,097	43,922,793,370	1.09
Total	1,017,190,636,316	2,013,758,017,366	464,045,786,884	370,396,444,311	54,282,059,916	98,702,687,275	7,425,328,121	2,077,091,013	**4,027,878,051,201**	100.00
%	**25.25**	**50.00**	**11.52**	9.20	1.35	2.45	0.18	0.05	100.00	
Discount rate 5%										
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,447,464,582	1,185,822,177	578,371,676	243,151,950	76,690,134	1,746,085,583	130,395,555	5,564,214	5,413,545,871	0.16
25-29	6,452,422,656	2,498,862,221	838,613,473	5,339,150,661	87,455,906	2,326,185,128	140,280,598	65,882,352	17,748,852,995	0.53
30-34	21,724,173,548	23,248,738,775	5,836,299,467	19,872,150,781	211,405,173	5,342,458,563	306,322,806	20,178,139	76,561,727,250	2.31

35-39	36,910,498,328	58,426,997,626	13,819,701,242	34,598,985,995	664,511,137	5,198,296,226	388,869,141	56,740,928	150,064,600,623	4.52
40-44	79,599,670,719	138,130,367,171	32,089,441,451	53,080,693,710	2,468,849,330	10,374,265,726	724,020,365	109,525,084	316,576,833,554	9.54
45-49	118,201,405,377	260,517,962,705	59,998,173,686	53,993,653,436	3,802,234,990	11,148,762,521	910,500,696	271,167,871	508,843,861,282	**15.34**
50-54	180,936,923,166	387,206,408,678	88,187,915,094	54,643,099,494	7,896,475,613	19,463,997,724	952,668,254	320,201,441	739,607,689,465	**22.29**
55-59	164,492,917,676	354,325,409,658	81,172,564,664	43,040,970,497	8,950,995,215	13,333,131,702	1,037,521,356	170,063,334	666,523,574,103	**20.09**
60-64	98,129,006,085	186,175,841,762	42,915,407,520	24,212,060,969	6,810,325,385	6,972,387,823	654,756,544	213,672,115	366,083,458,202	11.03
65-69	60,642,529,478	103,118,421,910	24,036,867,627	14,186,608,745	5,421,666,301	3,849,615,917	477,470,754	247,977,154	211,981,157,886	6.39
70-74	41,286,833,215	61,708,286,498	14,557,726,091	10,333,749,601	4,465,377,030	2,548,436,260	387,740,744	189,914,783	135,478,064,221	4.08
75-79	24,281,848,246	33,980,754,677	8,238,517,510	7,687,658,586	2,998,183,490	1,222,950,401	288,104,957	144,128,437	78,842,146,304	2.38
80&above	13,347,495,469	16,401,400,109	4,002,173,978	7,080,170,126	2,020,460,435	667,711,688	162,088,471	241,293,097	43,922,793,370	1.32
Total	847,453,188,545	1,626,925,273,966	376,271,773,477	328,312,104,550	45,874,630,136	84,194,285,262	6,560,740,241	2,056,308,949	**3,317,648,305,124**	100.00
%	**25.54**	**49.04**	**11.34**	9.90	1.38	2.54	0.20	0.06	100.00	

4.9.2 Sensitivity analysis by PAF

For sensitivity analysis by PAF, we estimated the cost changes of infection-related cancers by applying the lower and upper bound of the PAF 95% confidence interval (CI) by infectious agents. According to [14], the lower and upper limits of PAF sensitivity analysis were only performed for cancers attributed to HP, HBV, HCV, and Clonorchis sinensis. When applying the lower bound of PAF 95% CI, there was a decrease of nearly 17.3% compared with the original total infection-related costs. Furthermore, the most burdensome cancers relied on HBV, HP and HPV, rather than HCV. On the other hand, the costs of infection-attributable cancers adjusted by the upper bound of 95% CI of PAF stood at a high of 4,519 billion KRW, increasing by around 22%, of which HBV, HP and HCV remained as the top 3 infectious agents.

Table 16 Sensitivity analysis of infection-related cancers' costs by PAFs (Unit: KRW, %)

Lower bound of PAF										
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,535,642,876	1,250,993,167	326,008,063	246,257,732	39,259,786	1,917,432,351	156,000,480	5,564,214	5,477,158,670	0.19
25-29	6,692,434,578	2,842,946,962	358,664,332	5,873,458,224	41,994,623	2,625,085,030	152,446,393	65,882,352	18,652,912,492	0.64
30-34	21,509,024,853	27,205,571,371	1,770,732,426	21,242,723,261	93,872,213	6,065,687,763	330,668,367	20,178,139	78,238,458,394	2.67
35-39	34,796,245,249	66,102,762,153	3,741,448,816	37,145,819,636	280,749,495	5,495,156,691	411,770,935	56,740,928	148,030,693,903	5.05
40-44	72,412,070,836	150,298,908,656	8,324,684,401	56,559,537,573	1,029,860,295	11,157,520,472	777,362,867	109,525,083	300,669,470,183	10.27
45-49	104,945,133,510	275,037,158,217	14,710,255,636	55,958,933,174	1,523,954,051	11,647,850,344	960,502,639	271,167,871	465,054,955,443	**15.88**
50-54	158,204,909,390	394,710,849,843	20,701,944,555	56,522,679,920	3,094,474,390	20,510,298,008	984,611,694	320,201,441	655,049,969,241	**22.36**
55-59	140,313,422,544	350,319,503,643	18,897,848,297	43,867,587,430	3,407,449,791	13,734,532,249	1,062,949,584	170,063,334	571,773,356,872	**19.52**
60-64	82,928,375,784	178,923,369,610	10,064,985,992	24,474,264,480	2,547,334,283	7,128,794,475	665,839,237	213,672,115	306,946,635,975	10.48
65-69	50,874,524,966	96,212,430,098	5,785,197,917	14,279,642,292	1,999,505,221	3,915,432,027	482,546,640	254,997,600	173,804,276,762	5.93
70-74	34,322,771,334	55,715,646,493	3,635,216,681	10,371,473,705	1,621,340,600	2,567,666,124	390,009,403	190,208,603	108,814,332,944	3.72
75-79	19,965,942,073	29,491,448,904	2,140,151,339	7,687,658,586	1,072,037,904	1,222,950,401	288,104,957	144,128,437	62,012,422,602	2.12
80&above	10,922,457,402	13,553,384,416	1,092,477,696	7,080,170,125	719,286,022	667,711,688	162,088,470	241,293,098	34,438,868,918	1.18
Total	739,422,955,396	1,641,664,973,534	91,549,616,153	341,310,206,140	17,471,118,673	88,656,117,624	6,824,901,666	2,063,623,215	**2,928,963,512,399**	100.00
%	**25.25**	**56.05**	3.13	**11.65**	0.60	3.03	0.23	0.07	100.00	
Upper bound of PAF										
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	2,120,675,179	1,769,604,526	1,442,878,343	246,257,732	223,982,213	1,917,432,351	156,000,480	5,564,214	7,882,395,039	0.17
25-29	9,096,463,514	3,347,687,493	2,329,261,564	5,873,458,224	240,049,940	2,625,085,030	152,446,393	65,882,352	23,730,334,509	0.53
30-34	29,149,770,241	30,175,416,176	19,106,378,371	21,242,723,261	538,843,067	6,065,687,763	330,668,367	20,178,139	106,629,665,386	2.36

