Quantification of Transfusion Recipients at Risk of Receiving Hepatitis B Virus-Contaminated Blood Components: A Korean Study

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Received: 18 July 2014 / Accepted: 18 June 2015 / Published online: 26 June 2015
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Abstract Although there are lots of studies about the risk for the hepatitis B virus infection such as the residual risk for donated blood, there is no research on the risk of HBV infection, from the viewpoint of recipients in Korea. Using the data about HBsAg status of donated blood in 2008 and 2009, the distribution of blood components from the claim data of health insurance in 2009, the distribution of HBsAg and HBsAb of recipients, and some assumptions, we quantified the number of recipients in Korea that might be expected to receive HBV-contaminated blood components, as a proxy index for HBV infection by transfusion in 2009. Of the 376,211 recipients, the number who might be expected to receive blood components with HBV in 2009 was 23.2 (95 % CI 13.6, 36.8) in the basic model, 43.2 (95 % CI 25.4, 68.7) in extended model I, 55.2 (95 % CI 32.5, 87.7) in extended model II and 101.6 (95 % CI 59.8, 161.4) in extended model III. The number of HBV-positive

samples per 100,000 transfused units was 0.6 in the basic model (95 % CI 0.3, 0.9), 1.1 in extended model I (95 % CI 0.6, 1.8), 1.4 in extended model II (95 % CI 0.8, 2.2), and 2.6 in extended model III (95 % CI 1.5, 4.1). This study showed that a few recipients might receive HBV-contaminated blood component by transfusion. These results could be used as a scientific evidence for health policy on HBV transfusion infection.

Keywords Hepatitis B · Blood component · Transfusion · Residual risk

Introduction

Korea has one of the world's highest prevalences of hepatitis B virus (HBV), reported in 2011 as 3.2 % (male 3.6 %; female 2.7 %) [1]. HBV infection is a major causal factor in cirrhosis and liver cancer; thus it is important to both reduce HBV infection prevalence and provide effective treatment. Because transfusion is a major source of HBV transmission, several measures are applied at each step of the transfusion process—donation, screening for donated blood, and the transfusion procedure itself—to prevent HBV transmission [2].

The risk of HBV infection during transfusion is usually expressed as the residual risk (RR), which can be estimated by the incidence-window period model [3, 4]. Despite the reduction in the prevalence of HBV in the general population—and the window period of its screening test—the RR for HBV in Korea per 100,000 donations has remained high, at 2.18 in 2000/2001, increasing to 2.29 in 2009/2010 [5]. In addition to RR, the prevalence of occult carriage of HBV infection, or anti-HBc, also demonstrates the risk of HBV infection in the context of donated blood [6, 7]. To

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date, however, no research on the risk of HBV infection, from the viewpoint of recipients in Korea, has been conducted. Considering the high prevalence of HBV, the high RR for HBV from donated blood, and the magnitude of the risk of HBV infection among transfusion recipients, we might expect HBV-contaminated blood components to regularly be transfused to recipients.

The present study aimed to quantify the number of recipients in Korea that might be expected to receive HBV-contaminated blood components, as a proxy index for HBV infection by transfusion, and to provide a scientific evidence for health policy pertaining to prevention of HBV infection by transfusion.

Methods

Study Process and Data Resources

The blood donation and transfusion process, and the procedure of this study, are illustrated in Fig. 1. Phase I entailed calculation of the RR of HBV, via blood donation data obtained from two blood centers, and the number of HBV-contaminated blood components. In phase II, the distributions of recipients and blood components were ascertained using both the 2009 claim data of the Health Insurance Review and Assessment Service (HIRA), and the recipients' HBV surface antigen and antibody distribution (HBsAg and HBsAb). Finally, in phase III the number of recipients who might be expected to receive HBV-contaminated blood components was estimated by models based on the results of Phases I and II, together with some additional assumptions.

Measurement

Phase I: Calculation of the Residual Risk (RR) of HBV via Blood Donation Data Obtained from Two Blood Centers, and the Number of HBV-Contaminated Blood Components

RR refers to units of donated blood not classified as infected at the donation step due to the limitations of the screening test. This study employed an incidence methodology to calculate the RR (3, 4). The incidence method calculates RR by multiplying the incidence (incidence density) of HBV infection for donated blood by the window period of the screening test.

$$\text{RR of HBV} = \lambda \times \text{window period}$$

RR is the units of blood components not classified as infected, λ is the incidence density of HBV infection, and window period is the time (in days) between infection and first detection of the viral marker.

