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The lifetime cost estimation of human papillomavirus-related diseases in China: a modeling study

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ABSTRACT

Objectives: To estimate the lifetime treatment costs of patients with human papillomavirus (HPV) infection-related diseases in China and to provide cost estimates for the economic evaluation of HPV intervention strategies. **Methods:** We extracted real-world hospital data from 2012 to 2019 and screened for subjects who met the criteria of clinical diagnosis of HPV-related diseases to obtain country-specific inputs into a Markov decision model. The model simulated lifetime treatment costs for HPV from the perspective of a national payer. A 5% discount rate was applied. Costs were converted and inflated to 2020 US dollars (USD) **Results:** Using 2021 as the base year, the lifetime costs per patient for carcinoma in situ, local metastasis, and distant metastasis cervical cancer are $24,208 (95%CI: 18,793–30,897), $19,562 (95%CI: 14,456–25,567), and $17,599 (95%CI: 10,604–25,807), respectively. For carcinoma in situ, local metastasis, and distant metastasis vaginal cancer, the lifetime costs are $17,593 (95%CI: 14,962–23,596), $17,120 (95%CI: 13,215–22,417), and $22,411 (95%CI: 12,172–22,249), respectively. The base-case lifetime cost per patient for different stages of vulvar cancer/penile cancer/anal cancer/oral cancer/oropharyngeal cancer/laryngeal cancer falls within $17,120–$58,236. **Conclusions:** Using real-world data, we calculated lifetime treatment costs of HPV-related cancer in China and found that the lifetime cost for patients exceeded $17,000 for various stages of disease. The national burden of HPV-related disease could be significantly reduced by eliminating HPV infection.

Key words: human papillomavirus, economic burden of disease, real-world data

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INTRODUCTION

Approximately 200 genotypes of human papilloma virus (HPV) have been identified to date and are classified into high-risk and low-risk HPVs according to their pathogenicity. The most common high-risk HPVs are HPV 16, 18, 31, 33, 45, 52, and 58, which are associated with cervical cancer (CC), vaginal cancer (VaC), vulvar cancer (VC), anal cancer (AC), penile cancer (PC), and head-and-neck cancer. Low-risk HPVs variants include HPV 6 and 11, which have been linked to genital warts (GW) and recurrent respiratory papilloma (RRP).[1]

HPV-related diseases cause significant burden to society. Among them, CC is the most common disease caused by infection with high-risk HPVs, with its incidence and mortality exhibiting an upward trend throughout China. The standardized incidence of CC increased from 3.06/100,000 in 1988 to 10.7/100,000 in 2018 and the standardized mortality of this disease rose from 1.71/100,000 to

4.4/100,000 over the same time period.[2] In addition to CC, epidemiological data show that in 2015, high-risk HPV infections caused 1,087 new cases of AC, 1,128 new cases of PC, 694 new cases of VC, 364 new cases of VaC, 462 new cases of oropharyngeal cancer, 2,437 new cases of oral cancer, and 5,903 new cases of laryngeal cancer in China.[3] Low-risk HPV infections of GW reached an incidence of 24.65/100,000.[4] Previous research conducted in China suggests that the cost of hospitalization of CC is significant, approximately US $4,448 per patient in Zhejiang Province from 2009 to 2013[5] and US $4,444 from 2011 to 2016 among tertiary grade A hospitals located in Beijing.[6] In Taiwan of China, the undiscounted lifetime cost (10 years) for patients with CC was US $15,297 in 2002.[7] In 2008, a study from Changzhi in Shanxi Province of China showed that the average cost per patient for GW was US $90 in Changzhi.[8]

China has implemented a relatively complete three-grade prevention strategy for CC (including primary prevention strategies that mainly comprise HPV vaccination, health education, and safe sex practices; secondary prevention strategies that mainly include CC screening and precancerous lesion treatment; and tertiary prevention strategies that mainly involve treatment of invasive CC). However, the current vaccination rate of HPV is still relatively low[9] due to the low awareness, poor availability, and high price of the vaccines.[9,10] Presently, the approved HPV vaccines in China including Cervarix®, Gardasil®4, Gardasil®9, and Cecolin®, which have different protective efficacies according to researches.[11,12] Also, the prices of these four kinds of vaccines are distinctly different. So, to implement national immunization plan according to advice from the World Health Organization (WHO),[13] it is necessary to carry out economic and affordability evaluations of different vaccination strategies (combinations of vaccine valence with the population size and age range for vaccination), thereby choosing the strategy most suitable for national conditions and improving the allocation efficiency of health resources in China.

Because HPV is transmissible, economic evaluation of vaccination strategies requires the use of dynamic models (*e.g.*, transmission dynamics models) to simulate the cost and health benefits for the population at risk. However, owing to a lack of epidemiological investigations and real-world data mining, there are no validated studies on the economic burden of HPV-related diseases in China that can provide cost parameters for research based on the abovementioned models. As a result, only some HPV-related diseases have been included in the existing economic evaluations of HPV vaccines. For instance, when comparing the cost-effectiveness of different screening and HPV vaccination strategies in China, Levin *et al.*[14] and Zhang *et al.*[15] only considered cervical intraepithelial neoplasia (CIN) and CC, whereas Mo *et al.*[16] only included CIN, CC, and condyloma acuminatum. Owing to the incomplete disease spectrum, the models cannot simulate reality to the greatest extent, which affects the quality and accuracy of the evaluation results and increases the risk of uncertainty in health decision-making.