35-39	47,307,846,217	73,025,863,795	44,989,687,429	37,145,819,636	1,635,769,958	5,495,156,691	411,770,935	56,740,928	210,068,655,588	4.65
40-44	98,054,491,360	166,744,153,596	101,303,052,656	56,559,537,573	5,911,710,638	11,157,520,472	777,362,867	109,525,083	440,617,354,244	9.75
45-49	141,532,041,440	304,021,992,005	184,834,026,479	55,958,933,174	8,772,909,146	11,647,850,344	960,502,639	271,167,871	707,999,423,099	**15.67**
50-54	212,516,089,366	441,028,713,866	264,373,038,931	56,522,679,920	17,809,265,549	20,510,298,008	984,611,694	320,201,441	1,014,064,898,775	**22.44**
55-59	188,737,709,248	396,031,827,230	236,120,114,518	43,867,587,430	19,627,247,126	13,734,532,249	1,062,949,584	170,063,334	899,352,030,719	**19.90**
60-64	111,312,660,681	207,723,736,476	121,834,845,346	24,474,264,480	14,708,488,031	7,128,794,475	665,839,237	213,672,115	488,062,300,841	10.80
65-69	68,340,208,936	116,116,865,520	66,573,435,554	14,279,642,292	11,595,899,877	3,915,432,027	482,546,640	254,997,600	281,559,028,446	6.23
70-74	46,090,868,367	70,366,370,523	39,224,278,689	10,371,473,705	9,446,233,388	2,567,666,124	390,009,403	190,208,603	178,647,108,802	3.95
75-79	26,852,917,175	39,269,161,310	21,448,387,787	7,687,658,586	6,299,425,848	1,222,950,401	288,104,957	144,128,437	103,212,734,502	2.28
80&above	14,787,934,250	19,866,739,317	10,151,932,154	7,080,170,125	4,280,399,595	667,711,688	162,088,470	241,293,098	57,238,268,697	1.27
Total	995,899,675,974	1,869,488,131,832	1,113,731,317,821	341,310,206,140	101,090,224,376	88,656,117,624	6,824,901,666	2,063,623,215	**4,519,064,198,648**	100.00
%	**22.04**	**41.37**	**24.65**	7.55	2.24	1.96	0.15	0.05	100.00	

4.9.3 Sensitivity analysis by uncovered healthcare costs

After excluding the non-covered healthcare costs, the total costs of cancers attributed to infection in Korea in 2014 reduced by 3.8%, reaching around 3,410 billion KRW, of which the reduction amount came from direct medical costs whereas other cost components (direct non-medical costs and indirect costs) remained unchanged.

Table 17 Sensitivity analysis of infection-related cancers' costs by non-covered healthcare costs (Unit: KRW, %)

Including non-covered costs										
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,907,870,067	1,509,708,849	717,095,036	246,257,732	108,697,195	1,917,432,352	156,000,480	5,564,214	6,568,625,924	0.19
25-29	8,218,318,945	3,087,005,208	992,947,131	5,873,458,224	116,345,340	2,625,085,030	152,446,393	65,882,352	21,131,488,623	0.60
30-34	26,321,117,693	28,708,755,199	7,114,571,726	21,242,723,261	260,440,364	6,065,687,763	330,668,367	20,178,139	90,064,142,512	2.54
35-39	42,698,785,986	69,536,291,063	16,345,628,880	37,145,819,636	782,887,995	5,495,156,691	411,770,935	56,740,928	172,473,082,114	4.87
40-44	88,579,691,311	158,278,246,509	36,660,581,834	56,559,537,573	2,857,280,078	11,157,520,472	777,362,867	109,525,084	354,979,745,727	10.02
45-49	128,004,366,113	289,246,251,230	66,508,547,202	55,958,933,174	4,232,203,719	11,647,850,344	960,502,639	271,167,871	556,829,822,293	**15.71**
50-54	192,379,251,129	417,100,229,869	94,885,116,506	56,522,679,920	8,592,969,807	20,510,298,008	984,611,694	320,201,441	791,295,358,374	**22.33**
55-59	170,825,740,171	372,276,206,100	85,204,239,457	43,867,587,429	9,464,811,291	13,734,532,249	1,062,949,584	170,063,334	696,606,129,616	**19.66**
60-64	100,776,659,220	192,574,420,229	44,350,124,960	24,474,264,480	7,081,522,385	7,128,794,474	665,839,237	213,672,115	377,265,297,100	10.65
65-69	61,857,786,847	105,517,774,770	24,572,672,917	14,279,642,292	5,566,874,849	3,915,432,027	482,546,640	254,997,600	216,447,727,943	6.11
70-74	41,705,003,704	62,464,564,576	14,727,394,816	10,371,473,705	4,521,145,188	2,567,666,124	390,009,403	190,208,602	136,937,466,120	3.86
75-79	24,281,848,246	33,980,754,677	8,238,517,510	7,687,658,586	2,998,183,490	1,222,950,401	288,104,957	144,128,437	78,842,146,304	2.23
80&above	13,347,495,469	16,401,400,109	4,002,173,978	7,080,170,126	2,020,460,435	667,711,688	162,088,471	241,293,097	43,922,793,370	1.24
Total	900,903,934,902	1,750,681,608,388	404,319,611,953	341,310,206,138	48,603,822,134	88,656,117,623	6,824,901,668	2,063,623,215	**3,543,363,826,019**	100.00
%	**25.43**	**49.41**	**11.41**	9.63	1.37	2.50	0.19	0.06	100.00	
Excluding non-covered costs										
Overall	**H.pylori**	**HBV**	**HCV**	**HPV**	**C.sinensis**	**EBV**	**HIV**	**KSHV/HIV**	**Total**	**%**
20-24	1,886,076,047	1,474,740,819	689,052,215	225,814,751	108,064,659	1,761,769,101	146,650,380	5,269,682	6,297,437,652	0.18

