Age Distribution of Disease-Causal Human Papillomavirus Infection in Women With High-Grade Cervical Intraepithelial Neoplasia in South Korea

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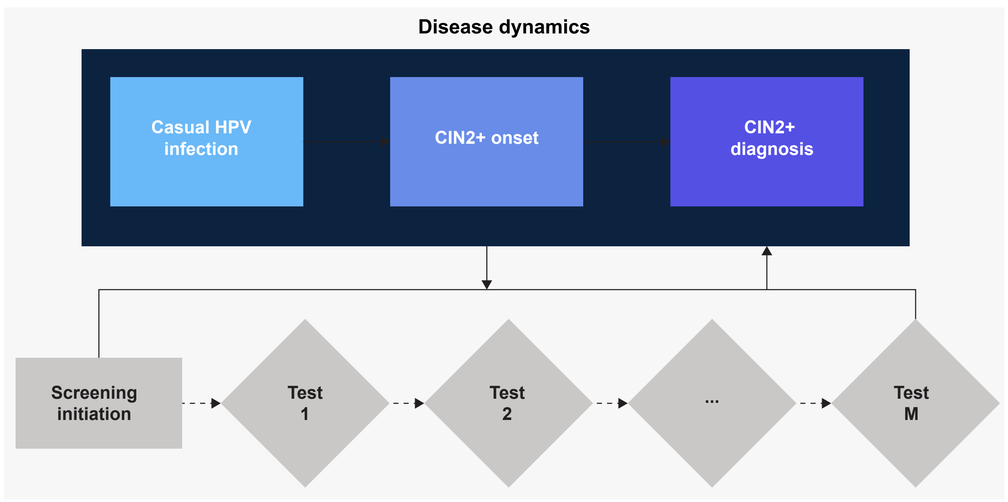
Background

- Human papillomavirus (HPV) is a significant public health issue, as it is the leading cause of cervical cancer worldwide[1]
- Prior to the introduction of the HPV vaccine into South Korea's National Immunization Program in 2016 for 12-year-old girls, the incidence of cervical carcinoma in situ was as high as 185.5 per 100,000 people,[2] while vaccination rates remained low[3]
- Consequently, many women in mid-adulthood continue to be vulnerable to new or persistent HPV infections due to insufficient prior vaccination coverage[4]
- Therefore, this study aims to estimate the distribution of age of causal persistent HPV infection leading to cervical intraepithelial neoplasia (CIN) grades 2, 3, and carcinoma in situ (CIN2+) in South Korea, to better understand infection timing and inform prevention strategies

Methods

Model structures and overview



- Time-to-event on disease onset
- Incidence of CIN2+
- Age of female at screening
- Sensitivity of primary screening test
- Age distribution of disease diagnosis
- Age distribution of casual infection

- A discrete event simulation developed by Prabhu et al (2021) was modified to estimate the age distribution of causal HPV infection for CIN2+ in South Korea[5]
- Data from 2015, before widespread HPV vaccination in South Korea, were used to minimize confounding factors
- Cases of CIN2+ were obtained from the Health Insurance Review and Assessment Service (HIRA) for 2015. The data included 3 diagnostic codes: N871 (moderate cervical dysplasia), N872 (severe cervical dysplasia), and D06 (cervical carcinoma in situ) (**Table 1**)[6]
- The model was further modified to incorporate annual screening rates, without limiting the total number of lifetime screenings, based on KOrean Statistical Information Service (KOSIS) data reporting screening starting at age 30—the minimum age for routine screening in South Korea in 2015[7]

Model inputs

Table 1. Number of CIN2+ cases in South Korea (2015 data)[a]

Age category, years		Number of cases of CIN2+	Cumulative distribution
15	19	57	0.2%
20	24	983	3.9%
25	29	2677	14.1%
30	34	4179	29.9%
35	39	3475	43.0%
40	44	3964	58.0%
45	49	3476	71.2%
50	54	2765	81.6%
55	59	1874	88.7%
60	64	1291	93.6%
65	69	810	96.7%
70	74	532	98.7%
75	79	247	99.6%
80	100	96	100.0%

[a]Source: Health Insurance Review & Assessment Service (HIRA).[6]

Key model assumptions

1. The shape of the distribution for the age of causal HPV infection is similar to the age distribution of CIN2+ diagnosis
2. The impact of HPV vaccination was minimized by using the data before the incorporation of HPV vaccination into Korea's NIP starting year, 2016
3. CIN2+ detection can only occur by routine screening tests for ages during which screening takes place (age 30 years and above in South Korea)[8]
4. The occurrence of screening for each woman simulated in the model at any given age is independent of their previous screening history, with the fractional age at which screening occurs determined under the assumption of at least 1 year between tests
5. To ensure consistency with the CIN2+ diagnosis data, a Pap smear screening sensitivity of 84%, informed by real-world data, was utilized for this period[9]

