1 # Changing Trends in the Incidence (1999-2011) and Mortality (1983-

2 2013) of Cervical Cancer in Republic of Korea

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23 *Key messages:*

24   한국의 자궁경부암 발생률과 사망률은 꾸준히 감소하고 있는 추세이다. 그러나
25 한국의 발생률은 여러 선진국에 비해 여전히 높은 수준에 머무르고 있다. 또한,
26 지난 10 년 동안 자궁경부암 사망률은 상대적으로 큰 감소를 보이지 않았다.
27 특히 35 세 미만에서는 자궁경부암 발생률이 감소하지 않았고, 사망률은 오히려
28 높아진 것으로 나타났다. 젊은 연령층의 자궁경부암 예방과 관리가 필요하다.

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Abstract

Objectives: Cervical cancer is a well-known preventable cancer worldwide, so that many countries including Korea have been tried to pursue the positive endpoint of mortality reduction. Our aim is to examine changing trends in cancer incidence and mortality after implementing the national effort in Korea.

Methods: The cervical cancer incidence data of duration from 1999 to 2011 and the mortality data from 1983 to 2013 were collected from Korean Statistical Information Service (KOSIS). The age-standardized rates (ASRs) per 100,000 were compared in the yearly comparison using Korea population of 2005 and in the worldwide comparison using the World standard population based on Segi's for incidence and WHO for mortality.

Results: In Korea, the age-standardized incidence per 100,000 populations declined from 17.2 in 2000 to 11.8 in 2011. However, the group aged 25 to 29 in 2011 showed higher rate (ASR: 6.5) than in 2000 (ASR: 3.6). The age-standardized mortality rate per 100,000 populations dropped from 2.81 in 2000 to 1.95 in 2013. In worldwide comparison, the incidence rates are remaining around the average incidence estimate of the more developed regions (ASR: 9.9). The decreasing mortality trend in Korea has observed towards to lower rate shown in Australia (ASR: 1.4) in 2010.

Conclusion: Although the incidence rates of cervical cancer are continuously declining in Korea, it still stands in a higher relatively to the other countries. Moreover, incidence and mortality rates in women aged under or around 30 increased in a recent year. It is necessary to find the effective policy to reduce both incidence and mortality especially in young aged group.

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Introduction

Globally, cervical cancer is a preventable cancer [1] and causally associated to infection by oncogenic Human Papillomavirus (HPV), two most common HPV 16 and 18 [2, 3]. Due to this necessary cause and increased sexual activity of the younger generation, cervical cancer is still considered as one of the major health concerns in female worldwide [4]. Development of various preventive strategies and clinical approaches has achieved in a number of developed countries reducing incidence, hence mortality [5]. Incidence and mortality rates have fallen over the past decades especially in many high-resource countries. Many previous studies proved that introduction of screening program plays a critical role in the control of cervical cancer [6].

In 1988, Korea introduced the practice of population-based cervical cancer screening using the Papanicolaou (Pap) smear, initially providing this service to selected people insured by the Korea National Health Insurance Program [4]. National Cancer Screening Program (NCSP) was established in 1999 and has provided free biennial Pap smear tests for females aged over 30 ever since. In 2000, the National Health Insurance Law mandated the Pap test as part of a nationwide screening program [7-9]. Several studies have reported positive outcomes related to cervical cancer screening that showed a significantly lower incidence of invasive cervical cancer (ICD-10: C53) and carcinoma *in situ* (CIS; ICD-10: D06) among Korean females who were screened 2 or more times compared with unscreened females [10]. Since around 2000, implementation of population-based screening program has made a difference in lowering the overall incidence and mortality rates in Korea. However, there may be different trends between age groups in female that could influence on incidence and mortality rates.

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91   The aim of the present study was to examine changing trends in incidence and mortality of

92   cervical cancer in Korea. The patterns both in incidence and mortality will be discussed with

93   respect to the yearly comparison by specified age groups and the worldwide comparison.

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95   **Methods**

96   The type of cancer was classified according to the International Classification of Diseases

97   for Oncology, third edition [11] and converted according to the International Classification of

98   Diseases, 10th edition (ICD-10) [12]. The code for invasive cervical cancer is C53 classified

99   in malignant neoplasm of cervix uteri. Statistical data used in this study only included cases

100   of invasive cervical carcinoma. We have collected the incidence and mortality data directly

101   from Korean Statistical Information Service (KOSIS) [13, 14] and also indirectly from Korea

102   Ministry of Health and Welfare, National Health Insurance Service, and Korean Central

103   Cancer Registry [15]. The incidence and mortality rates were compared by age over years

104   from the 1999 to 2011, and 1983 to 2013 respectively. Both incidence and mortality data

105   were gathered from the online database that showed the selectively chosen datasets by

106   choosing certain type of cancer, required statistical unit, age, gender, and duration of time.

107   Age-standardized rates calculated using the Korean population of 2005 (ASR, K), were

108   mainly used to compare difference in yearly comparison. The reference population data were

109   collected from Korea National Statistical Office [16]. To analyze the age-specific incidence

110   trends over time duration from 2000 to 2010, we used ASRs from three different years, 2000,

111   2005, and 2010.

112   For the worldwide comparison regarding cervical cancer, age-standardized incidence rates

113   of more developed regions that GLOBOCAN classified as following were collected: All

114   regions of Europe, Northern America, Australia, New Zealand, and Japan [17]. We

115 selectively collected the list of countries from the series of Cancer Incidence in Five

116 Continents (CI-5) [18]: France (8 registries), United Kingdom (9 registries), United States

117 (SEER, 9 registries), Canada (3 registries), Australia (6 registries), New Zealand, and Japan

118 (3 registries). Since the provided available data were limited until year of 2007, we collected

119 the estimated incidence data from the GLOBOCAN 2012 [17]. The incidence rates (Table 1)

120 in Korea were converted based on Segi's World standard population (ASR, W) [19, 20].

121 Comparing global trends of mortality rates, age-specific data were only available from three

122 of more developed countries mentioned above. We collected data directly from New Zealand

123 cancer registry [21], Australian Association of Cancer Registries (AACR) [22], and National

124 Cancer Center in Japan [23]. For mortality, ASRs were determined using the World Health

125 Organization (WHO) world standard population (ASR, W) [24].

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127 **Results**

128 Incidence rates of cervical cancer

129 In Korea, the incidence rates of cervical cancer have significantly declined since 2001. The

130 yearly incidence cases declined from 4,443 cases in 1999 to 3,760 cases in 2011. Crude rates

131 and ASRs per 100,000 decreased from 18.9 and 18.6 in 1999 to 15.0 and 11.8 in 2011,

132 respectively (Table 1). Compared to 2000, lower incidence was shown in all age groups

133 except the aged under 30 in the recent year of 2011. The group aged 25 to 29 showed higher

134 incidence of 6.5 in 2011 compared to 3.6 in 2000 (Figure 1).

135 In Figure 2, each birth cohort group represents 3 points based on the incidence rates in

136 2000, 2005, and 2010. The birth cohort group born during 1976-1980 and the other group

137 born during 1966-1970 have shown the same rates of 13.3 and 13.2, respectively in aged 30-

138 34. Those in earlier birth cohort groups have shown higher incidence rates when they were in

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139 same age range. Specifically, for aged 40 to 44, the higher rate of 33.0 was shown in 1955-

140 1960 compared to the rate of 23.0 in 1966-1970. Likewise, the rate of 35.5 in 1945-1950 was

141 higher than 25.4 in 1955-1960 for aged 50 to 54 and the rate of 42.4 in 1935-1940 was higher

142 than 26.9 in 1945-1950 for aged 60-64.

143 For the worldwide comparison, the converted rates using Segi's world population became

144 relatively lower than the rates using Korea population of 2005. The declining incidence rates

145 were changed from 18.6 (ASR, K) per 100,000 to 16.3 (ASR, W) per 100,000 in 1999 and

146 from 11.7 (ASR, K) per 100,000 to 10.1 (ASR, W) per 100,000 in 2011. Compared to more

147 developed countries, incidence rates in Korea are relatively high (Figure 3). For instance,

148 12.4 in ASR per 100,000 in 2005 is similar to that of New Zealand in 1990 (ASR, W: 12.65

149 per 100,000), which reported rate is the highest in 1990 among other comparable countries.

150 From 1990s to 2007, all other 7 countries scored lower incidence rates than those of Korea

151 showing steady decreasing pattern through years. The GLOBOCAN estimated the incidence

152 rates in 2012. Due to different regional classifications used in GLOBOCAN and CI-5, two

153 countries among 8 countries were able to be compared in this study (Figure 3): 9.5 in ASR

154 per 100,000 (Korea) and 5.3 (New Zealand).

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156 Mortality rates of cervical cancer

157 In Korea, the yearly mortality cases were from 129 in 1983 to 892 in 2013. The crude rates

158 and ASRs per 100,000 were from 0.7 and 0.98 in 1983 to 3.5 and 1.95 in 2013, respectively

159 (Table 1). Before investigating mortality trend, a limitation of this study should be

160 understood that is the use of uncorrected mortality records from death certificates that

161 misclassified cervical cancer in Korea. A study conducted in 2007 corrected the number of

162 cervical cancer death by comparing death certificate cases of unspecified uterine cancer data

163 with the national cancer incidence databases of entire cancer registries in Korea. After the

164 correction, there was an apparent reduction in mortality; the overall age-standardized

165 mortality rates per 100,000 persons decreased from 5.2 in 1993 to 3.9 in 2002 based on 1967

166 WHO world standard population [4]. From 2003 to 2013, there was a gradual reduction of

167 cervical cancer deaths in Korean women.

168   Age-specifically, the older groups aged 50 and over generally had high proportion of

169 overall mortality from cervical cancer. From the group aged mid 30s to mid 40s, the mortality

170 rates increased significantly. During a decade from 2000 to 2011, the mortality rates have not

171 been changed or improved much through all age groups, except the older group aged mid 50s

172 and over. For certain age groups, the mortality rates were even higher in a recent year of 2011

173 compared to 2000. The age groups of 30-34 and 50-54 showed significantly higher mortality

174 rates in 2011 with 0.13 per 100,000 and 0.36 per 100,000, respectively, compared to 0.06 per

175 100,000 and 0.30 per 100,000 in 2000 (Figure 4).