25-29	8,139,351,889	2,996,374,828	952,432,495	5,644,939,198	116,030,379	2,520,415,654	142,977,374	57,958,465	20,570,480,282	0.60
30-34	26,020,773,011	28,376,464,862	7,004,760,730	20,370,384,365	257,353,090	5,880,018,749	313,616,899	19,951,853	88,243,323,558	2.59
35-39	42,172,308,620	68,737,582,617	16,122,185,062	35,661,026,195	769,930,226	5,258,448,971	390,737,701	55,805,563	169,168,024,955	4.96
40-44	87,249,104,894	156,341,949,969	36,165,203,057	54,347,475,863	2,827,531,522	10,780,176,359	746,666,243	107,548,111	348,565,656,019	10.22
45-49	126,050,080,878	284,887,787,729	65,440,520,827	53,321,789,635	4,167,007,525	11,200,536,224	918,084,350	264,339,428	546,250,146,596	**16.02**
50-54	189,177,833,442	407,814,551,270	92,672,860,843	53,361,425,975	8,428,444,647	19,886,889,112	930,526,668	304,452,797	772,576,984,754	**22.65**
55-59	166,881,843,934	360,348,527,863	82,363,294,747	41,088,388,655	9,170,784,647	13,136,467,434	995,068,513	165,972,135	674,150,347,929	**19.77**
60-64	97,084,210,457	182,643,355,122	41,980,176,544	22,435,475,979	6,716,000,533	6,709,011,424	608,019,679	202,592,751	358,378,842,491	10.51
65-69	57,960,276,175	96,880,899,170	22,494,032,583	12,622,089,854	5,114,371,711	3,575,620,692	425,834,094	244,624,954	199,317,749,235	5.84
70-74	37,629,663,212	55,724,174,469	13,100,660,626	8,997,592,295	4,007,613,257	2,260,264,957	336,291,737	172,424,375	122,228,684,928	3.58
75-79	21,153,889,488	29,218,526,970	7,066,713,748	6,532,531,059	2,565,985,945	1,046,179,104	242,330,041	127,047,219	67,953,203,575	1.99
80&above	11,108,095,084	13,624,245,231	3,324,308,740	5,952,155,530	1,676,794,706	556,024,447	134,076,919	200,752,450	36,576,453,108	1.07
Total	872,513,507,132	1,689,069,180,920	389,376,202,216	320,561,089,353	45,925,912,848	84,571,822,229	6,330,880,597	1,928,739,785	**3,410,277,335,081**	100.00
%	**25.58**	**49.53**	**11.42**	9.40	1.35	2.48	0.19	0.06	100.00	

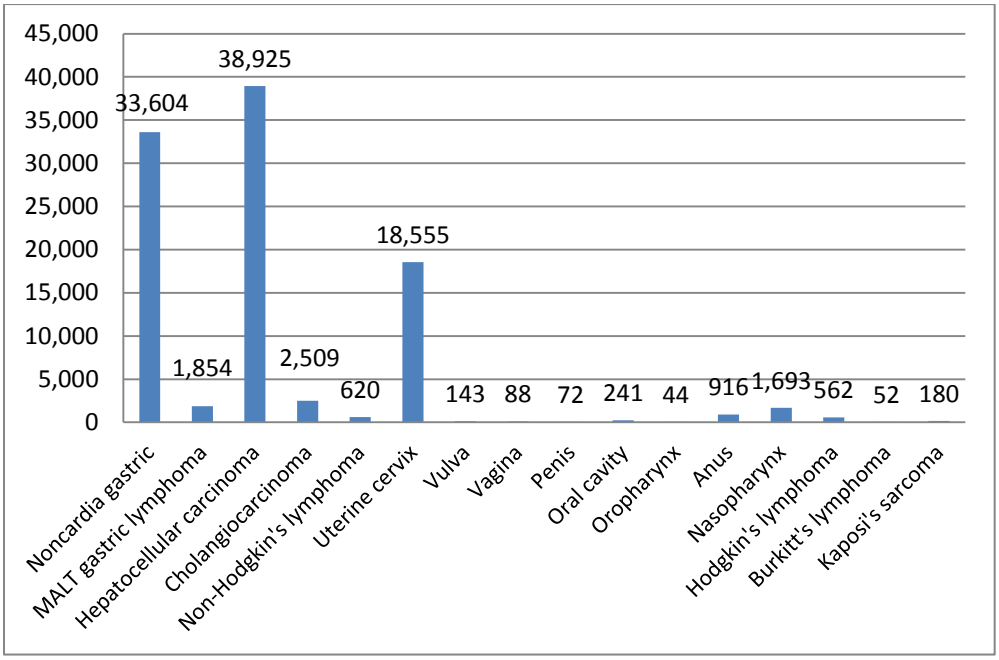

Figure 1 Number of prevalent cases of infection-related cancers by infection types

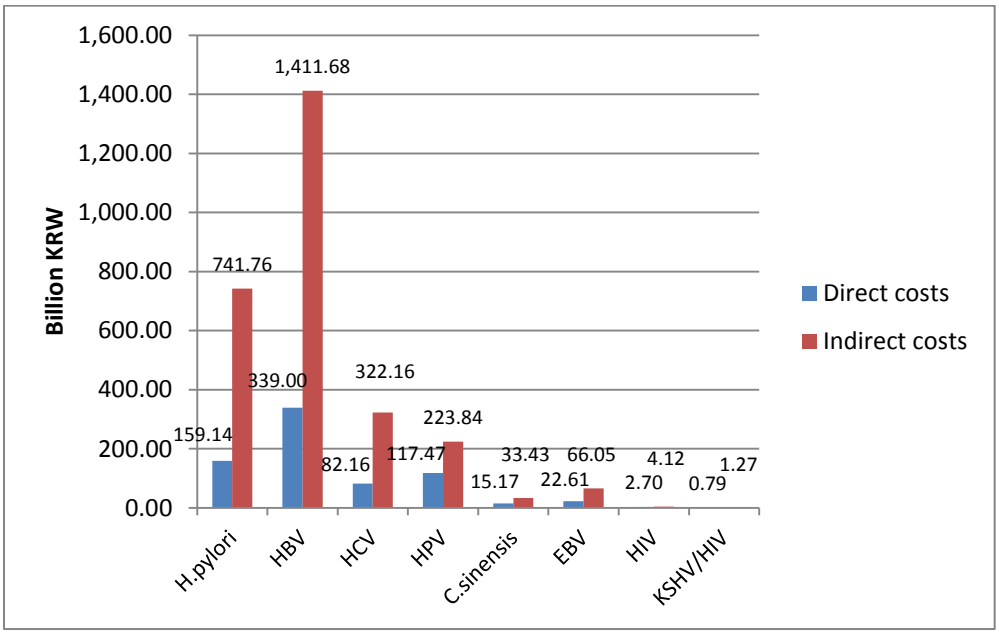

Figure 2 Direct and indirect costs of infection-related cancers by infection types (Unit: billion KRW)