The incidence, calculated by dividing the number of positive seroconvertors of HBV by person-year, is an index of the number of seroconvertors per 1 million person-years. If the incidence rate is 6 per 1 million person-years, and the window period is 30 days, then the RR is $6/1,000,000 \text{ person-years} \times 30/365 = 0.49/1,000,000$. This translates to screening tests failing to identify 0.49 infected blood units per 1,000,000 blood donations.

Donors were classified as first-time donors who donated on a single occasion, or as repeated donors who donated more than twice between 2008 and 2009. Using the number of HBsAg seroconvertors and follow-up periods among repeat donors at the Korea Red Cross Blood Center

Fig. 1 Process of donation and transfusion and this study. *RR* Residual risk, *HBsAg* Hepatitis B surface antigen, *HBsAb* Hepatitis B surface antibody

between 2008 and 2009, the incidence of HBV infection of the donated blood was calculated. The operational definition for a seroconverter of HBsAg is that HBsAg, for repeated donors, was negative at the first donation but positive at the second donation.

Since July 2007, the Korean Red Cross Blood Center has screened all donated blood using the chemiluminescence immunoassay (CLIA) (Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA), which has a window period of approximately 45 days [8]. The number of confirmed HBV infections was estimated from the confirmatory rate (87.5 %) of HBsAg among Korean blood donors using a HBsAg neutralization test (PRISM, Abbott Diagnostics, Chicago, IL, USA) [9]. However, estimation of the incidence of HBV infection using repeated donation data is limited in that the incidence of HBV infection in repeated donors may differ from that in first-time donors. Accordingly, we assumed that the incidence of HBV infection in these two types of donor was identical. There are two major blood centers in Korea; the Korean Red Cross Blood Center and the Hanmaeum Blood Center. This study analyzed data only from the former center. We assumed that total RR, and amount of donated blood positive for HBV, were identical in both centers. The incidence, RR, and amount of donated blood were used to calculate the proportion of HBV-positive blood.

Phase II: Distribution of Recipients, Blood Components and HBV Risk

Data on the gender- and age-distribution of recipients and blood components were calculated based on the 2009 claim data of HIRA. Accordingly, the number of blood components delivered to recipients was operationally defined as the quantity of blood components supplied by the two blood centers to medical institutions. We assumed that the distribution of HBsAg and HBsAb to all recipients in 2009 was identical to that of a previous report of HBsAg and HBsAb distribution of 6037 recipients from a single university [10]. If a recipient had HBsAb, we assumed that they would not be infected by transfusion. If they possessed HBsAg prior to transfusion, we assumed that their infection was not related to transfusion with HBV-contaminated blood components. The operational definition of the HBV transmission-through-transfusion risk group was 'those whose HBsAg and HBsAb were negative before transfusion.' In addition, we assumed that all medical institutions discarded 1.2 % of the blood components due to several reasons, including changes in patient status and lapses in storage period, etc. [11].

Phase III: Estimation on the Number of Recipients to Contract HBV by Contaminated Blood Products

To quantify the recipients that might be expected to receive HBV-contaminated blood components via transfusion, we considered principally the following three factors: the number of HBV-contaminated blood components at the medical institutions, their blood component disposal rates, and the magnitude of the at risk population for HBV transmission among recipients.

Number of recipients of HBV

$$\begin{aligned} & - \text{contaminated blood components} \\ & = (\text{Contaminated blood components with HBV} \\ & - \text{Disposed blood components}) \times \text{HBV risk group} \end{aligned}$$

Based on the above equation, the number of recipients of an HBV-contaminated blood component will depend upon the number of HBV-contaminated blood components, because the values of disposed blood components and HBV risk groups were fixed. Using the above equation, and some additional assumptions, we developed four models for estimation.