176   For the worldwide comparison, three countries including Korea have shown a decreasing

177 pattern over years (Figure 5). For instance, 3.1 in ASR per 100,000 in 1991 of Australia is

178 similar to that of Korea in 2003 and of New Zealand in 2001 (ASR, W: 3.09 per 100,000 and

179 3.0 per 100,000, respectively), which different years of each country were on a decreasing

180 trend of mortality rates. Although the mortality rates showed a gradual decline in Korea, the

181 mortality rate in 2013 (ASR, W: 1.65 per 100,000) is still higher than that of Australia in

182 2010 (ASR, W: 1.4 per 100,000).

183   A slight increasing pattern has been observed in Japan reporting higher mortality rate

184 (ASR, W: 1.97 per 100,000) since 2010 than that of Korea (ASR, W: 1.88 per 100,000).

185 **Discussion**

186 Both incidence and mortality rates of cervical cancer in Korea have been declining since

187 the nationwide cancer screening program implemented [10]. With a decrease in cervical

188 cancer cases, age-standardized incidence rates using Korea population were higher than the

189 results using world standard population. It is due to relatively higher distribution of the

190 elderly in Korea, comparing to demographics of the world scale.

191 In Korea, invasive cervical cancer appears to have increased predominantly among

192 younger age group [25]. The increasing incidence rates in aged 20 to 29 and relatively slight

193 reducing trends in mortality through all age groups might be the outcome of more advanced

194 cancer cases at diagnosis and consequent poor prognosis with low survival rates [26, 27].

195 Since cure rates depend strongly on the stage at diagnosis [28], the detection at advanced

196 stage might be closely related to unchanged mortality rates over time. At this late stage,

197 cancer detection might be reported by voluntary hospital visits after suspecting signs or

198 symptoms [29], rather than by regular screening tests.

199 The significantly high mortality in groups aged 30s, late 40s and over may reflect potential

200 risk factors. The early initiating sexual activities in young generation might cause early

201 exposure to HPV infection [30]. Women infected with an oncogenic HPV type, will progress

202 to high-grade cervical intraepithelial neoplasia in their 20s or early 30s. Since the latency

203 period from HPV infection to cancer development is long, it may progress to invasive cancer

204 10 or more years later [28]. Moreover, elderly women might have more exposure to low

205 hygiene environment regarding HPV infection [31] while they have less opportunity to start

206 preventive programs from young age. Despite of introduction of HPV vaccination, the current

207 vaccines do not cover all potential oncogenic HPV types [28] and it does not guarantee to

208 prevent cancer among those who had already been exposed to HPV.

209   In countries where organized cytological screening has been implemented over the last 3 or

210   4 decades, the incidence of and mortality from cervical cancer have declined steadily [32, 33]

211   so far. In the United States (US), for example, the incidence rates were stable across most

212   states declining 1.9% per year. In while, overall mortality in cervical cancer has remained

213   stable at certain point and this pattern in mortality is similar to that of Korea at present [34].

214   To obtain reduction in mortality ultimately, the US has provided free or low-cost screening

215   and cervical cancer services for more than 20 years. Moreover, they continuously are making

216   an effort to increase the cervical cancer screening proportion from 83% in 2010 to the

217   Healthy People 2020 target of 93% [35]. They also emphasize that nonfinancial barriers, such

218   as lack of awareness of disease, need to be addressed to save more lives continuously [36].

219   Exploring changing trends in cervical cancer raises an important question about

220   effectiveness of cervical cancer screening. The routine screening solely might not be an

221   efficient way against cervical cancer, especially in relatively younger age group of 20 to 40 in

222   Korea. A combination of public awareness of causal factors, early cancer detection by regular

223   screening with the incorporation of HPV DNA testing, and vaccination at reasonable costs

224   will remain as a key preventive tool of cervical cancer [37] in Korea, as well as on a global

225   scale.

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Table 1. Incidence rate (1999-2011) and mortality rate (1983-2013) by year of cervical cancer in Republic of Korea

Year	Incidence			Mortality		
	Cases	Crude Rate (per 100.000)	ASR[a] (per 100.000)	Cases	Crude Rate (per 100.000)	ASR[a] (per 100.000)
1983	-	-	-	129	0.7	0.98
1984	-	-	-	147	0.7	1.09
1985	-	-	-	177	0.9	1.26
1986	-	-	-	189	0.9	1.26
1987	-	-	-	222	1.1	1.49
1988	-	-	-	265	1.3	1.67
1989	-	-	-	359	1.7	2.21
1990	-	-	-	343	1.6	2.07
1991	-	-	-	360	1.7	2.11
1992	-	-	-	439	2.0	2.38
1993	-	-	-	425	1.9	2.25*
1994	-	-	-	560	2.5	2.91*
1995	-	-	-	554	2.4	2.76*
1996	-	-	-	668	2.9	3.28*
1997	-	-	-	680	2.9	3.11*
1998	-	-	-	610	2.6	2.56*
1999	4,443	18.9	18.6	690	2.9	2.87*
2000	4,253	18.0	17.2	726	3.1	2.81*
2001	4,572	19.2	18.0	807	3.4	2.84*
2002	4,402	18.4	16.8	1,009	4.2	3.42*
2003	4,373	18.2	16.2	1,111	4.6	3.60
2004	4,130	17.1	14.9	1,078	4.5	3.28
2005	4,014	16.5	14.1	1,066	4.4	3.05
2006	4,047	16.6	13.9	1,002	4.1	2.78
2007	3,755	15.3	12.7	987	4.0	2.72
2008	4,004	16.2	13.2	954	3.9	2.48
2009	3,803	15.3	12.2	950	3.8	2.32
2010	3,956	15.9	12.6	956	3.8	2.21
2011	3,760	15.0	11.8	989	4.0	2.31
2012	-	-	-	889	3.5	2.06
2013	-	-	-	892	3.5	1.95

Data Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.
[a] *Age-Standardized Rate per 100,000 using the Korea population of 2005.*
* *Corrected mortality using national death certification data. ASR using direct method based on 1967 WHO world standard population (From 1993 to 2002 by year: 5.20, 5.60, 5.10, 5.10, 4.90, 4.30, 4.20, 4.10, 4.00, 3.90, respectively). Adapted from: Shin HR, Park S, Hwang SY, Kim JE, Jung KW, Won YJ, et al. Trends in cervical cancer mortality in Korea 1993–2002: corrected mortality using national death certification data and national cancer incidence data. Int J Cancer 2008;122:393-397 [4].*
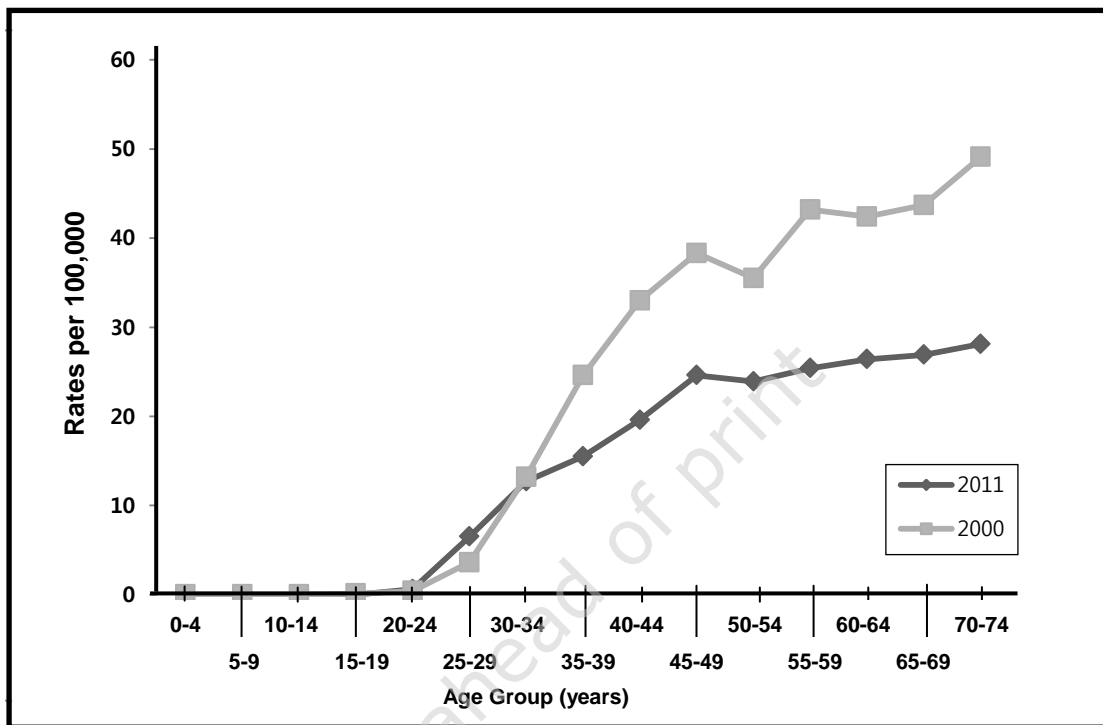
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Figure 1. Age-specific incidence rates per 100,000 populations of cervical cancer in Republic of Korea, 2000 and 2011.

Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.
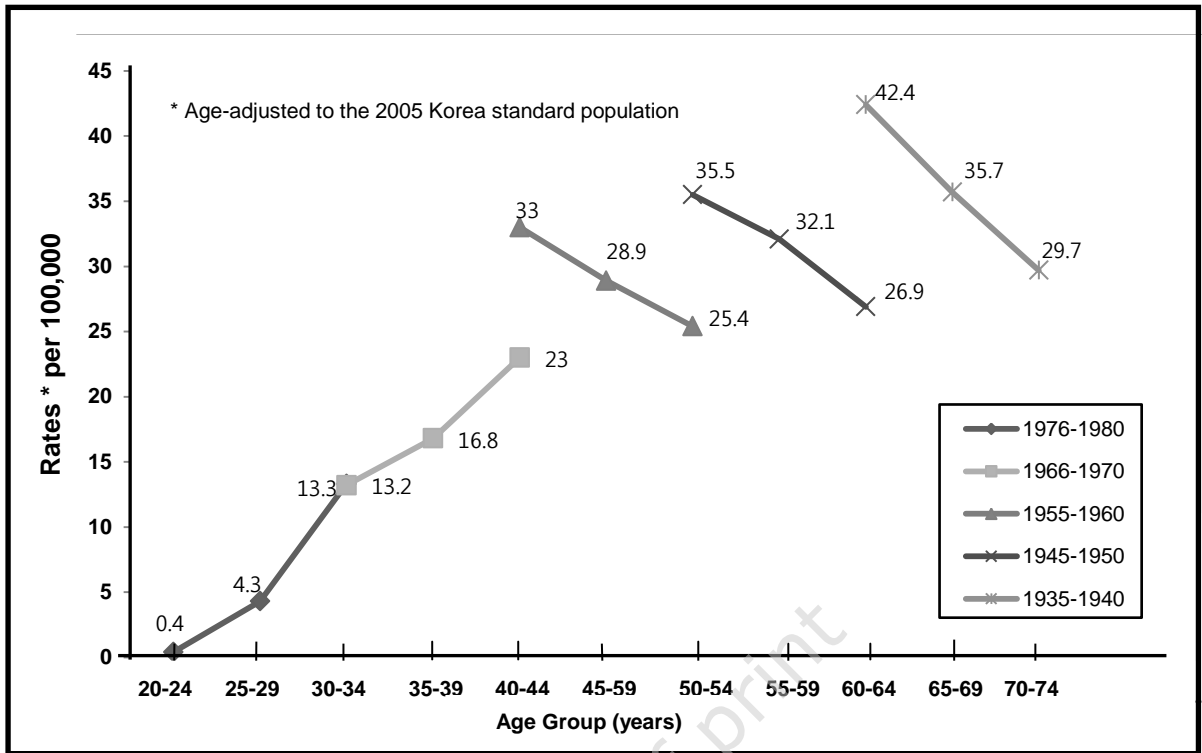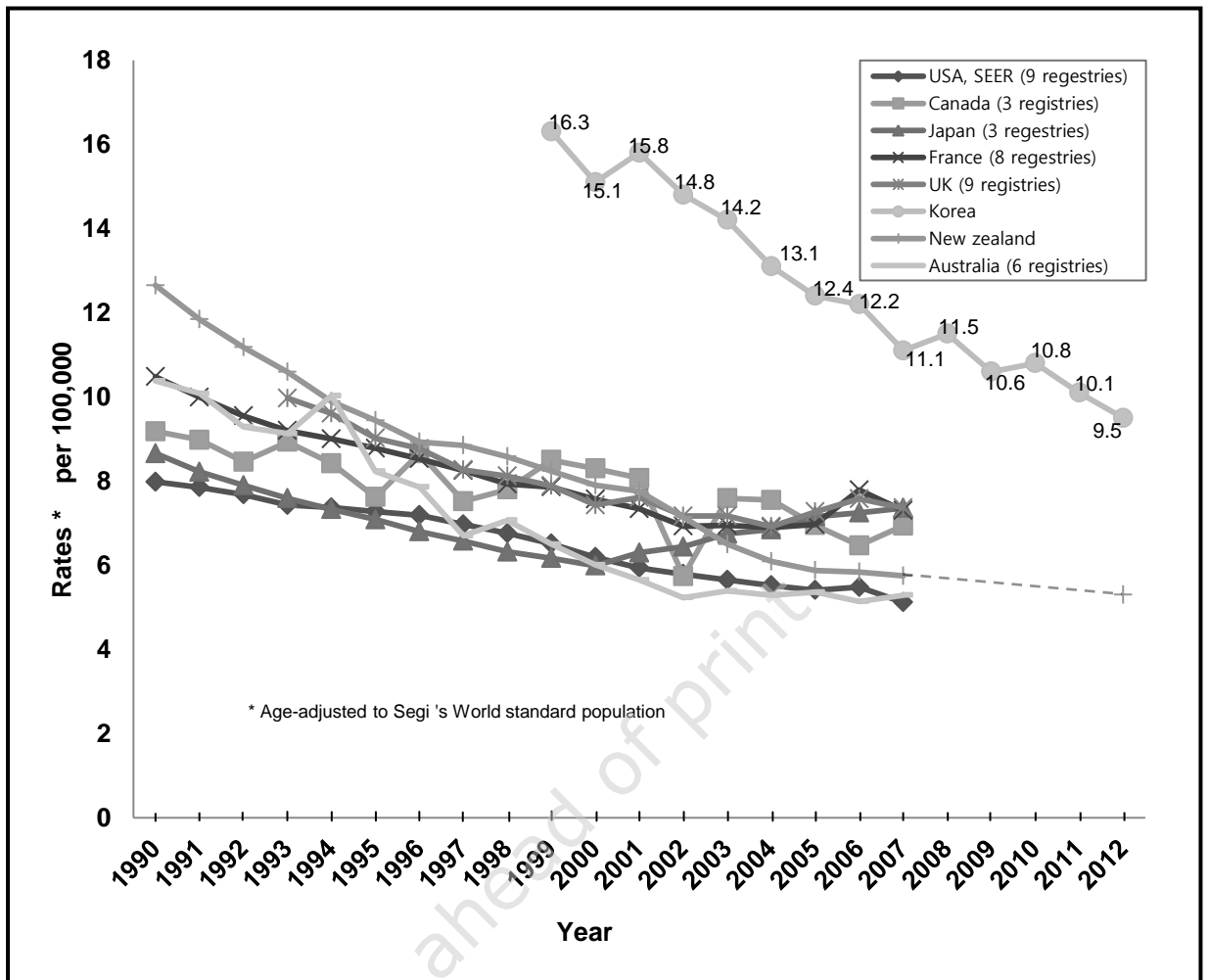
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Figure 2. Trends in age-specific incidence rates of cervical cancer by birth cohort group in Republic of Korea, 2000, 2005 and 2010.

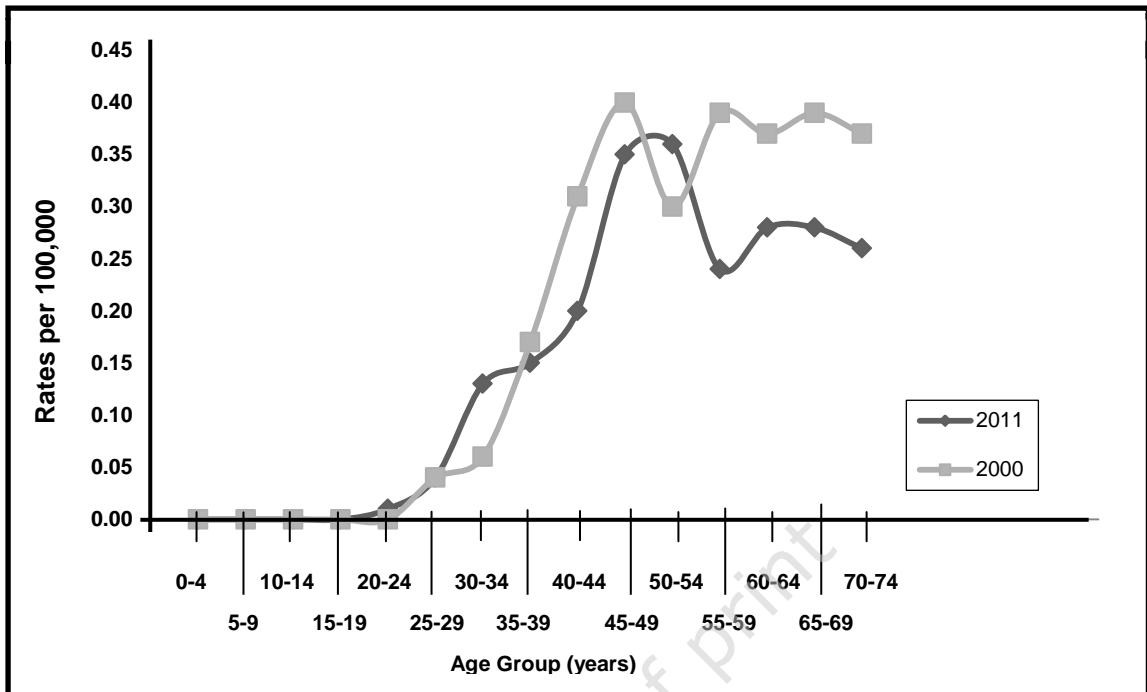*Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.*

Figure 3. Trends of incidence rates of cervical cancer, worldwide, 1990-2012†.

Source: International Agency for Research on Cancer (IARC), WHO. Cancer Incidence in Five Continents (CI-5) and GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012.   Available from: http://www.ci5.iarc.fr and http://www.globocan.iarc.fr
† Estimated Incidence rate in ASR (W), 2012: The estimates incidence rates in the year of 2012 are representable for each country as a whole while the data from CI-5 were collected selectively by cancer registry regions.

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Figure 4. Age-specific mortality rates per 100,000 populations of cervical cancer in Republic of Korea, 2000 and 2011.

Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.

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* Age-adjusted to World Health Organization (WHO) World standard population

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322 **Figure 5. Trends of mortality rates of cervical cancer, worldwide, 1990-2013.**

323 *Source: New Zealand cancer registry, New Zealand mortality collection. Available from http://data-*
324 *enquiries@moh.govt.nz. Australian Cancer Incidence and Mortality (ACIM) book for cervical cancer,*
325 *Australian Government and Australian Institute of Health and Welfare, Australian Association of*
326 *Cancer Registries (AACR). Korea Statistical Office, Korean Statistical Information Service (KOSIS).*
327 *Available from http://kosis.kr.   Vital Statistic in Japan, tabulated by Center for Cancer Control and*
Information Services, National Cancer Center, Japan. Available from http://qanjoho.jp.