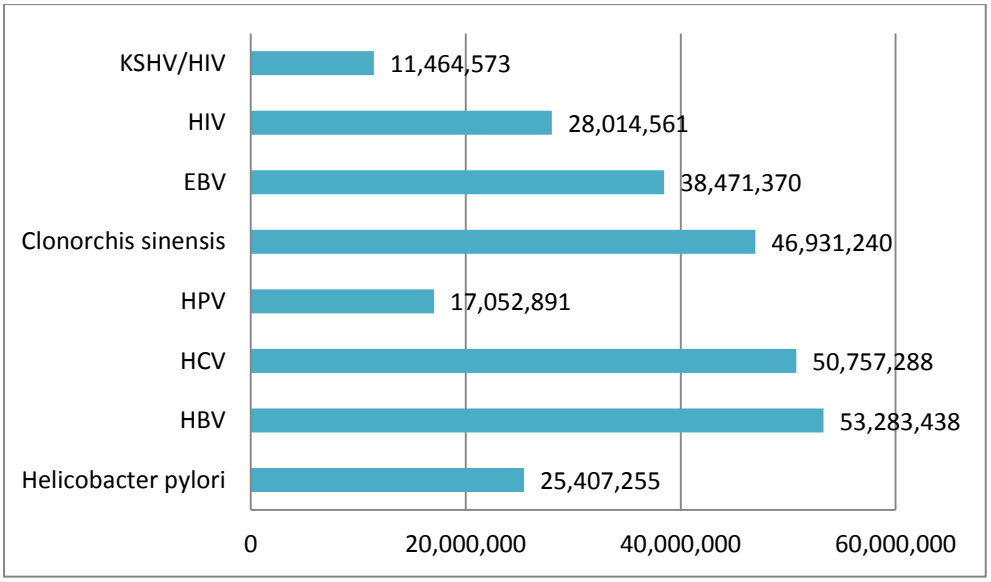

Figure 3 Cost per patient by infectious agents (Unit: KRW), 2014

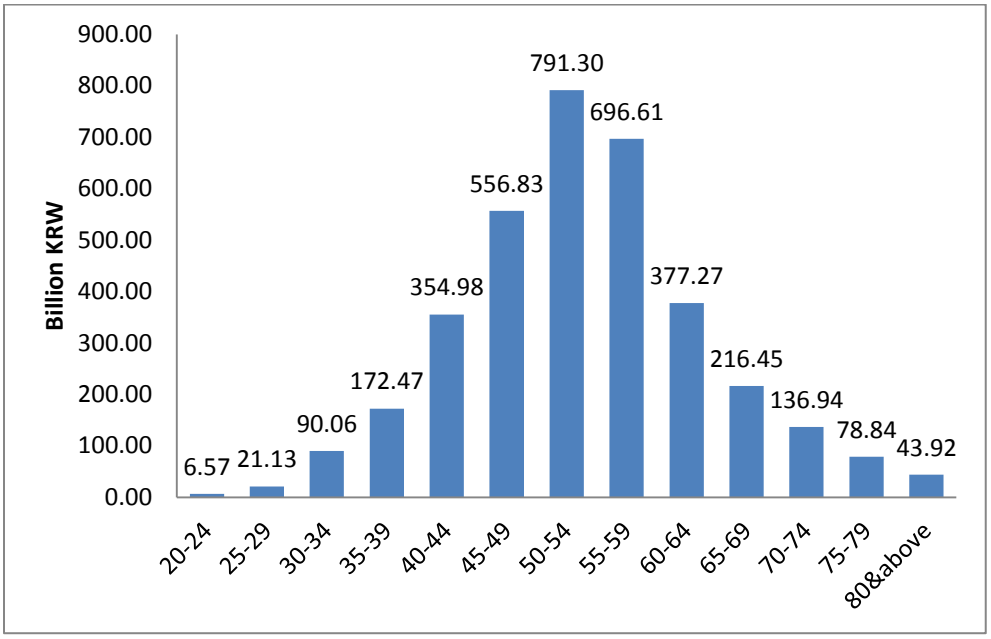

Figure 4 Total costs of infection-related cancers by 5-year age groups (Unit: billion KRW)

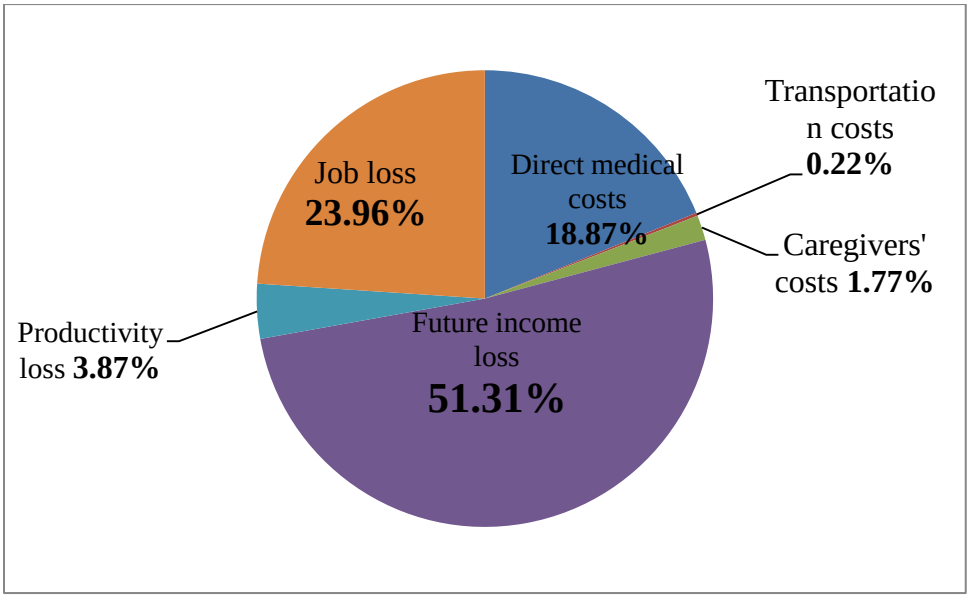

Figure 5 Proportions of cost components (%)

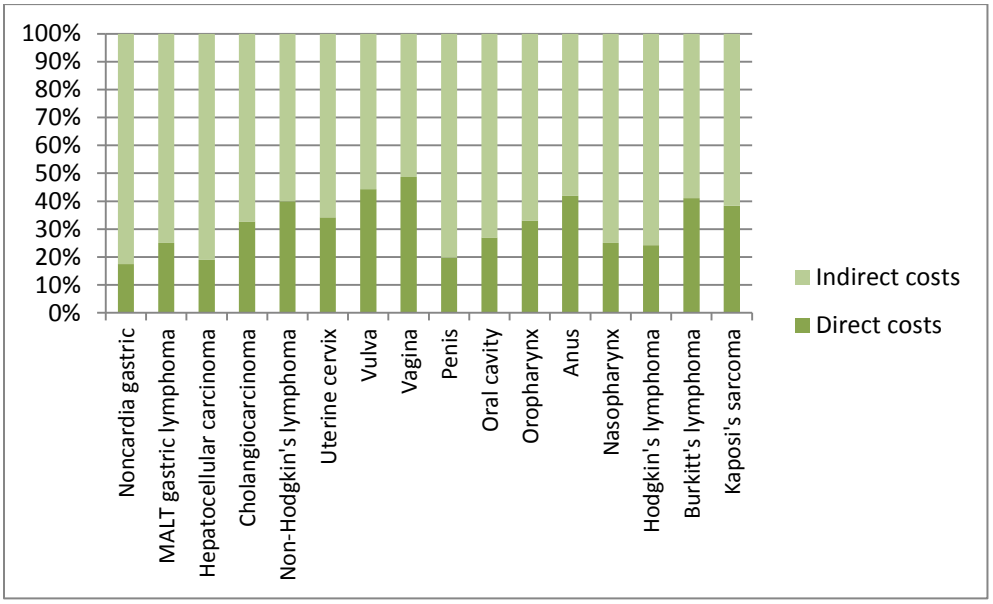

Figure 6 Proportions of direct and indirect costs by each cancer type (%)

