**The Economic Burden of Cancers Attributable to Infection in the Republic of Korea: A Prevalence-Based Study**

Thi Xuan Trinh Nguyen 1, Minji Han 1, Moran Ki 1, Young Ae Kim 2 and Jin-Kyoung Oh 1,2,*

1 Department of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, 323 Ilsan-ro, Ilsandong-gu, Goyang-si 410-769, Korea; xuantrinh93@gmail.com (T.X.T.N.); mjhan@ncc.re.kr (M.H.); moranki@ncc.re.kr (M.K.)

2 National Cancer Control Institute, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang-si 410-769, Korea; 12274@ncc.re.kr

*Correspondence: jkoh@ncc.re.kr; Tel.: +82-319-202-921

Received: 28 September 2020; Accepted: 14 October 2020; Published: 19 October 2020

**Abstract:** Infection is a major cause of cancers. We estimated the economic burden of cancers attributable to infection in 2014 in Korea, where cancer causing infection is prevalent, but the economic burden of it has never been examined. Cancer patients were defined as those having made medical claims as recorded by the National Health Insurance Service, which is a mandatory insurance for all citizen. We multiplied the costs by the population-attributable fraction for each type of cancer. The study included direct and indirect costs, where direct costs comprised direct medical and non-medical costs of inpatients and outpatients, while indirect costs were estimated by identifying future income loss due to premature death, productivity loss during hospitalization/outpatient visits, and job loss. In 2014, there were 100,054 infection-related cancer patients, accounting for 10.7% of all Korean cancer cases for that year. Direct costs of cancers associated with infection stood at nearly USD 676.9 million, while indirect costs were much higher at USD 2.57 billion. The average expenditure of a typical patient was USD 32,435. Economic burden of cancers attributable to infection is substantial in Korea, accounting for 0.23% of the national gross domestic product and 1.36% of national healthcare expenditure in 2014.

**Keywords:** cancer; infection; economic burden; Korea

1. **Introduction**

Cancer places an enormous burden on society regardless of countries’ development. Overall, the numbers of new cancer cases and deaths reported worldwide in 2012 were 14.1 and 8.2 million, respectively [1]. Korean age-standardized cancer incidence rates were among the highest globally at an average of 253.8 per 100,000 population [2], while a remarkable improvement in 5-year survival rates was seen between 1993 and 1995 and in the next 4 years from 2010 to 2014 [3]. In 2015, the national cancer burden was predicted to increase to nearly 280,556 new cancer cases and 76,698 cancer deaths with the increasing population age [4].

A significant number of infectious agents, namely helicobacter pylori (HP), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), *Clonorchis sinensis* (*C. sinensis*), Epstein Barr virus (EBV), human immunodeficiency virus (HIV), and Kaposi sarcoma-associated herpes virus (KSHV) have been categorized as Group 1 human carcinogens by the International Agency for Research on Cancer (IARC) [5]. With respect to the global population, the health burden of infection-associated cancers has been recorded on a yearly basis, with 1.9 million cases witnessed in 2002 [6]. Thereafter, the number of cancer cases associated with infectious agents increased to 2 million in 2008 [7] and
2.2 million in 2012 [8], constituting over 15% of all new cancer cases in both years. The proportion of cancer deaths attributed to these infections in low- and middle-income countries was higher relative to that reported for high-income countries; in addition, the proportions of cancer deaths attributed to infection in developed and developing countries were 9% and 20%, respectively [9].

In 2007, the estimated proportions of all cancers in Korea attributable to infection were 25.1% and 16.8% for cancer incidence in men and women, respectively [10]. In addition, those for cancer mortality in men and women were 25.85% and 22.7%, respectively. Furthermore, the proportion of infection-related cancers attributable to infection with HP, HBV, HCV, and HPV was over 97% [10]. Primary and secondary prevention programs to control infections have been implemented. For example, immunization programs against viral hepatitis B and human papillomavirus has been established in 1995 and in 2016, respectively, through the national immunization program, which shows very high vaccination rate [11]. The national screening program provides screening for stomach, liver, colorectal, breast, and cervical cancer for adults in every 2 years, free of charge [12]. Despite those preventable interventions, stomach and liver cancers were predicted to become among the most burdensome for Korean men in 2015, with cervical cancer expected to account for an overwhelming proportion of the cancer burden in Korean women [4]. Importantly, there is sufficient evidence indicating that all these types of cancer are caused by infectious agents.

To date, several cost-of-illness studies have emphasized the large burden incurred by specific types of cancer and groups of cancers linked to risk factors such as smoking [13]. However, no studies have examined the economic burden of cancer associated with infection in Korea. Therefore, research examining the economic cost of infection-related cancer is required to reveal new findings.

2. Materials and Methods

2.1. Infectious Agents Related to Cancer

The list of infection-causing agents includes HP, HBV, HCV, HPV, Clonorchis sinensis, EBV, HIV, and KSHV/HIV. The current study used the population-attributable fraction (PAF), based on previous research conducted in Korea [10].