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445   screening in the era of HPV vaccination. Vaccine 2006;24:S171-S177.
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Epub ahead of print

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3 **<u>Abstract</u>**
4
5 ***Objectives:*** Cervical cancer is a well-known preventable cancer worldwide, so that many
6 countries including Korea have been tried to pursue the positive endpoint of mortality
7 reduction. Our aim is to examine changing trends in cancer incidence and mortality after
8 implementing the national effort in Korea.
9
10 ***Methods:*** The cervical cancer incidence data of duration from 1999 to 2011 and the mortality
11 data from 1983 to 2013 were collected from Korean Statistical Information Service (KOSIS).
12 The age-standardized rates (ASRs) per 100,000 were compared in the yearly comparison
13 using Korea population of 2005 and in the worldwide comparison using the World standard
14 population based on Segi's for incidence and WHO for mortality.
15
16 ***Results:*** In Korea, the age-standardized incidence per 100,000 populations declined from
17 17.2 in 2000 to 11.8 in 2011. However, the group aged 25 to 29 in 2011 showed higher rate
18 (ASR: 6.5) than in 2000 (ASR: 3.6). The age-standardized mortality rate per 100,000
19 populations dropped from 2.81 in 2000 to 1.95 in 2013. In worldwide comparison, the
20 incidence rates are remaining around the average incidence estimate of the more developed
21 regions (ASR: 9.9). The decreasing mortality trend in Korea has observed towards to lower
22 rate shown in Australia (ASR: 1.4) in 2010.
23
24 ***Conclusion:*** Although the incidence rates of cervical cancer are continuously declining in
25 Korea, it still stands in a higher relatively to the other countries. Moreover, incidence and
26 mortality rates in women aged under or around 30 increased in a recent year. It is necessary
27 to find the effective policy to reduce both incidence and mortality especially in young aged
28 group.
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Introduction

Globally, cervical cancer is a preventable cancer [1] and causally associated to infection by oncogenic Human Papillomavirus (HPV), two most common HPV 16 and 18 [2, 3]. Due to this necessary cause and increased sexual activity of the younger generation, cervical cancer is still considered as one of the major health concerns in female worldwide [4]. Development of various preventive strategies and clinical approaches has achieved in a number of developed countries reducing incidence, hence mortality [5]. Incidence and mortality rates have fallen over the past decades especially in many high-resource countries. Many previous studies proved that introduction of screening program plays a critical role in the control of cervical cancer [6].

In 1988, Korea introduced the practice of population-based cervical cancer screening using the Papanicolaou (Pap) smear, initially providing this service to selected people insured by the Korea National Health Insurance Program [4]. National Cancer Screening Program (NCSP) was established in 1999 and has provided free biennial Pap smear tests for females aged over 30 ever since. In 2000, the National Health Insurance Law mandated the Pap test as part of a nationwide screening program [7-9]. Several studies have reported positive outcomes related to cervical cancer screening that showed a significantly lower incidence of invasive cervical cancer (ICD-10: C53) and carcinoma *in situ* (CIS; ICD-10: D06) among Korean females who were screened 2 or more times compared with unscreened females [10]. Since around 2000, implementation of population-based screening program has made a difference in lowering the overall incidence and mortality rates in Korea. However, there may be different trends between age groups in female that could influence on incidence and mortality rates.

62   The aim of the present study was to examine changing trends in incidence and mortality of

63   cervical cancer in Korea. The patterns both in incidence and mortality will be discussed with

64   respect to the yearly comparison by specified age groups and the worldwide comparison.

65

66   **Methods**

67   The type of cancer was classified according to the International Classification of Diseases

68   for Oncology, third edition [11] and converted according to the International Classification of

69   Diseases, 10th edition (ICD-10) [12]. The code for invasive cervical cancer is C53 classified

70   in malignant neoplasm of cervix uteri. Statistical data used in this study only included cases

71   of invasive cervical carcinoma. We have collected the incidence and mortality data directly

72   from Korean Statistical Information Service (KOSIS) [13, 14] and also indirectly from Korea

73   Ministry of Health and Welfare, National Health Insurance Service, and Korean Central

74   Cancer Registry [15]. The incidence and mortality rates were compared by age over years

75   from the 1999 to 2011, and 1983 to 2013 respectively. Both incidence and mortality data

76   were gathered from the online database that showed the selectively chosen datasets by

77   choosing certain type of cancer, required statistical unit, age, gender, and duration of time.

78   Age-standardized rates calculated using the Korean population of 2005 (ASR, K), were

79   mainly used to compare difference in yearly comparison. The reference population data were

80   collected from Korea National Statistical Office [16]. To analyze the age-specific incidence

81   trends over time duration from 2000 to 2010, we used ASRs from three different years, 2000,

82   2005, and 2010.

83   For the worldwide comparison regarding cervical cancer, age-standardized incidence rates

84   of more developed regions that GLOBOCAN classified as following were collected: All

85   regions of Europe, Northern America, Australia, New Zealand, and Japan [17]. We

86 selectively collected the list of countries from the series of Cancer Incidence in Five

87 Continents (CI-5) [18]: France (8 registries), United Kingdom (9 registries), United States

88 (SEER, 9 registries), Canada (3 registries), Australia (6 registries), New Zealand, and Japan

89 (3 registries). Since the provided available data were limited until year of 2007, we collected

90 the estimated incidence data from the GLOBOCAN 2012 [17]. The incidence rates (Table 1)

91 in Korea were converted based on Segi's World standard population (ASR, W) [19, 20].

92 Comparing global trends of mortality rates, age-specific data were only available from three

93 of more developed countries mentioned above. We collected data directly from New Zealand

94 cancer registry [21], Australian Association of Cancer Registries (AACR) [22], and National

95 Cancer Center in Japan [23]. For mortality, ASRs were determined using the World Health

96 Organization (WHO) world standard population (ASR, W) [24].

97

98 **Results**

99 Incidence rates of cervical cancer

100 In Korea, the incidence rates of cervical cancer have significantly declined since 2001. The

101 yearly incidence cases declined from 4,443 cases in 1999 to 3,760 cases in 2011. Crude rates

102 and ASRs per 100,000 decreased from 18.9 and 18.6 in 1999 to 15.0 and 11.8 in 2011,

103 respectively (Table 1). Compared to 2000, lower incidence was shown in all age groups

104 except the aged under 30 in the recent year of 2011. The group aged 25 to 29 showed higher

105 incidence of 6.5 in 2011 compared to 3.6 in 2000 (Figure 1).

106 In Figure 2, each birth cohort group represents 3 points based on the incidence rates in

107 2000, 2005, and 2010. The birth cohort group born during 1976-1980 and the other group

108 born during 1966-1970 have shown the same rates of 13.3 and 13.2, respectively in aged 30-

109 34. Those in earlier birth cohort groups have shown higher incidence rates when they were in

110 same age range. Specifically, for aged 40 to 44, the higher rate of 33.0 was shown in 1955-

111 1960 compared to the rate of 23.0 in 1966-1970. Likewise, the rate of 35.5 in 1945-1950 was

112 higher than 25.4 in 1955-1960 for aged 50 to 54 and the rate of 42.4 in 1935-1940 was higher

113 than 26.9 in 1945-1950 for aged 60-64.

114 For the worldwide comparison, the converted rates using Segi's world population became

115 relatively lower than the rates using Korea population of 2005. The declining incidence rates

116 were changed from 18.6 (ASR, K) per 100,000 to 16.3 (ASR, W) per 100,000 in 1999 and

117 from 11.7 (ASR, K) per 100,000 to 10.1 (ASR, W) per 100,000 in 2011. Compared to more

118 developed countries, incidence rates in Korea are relatively high (Figure 3). For instance,

119 12.4 in ASR per 100,000 in 2005 is similar to that of New Zealand in 1990 (ASR, W: 12.65

120 per 100,000), which reported rate is the highest in 1990 among other comparable countries.

121 From 1990s to 2007, all other 7 countries scored lower incidence rates than those of Korea

122 showing steady decreasing pattern through years. The GLOBOCAN estimated the incidence

123 rates in 2012. Due to different regional classifications used in GLOBOCAN and CI-5, two

124 countries among 8 countries were able to be compared in this study (Figure 3): 9.5 in ASR

125 per 100,000 (Korea) and 5.3 (New Zealand).

126

127 Mortality rates of cervical cancer

128 In Korea, the yearly mortality cases were from 129 in 1983 to 892 in 2013. The crude rates

129 and ASRs per 100,000 were from 0.7 and 0.98 in 1983 to 3.5 and 1.95 in 2013, respectively

130 (Table 1). Before investigating mortality trend, a limitation of this study should be

131 understood that is the use of uncorrected mortality records from death certificates that

132 misclassified cervical cancer in Korea. A study conducted in 2007 corrected the number of

133 cervical cancer death by comparing death certificate cases of unspecified uterine cancer data

134 with the national cancer incidence databases of entire cancer registries in Korea. After the

135 correction, there was an apparent reduction in mortality; the overall age-standardized

136 mortality rates per 100,000 persons decreased from 5.2 in 1993 to 3.9 in 2002 based on 1967

137 WHO world standard population [4]. From 2003 to 2013, there was a gradual reduction of

138 cervical cancer deaths in Korean women.

139 Age-specifically, the older groups aged 50 and over generally had high proportion of

140 overall mortality from cervical cancer. From the group aged mid 30s to mid 40s, the mortality

141 rates increased significantly. During a decade from 2000 to 2011, the mortality rates have not

142 been changed or improved much through all age groups, except the older group aged mid 50s

143 and over. For certain age groups, the mortality rates were even higher in a recent year of 2011

144 compared to 2000. The age groups of 30-34 and 50-54 showed significantly higher mortality

145 rates in 2011 with 0.13 per 100,000 and 0.36 per 100,000, respectively, compared to 0.06 per

146 100,000 and 0.30 per 100,000 in 2000 (Figure 4).