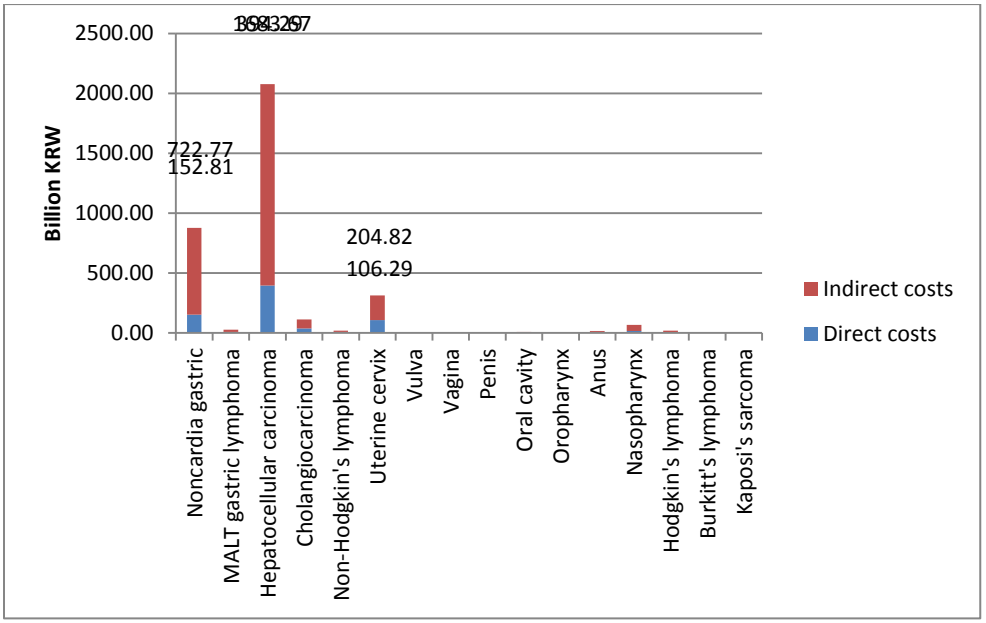

Figure 7 Total costs by cancer types (Unit: billion KRW)

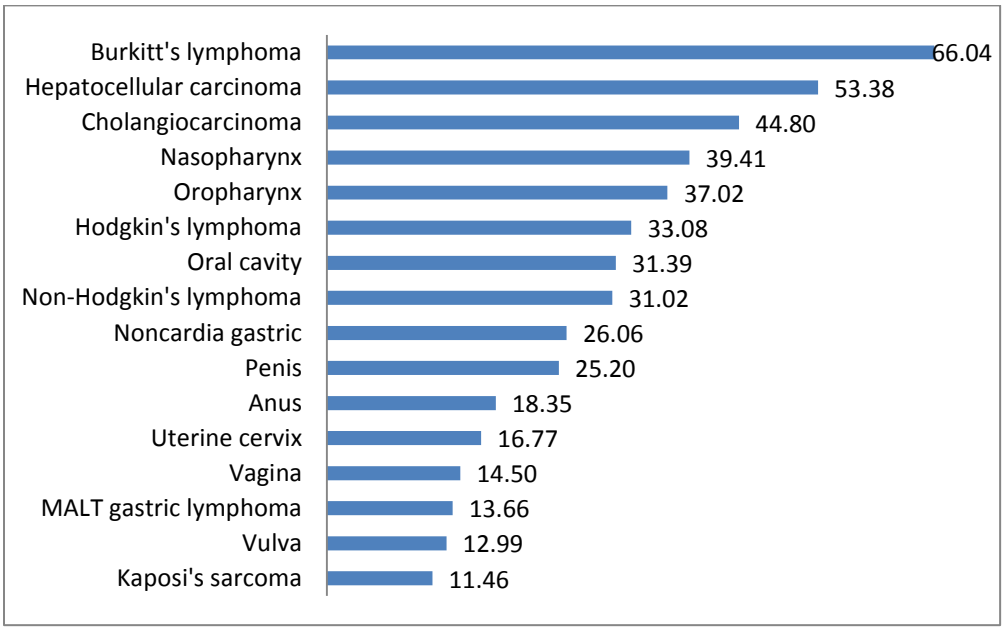

Figure 8 Costs per patient by cancer types, 2014 (Unit: million KRW)

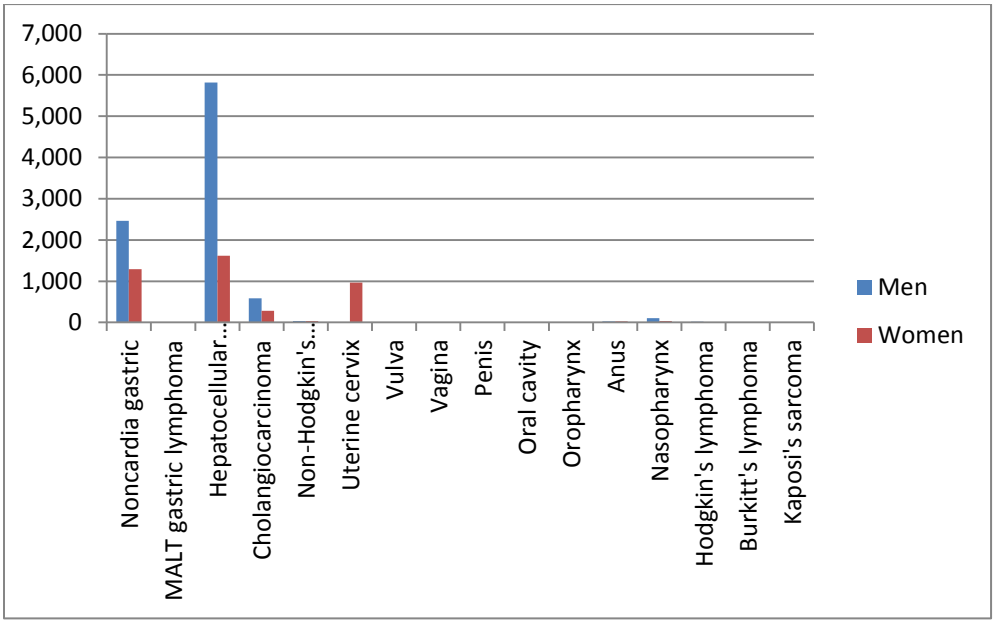

Figure 9 Estimate of number of deaths of infection-related cancers by cancer types by sex in 2014, applying PAF

4.10 Figure explanation

Fig 1 provides information about the number of prevalent cases by infection-related cancer types in Korea in 2014. Noticeably, the figures for cases of hepatocellular carcinoma, non-cardia gastric cancer and uterine cervical cancer were considerably higher than those of other cancers, representing nearly 91% of total cases attributed to infection. This result was in consistency with what was described in the first part of results section which shows a much higher prevalence in cancers due to HBV, HP and HPV.