- (1) *Basic model* Here, we assumed that one donated blood unit positive for HBV results in one HBV-contaminated blood component. Accordingly, the number of HBV-contaminated blood components supplied to medical institutions would correspond to the number of donated blood units positive for HBV. The patients receiving blood units in excess of one has not been classified in terms of confidence index or 95 % probability of getting a HBV blood unit in transfusion. Assuming a unscreened fixed blood unit number is acquired in a medical institution, the probability of the high-risk recipient getting infected increases with multiple transfusions.
- (2) *Extended model I* Here, one donated blood unit yields more than one blood component. In this model, we compared the number of donated blood units with the number of blood components supplied to medical institutions in 2009, and assumed that one donated blood unit positive for HBV would produce HBV-contaminated blood components according to that ratio. The number of HBV-contaminated blood components was derived by multiplying the donated blood positive for HBV by this ratio. The total number of donated blood units was 2,569,954 in 2009 [12], and the total number of blood components supplied from two blood centers to medical institutions was 4,724,472 units. Thus the ratio of supplied blood components to donated blood units was 1.84.

- (3) *Extended model II* Some papers have alluded to the limitations of the serological screening test itself, and suggest that a correcting value, for the incidence of HBV infection of donated blood, be employed [13, 14]. In this model, the number of HBV-contaminated blood components equates to the product of donated blood positive for HBV and a corrective value. We took 2.38 to be the corrective value, based on a previous study [15].
- (4) *Extended model III* This model uses ratio and corrective values simultaneously, such that the number of HBV-contaminated blood components is equal to the product of the donated blood positive for HBV and the ratio and corrective values.

Ethics Statement

This paper was approved by the Korea Red Cross Blood Services Ethics Review Committee in 2010.

Data Analysis

Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and SAS (Version 9.1, SAS Institute, Cary, NC, USA) were employed for data analysis and estimation purposes.

Results

Calculation of the RR of HBV of Donated Blood and the Quantity of Blood Components with HBV

The number of donated blood units from the Korea Red Cross Blood Center (Table 1) in 2008 and 2009 was 4,724,472. Of these units, 972,902 were from repeat donors; the follow-up period for repeat donors totaled 319,221,583 days. The number of cases HBV-positive in screening tests, was 226; thus confirmatory cases of HBsAg may be estimated at 197.8 ($=226 \times 0.875$) units. Accordingly, the incidence of HBV infection was 22.6 per 100,000 person-years between 2008 and 2009 [95 % confidence interval (CI) 13.3, 35.9]. When applying the CLIA window period of 45 days, the RR of HBV was 2.79 units/100,000 donations (95 % CI 1.64, 4.43). So, donated blood, positive for HBV and not detected, totaled 68.6 units at the Korea Red Cross Blood Center. When these were applied to the Hanmaeum Blood Center again, donated blood, positive for HBV and not detected could be 3 units in 2009 (Table 1). The number of blood components positive for HBV and supplied from two blood centers to medical institutions was estimated to be 71.6 (95 % CI 42.1, 113.7) in the basic model. Based on their assumptions, the number

of blood components positive for HBV supplied from two blood centers to medical institutions was 131.9 units (95 % CI 77.5, 209.3) in extended model I; 170.4 units (95 % CI 100.3, 270.7) in extended model II; and 314 units (95 % CI 184.5, 498.1) in extended model III (Table 1).

Distribution of Recipients, Blood Components and HBV Transmission Risk Groups

Based on health insurance claims data, 376,111 individuals received a blood transfusion in 2009, which involved a total of 3,916,956 blood components. The gender and age distribution of recipients and blood components are shown in Table 2. According to pre-transfusion HBsAg/anti-HBs tests conducted in 6037 blood transfusion recipients, the negative/negative rate was 32.8 % in the HBV transmission risk group. The gender and age distributions of the HBV transmission risk group are provided in Table 3.

Number of Recipients of HBV-Contaminated Blood Components

Of the 376,211 recipients, the number who might be expected to receive blood components with HBV in 2009 was 23.2 (95 % CI 13.6, 36.8) in the basic model, 43.2 (95 % CI 25.4, 68.7) in extended model I, 55.2 (95 % CI 32.5, 87.7) in extended model II and 101.6 (95 % CI 59.8, 161.4) in extended model III (Table 3).

The number of HBV-positive samples per 100,000 transfused units was 0.6 in the basic model (95 % CI 0.3, 0.9), 1.1 in extended model I (95 % CI 0.6, 1.8), 1.4 in extended model II (95 % CI 0.8, 2.2), and 2.6 in extended model III (95 % CI 1.5, 4.1).