147 For the worldwide comparison, three countries including Korea have shown a decreasing

148 pattern over years (Figure 5). For instance, 3.1 in ASR per 100,000 in 1991 of Australia is

149 similar to that of Korea in 2003 and of New Zealand in 2001 (ASR, W: 3.09 per 100,000 and

150 3.0 per 100,000, respectively), which different years of each country were on a decreasing

151 trend of mortality rates. Although the mortality rates showed a gradual decline in Korea, the

152 mortality rate in 2013 (ASR, W: 1.65 per 100,000) is still higher than that of Australia in

153 2010 (ASR, W: 1.4 per 100,000).

154 A slight increasing pattern has been observed in Japan reporting higher mortality rate

155 (ASR, W: 1.97 per 100,000) since 2010 than that of Korea (ASR, W: 1.88 per 100,000).

156 **Discussion**

157   Both incidence and mortality rates of cervical cancer in Korea have been declining since

158   the nationwide cancer screening program implemented [10]. With a decrease in cervical

159   cancer cases, age-standardized incidence rates using Korea population were higher than the

160   results using world standard population. It is due to relatively higher distribution of the

161   elderly in Korea, comparing to demographics of the world scale.

162   In Korea, invasive cervical cancer appears to have increased predominantly among

163   younger age group [25]. The increasing incidence rates in aged 20 to 29 and relatively slight

164   reducing trends in mortality through all age groups might be the outcome of more advanced

165   cancer cases at diagnosis and consequent poor prognosis with low survival rates [26, 27].

166   Since cure rates depend strongly on the stage at diagnosis [28], the detection at advanced

167   stage might be closely related to unchanged mortality rates over time. At this late stage,

168   cancer detection might be reported by voluntary hospital visits after suspecting signs or

169   symptoms [29], rather than by regular screening tests.

170   The significantly high mortality in groups aged 30s, late 40s and over may reflect potential

171   risk factors. The early initiating sexual activities in young generation might cause early

172   exposure to HPV infection [30]. Women infected with an oncogenic HPV type, will progress

173   to high-grade cervical intraepithelial neoplasia in their 20s or early 30s. Since the latency

174   period from HPV infection to cancer development is long, it may progress to invasive cancer

175   10 or more years later [28]. Moreover, elderly women might have more exposure to low

176   hygiene environment regarding HPV infection [31] while they have less opportunity to start

177   preventive programs from young age. Despite of introduction of HPV vaccination, the current

178   vaccines do not cover all potential oncogenic HPV types [28] and it does not guarantee to

179   prevent cancer among those who had already been exposed to HPV.

180   In countries where organized cytological screening has been implemented over the last 3 or

181   4 decades, the incidence of and mortality from cervical cancer have declined steadily [32, 33]

182   so far. In the United States (US), for example, the incidence rates were stable across most

183   states declining 1.9% per year. In while, overall mortality in cervical cancer has remained

184   stable at certain point and this pattern in mortality is similar to that of Korea at present [34].

185   To obtain reduction in mortality ultimately, the US has provided free or low-cost screening

186   and cervical cancer services for more than 20 years. Moreover, they continuously are making

187   an effort to increase the cervical cancer screening proportion from 83% in 2010 to the

188   Healthy People 2020 target of 93% [35]. They also emphasize that nonfinancial barriers, such

189   as lack of awareness of disease, need to be addressed to save more lives continuously [36].

190   Exploring changing trends in cervical cancer raises an important question about

191   effectiveness of cervical cancer screening. The routine screening solely might not be an

192   efficient way against cervical cancer, especially in relatively younger age group of 20 to 40 in

193   Korea. A combination of public awareness of causal factors, early cancer detection by regular

194   screening with the incorporation of HPV DNA testing, and vaccination at reasonable costs

195   will remain as a key preventive tool of cervical cancer [37] in Korea, as well as on a global

196   scale.

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204 **Table 1. Incidence rate (1999-2011) and mortality rate (1983-2013) by year of**
205 **cervical cancer in Republic of Korea**
206

Year	Incidence			Mortality		
	Cases	Crude Rate (per 100.000)	ASR[a] (per 100.000)	Cases	Crude Rate (per 100.000)	ASR[a] (per 100.000)
1983	-	-	-	129	0.7	0.98
1984	-	-	-	147	0.7	1.09
1985	-	-	-	177	0.9	1.26
1986	-	-	-	189	0.9	1.26
1987	-	-	-	222	1.1	1.49
1988	-	-	-	265	1.3	1.67
1989	-	-	-	359	1.7	2.21
1990	-	-	-	343	1.6	2.07
1991	-	-	-	360	1.7	2.11
1992	-	-	-	439	2.0	2.38
1993	-	-	-	425	1.9	2.25*
1994	-	-	-	560	2.5	2.91*
1995	-	-	-	554	2.4	2.76*
1996	-	-	-	668	2.9	3.28*
1997	-	-	-	680	2.9	3.11*
1998	-	-	-	610	2.6	2.56*
1999	4,443	18.9	18.6	690	2.9	2.87*
2000	4,253	18.0	17.2	726	3.1	2.81*
2001	4,572	19.2	18.0	807	3.4	2.84*
2002	4,402	18.4	16.8	1,009	4.2	3.42*
2003	4,373	18.2	16.2	1,111	4.6	3.60
2004	4,130	17.1	14.9	1,078	4.5	3.28
2005	4,014	16.5	14.1	1,066	4.4	3.05
2006	4,047	16.6	13.9	1,002	4.1	2.78
2007	3,755	15.3	12.7	987	4.0	2.72
2008	4,004	16.2	13.2	954	3.9	2.48
2009	3,803	15.3	12.2	950	3.8	2.32
2010	3,956	15.9	12.6	956	3.8	2.21
2011	3,760	15.0	11.8	989	4.0	2.31
2012	-	-	-	889	3.5	2.06
2013	-	-	-	892	3.5	1.95

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208 *Data Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from:*
209 *http://www.kosis.kr.*
210 *[a] Age-Standardized Rate per 100,000 using the Korea population of 2005.*
211 ** Corrected mortality using national death certification data. ASR using direct method based on 1967*
212 *WHO world standard population (From 1993 to 2002 by year: 5.20, 5.60, 5.10, 5.10, 4.90, 4.30,*
213 *4.20, 4.10, 4.00, 3.90, respectively). Adapted from: Shin HR, Park S, Hwang SY, Kim JE, Jung KW,*
214 *Won YJ, et al. Trends in cervical cancer mortality in Korea 1993–2002: corrected mortality using*
215 *national death certification data and national cancer incidence data. Int J Cancer 2008;122:393-397*
216 *[4].*
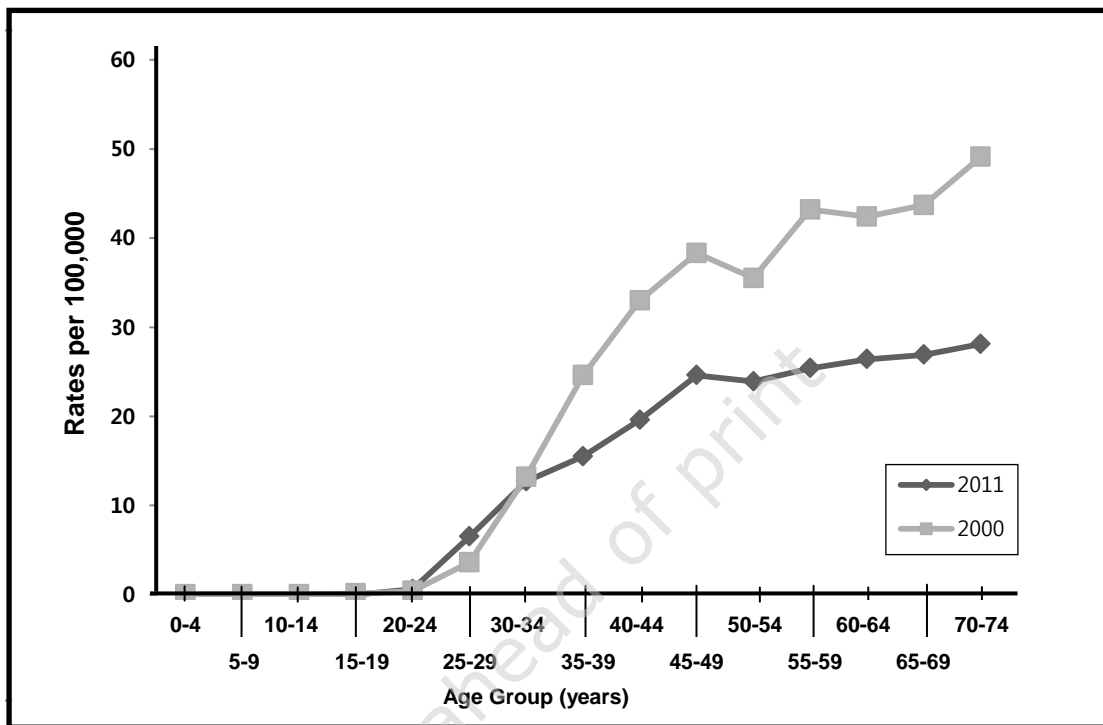217

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Figure 1. Age-specific incidence rates per 100,000 populations of cervical cancer in Republic of Korea, 2000 and 2011.

Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.
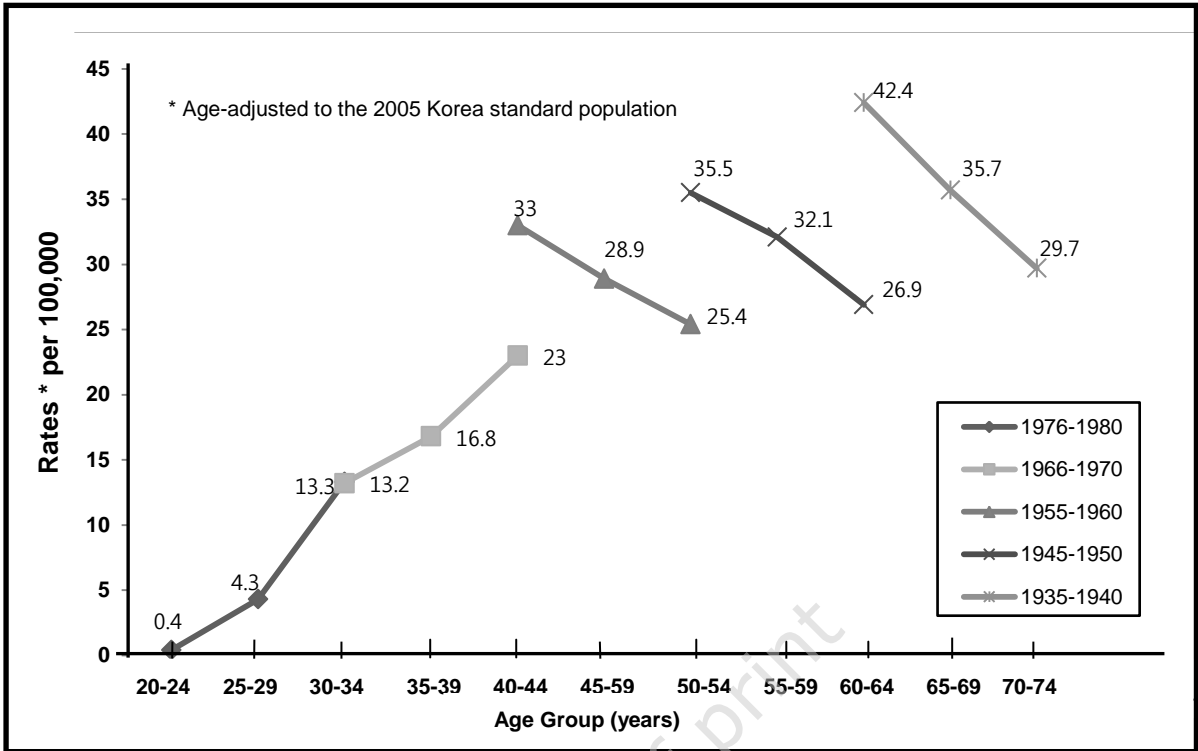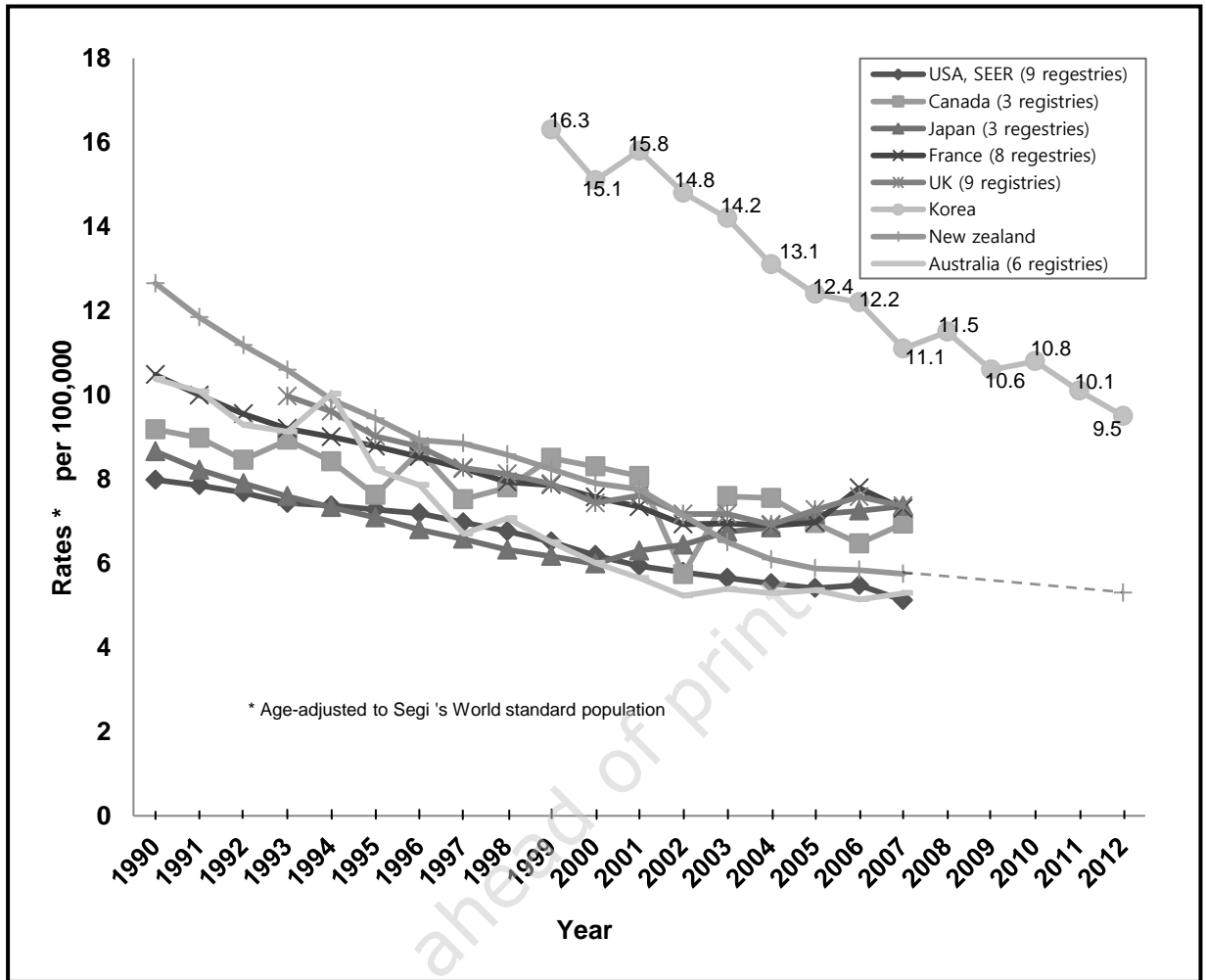
Figure 2. Trends in age-specific incidence rates of cervical cancer by birth cohort group in Republic of Korea, 2000, 2005 and 2010.

Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.

Figure 3. Trends of incidence rates of cervical cancer, worldwide, 1990-2012†.

Source: International Agency for Research on Cancer (IARC), WHO. Cancer Incidence in Five Continents (CI-5) and GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012.   Available from: http://www.ci5.iarc.fr and http://www.globocan.iarc.fr
† Estimated Incidence rate in ASR (W), 2012: The estimates incidence rates in the year of 2012 are representable for each country as a whole while the data from CI-5 were collected selectively by cancer registry regions.

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Figure 4. Age-specific mortality rates per 100,000 populations of cervical cancer in Republic of Korea, 2000 and 2011.

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Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.
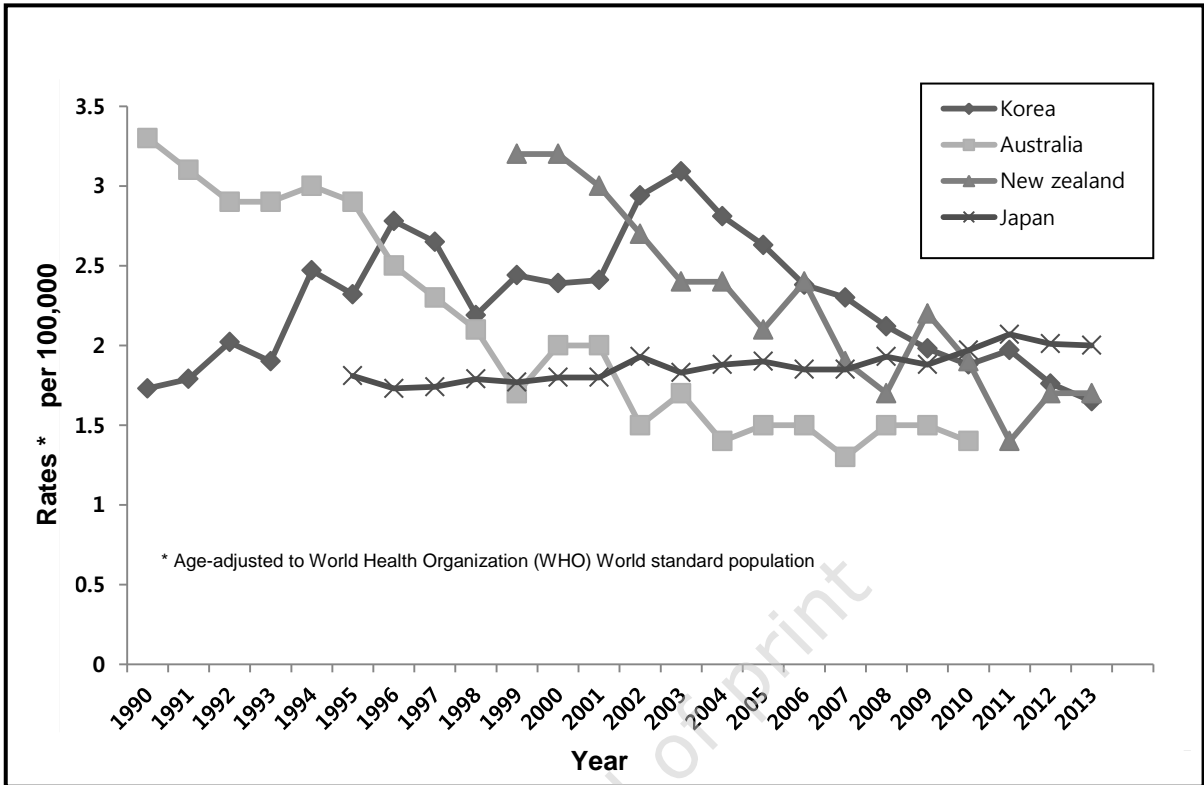
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Figure 5. Trends of mortality rates of cervical cancer, worldwide, 1990-2013.