According to Fig 2, the gap between indirect and direct costs widened from HP to HBV before getting narrower alongside until KSHV/HIV. The biggest difference was seen in the economic burden caused by HBV and HP, reflecting that patients

with cancers attributed to HBV and HP being more liable to experience economic impact of job loss, lost incomes during treatment and premature deaths. This can be explained by the fact that the number of cancers attributed to HP and HBV in Korea in 2014 accounted for the highest portion in the total figure for infection-related cancers, at 35.44% and 32.84% respectively. Stomach and liver cancers were the most common cancers [8] and being responsible for high portion of mortality in men, with the age-standardized mortality rate per 100,000 at 15.4 and 22.4 respectively, while in women these cancer types were also listed in the top 5 causes of death, with respective ASRs at 5.7 and 5.6 per 100,000.

With respect to Fig 3, an average infection-related cancer patient had to pay significantly more budget on cancer types attributed to HBV, HCV and C.sinensis, compared with cancers associated with other infectious agents. In particular, nearly 53 million KRW was expended by a typical HBV-related cancer patient, followed closely by 51 and 47 million KRW being spent by an average HCV and C.sinensis-related cancer patient respectively. Overall, this result expressed that the per-person economic costs of liver cancers was relatively higher than those of other cancer types related to infection. Also, it is noticeable that although the number of HIV patients was significantly low, at around 244 in 2014, the expenditure incurred by each person was quite high, at more than 28 million KRW, which can be unravelled by the fact that antiretroviral therapies for HIV patients were extremely costly, and not easily accessed [115].

According to Fig.4, the total costs of cancers attributed to infection increased with age, reaching a peak of nearly 791.30 billion KRW among people aged

between 50 and 54. It then declined to around 43.92 billion KRW among those of 80 & above age group. It can be clearly seen that people in the mid-20s to 30s were the least likely to be engaged in infection-related cancers, whereas working aged people and the elderly were more susceptible to contract cancers linked to infection. This pattern provides a firm ground for the assumption that it would take at least 20-year time lag for an average person to develop cancer from the time of being infected.

In relation to Fig 5, it can be noted that the largest burden of economic costs of infection-associated cancers was due to the potential future earnings lost due to premature death (51.31%). The second and largest percentages went on job loss (23.96%) and direct medical costs (18.87%) respectively. Furthermore, lost incomes due to hospitalization/outpatient visits and direct non-medical costs (transportation and caregiver's costs) were found to account for the least proportion of the total costs, ranging from 0.2-1.8% for each, which were quite similar with a previous study [23].

On the other hand, it is of compelling necessity to make critical comparisons in costs of cancers associated with infection by cancer types. From what can be seen in Fig 6, indirect costs always take up greater proportions than direct costs in each cancer type. The biggest difference in indirect and direct costs was seen in non-cardia gastric cancer, hepatocellular carcinoma and penis cancer as potential incomes lost due to morbidity and mortality accounted for nearly 89% of the total costs, while vagina cancer's cost has similar portion of direct and indirect costs. The top three cancers with gigantic economic costs consisted of hepatocellular

carcinoma, non-cardia gastric cancer and uterine cervical cancer with regards to Fig 7. This observation was contingently matched with previous results of significant costs relying on HBV, HP, HCV and HPV.

Furthermore, according to Fig 8, the average expenditure of a typical patient of Burkitt's lymphoma, hepatocellular carcinoma, and cholangiocarcinoma were shown to be highest compared with other infection-associated cancer types, which were appropriately matched with the per person spending pattern caused by HBV, HCV, and C.sinensis. Turning to Fig 9, the number of cancer deaths due to infection was considerably higher in hepatocellular carcinoma, non-cardia gastric cancer and cervical cancer. These results were reflected in an enormous burden of indirect costs of these 3 cancer types regarding Fig 7.

5. Discussion

5.1 Overall results

The economic burden of cancers attributed to infection in Korea in 2014 stood at approximately 3,543 billion KRW. Regarding direct medical and non-healthcare costs, HBV, HP and HCV took responsibility for the majority of this type of burden consecutively in men, whereas in women most of the direct costs relied on HPV, HBV and HP. Regardless of gender, nearly half of costs related to medical treatment and non-medical components including guardians' payment and transportation fees (45.87%) were spent by patients of HBV-related cancers, followed by HP (21.53%) and HPV (15.89%). Trends of the top three cancers in each sex remained the same in terms of indirect costs; however, HBV became responsible for the largest economic burden of morbidity and mortality of infection-related cancers, constituting almost half, while the second and third top cancers were associated with HP and HCV respectively. These patterns results in an overall outcome of HBV, HP and HCV sharing the most burden of infection-attributable cancers. The indirect costs (2,804 billion KRW) were significantly much higher than the direct costs (739 billion KRW) as nearly 3.79 times large. Indirect costs were evidenced as considerably more burdensome 2-3 times compared with direct costs by two previous studies calculating the economic burden of smoking-related cancers and liver disease in Korea [20, 22].

5.2 Further evaluation by infectious agents

HBV became the leading cause of cancers attributed to infection in all categories of costs in men and overall, except in women. Korea has focused on reducing the health impact of HBV by launching the National Cancer Screening Program for 5 leading sites of cancer, liver included, in 1999 in addition to their well-established vaccination efforts. As a consequence, the 5-year liver cancer survival rate increased from 13.2% (1996-2000) to 23.3% (2003-2008) [116]. There was a marked decline in the prevalence of HBV carriers after the implementation of the universal HBV vaccination program [117]. Despite the gradual decreasing trend of HBV prevalence, Korea is still classified as an intermediate endemic area of HBV infection [118]. A huge discrepancy in economic costs of cancers linked to HBV was recorded between both sexes. The expenditure related to HBV in men stood at approximately 1,607 billion KRW, which was almost 11 times higher compared with that in women. One possible explanation for that lies in a considerable gap between males and females with liver cancer. Males had a 3-4 times higher incidence of liver cancer than females did from 1999 to 2011 [119]. The prevalence gap increased with age and 50-59 year old males saw a 5 times higher incidence than female of the same age group did.

One common type of liver cancer in Korea is hepatocellular carcinoma (HCC) with a high incidence rate [120], of which HBV accounted for 68%-78% of all HCC diagnosed [118], while 10%-15% were made up by HCV [121]. Consequently, high incidence of HCC closely reflects a high prevalence of HBV or HCV infection [122]. The expenses of HBV-related cancers were much higher than those of HCV-

related cancers in every cost component. One potential explanation is that the mean age at diagnosis was much younger in HBV than HCV-related HCC [123]. In HCC cases attributed to HBV, a considerable percentage of patients were below the age of 60. By contrast, those below the age of 40 diagnosed with HCV-related HCC were rare (1%) and most patients (77%) were over 60 years. As a time lag is required for a typical person from being infected by HBV to associated cancer development, the higher proportion of young patients with HBV infection partly leads to a more significant portion of costs related to infection by total, compared with HCV. Furthermore, the lower prevalence combining with higher survival rate of HCV-related HCC can underpin that statement. According to treatment modality, there was no difference of initial treatment methods between HBV- and HCV-related HCC [123]. The 1, 3, 5 year survival rates of HCV-related HCC (68%, 40% and 28%) were relatively higher than those of HBV-related HCC (55%, 35% and 27%).