Discussion

This study has demonstrated that the number of blood transfusion recipients in Korea in 2009 who might be expected to receive HBV-contaminated blood components ranged from 23.2 (95 % CI 13.6, 36.8) to 101.8 (95 % CI 59.8, 161.4). The number, per 100,000 transfused units, that might be expected to be transfused to recipients ranged from 0.6 (95 % CI 0.3, 0.9) to 2.6 (95 % CI 1.5, 4.1). This study represents the first attempt to estimate the number of recipients who might receive HBV-contaminated blood components based on epidemiological data and objective evidence.

The likelihood of a recipient being infected with HBV was examined in the context of the Korea Centers for Disease Control and Prevention's data pertaining to adverse transfusion reactions and transfusion-transmitted infections. According to their investigation of adverse

Table 1 Residual risk of hepatitis B virus in donation and blood components with contaminated HBV in 2009

Year	Korea Red Cross Blood Center							
	Donated blood (units, A)	Donor (people)		Repeat donor		IR (/10 ⁵ P-Y)	RR (/10 ⁵ donations)	Corrected RR (/10 ⁵ donations)
		One-time/ HBsAg (+)	Repeat/ HBsAg (+)	Confirmed HBsAg (+)	Follow-up period (days)			
Basic model								
2008	2,265,592							
2009	2,461,880							
2008–2009	4,724,472	1,409,146/4,610	972,902/226	197.8	319,221,583	22.6 (13.3–35.9)	2.79 (1.64–4.43)	
Extended model I in 2009								
Extended model II in 2009								6.63
Extended model III in 2009								6.63
Year	Hanmaeum Blood Center			Total No. of donated blood with HBV (units)	No. of blood components supplied to medical institutions (units, C)	C/(A + B)	No. of blood components supplied to medical institutions with contaminated HBV (units)	
	No. of donated blood with HBV (units)	Donated blood (units, B)	No. of donated blood with HBV (units)					
Basic model								
2008								
2009	68.6	108,074	3.0	71.6	4,724,472		71.6 (42.1–113.7)	
2008–2009								
Extended model I in 2009				71.6		1.84	131.8 (77.5–209.3)	
Extended model II in 2009	163.2		7.2	170.4			170.4 (100.3–270.7)	
Extended model III in 2009	163.2		7.2	170.4		1.84	313.6 (184.5–498.1)	

HBsAg Hepatitis B surface antigen, IR incidence rate, RR residual rate, P-Y Person-years, HBV Hepatitis B virus

transfusion reactions occurring between 2006 and 2013, 24 recipients reported that their HBV infection was related to transfusion [16, 17]. Among these cases, only one was subsequently confirmed as being a transfusion-transmitted infection. According to lookback for transfusion-transmitted HBV infection between May 2011 and May 2013, 59 of 1742 specimens in storage tested positive, amounting to 95 units of donated blood, or 204 units of blood components [18]. Of a total of 204 recipients, 102 were deceased, 35 were uncooperative, and 4 were unidentifiable. Among the remainder (5 = negative; 9 = infected with HBV prior to the transfusion; 10 = positive for antibody against HBV prior to the transfusion; 39 = not investigated), no HBV transfusion-transmitted infection was detected.

Overall, a significant number of recipients have been exposed to HBV-contaminated blood components. However, rates of transfusion transmission of HBV infection are

low for the following reasons: firstly, although recipients received HBV-contaminated blood components, this may not result in HBV infection. HBV infectivity is essentially related to the viral load in the product [19]. In fact, HBV transmission has been reported, from WP and OBI donors, with an HBV DNA load of <20 IU/mL in humans [20, 21]. However, in some cases, units from WP and OBI donors were not infectious even though a viral load of <20 and >500 IU/mL (<100 and >2500 geq/mL) was transfused [22, 23]. The lack of a clear relationship between infectivity and viral load in blood components may be related to immune factors in recipients that affect their susceptibility to infection [19]. Secondly, even when transfusion-transmitted infection actually occurs, it may not always be detected due to the absence of an active system for investigation of HBV infection. The investigation of adverse reactions from transfusions is conducted only when