Source: New Zealand cancer registry, New Zealand mortality collection. Available from http://data-enquiries@moh.govt.nz. Australian Cancer Incidence and Mortality (ACIM) book for cervical cancer, Australian Government and Australian Institute of Health and Welfare, Australian Association of Cancer Registries (AACR). Korea Statistical Office, Korean Statistical Information Service (KOSIS). Available from http://kosis.kr.   Vital Statistic in Japan, tabulated by Center for Cancer Control and Information Services, National Cancer Center, Japan. Available from http://ganjoho.jp.

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416   screening in the era of HPV vaccination. Vaccine 2006;24:S171-S177.
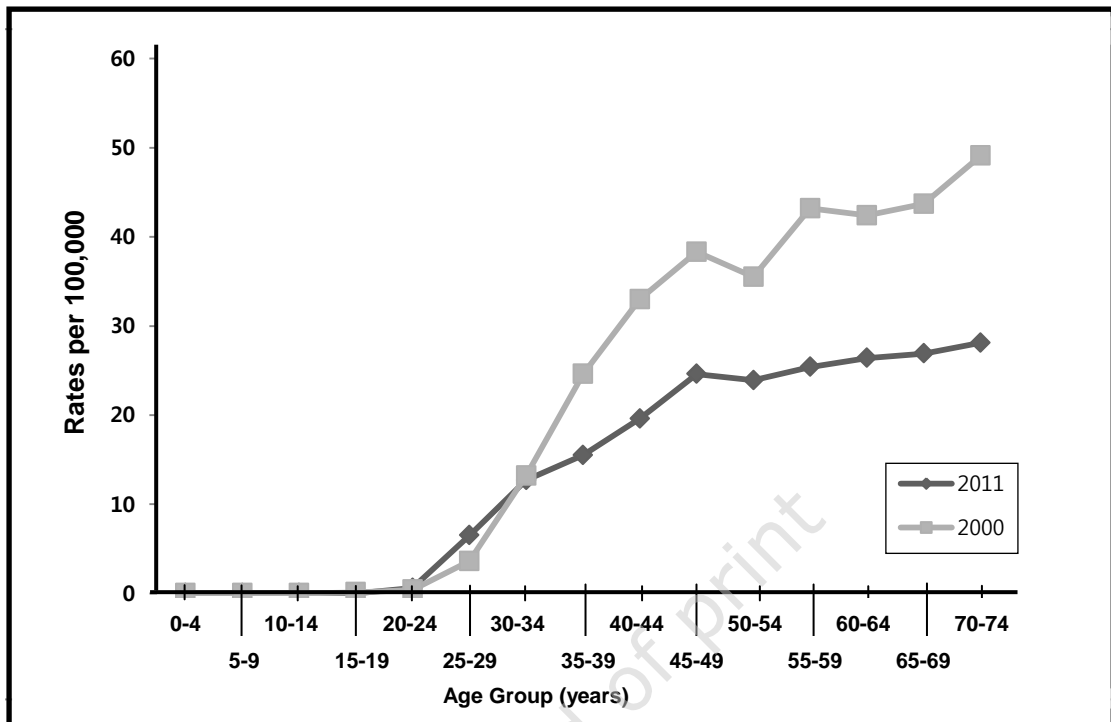417

Table 1. Incidence rate (1999-2011) and mortality rate (1983-2013) by year of cervical cancer in Republic of Korea

Year	Incidence			Mortality		
	Cases	Crude Rate (per 100.000)	ASR[a] (per 100.000)	Cases	Crude Rate (per 100.000)	ASR[a] (per 100.000)
1983	-	-	-	129	0.7	0.98
1984	-	-	-	147	0.7	1.09
1985	-	-	-	177	0.9	1.26
1986	-	-	-	189	0.9	1.26
1987	-	-	-	222	1.1	1.49
1988	-	-	-	265	1.3	1.67
1989	-	-	-	359	1.7	2.21
1990	-	-	-	343	1.6	2.07
1991	-	-	-	360	1.7	2.11
1992	-	-	-	439	2.0	2.38
1993	-	-	-	425	1.9	2.25*
1994	-	-	-	560	2.5	2.91*
1995	-	-	-	554	2.4	2.76*
1996	-	-	-	668	2.9	3.28*
1997	-	-	-	680	2.9	3.11*
1998	-	-	-	610	2.6	2.56*
1999	4,443	18.9	18.6	690	2.9	2.87*
2000	4,253	18.0	17.2	726	3.1	2.81*
2001	4,572	19.2	18.0	807	3.4	2.84*
2002	4,402	18.4	16.8	1,009	4.2	3.42*
2003	4,373	18.2	16.2	1,111	4.6	3.60
2004	4,130	17.1	14.9	1,078	4.5	3.28
2005	4,014	16.5	14.1	1,066	4.4	3.05
2006	4,047	16.6	13.9	1,002	4.1	2.78
2007	3,755	15.3	12.7	987	4.0	2.72
2008	4,004	16.2	13.2	954	3.9	2.48
2009	3,803	15.3	12.2	950	3.8	2.32
2010	3,956	15.9	12.6	956	3.8	2.21
2011	3,760	15.0	11.8	989	4.0	2.31
2012	-	-	-	889	3.5	2.06
2013	-	-	-	892	3.5	1.95

Data Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.
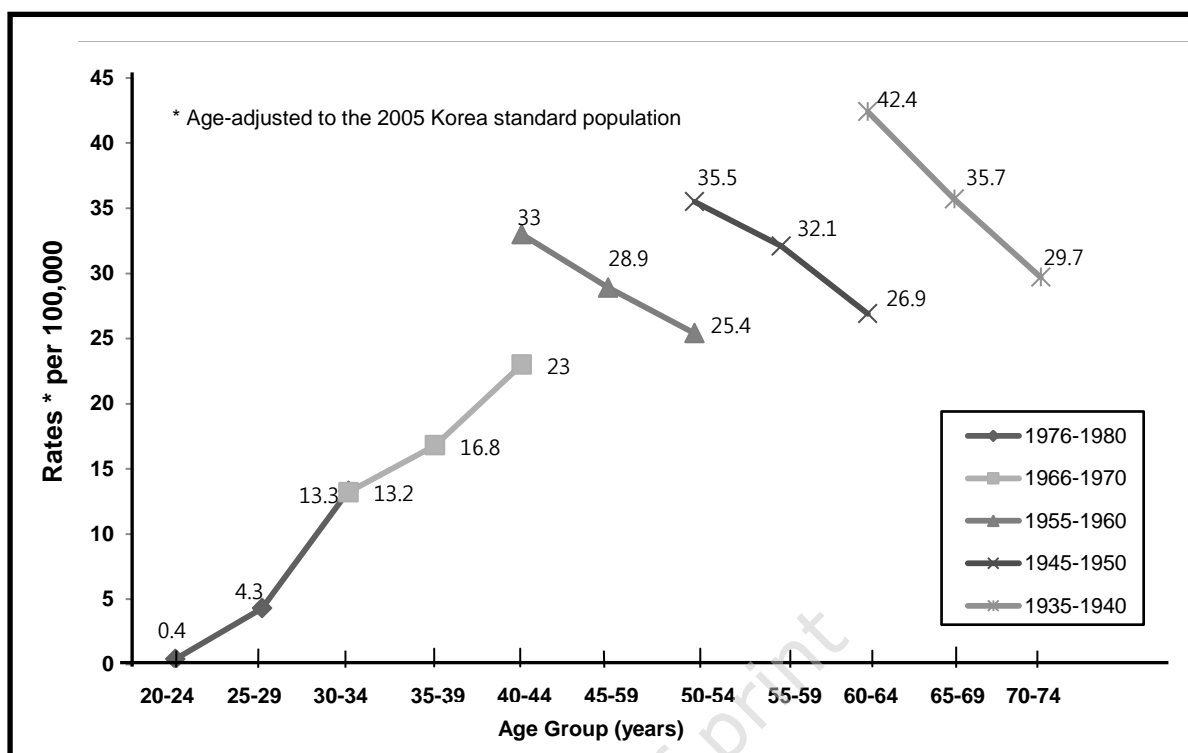
[a] *Age-Standardized Rate per 100,000 using the Korea population of 2005.*

* *Corrected mortality using national death certification data. ASR using direct method based on 1967 WHO world standard population (From 1993 to 2002 by year: 5.20, 5.60, 5.10, 5.10, 4.90, 4.30, 4.20, 4.10, 4.00, 3.90, respectively). Adapted from: Shin HR, Park S, Hwang SY, Kim JE, Jung KW, Won YJ, et al. Trends in cervical cancer mortality in Korea 1993–2002: corrected mortality using national death certification data and national cancer incidence data. Int J Cancer 2008;122:393-397* [4].