The total economic cost of cancer due to infection was measured by multiplying the cost of each cancer site by the respective PAF, as described in the following formula:

\[
\text{Infection-attributable costs} = \text{Total costs per cancer site} \times \text{PAF}
\]

2.2. Data Source

Health insurance claims data provided by the National Health Insurance Service (NHIS) were analyzed. NHIS insurance is a mandatory single-payer system that provides benefits for medical services. All South Korean citizens must either enroll in the NHIS (97% of the entire population) or receive medical aid (3%) [14]. The NHIS database contains information regarding both those enrolled in the service and medical aid subjects; therefore, it includes data for the entire Korean population. The NHIS currently maintains and stores national records for healthcare utilization and prescriptions. The NHIS claims data contain details of the cost of care, attended medical institutions, income distribution, and residence for all insurance subscribers [15].

2.3. Ethics Approval

This study used anonymous secondary data and was exempted from the Institutional Review Board of the National Cancer Center, Korea (approval date: 13 June 2017; approval number: NCC2017-0131). The requirement for obtaining consent was waived.
2.4. Estimation of Economic Burden

We conducted a cost-of-illness study to assess the economic burden of cancer due to infection based on a prevalence-based approach aiming at existing and newly diagnosed patients in 2014. Major cancers attributable to infection were selected with regards to the IARC Monograph Evaluation Carcinogenic Risks to Humans 2012 [16]. Infection-related cancers were defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision and included cancers of the oral cavity (C00–C09), oropharynx (C10), nasopharynx (C11), anus (C21), vulva (C51), vagina (C52), uterine cervix (C53), and penis (C60); Kaposi’s sarcoma (C46); Hodgkin’s sarcoma (C81); non-Hodgkin’s lymphoma (C82–85, C96); non-cardia gastric cancer (C161–C168); hepatocellular carcinoma (C220); cholangiocarcinoma (C221 + C240); Burkitt’s lymphoma (C837); and mucosa-associated lymphoid tissue gastric lymphoma (C884) [15]. The target participants were patients who had claimed health insurance benefits with these International Statistical Classification of Diseases and Related Health Problems 10th Revision codes as a primary diagnosis and the special cancer claim code, V193 (a cancer-specific code for expanded benefits), in 2014. Because of the time lag in cancers attributable to infection, the study sample included only patients aged ≥20 years.

The total economic burden of infection-related cancers included direct and indirect costs. 

Total costs = Direct costs + Indirect costs

Direct costs are costs incurred during medical treatment and consist of direct medical and nonmedical costs. Medical claim records from the 2014 NHIS were used to obtain direct medical care costs, and existing and newly diagnosed patients with infection-related cancer were targeted. The non-covered medical costs were estimated at 19.9% of the total direct medical costs [17]. Direct nonmedical care costs were quantified by acquiring transportation costs for inpatient and outpatient visits and total caregiver payments. One-way transportation fees for inpatient and outpatient visits, obtained from the 2014 Korea Health Panel Survey, were KRW 15,000 and KRW 4000, respectively [18]; these were used with visit frequency, to achieve transportation costs. Based on the 2014 Korea Health Panel Survey, caregivers’ overall daily wage was estimated at KRW 63,000, with a utilization rate of 67% for inpatients [18]. To obtain inpatient caregiver costs, we assumed that each patient was accompanied by a guardian for the entire day; therefore, the cost was calculated by including the daily caregiver payment, duration of hospitalization, and nursing utilization rate. Costs for outpatients aged ≥65 years were determined by multiplying the duration of outpatient visits (in days) by one third of caregivers’ daily wages (see Table A1 in Appendix A).

Formula:

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

DC = direct costs; j = age; i = gender; y = cancer type
IP = total treatment duration for inpatients of i and j in NHIS data
OP = total treatment duration for outpatients of i and j in NHIS data
\( \alpha \) = the ratio of noncoverage and coverage rates (in this study, \( \alpha = 19.9:80.1 \))
IV = duration of inpatient visits (in days)
OV = duration of outpatient visits (in days)
TIV = cost of one-way trip to hospital for inpatients
TOV = cost of one-way trip to hospital for outpatients
CGR = caregivers’ average wage per day
C = utilization rate
OV’ = durations of outpatient visits (in days) for those aged ≥65 years
PAF = population-attributable fraction
Indirect costs included future income loss (FIL) because of premature death, productivity loss (PL) due to inpatient or outpatient hospital visits, and job loss (JL) after cancer diagnosis. A human capital approach was applied to the estimate FIL by calculating the income each person would have earned during the period from earlier death to normal life expectancy for the age cohort. A human capital approach based on the assumption that future income acts as a substitute for future productivity was used to determine future income loss, but it does provide an accurate representation in some cases [19]. FIL following premature deaths by year and by cancer types was calculated using data from cause of death statistics [20], and employment rates and annual average wage by sex and age was provided by the Ministry of Employment and Labor [21], with an annual discount rate of 3%. To estimate the loss of productivity due to visits to medical institutions and hospitalization, the total numbers of outpatient visits and days of inpatient admission were obtained from NHIS claims data, which were combined with age and sex-specific employment rates and monthly wages. The rate of job loss due to cancer was estimated at 47%, based on previous research [22]. These figures were used with employment rates and daily average wages according to age and sex, to determine costs incurred due to unemployment following diagnosis (see Table A1). We assumed that the employment rates in age 70–74 years and in age 75 years or older are half of and one quarter of the employment rate in age 65–69 years, respectively, which is the oldest age group available from the Ministry of Employment and Labor.