Stability, sensitivity, and scenario analysis

1. To test the stability of the base case result, the model was run 10 times using the same input as the base case, but with a unique set of random numbers representing the simulated females
2. The sensitivity analysis investigated the impact of relaxing the assumption that time from causal infection to CIN2+ onset is independent of age at causal infection. We explored scenarios where the time increased with increasing age of causal infection (age coefficients of 0.025, 0.05, 0.1, 0.2; coefficient of 0 implies independence). The mean age of 20 years is the average age of infection
3. Scenario analysis (**Table 2**) tested the impact of using an alternate distribution for the HPV causal persistent infection to CIN2+ onset on model results. Scenarios 1-4 used alternative gamma distributions derived from FUTURE I by accounting for females "censored" (females with persistent HPV infection that had not cleared or progressed to CIN2+ by 3 years) and assuming 0%, 5%, 10%, or 20% would progress to CIN2+ beyond 3 years

Table 2. Description of scenario analysis

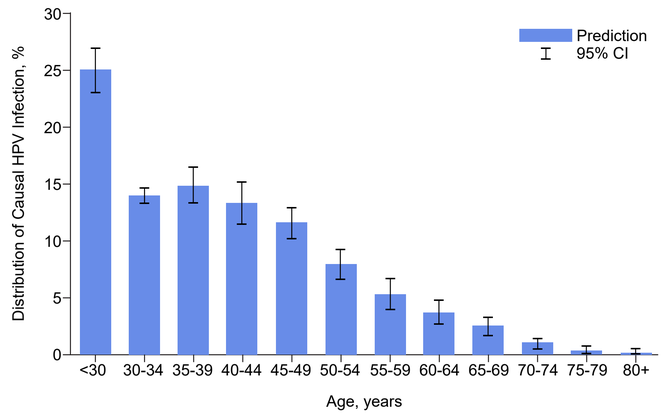
Scenario	Description
1	0% censoring + gamma distribution (0.7, 1.1)
2	5% censoring + gamma distribution (0.5, 2.0)
3	10% censoring + gamma distribution (0.5, 2.75)
4	20% censoring + gamma distribution (0.5, 4.0)
5	Exponential distribution

Results

Base case

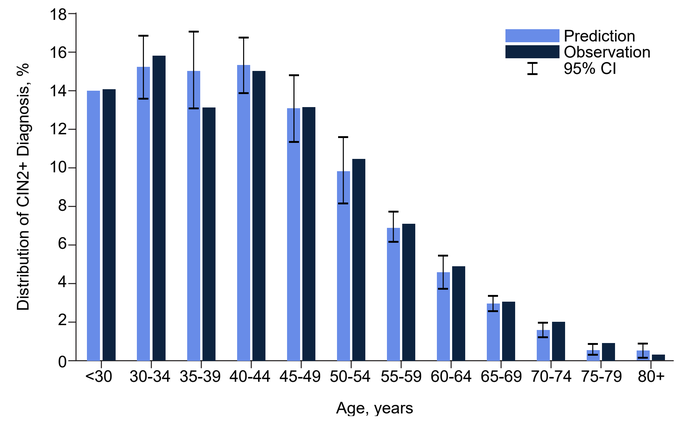
- The proportion of HPV infections leading to CIN2+ was 25.5% and 42.3% in females under 30 years and 30-44 years, respectively. Women aged 45 years and older accounted for 32.6% of infections, distributed across older age groups with decreasing proportions. The predicted and observed proportions of CIN2+ diagnoses were closely aligned across most age groups, with a calculated mean absolute error of 0.0051, indicating strong agreement between the model and observed data (**Figure 1**)
- The predicted and observed CIN2+ diagnosis curves were closely aligned across most age groups (**Figure 2**)

Figure 1. Predicted distribution of age at causal HPV infection



CI, confidence interval.

Figure 2. Predicted and observed distributions of age at CIN2+ diagnosis

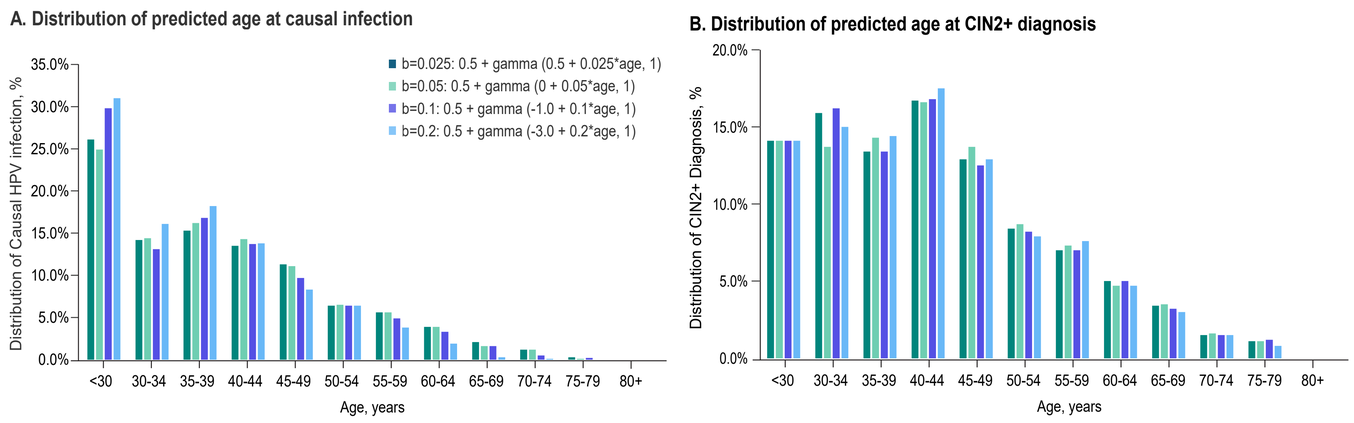


CI, confidence interval.