Figure 1. Age-specific incidence rates per 100,000 populations of cervical cancer in Republic of Korea, 2000 and 2011.
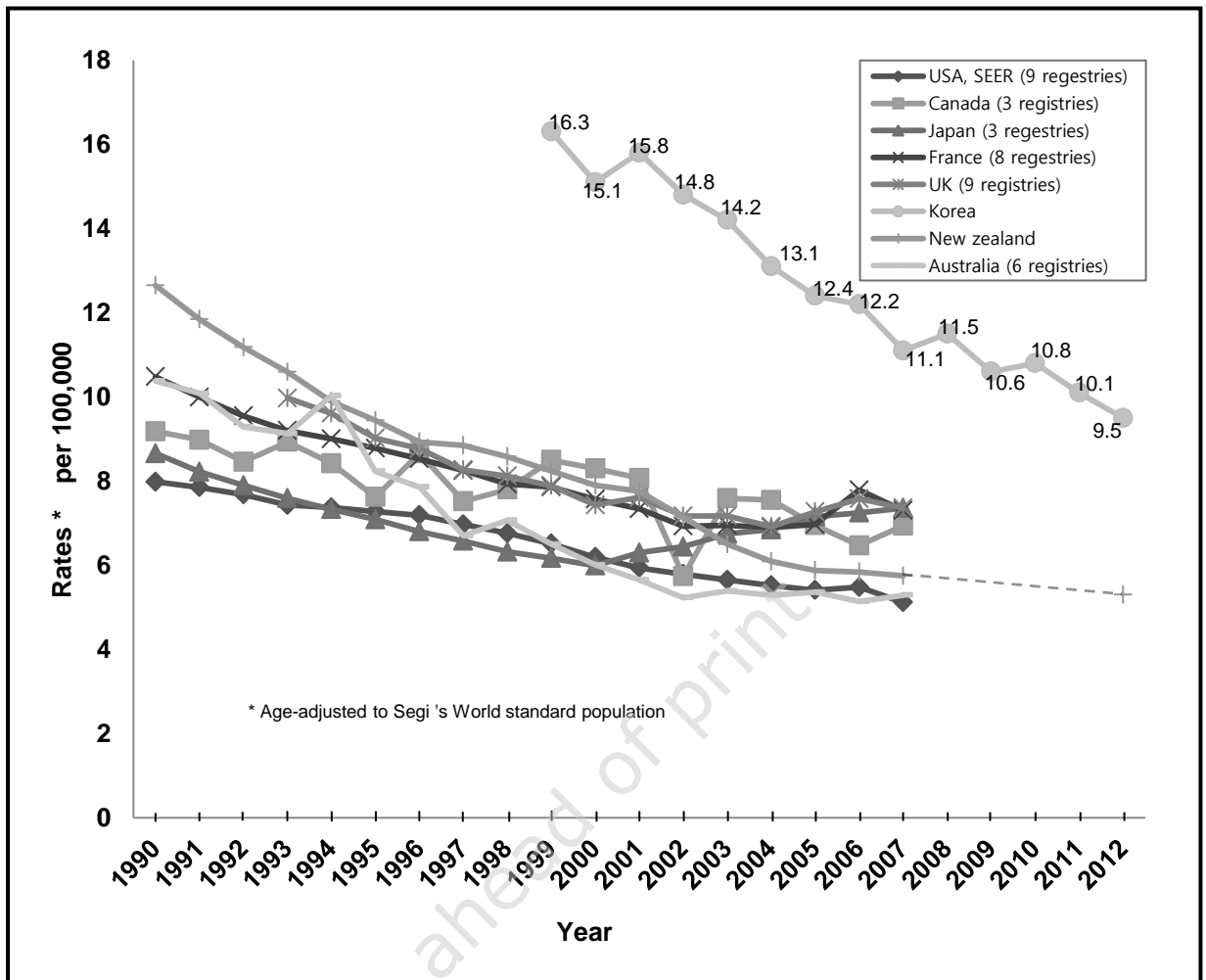
Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.

Figure 2. Trends in age-specific incidence rates of cervical cancer by birth cohort group in Republic of Korea, 2000, 2005 and 2010.

Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.
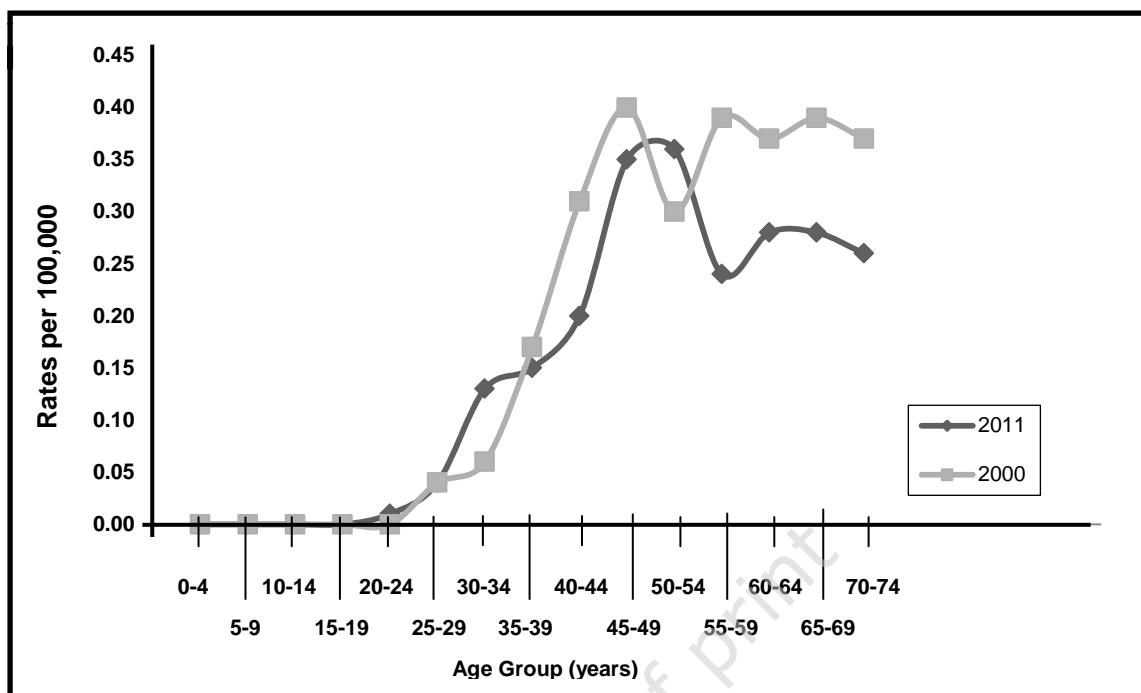
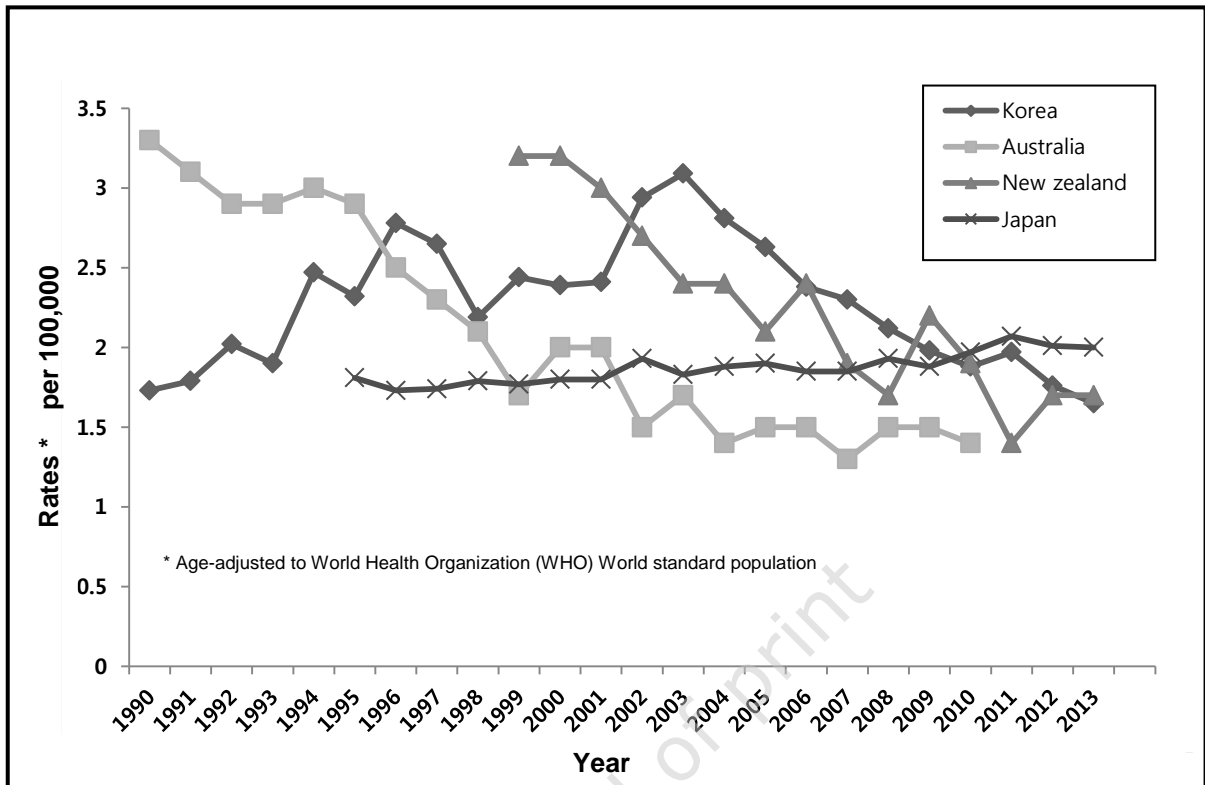**Figure 3. Trends of incidence rates of cervical cancer, worldwide, 1990-2012†.**

Source: International Agency for Research on Cancer (IARC), WHO. Cancer Incidence in Five Continents (CI-5) and GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available from: http://www.ci5.iarc.fr and http://www.globocan.iarc.fr
† Estimated Incidence rate in ASR (W), 2012: The estimates incidence rates in the year of 2012 are representable for each country as a whole while the data from CI-5 were collected selectively by cancer registry regions.

Figure 4. Age-specific mortality rates per 100,000 populations of cervical cancer in Republic of Korea, 2000 and 2011.

Source: Korean Statistical Information Service (KOSIS) [Internet]. Available from: http://www.kosis.kr.

Figure 5. Trends of mortality rates of cervical cancer, worldwide, 1990-2013.

Source: New Zealand cancer registry, New Zealand mortality collection. Available from http://data-enquiries@moh.govt.nz. Australian Cancer Incidence and Mortality (ACIM) book for cervical cancer, Australian Government and Australian Institute of Health and Welfare, Australian Association of Cancer Registries (AACR). Korea Statistical Office, Korean Statistical Information Service (KOSIS). Available from http://kosis.kr.   Vital Statistic in Japan, tabulated by Center for Cancer Control and Information Services, National Cancer Center, Japan. Available from http://qanjoho.jp.