\[
Indirect\ costs = Future\ income\ loss + Productivity\ loss + Job\ loss
\]

Formula:

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

FIL = future income loss
i = sex; j = age; t = age at death
y = cancer type
k = 1, 2, \ldots, 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

\[
PL = \sum_i \sum_j \sum_y \left\{ \left( IV_{ijy} + \frac{1}{2} OV_{ijy} \right) \times PA\frac{F}{iy} \times E_{ij} \times DW_{ij} \right\}
\]

PL = productivity loss
i = sex; j = age; y = cancer type
IV = number of inpatient visits
OV = number of outpatient visits
E = employment rate
DW = daily wage
PAF = population-attributable fraction

\[
JL = \sum_i \sum_j \sum_y \left\{ N_{ijy} \times YW_{ij} \times E_{ij} \times L \times PA\frac{F}{iy} \right\}
\]

JL = job loss
N = number of prevalent cancer cases
i = sex; j = age; y = cancer type
YW = yearly wage  
E = employment rate  
L = job loss rate  
PAF = population-attributable fraction

Sensitivity analysis was performed to examine productivity loss following premature death, with 0% and 5% annual discount rates. Furthermore, sensitivity analysis was stratified according to noninsured healthcare costs and the upper and lower bounds of the 95% confidence interval for the PAF. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2013. All costs were converted from KRW to USD based on the exchange rate in 2014 (1 USD = 1091.85 KRW) [23].

3. Results

There were approximately 100,054 patients with infection-related cancer in Korea in 2014, accounting for almost 10.7% of all cancer cases that year in which no remarkable differences in the figures for males and females were recorded, with relatively equal numbers of patients (approximately 50,000) of each sex (Table 1). Overall, the largest numbers of prevalent cancers attributed to infection were observed in people in their 50s and 60s. With respect to infection types, HP was the most common factor, associated with almost 35% of all infection-related cancers, followed by HBV and HPV, irrespective of sex.

Table 1. The estimated number of cases of infection-related cancers according to infectious agent in 2014, South Korea.

| Infectious Agent | Gender | Age | Total N |
|------------------|--------|-----|---------|
|                  |        | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80+ |       |
| HP               | Men    | 38    | 370   | 2077  | 6041  | 7398  | 6228  | 1503 | 23,655 |
|                  | Women  | 72    | 441   | 1555  | 2651  | 2673  | 3188  | 1223 | 11,803 |
| HBV              | Men    | 24    | 341   | 2455  | 8266  | 7896  | 5110  | 1158 | 25,250 |
|                  | Women  | 18    | 118   | 442   | 1596  | 2299  | 2340  | 791  | 7604   |
| HCV              | Men    | 15    | 92    | 575   | 1881  | 1783  | 1147  | 256  | 5749   |
|                  | Women  | 13    | 48    | 147   | 477   | 656   | 659   | 218  | 2218   |
| HPV              | Men    | 6     | 18    | 47    | 146   | 182   | 170   | 66   | 635    |
|                  | Women  | 237   | 2454  | 4832  | 5183  | 3373  | 2443  | 857  | 19,379 |
| C. sinensis      | Men    | 0     | 3     | 27    | 125   | 236   | 298   | 109  | 798    |
|                  | Women  | 0     | 1     | 6     | 26    | 55    | 91    | 56   | 235    |
| EBV              | Men    | 110   | 150   | 287   | 491   | 368   | 195   | 32   | 1633   |
|                  | Women  | 72    | 85    | 131   | 168   | 98    | 89    | 28   | 671    |
| HIV              | Men    | 4     | 7     | 13    | 23    | 22    | 19    | 5    | 93     |
|                  | Women  | 5     | 14    | 26    | 38    | 31    | 28    | 9    | 151    |
| KSHV/HIV         | Men    | 3     | 3     | 12    | 12    | 25    | 56    | 32   | 143    |
|                  | Women  | 0     | 1     | 1     | 12    | 6     | 8     | 9    | 37     |

Total N 617 4146 12,633 27,136 27,101 22,069 6352 100,054

Abbreviations. HP, helicobacter pylori; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; C. sinensis, Clonorchis sinensis; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; KSHV, Kaposi’s sarcoma herpes virus.