HP-related cancers remained stable as the next highest burdensome compared with cancers attributed to HBV in terms of direct and indirect costs. Most of gastric cancers are non-cardia cancer [14] and nearly 80% of all non-cardia cancer cases and deaths were attributed by HP in both sexes. Gastric cancer has been recorded as the most frequently cited diagnosed cancer in Korea since 1999 when the Korea Central Cancer Registry produced a nationwide report of cancer incidence data for the first time [124]. Though not a statistically dramatic change, gastric cancer incidence has dropped in both males and females with the annual percentage change in ASR being -0.5% in males and -0.6% in females respectively. The attributable

fraction of HP is predicted to be smaller recently as a consequence of a decline in HP prevalence [125]. Nonetheless, it is important to note that the generations between 40 and 54 experienced a rising incidence pattern, more significantly in women despite the overall decreasing trend for both incidence and mortality in both sexes [126]. This evidence was solidified by the increasingly high economic burden of cancers linked to HP by older ages, specifically in people in the age groups of 45-59.

While HBV asserted the first place of infection-related cancers in terms of monetary terms in men and overall, HPV became the infectious agent with highest share of costs in women in each cost sector. Regarding a prior study conducted in 2012, among 60,775 women aged from 18 to 79, 34.2% of them were shown with HPV positive rate of total patients in Korea [127]. High risk HPV infection is common among Korean women [60]. From this research, the prevalence of genital high-risk HPV was highest among those aged 20-59 years, falling thereafter before growing again to 12.4% among 50-59 year-olds. The total economic costs of cancers attributable to HPV were estimated at nearly 341 billion KRW, of which a huge proportion (94.2%) was contributed by females. People in the mid-40s and 50s were the most likely group of age to be affected by HPV-related cancers.

The least burdensome infection-attributable cancer types were those associated with HIV and KSHV with their respective economic costs accounting for 0.19% and 0.06% of the total. In terms of HIV, despite very low HIV prevalence recorded in Korea, the number of new HIV cases was reported to increase steadily since 2000, from 219 to 868 in 2012 [128]. There was not much difference between direct

and indirect costs in HPV-related cancer patients. One main reason is that though HIV survival rates had certain signs of improvement, HIV patients still become susceptible to higher mortality at early times after diagnosis [129]. Specifically, regarding a previous study [130], 38.2% of total HIV-infected patients died during the first year of antiretroviral therapy (ART), while the remaining's death occurred between 1 and 5 year after that start of ART. Furthermore, it is noticeable that men spent significantly higher budget on infection-related cancer treatment than women as well as larger lost income due to absences from work/premature deaths in every category of infectious agents, apart from HPV and HIV. The number of HIV-related cancers in Korean males (93) in 2014 was found to be nearly 1.6 times smaller than that in females (151). This interpretation is consolidated by another study [131] showing that gender distribution among public health centers' visitors was larger in women although HIV prevalence was higher in men. In terms of KSHV, Kaposi sarcoma is categorized as a relatively rare cancer type with around 44,427 incident cases and 26,974 deaths being identified worldwide in 2012 [12]. Therefore, it hardly becomes doubtful of the lowest economic burden of infection-related cancers being KSHV-associated.

In this study, we included job loss as part of the indirect costs. Although in Korea several studies of economic burden determination did not cover incomes lost due to unemployment after cancer diagnosis, job loss needs to be carefully considered because of the high proportion it accounted for in the total costs endured. From what is shown in the result section, a significant 23.96% of the overall infection-related costs was contributed by job loss. In Korea, the all-cancer

incidence rate has started to decreased after 2012 along with an annually decreasing trend of mortality rate since 2002 [8]. These patterns combing with an improvement of 5-year relative survival rate for cancer patients lead to questioning how cancers impact their daily lives, such as employment and work abilities. Cancer survivors experienced a considerably higher risk of unemployment, early retirement and delayed re-employment. An estimated proportion of cancer survivors, ranging from 26% to 53%, lost their job or quit their current occupations during a 72-month period post diagnosis, of which between 23% and 75% were re-recruited [132]. Several studies taking job loss situation into account have been conducted in some countries [133, 134]. According to a study researching Korean job loss rate post cancer diagnosis [114] , of 5,396 patients being engaged at the baseline, a high of 47% lost their job over a 72-month follow up period, and 25.9% were unemployed within the first year after cancer diagnosis. Until now, that article was the most recent one in terms of job loss post cancer diagnosis in Korea, covering almost all cancer sites and taking the employment status of the entire Korean population into consideration. That is the primary reason why we decided to involve job loss as an essential component of the indirect costs.

On the other hand, our study selected cancer patients in accordance with their special code-V193 provided by medical providers during inpatient stay/outpatient visits. One main reason for that is that Korea utilized fee-for-service system for hospital fee charge in most circumstances, of which a fee reduction system is employed for medical costs paid by patients with serious diseases such as cancer, stroke, and myocardial infarction has been in place since 2005 [135]. In particular,

without the policy of Expanding Benefit Coverage, patients with severe diseases would have to spend considerably regardless of their insurance because of huge healthcare expenses involved. According to this policy, in the case of inpatient hospital stays or doctor office visits due to their disease or complications, the patients would only need to pay for 5% of their total bill [136, 137]. This policy is applied for patients with serious diseases as mentioned above for 5 years following the first registration date, and can be re-applied for those who still have cancers or suffer from metastasis or recurrence after 5 years. On the other hand, several articles determining the economic burden of cancers specifically or overall have defined a cancer patient as experiencing at least one inpatient admission and three times of outpatient visits [19, 138]. Regarding the article named "Economic burden of cancers attributable to metabolic syndrome in Korea", it was hypothesized that the number of the cancer patients indicated by this code would be more accurate than that calculated using the frequency of visits as similarly in another previous study [23], a sensitivity analysis was conducted to assess the differences in results obtained by applying special code versus the frequently used definition of a cancer patient. A slight discrepancy was seen in results obtained by this sensitivity analysis, of which the total costs in patients with special code were insignificantly lower than that in patients defined as usual, along with a smaller proportion of the number of cancer patients observed by using V-193 (7% fewer). As a result, it can be understood clearly that involving special code V-193 in the analysis can underestimate the total costs of cancers attributed to infection in this study. However, the difference is predicted not to be substantial.