Table 2 Gender and age distribution of recipients and blood components

Gender	Age group	Recipients (%)	Blood components (%)
Male	Total	376,211 (100)	3,916,956 (100)
	0–9	4921 (1.3)	57,021 (1.5)
	10–19	2719 (0.7)	67,590 (1.7)
	20–29	3843 (1.0)	72,339 (1.8)
	30–39	7866 (2.1)	133,564 (3.4)
	40–49	20,358 (5.4)	316,141 (8.1)
	50–59	31,943 (8.5)	472,111 (12.1)
	60–69	40,802 (10.8)	515,651 (13.2)
	70–79	37,616 (10.0)	380,519 (9.7)
	≥80	14,092 (3.7)	111,184 (2.8)
Female	Subtotal	163,097 (43.6)	2,126,120 (54.3)
	0–9	3991 (1.1)	40,326 (1.0)
	10–19	2604 (0.7)	47,217 (1.2)
	20–29	8132 (2.2)	79,836 (2.0)
	30–39	16,628 (4.4)	161,106 (4.1)
	40–49	24,465 (6.5)	235,119 (6.0)
	50–59	25,420 (6.8)	291,498 (7.4)
	60–69	44,972 (12.0)	391,860 (10.0)
	70–79	56,525 (15.0)	390,695 (10.0)
	≥80	29,314 (7.8)	153,178 (3.9)
	Subtotal	211,139 (56.4)	1,790,836 (45.7)

a sign of an adverse reaction, such as infection, death, handicap or hospitalization, is reported by the recipient. Considering the low rates of examination for markers of HBV infection (77.6 % prior to transfusion and 22.0 % after transfusion in the at-risk group), and the asymptomatic HBV infection rate of 65–80 % [7, 24], a recipient is unlikely to perceive HBV infection by infection markers or symptoms. Moreover, although assessment of transfusion-transmitted infections is more rigorous than is investigation of transfusion-related adverse reactions (in the context of transfusion-transmitted infection), the response is not prompt considering the timeframe of the investigation. At the time of investigation, approximately half of the recipients were dead [18]. Therefore, it was difficult to determine whether a recipient was infected with HBV via transfusion. Thirdly, the risk of developing chronic HBV infection after acute exposure ranges from 90 % in newborns of HbeAg-positive mothers to 25–30 % in infants and children under 5 and <10 % in adults [25]. Therefore, the likelihood of transfusion-transmitted HBV infection developing into chronic hepatitis B may be very low, or even zero, due to uncertainty regarding the viral load and the high death rates of recipients. In addition, although antibody is produced following hepatitis B vaccination, the titer of which decreases with age, such changes do not result in a loss of protection against HBV [26]. Therefore,

the size of the at-risk group for HBV infection in the present study could have been overestimated.

To date there have been few studies on the prevalence of HBV infection following blood transfusion. In the U.S., for example, HBV infection occurs once for every 100,000–200,000 units of transfusion, a higher incidence compared to the 1 per 1–2 million units of HCV or 2–3 million units of HIV [27]. By lookback, using data gathered between 1997 and 2004 in Japan [21], serological responses demonstrating acute infection were detected in 12 (19 %) of 158 patients transfused with HBV-infected blood. The serological response in an acute infection is in the form of HbsAg in the acute or a chronic phase of hepatitis B. IgM anti HBc, is the antibody to distinguish acute from the chronic hepatitis B infection. OBI and window period viremic response may vary depending on the loading dose, patient immune status, latent interval between the previous donations etc.

However, all forms have proven to be infectious in immunocompromised individuals, including organ- and bone-marrow-transplant recipients. Of the 279 components included in a lookback study in Canada [28], no traced recipients were HBsAg-positive; 7 recipients were anti-HBc-reactive. In the UK [29], 20 cases of transfusion-transmission of HBV were reported between 1991 and 2001, via a surveillance system, for all post-transfusion infections. However, because the prevalence of HBV, screening methods for donated blood, and the number of recipients and blood components differ among countries, retrospective comparison of the number of transfusion-transmitted HBV infections is subject to a number of limitations.

In an effort to prevent transfusion-transmitted infection, individual HBV-NAT, using a Procleix Ultrio Plus assay (Novartis Diagnostics), was implemented in Korea in July 2012. This method is known to reduce the window period significantly and aids detection of occult HBV carriage. Using individual HBV-NAT, a total of 374 cases that were not detected by CLIA were confirmed 1 year after the introduction of the HBV-NAT [30]. Therefore, it appears that the introduction of individual HBV-NAT has reduced the likelihood of infection from HBV-contaminated transfusions.