The estimated number of deaths with infection-related cancer was 13,380 deaths, accounting for 13.4% of prevalent cases in that year (Table 2).
Table 2. The estimated number of deaths with infection-related cancers according to infectious agent in 2014, South Korea.

| Infectious Agent | Gender | Age       | Total N |
|------------------|--------|-----------|---------|
|                  |        | 20–29     | 30–39   | 40–49   | 50–59   | 60–69   | 70–79   | 80+     |        |
| HP               | Men    | 7         | 38      | 155     | 495     | 593     | 748     | 428     | 2463    |
|                  | Women  | 5         | 59      | 139     | 160     | 138     | 383     | 410     | 1292    |
| HBV              | Men    | 2         | 89      | 518     | 1439    | 1295    | 1238    | 461     | 5043    |
|                  | Women  | 3         | 17      | 55      | 180     | 281     | 510     | 394     | 1440    |
| HCV              | Men    | 1         | 20      | 116     | 320     | 286     | 272     | 100     | 1115    |
|                  | Women  | 1         | 5       | 16      | 49      | 76      | 139     | 107     | 393     |
| HPV              | Men    | 0         | 1       | 4       | 10      | 10      | 15      | 13      | 52      |
|                  | Women  | 6         | 63      | 154     | 205     | 143     | 233     | 212     | 1016    |
| C. sinensis      | Men    | 0         | 1       | 8       | 37      | 66      | 100     | 54      | 267     |
|                  | Women  | 0         | 0       | 2       | 7       | 16      | 32      | 30      | 87      |
| EBV              | Men    | 1         | 5       | 11      | 39      | 33      | 26      | 12      | 127     |
|                  | Women  | 1         | 2       | 5       | 10      | 8       | 14      | 12      | 52      |
| HIV              | Men    | 0         | 0       | 1       | 1       | 2       | 4       | 2       | 10      |
|                  | Women  | 0         | 0       | 1       | 2       | 2       | 4       | 3       | 13      |
| KSHV/HIV         | Men    | 0         | 0       | 0       | 0       | 2       | 1       | 3       | 6       |
|                  | Women  | 0         | 0       | 0       | 0       | 2       | 2       | 4       |         |
| Total N          |        | 29        | 300     | 1184    | 2953    | 2951    | 3720    | 2243    | 13,380  |

Abbreviations. HP, helicobacter pylori; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; C. sinensis, Clonorchis sinensis; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; KSHV, Kaposi’s sarcoma herpes virus.

The economic burden of cancer attributable to infection in 2014 was USD 3.25 billion, and the majority of the total indirect cost was incurred for HBV, HP, and HCV. The direct cost of cancer attributable to infection in Korean adults aged ≥20 years was estimated at approximately USD 676.9 million (Table 3). The estimated cost incurred during medical treatment was high at almost USD 612.5 million, which accounted for 90.5% of direct costs. Men endured much higher costs, relative to those observed in women, for each infection type, regardless of HPV and HIV status. Noticeably, HBV, HP, and HCV were responsible for the greatest expenditure incurred by men, while HPV accounted for the highest infection-related cancer costs in women, followed closely by HBV and HP.

In contrast, the indirect cost of cancer attributable to infection in Korean adults aged ≥20 years was approximately USD 2.57 billion (Table 3). Regardless of sex, the most burdensome indirect costs were incurred for HBV, HP, and HCV. In particular, the greatest expenses resulting from premature death and lost productivity in men were observed for cancers attributed to HBV, HP, and HCV, while HPV accounted for the highest indirect cost, followed closely by HP and HBV, in women. Economic loss of productivity because of premature death, inpatient/outpatient visits, and unemployment following cancer diagnosis were estimated at USD 1.67 billion, USD 125.7 million, and USD 777.4 million, respectively.

The largest burden resulting from the economic costs of infection-associated cancers was due to potential future earnings lost because of premature death (51.3%), followed by job loss (24.0%) and direct medical costs (18.9%) (Figure A1).
Table 3. Estimated direct and indirect costs of infection-related cancers regarding infectious agent in 2014, South Korea (Unit: 1000 USD).

| Infectious Agent | Gender | Direct Cost | Indirect Cost | Total |
|------------------|--------|-------------|---------------|-------|
|                  |        | Medical Costs | Transportation Cost | Caregiver Costs | Subtotal | Future Income Loss | Productivity Loss during Hospital Visits | Job Loss | Subtotal |
| HP               | Men    | 89,642       | 1134            | 8840            | 99,616   | 318,892         | 23,057                        | 226,787 | 568,736 | 668,352 |
|                  | Women  | 41,025       | 356             | 4564            | 46,145   | 66,245          | 4275                         | 40,122  | 110,641 | 156,786 |
| HBV              | Men    | 224,517      | 2141            | 18,200          | 244,858  | 890,949         | 56,394                        | 279,422 | 1,226,765 | 1,471,623 |
|                  | Women  | 59,055       | 599             | 5976            | 65,630   | 41,623          | 3886                         | 20,688  | 66,197  | 131,827 |
| HCV              | Men    | 51,312       | 487             | 4092            | 55,891   | 198,980         | 12,823                        | 64,139  | 275,941 | 331,832 |
|                  | Women  | 17,465       | 176             | 1715            | 19,357   | 11,592          | 1181                          | 6354    | 19,128  | 38,485  |
| HPV              | Men    | 4353         | 60              | 530             | 4943     | 6267            | 1360                         | 5714    | 13,341  | 18,284  |
|                  | Women  | 91,145       | 1430            | 10,073          | 102,647  | 76,219          | 14,645                        | 100,810 | 191,675 | 294,322 |
| C. sinensis      | Men    | 9335         | 97              | 1081            | 10,714   | 21,643          | 1873                         | 5007    | 28,522  | 39,236  |
|                  | Women  | 2790         | 28              | 366             | 3184     | 1564            | 150                          | 383     | 2096    | 5280    |
| EBV              | Men    | 13,853       | 185             | 1182            | 15,221   | 25,900          | 4959                         | 21,895  | 52,735  | 67,976  |
|                  | Women  | 4945         | 66              | 475             | 5487     | 3582            | 691                          | 3465    | 7738    | 13,225  |
| HIV              | Men    | 1036         | 9               | 71              | 1116     | 1223            | 205                          | 1053    | 2481    | 3597    |
|                  | Women  | 1238         | 13              | 108             | 1360     | 515             | 115                          | 664     | 1294    | 2654    |
| KSHV/HIV         | Men    | 489          | 9               | 71              | 569      | 96              | 113                          | 836     | 1045    | 1614    |
|                  | Women  | 132          | 2               | 21              | 135      | 7               | 11                           | 102     | 120     | 275     |
| Subtotal         |        | 612,532      | 6993            | 57,367          | 676,892  | 1,665,298       | 125,737                       | 777,440 | 2,568,475 | 3,245,367 |