5.3 Comparison with other diseases and nations

In Korea, the health burden of cancers attributed to infection in monetary terms took up 0.22% of national gross domestic product (GDP) and nearly 1.36% of national healthcare expenditure in 2014. It would be extremely useful to make several comparisons between infection-related cancers and other diseases with regards to economic costs. Firstly, in terms of acute myocardial infarction (AMI), the prevalence of AMI is on the rise in aging populations as decreasing mortality resulting from improved early detection and treatment modality, without an except case of South Korea [139]. Compared with cancers linked to infection, the number of patients diagnosed with AMI in 2012 stood at 236,339, being nearly twice as high as that with infection-related cancers (100,059), whereas only a relative higher economic burden was seen in AMI, accounting for 1.58% of NHI healthcare expenditure. Secondly, in terms of acute coronary syndrome (ACS), ACS was significantly prevalent in Korea and it became the third leading cause of death as the figures for morbidity and mortality linked with ACS has increased rapidly in the last 10 years [140]. ACS impacted a considerably larger number of patients (309,384) in 2009 compared with infection-related cancers (100,059). By contrast, direct costs of ACS accounted for around 1.1% of national medical spending, quite lower than that of infection-attributable cancers. Thirdly, it is worth making a comparable picture of the economic burden of infection-related cancers and rheumatic heart disease (RHD) in Korea as the role of RHD is increasingly being concerned by public health policy makers in high income countries [141]. The proportion of RHD economic costs in total expenditure (0.13%) in 2008 was much

lower than that of infection-related cancer costs, whereas the number of patients with both diseases was quite similar (around 100,000 for each). Finally, the economic burden of asthma is put into consideration compared with that of cancers attributed to infection. One main reason is that Korea has experienced a large and rising burden of asthma regarding prevalence and mortality rates [142, 143]. It is highly noticeable that the number of asthma patients in 2008 (2,273,290) [144] was dramatically larger than that of infection-related cancers patients as almost 23 times though asthma's shared burden over national healthcare expenses (1.69%) was not much higher than infection-associated cancers' (1.36%). In conclusion, it is of great necessity to draw a more considerable concern on infection-related cancers in addition to ACS, RHD and asthma.

Measuring the economic burden of cancers associated with infection is not paid as much attention in the Western world or America as in Korea since infection-related cancers were not common in highly developed countries with the proportion of incident cases fluctuating between 5% and less than 10%, while nearly 20% of prevalent cancer cases and deaths in Korea relied on infection [34]. However, a few studies were carried out with the purpose of determining the costs of HPV-related diseases and cancers, driving the making of informed decisions about future investments in programs of HPV prevention [145]. In particular, Finland is renowned for its far-reaching screening performance which results in the low cervical cancer incidence rate [146], while a study topic of Economic Burden of HPV-related cancers in France was executed to update a certain contribution of cancers attributable to HPV as well as assessing the possible advantages of HPV

vaccination programs in both sexes [147]. By gender, Korean females represent the majority of economic burden, with nearly 94.2%, compared with relatively lower 84% attributed by women in Sweden [148].

To date, there was no separate paper carried out to examine the burden of cancers attributed to each type of infectious agents in Korea. Only one study was realized in terms of demonstrating economic costs of diseases related to HBV [149]. Infection is one of the modifiable risk factors, meaning that primary prevention can help diminish the heavy strain of cancers in the long term. Two studies were executed in the measurement of the economic burden of cancers attributed to modifiable risk factors, i.e. metabolic syndrome and smoking in Korea [22, 23].

5.4 Limitations and strengths

There are several limitations in our study. The first shortcoming is the potential overestimation of productivity loss in accordance with the human capital approach employed in the measurement of future income loss since this method has been criticized for its assumption that a worker cannot be replaced even if the unemployment is significantly high. Secondly, the cost of alternative and complementary medicine was not included due to the absence of data, and also, outpatient pharmaceutical costs and other non-covered healthcare costs (i.e. equipment costs) were excluded because of lack of available accurate data. Finally, cancer costs attributed to infection might have been underestimated as only primary diagnoses were included in this study.

However, it is of great importance to recognize the strengths of our study. One main advantage is the utilization of NHIS claims data as this data source has been

affirmed for its comprehensiveness and extension in calculating per-person medical cost with specific disease. Another strength that is worth mentioning is that this study is the originality itself as it is the first-ever conducted in terms of the estimation of infection-related cancers in economic costs in Korea.

6. Conclusions & Implications

6.1 Conclusions

In conclusions, we determined the economic costs of cancers attributed to infection in Korea in 2014, utilizing the representative dataset from NHIS which covers most Korean populations. Despite a gradually decreasing trend of infection incidence, it is noticeable that the economic burden of infection-related cancers is quite substantial and projected to be significant in the near future as it takes a time-lag period from getting infection to cancer development and population growth. Our results act as a practically useful tool for policy making in terms of stringent reinforcement and extensive promotion of infection prevention programs nationwide. Furthermore, this study can be used as a baseline for further research conducted to examine the effectiveness of ongoing preventive policies in Korea.

6.2 Implications

This study has several important implications. Firstly, it serves as a solid platform for more far-reaching infection prevention programs and highly extensive efforts of Korean governments in terms of consolidating infection-associated cancers reduction. In order to address infection-attributable cancer burden as well as eradicating chronic infections, primary prevention is of critical importance, of which vaccines play an important role in the prevention of infectious diseases and related cancers [150]. In particular, the widespread coverage of HBV vaccination has given rise to a favourable effect of decreasing primary hepatocellular

carcinoma. In Korea, it has been shown that HBV control goals have been achieved successfully thanks to the constructively well-established National Immunization Program (NIP) [151]. From our study results, HBV, HP, HCV and HPV were responsible for the most burdensome infection-related cancers, i.e. hepatocellular carcinoma, gastric cancer and cervical cancer, and had significant effect on working-aged people in Korea. Since June 2016, HPV vaccination has become part of the fully funded NIP [152]. Because the HPV vaccination program was nationally implemented not long time, it is still of great necessity to enhance the awareness of the use of vaccination as a cervical cancer preventive method further. While HBV and HPV vaccines have been well-developed and extensively used, promising vaccines against HCV, HP, and HIV is still in progress. As a result, a further primary prevention strategy is to abandon the chronicization of infection [150]. In particular, the primary prevention of HIV-associated cancers is based on the therapy of AIDS (high active anti-retroviral therapy-HAART), whereas HCV and HP infection are eradicated relying on drugs and available treatments. In terms of other infection types, to reduce Clonorchis sinensis, in addition to mass health campaigns of eating behavior modification and praziquantel distribution, it is recommended to include community leader or individual health education in the parasitic national control programs [153]. EBV vaccination has not been discovered yet; therefore, the only way to prevent EBV infection is to keep personal hygiene and sanitation at high levels. Similarly, to date, there is no way of preventing KSHV infection; in order to hasten the burden of KSHV-related cancers, the only way is to strengthen the ongoing developed treatment of KSHV/HIV-related Kaposi's

sarcoma and to hamper the chance of getting KSHV on HIV-infected patients by using HAART. On the other hand, secondary prevention is worth applying in case the carcinogenic process is about to happen [150]. Korea has adapting its National Cancer Screening Program with free cancer screenings for the five major types of cancers (stomach, liver, colorectal, breast, and cervical cancer) since 1999 [154]. Secondary prevention helps to reduce the mortality of infection-associated cancers; however, its long-term effect takes time to be examined. Secondly, it is noticeable that job loss accounted for the second highest burden of the total economic costs of infection-related cancers in Korea, which highlights the need to assist cancer patients' employment status post-diagnosis, for example, increasing the rate of re-employment of cancer survivors. Finally, our study provides useful baseline data for further research regarding the examination and assessment of the effectiveness and long-term impact of infection control programs in Korea as well as nationwide screening implementation.

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