Therefore, to reduce the incidence of infection from HBV-contaminated transfusions, attention must be paid to recipients. First of all their immune systems should be strengthened by acquisition of antibodies against HBV prior to transfusion. Furthermore, HBV infection markers should be screened for before and after transfusion, to allow early detection of transfusion-transmitted infection and the taking of appropriate action.

This study had several limitations. Firstly, although the distribution of recipients and blood components according

Table 3 Number of recipients with HBV-contaminated blood components

Gender	Age group	Distribution of blood components (%)	Distribution of risk group of hepatitis B infection (%)	No. of recipients with HBV-contaminated blood components			
				Basic model	Extended model I	Extended model II	Extended model III
Total		100.0	32.8	23.2 (13.6–36.8)	43.2 (25.4–68.7)	55.2 (32.5–87.7)	101.6 (59.8–161.4)
Male	0–9	1.5	24.0	0.2	0.5	0.6	1.1
	10–19	1.7	39.0	0.5	0.9	1.1	2.1
	20–29	1.8	33.3	0.4	0.8	1.0	1.9
	30–39	3.4	35.8	0.9	1.6	2.1	3.8
	40–49	8.1	34.1	1.9	3.6	4.6	8.5
	50–59	12.1	26.1	2.2	4.1	5.3	9.7
	60–69	13.2	31.5	2.9	5.5	7.0	12.8
	70–79	9.7	36.8	2.5	4.7	6.0	11.1
	≥80	2.8	36.6	0.7	1.4	1.7	3.2
	Subtotal	54.3	32.6	12.5 (7.4–19.9)	23.3 (13.7–37.0)	29.8 (17.5–47.3)	54.9 (32.3–87.1)
Female	0–9	1.0	23.5	0.2	0.3	0.4	0.7
	10–19	1.2	57.7	0.5	0.9	1.2	2.2
	20–29	2.0	28.6	0.4	0.8	1.0	1.8
	30–39	4.1	26.6	0.8	1.4	1.8	3.4
	40–49	6.0	28.7	1.2	2.3	2.9	5.3
	50–59	7.4	29.9	1.6	2.9	3.7	6.9
	60–69	10.0	33.0	2.3	4.4	5.6	10.2
	70–79	10.0	38.7	2.7	5.1	6.5	12.0
	≥80	3.9	39.8	1.1	2.1	2.6	4.8
	Subtotal	45.7	33.1	10.7 (6.4–17.0)	19.9 (11.7–31.7)	25.5 (15.0–40.5)	46.9 (27.6–74.5)

to car insurance and occupational health and safety insurance data might differ compared to the HIRA data, they were nonetheless assumed to be identical. This limitation could be addressed by using data from these areas in the future. Secondly, while objective data were used, some assumptions were still applied. However, those assumptions were deemed acceptable, and may also be amenable to correction when objective data are available. Thirdly, the transfusion-transmitted infection risk groups were limited to those who were antigen- and antibody-negative. Several studies have reported transfusion-transmitted infection even in individuals with anti-HBV antibodies [31]. High risk recipients with negative Hbs Ag/HbsAb have been classified as having an increased risk of viral acquisition but the data on high risk donors with HbsAg/HbsAb negative status may also be incorporated in our study as a potential source of HBV blood. In addition, the patients receiving blood units in excess of one has not been classified in terms of confidence index or 95 % probability of getting a HBV blood unit in transfusion. Assuming a HBV positive blood unit is acquired in a medical institution, the probability of the high-risk recipient getting infected increases with multiple transfusions. These limitations

should be addressed by conducting retrospective or pre- and post-transfusion marker studies. Finally, this study used data from two main blood centers. Although blood donation and transfusion are conducted internally in other medical institutions, their data were not considered in this study. However, the proportion of blood donations at these medical institutions is negligible: 1.48 % (37,406 cases) in 2003 and 0.28 % (7417 cases) in 2010 [32]; thus their inclusion would have had an only minor impact on the results.

Acknowledgments This work was supported by Konkuk University in 2014.

Compliance with Ethical Standards

Conflict of interest No potential conflict of interest relevant to this article was reported.

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