Abbreviations. HP, helicobacter pylori; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; C. sinensis, Clonorchis sinensis; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; KSHV, Kaposi’s sarcoma herpes virus.
Regarding cancer types, the costs incurred for hepatocellular carcinoma accounted for the largest proportion of the total cost (USD 1.9 billion), followed by uterine cervical cancer (USD 285 million) and cholangiocarcinoma (USD 103 million; Table 4). With respect to infectious agents and sex, the largest economic burden was associated with cancers attributed to HBV in men (approximately USD 1.47 billion), followed by HP- and HCV-related cancers in men and HPV-related cancers in women. The economic burden per patient was highest for cancers related to HBV (USD 48,802) and noticeably greater for Burkitt’s lymphoma and hepatocellular carcinoma, relative to that for other cancer types.

The results of the sensitivity analysis performed to examine different discount rates showed that the economic burden was USD 3.69 billion with a discount rate of 0% and USD 3.04 billion with a discount rate of 5%. The sensitivity analysis involving the lower and upper bounds of PAF showed that the economic burden ranged from USD 2.68 billion using the lower bound to USD 4.14 billion with the upper bound (Table A2).

Table 4. Estimated cost of infection-related cancers according to cancer type in 2014, South Korea (Unit: 1000 USD).

| Cancer Types              | Direct Costs | Indirect Costs | Total   |
|---------------------------|--------------|----------------|---------|
| Anus                      | 6456         | 8934           | 15,390  |
| Burkitt’s lymphoma        | 1288         | 1842           | 3130    |
| Cholangiocarcinoma        | 33,687       | 69,265         | 102,952 |
| Hepatocellular carcinoma  | 361,129      | 1,542,072      | 1,903,201|
| Hodgkin’s lymphoma        | 4128         | 12,903         | 17,031  |
| Kaposi’s sarcoma          | 725          | 1165           | 1890    |
| MALT gastric lymphoma     | 5806         | 17,393         | 23,199  |
| Nasopharynx               | 15,308       | 45,804         | 61,112  |
| Noncardia gastric         | 139,954      | 661,985        | 801,939 |
| Non-Hodgkin’s lymphoma    | 7037         | 10,575         | 17,612  |
| Oral cavity               | 1870         | 5067           | 6937    |
| Oropharynx                | 494          | 1000           | 1494    |
| Penis                     | 329          | 1333           | 1662    |
| Uterine cervix            | 97,354       | 187,590        | 284,944 |
| Vagina                    | 569          | 599            | 1168    |
| Vulva                     | 755          | 948            | 1703    |

Abbreviations. MALT, mucosa-associated lymphoid tissue.

4. Discussion

The economic burden of cancers attributed to infection in Korea in 2014 was approximately USD 3.25 billion, and indirect costs were 3.8 times higher than direct costs. Indirect costs were significantly more burdensome and 2–3 times higher than direct costs reported in previous studies [13,24]. Furthermore, the financial health burden of cancers attributed to infection accounted for 0.23% of the national gross domestic product and almost 1.36% of national healthcare expenditure in 2014 [14,25].

Regarding direct costs, HBV, HP, and HCV accounted for the majority of infection-related cancers in men, while women’s direct costs were incurred for HPV, HBV, and HP. Trends for indirect costs incurred for the top three infectious agents were similar for both sexes. Overall, HBV accounted for the greatest economic burden of morbidity and mortality resulting from infection-related cancers, followed by HP and HCV. The costs incurred by men for infection-related cancers were four times higher than those incurred by women.

The current study included the cost of job loss as an essential part of indirect costs. Although several Korean studies involving economic burden estimation did not examine income lost through unemployment following cancer diagnosis, job loss should be considered carefully because of the high proportion of the total cost attributable to this factor. The current results suggested that 23.96% of the overall infection-related cancer costs were attributable to job loss. The annual decrease in the mortality
rate since 2002, combined with the improvement of 5-year survival rates in cancer patients in Korea [4], raises questions regarding the impact of cancer on patients’ daily lives including employment and work capability. Of the 5396 patients assessed at baseline, 47% lost their jobs over the 3-year follow-up period [22]. This was the primary reason for the inclusion of job loss as a fundamental component of indirect costs in the current study.