Sensitivity analysis

- The effects of an age-dependent gamma distribution on the age distribution of causal HPV infection and CIN2+ diagnosis were examined (**Figure 3**)
- A steeper age distribution was observed, with a higher proportion of causal infections predicted among younger age groups, when the association between age and progression rate was stronger
- The proportion of causal infections among women aged 30 years and older was maintained at ≥69% across all analyses

Figure 3. Sensitivity analysis results: predicted distribution of age at A, causal HPV infection and B, CIN2+ diagnosis, by age-dependent gamma distribution



Scenario analysis

Scenario analysis demonstrated the model results to be robust to changes in the distribution for causal HPV infection and CIN2+ diagnosis (**Table 3**). The base case is the average of 10 runs of the model.

Table 3. Scenario analysis: proportion of causal HPV infection by age group

Age, years	Base case	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
<30	25.06	23.00	24.98	25.41	27.13	25.32
30-34	14.02	14.01	14.18	14.27	13.32	14.01
35-39	14.93	15.81	14.87	15.38	15.98	15.04
40-44	13.36	14.09	14.18	13.49	13.15	13.84
45-49	11.57	11.09	11.26	11.52	10.91	11.52
50-54	8.01	7.22	6.62	6.36	6.53	6.62
55-59	5.33	6.36	5.93	5.76	5.33	5.76
60-64	3.74	3.44	3.78	3.78	3.87	3.78
65-69	2.46	3.09	2.41	2.23	2.06	2.32
70-74	0.99	1.37	1.29	1.29	1.20	1.29
75-79	0.32	0.26	0.34	0.34	0.34	0.34
80-84	0.20	0.26	0.17	0.17	0.17	0.17

Discussion

- **Summary**
  - The study estimated that 74.9% of HPV infections causing CIN2+ occur in women aged 30 years and older, and a significant proportion of causal infections was predicted to occur in women aged 30-44 years (42.3%) and women ≥45 years and older (32.6%)
  - The findings support the implementation of catch-up HPV vaccination programs for adult women to protect from new HPV infections that cause cervical diseases
- **Strengths**
  - This study uses real-world CIN2+ diagnosis and screening data from South Korea
  - The time from infection to disease onset is based on vaccine trial controls, accurately reflecting the natural progression of HPV
- **Limitations**
  - The model lacks HPV genotype data associated with CIN2+ and does not account for potential changes in genotype distribution or progression timing due to vaccination, although vaccination rates were low in 2015
  - It assumes all CIN2+ cases are detected through screening without distinguishing between new or persistent reinfections, or reactivations, and does not consider variations in screening behaviors or individual risk factors

Conclusions

- The analysis indicates that a significant proportion of causal HPV infections for CIN2+ in South Korea occur among women ≥30 years of age
- These findings highlight the need for catch-up HPV vaccination to protect adult women from new HPV infections that cause cervical diseases

References

1. Kim M-A, et al. *J Korean Med Sci.* 2018;33(52):e331.
2. Yu SY. Cost-effectiveness of introducing new vaccines or expanding beneficiaries to the national immunization program. Korea Centers for Disease Control and Prevention; 2024
3. Choi JY, et al. *Clin Exp Obstet Gynecol.* 2022;49(1):22.
4. Ferris DG, et al. *Papillomavirus Res.* 2020;10:100202
5. Prabhu vs, et al. *Open Forum Infect Dis.* 2021;8:(7)
6. Health Insurance Review & Assessment Service (HIRA) "HIRA Opendata Disease Code" [in Korean]. Data for 2015. Updated July 02, 2024. Accessed August 30, 2024. https://opendata.hira.or.kr/op/opc/olap4thDsInfoTab3.do
7. KOSIS. KOrean Statistical Information Service (KOSIS) Available from: https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1IN1503&vw_cd=MT_ZTITLE&list_id=A11_2015_1_10_10. Accessed 2023 Dec 4. https://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1IN1503&vw_cd=MT_ZTITLE&list_id=A11_2015_1_10_10.
8. Lee JK, et al. *J Gynecol Oncol.* 2013;24(2):186-203.
9. Ko M, et al. Cost-effectiveness of conventional cytology and HPV DNA testing for cervical cancer screening in South Korea. Seoul: National Evidence-based Healthcare Collaborating Agency. 2014.

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