From the results of our study, a combination of productivity loss and job loss burden accounts for a substantial fraction of the total infection-related cancer costs (27.8%). There is also other research placing an importance on the burden of productivity loss and job loss in terms of cancer costs. In a study on the economic burden of cancer survivorship among adults in the US [26], indirect morbidity costs were estimated from lost productivity as a result of employment disability, missed work days, and lost household productivity. In particular, mean adjusted annual lost productivity among adults recently diagnosed with cancer was 4694 USD, compared with 17,170 USD of medical expenditure, taking up around 21.5%. In a study on the economic burden of lung cancer and mesothelioma due to occupational and para-occupational asbestos exposure in Canada [27], both human capital and friction cost approaches are employed to determine lost productivity due to cancer, which constitutes 24.4% of total cancer costs. In a Japanese study on the cost of illness of breast cancer trends and future projections [28], productivity loss (morbidity costs) is included, consisting of costs associated with inpatient and outpatient care, holding nearly 6.7% of total costs in 2011 (46.8/697 billion JPY).

In our study, we selected patients based on the special code V193 claimed by medical providers for inpatient stays and outpatient visits. The main reason for this was that, in accordance with the policy of expanding benefit coverage, special codes are provided for patients with severe diseases, such as cancer and myocardial infarction, to reduce the substantial healthcare expenses that could be incurred. In contrast, with the exception of one study that estimated the economic burden of metabolic syndrome-related cancers [29] and used special code V193, studies examining the economic burden of cancer in Korea have defined cancer patients based on the frequency of visits (i.e., at least one inpatient admission and three outpatient visits) [30]. According to the above-mentioned study, there was a slight discrepancy between the economic cost calculated using the frequency of visits and that observed for the special code. Consequently, the use of the special code, V193, in the current analysis could have led to slight underestimation of the total cost; however, this would not have been substantial.

Measurement of the economic burden of cancers associated with infection has not received a considerable attention in developed countries, because these types of cancer are uncommon in highly industrialized nations, with the proportion of cases fluctuating between 5% and 10% [31], while nearly 20% of cancer cases and deaths in Korea have been associated with infection [10]. Many infection-related cancers, particularly those associated with HBV, HCV, HP, HPV, and liver flukes are primarily or secondarily preventable through vaccination, health education for safe sex, changes in eating habits, and early screening. The implementation of the HBV vaccination, for example, started to be packaged into the National Immunization Program in Korea in 1995 [11]. Moreover, there was a marked decline, from 4.6% in 1998 to 2.9% in 2016, in the seroprevalence of hepatitis B surface antigens. Although HPV vaccines have been used in Korea since 2007, HPV vaccination was involved in the National Immunization Program for girls in 2016 [11]. A recent study in Korea reported that, while the prevalence of anogenital warts in men increased continuously over time, that observed in women declined after 2012, reflecting the effect of the vaccine [32]. Korea has adapted its National Cancer Screening Program for the five major types of cancer (i.e., stomach, liver, colorectal, breast, and cervical) since 1999 [12]. However, considering the time lag involved, the long-term effects, including reduced economic burden because of primary and secondary prevention, require sufficient time for examination.

The study was subject to several limitations. The first was the potential overestimation of productivity loss based on the human capital approach used to measure future income loss, as this method has been criticized for its assumption that workers cannot be replaced, even if unemployment is significantly high. However, the human capital approach is one of the most widely used methods in the estimation of indirect costs of diseases. In addition, medical costs could have been underestimated,
because the outpatient pharmaceutical costs of cancer-specific treatment could not be verified via the NHIS claim data, and the cost of alternative and complementary medicine was excluded because of an absence of data. Furthermore, cancer costs attributed to infection could have been underestimated, as only primary diagnoses were included in the study. Despite these limitations, this was the first study to focus on the estimation of the economic burden of infection-related cancers in Korea, using NHIS claim data for the entire Korean population. Further investigation on economic burden of infection-specific cancer for evaluating impact of intervention programs of infection control and prevention is needed.

5. Conclusions

In the current study, we calculated the economic cost of cancers attributed to infection in Korea in 2014, using a representative dataset from the NHIS, which reflects the entire Korean population. Despite a gradually decreasing trend in the incidence of infection, the results showed a substantial economic burden resulting from infection-related cancers, and this is expected to increase in the near future because of population growth and the time lag between infection and cancer development. These results could assist policymakers to reinforce and promote infection prevention programs and early treatment for infectious diseases nationwide. In addition, the findings could provide a useful baseline for further research examining the effectiveness of ongoing preventive policies in Korea.

Author Contributions: Conceptualization, J.-K.O.; methodology, M.H.; formal analysis, M.H., T.X.T.N.; investigation, M.H., J.-K.O., and T.X.T.N., writing—original draft, T.X.T.N.; writing—review and editing, M.K., Y.A.K., and J.-K.O.; supervision and funding acquisition, J.-K.O. All authors have read and agreed to the final version of the manuscript.

Funding: This study was supported by the National Cancer Center (NCC-1610410; 2010303). The first author, T.X.T.N., received funding from the “International Cooperation & Education Program (NCCRI·NCCI 52210-52211, 2018)” at the National Cancer Center, Korea.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

HP, helicobacter pylori; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; C. sinensis, Clonorchis sinensis; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; KSHV, Kaposi’s sarcoma herpes virus; IARC, International Agency for Research on Cancer; KRW, Korean won; MALT, mucosa-associated lymphoid tissue; NHIS, National Health Insurance Services; PAF, population-attributable fraction; USD, United States dollar.
Appendix A

Table A1. Data sources that are used in direct and indirect costs estimation of infection-related cancers in the Republic of Korea.

| 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) |
|               | Direct non-medical costs | One-way cost per visit: Korea Health Panel Survey (2014) | Frequency of inpatient/outpatient visits: NHIS claims data (2014) |
|               | Transportation costs | Days of inpatient admission: NHIS claims data (2014) | Frequency of over-65-year-old outpatients: NHIS claims data (2014) |
|               | Caregivers’ costs | Caregivers’ daily wage and utilization rate: Korea Health Panel Survey (2014) | Days of inpatient admission: NHIS claims data (2014) |
|               | Future income loss | Number of cancer specific deaths: Cause of death statistics, Korea (2014) | Employment rates: Ministry of Employment and Labor, Korea (2014) |
|               | Indirect costs | 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) |
|               | Job loss | Number of cancer cases: NHIS claims data (2014) | Job loss average rate: Park J.H. et al. (2008) |
|               |               | Average daily wage: Ministry of Employment and Labor, Korea (2014) | Average daily wage: Ministry of Employment and Labor, Korea (2014) |

Table A2. Sensitivity analysis of infection-related cancer costs regarding discount rates and PAF range (Unit: 1000 USD).

| Economic Burden for a Given Discount Rate | Economic Burden within PAF Range |
|------------------------------------------|---------------------------------|
| 0%           | 3%                | 5%                | Lower Bound | Base Estimate | Upper Bound       |
| 3,689,134    | 3,245,367         | 3,038,634         | 2,682,638   | 3,245,367     | 4,139,011         |

Abbreviations. PAF, population-attributable fraction.
Figure A1. Proportions of cost components.

References

1. World Health Organization. Global Healthy Observatory Data Repository. Available online: http://apps.who.int/gho/data/node.main.CODWORLD?lang=en (accessed on 14 June 2018).
2. Korea Central Cancer Registry; Ministry of Health and Welfare (South Korea); National Cancer Center (South Korea). Annual Report of Cancer Statistics in Korea in 2013; National Cancer Center (South Korea): Goyang-si, Korea, 2015.
3. Jung, K.W.; Won, Y.J.; Oh, C.M.; Kong, H.J.; Lee, D.H.; Lee, K.H. Community of Population-Based Regional Cancer, R. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2014. Cancer Res. Treat. 2017, 49, 292–305. [CrossRef] [PubMed]
4. Jung, K.W.; Won, Y.J.; Oh, C.M.; Kong, H.J.; Cho, H.; Lee, D.H.; Lee, K.H. Prediction of cancer incidence and mortality in Korea, 2015. Cancer Res. Treat. 2015, 47, 142–148. [CrossRef] [PubMed]
5. Bouvard, V.; Baan, R.; Straif, K.; Grosse, Y.; Secretan, B.; El Ghissassi, F.; Benbrahim-Tallaa, L.; Guha, N.; Freeman, C.; Galichet, L.; et al. A review of human carcinogens—Part B: Biological agents. Lancet Oncol. 2009, 10, 321–322. [CrossRef]
6. Parkin, D.M. The global health burden of infection-associated cancers in the year 2002. Int. J. Cancer 2006, 118, 3030–3044. [CrossRef] [PubMed]
7. De Martel, C.; Ferlay, J.; Franceschi, S.; Vignat, J.; Bray, F.; Forman, D.; Plummer, M. Global burden of cancers attributable to infections in 2008: A review and synthetic analysis. Lancet Oncol. 2012, 13, 607–615. [CrossRef]
8. Plummer, M.; de Martel, C.; Vignat, J.; Ferlay, J.; Bray, F.; Franceschi, S. Global burden of cancers attributable to infections in 2012: A synthetic analysis. Lancet Glob. Health 2016, 4, e609–e616. [CrossRef]
9. Ott, J.J.; Ulrich, A.; Mascarenhas, M.; Stevens, G.A. Global cancer incidence and mortality caused by behavior and infection. J. Public Health (Oxf.) 2011, 33, 223–233. [CrossRef] [PubMed]
10. Shin, A.; Park, S.; Shin, H.R.; Park, E.H.; Park, S.K.; Oh, J.K.; Lim, M.K.; Choi, B.Y.; Boniol, M.; Boffetta, P. Population attributable fraction of infection-related cancers in Korea. Ann. Oncol. 2011, 22, 1435–1442. [CrossRef] [PubMed]
11. Korean Centers for Disease Control and Prevention. Guidelines for the National Immunization Program. Available online: https://nip.cdc.go.kr (accessed on 14 June 2018).

12. Jung, M. National Cancer Screening Programs and evidence-based healthcare policy in South Korea. Health Policy 2015, 119, 26–32. [CrossRef] [PubMed]

13. Oh, I.H.; Yoon, S.J.; Yoon, T.Y.; Choi, J.M.; Choe, B.K.; Kim, E.J.; Kim, Y.A.; Seo, H.Y.; Park, Y.H. Health and economic burden of major cancers due to smoking in Korea. Asian Pac. J. Cancer Prev. 2012, 13, 1525–1531. [CrossRef] [PubMed]

14. National Health Insurance Service. National Health Insurance Statistical Yearbook; Health Insurance Review & Assessment Service: Wonju, Korea, 2016.

15. Seong, S.C.; Kim, Y.Y.; Khang, Y.H.; Park, J.H.; Kang, H.J.; Lee, H.; Do, C.H.; Song, J.S.; Bang, J.H.; Ha, S.; et al. Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. Int. J. Epidemiol. 2017, 46, 799–800. [CrossRef]

16. International Agency for Research on Cancer. Biological Agents. In IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; International Agency for Research on Cancer: Lyon, France, 2012.

17. National Health Insurance Services. Survey on the Benefit Coverage Rate of National Health Insurance in 2014; National Health Insurance Services: Richardson, TX, USA, 2014.

18. Korea Health Panel Study. Available online: https://www.khp.re.kr:444/eng/main.do (accessed on 14 June 2018).

19. Jo, C. Cost-of-illness studies: Concepts, scopes, and methods. Clin. Mol. Hepatol. 2014, 20, 327–337. [CrossRef] [PubMed]

20. Statistics Korea. Cause of Death Statistics in 2014. Available online: http://kostat.go.kr/portal/eng/pressReleases/8/10/index.board?bmode=read&bSeq=&aSeq=349053&pageNo=1&rowNum=10&navCount=10&currlPg=&sTarget=title&sTxt (accessed on 14 June 2018).

21. Korea Ministry of Employment and Labor. Survey Report on Labor Conditions by Employment Type; Korea Ministry of Employment and Labor: Sejong-si, Korea, 2015.

22. Park, J.H.; Park, E.C.; Park, J.H.; Kim, S.G.; Lee, S.Y. Job loss and re-employment of cancer patients in Korean employees: A nationwide retrospective cohort study. J. Clin. Oncol. 2008, 26, 1302–1309. [CrossRef] [PubMed]

23. Exchange Rates. Korean Won Rates for 12/31/2014/ US Dollar. Available online: https://www.exchange-rates.org/Rate/KRW/USD/12-31-2014 (accessed on 14 June 2018).

24. Lee, S.; Chung, W.; Hyun, K.R. Socioeconomic costs of liver disease in Korea. Korean J. Hepatol. 2011, 17, 274–291. [CrossRef] [PubMed]

25. South Korea GDP—Gross Domestic Product. Available online: https://countryeconomy.com/gdp/south-korea?year=2014 (accessed on 14 June 2018).

26. Guy, G.P., Jr.; Ekwueme, D.U.; Yabroff, K.R.; Dowling, E.C.; Li, C.; Rodriguez, J.L.; de Moor, J.S.; Virgo, K.S. Economic burden of cancer survivorship among adults in the United States. J. Clin. Oncol. 2013, 31, 3749–3757. [CrossRef]

27. Tompa, E.; Kalcevich, C.; McLeod, C.; Lebeau, M.; Song, C.; McLeod, K.; Kim, J.; Demers, P.A. The economic burden of lung cancer and mesothelioma due to occupational and para-occupational asbestos exposure. Occup. Environ. Med. 2017, 74, 816–822. [CrossRef] [PubMed]

28. Matsumoto, K.; Haqa, K.; Kitazawa, T.; Seto, K.; Fujita, S.; Hasegawa, T. Cost of illness of breast cancer in Japan: Trends and future projections. BMC Res. Notes 2015, 8, 539. [CrossRef] [PubMed]

29. Kim, D.; Yoon, S.J.; Gong, Y.H.; Kim, Y.A.; Seo, H.Y.; Yoon, J.; Kim, A.R. The Economic Burden of Cancers Attributable to Metabolic Syndrome in Korea. J. Prev. Med. Public Health 2015, 48, 180–187. [CrossRef] [PubMed]

30. Yoon, S.J. A Study on Measuring and Forecasting the Burden of Disease in Korea; Cardiovascular and Metabolic Diseases Etiology Research Center: Seoul, Korea, 2015.
31. Schottenfeld, D.; Beebe-Dimmer, J. The cancer burden attributable to biologic agents. *Ann. Epidemiol.* 2015, 25, 183–187. [CrossRef] [PubMed]

32. Oh, J.K.; Choi, H.Y.; Han, M.; Lee, J.K.; Min, K.J.; Ko, M. Prevalence of human papillomavirus-related diseases in the Republic of Korea: A cross-sectional study. *Sex. Transm. Infect.* 2019, 95, 292–299. [CrossRef]

**Publisher’s Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).