In this study, we selected representative hospital databases in China and captured a number of HPV-related diseases that met the diagnostic criteria and also had completely qualified data at the same time. Markov models were constructed to predict the lifetime treatment costs (only cost in the hospital because of data source) of HPV-related conditions, which were then used to estimate the economic burden of HPV-related diseases on a per person basis using national cost inputs. Since few patients suffer from more than one HPV-related disease at the same time and the current economic evaluations only consider single diseases, the lifetime treatment cost of comorbidity was not considered in our study.

METHODS

Overview

HPV is known to cause both short-term and long-term diseases. In our study, we included GW and RRP for short-term HPV-related diseases. Markov models with four to eight health states were constructed to estimate lifetime costs of patients who developed long-term diseases after infection, including CIN, vaginal intraepithelial neoplasia (VaIN), CC, VaC, VC, PC, AC, oral cavity cancer (OcC), oropharynx cancer (OrC), and larynx cancer (LC). The treatment cost per patient over the full course of short-term diseases was taken as the lifetime treatment cost. Transition probabilities were taken from published literature (see Table 1). For short-term conditions such as GW and RRP, the average annual treatment costs were also calculated. To estimate national-level lifetime treatment costs of these diseases, extrapolation of the per person models was made based on the ratio of the medical cost per patient in the source region of disease data to the medical cost per patient for the whole country. The hypotheses of this model were as follows: (1) It is possible for patients with CIN/VaIN to return to the disease-free healthy state, whereas those with other HPV-related diseases cannot return to the disease-free healthy state and (2) costs in the first-diagnosed year are higher than those in the following years,[17] and the rules could be applied to all the diseases. Figure 1 shows the technical procedures in this study.

Model structure

According to the natural progression of different diseases, we established a total of eight Markov models consisting

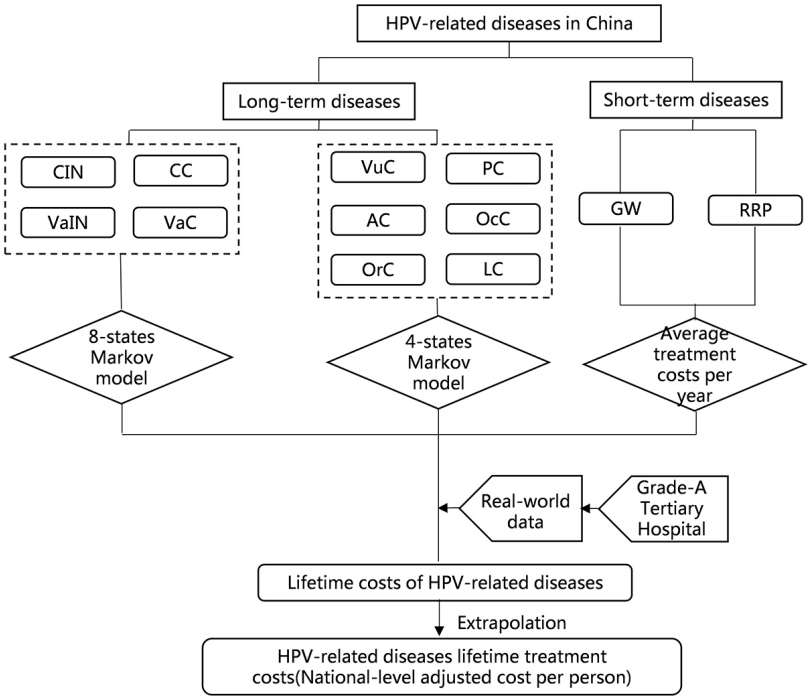

Figure 1: Technology roadmap.CC: cervical cancer; CIN: cervical intraepithelial neoplasia; GW: genital warts; HPV: human papillomavirus; RRP: recurrent respiratory papillomatosis; VaC: vaginal cancer; VaIN: vaginal intraepithelial neoplasia. Other related cancers are anal cancer, larynx cancer, oral cavity cancer, oropharynx cancer, penile cancer, and vulvar cancer.

of 40 health states, and patients in each state received relevant treatments to simulate the lifetime treatment costs of patients with different diseases and in different stages.

Eight-state Markov model: For CC and VaC, precancerous lesions and cancer stage were taken into account[18–21] to construct an eight-state Markov model[22–24]: disease-free healthy state, grades 1–3 intraepithelial neoplasia, carcinoma in situ (localized cancer), local metastasis (regional cancer), distant metastasis (distant cancer), and death. Because CIN/VaIN are mild diseases compared with CC/VC, we considered it a disease-free state. It was assumed that among patients with CIN/VaIN, some cases of each grade will be cured to the disease-free healthy state and will have no need of treatment after recovery. Additionally, because some patients may develop CC/VaC when CIN/VaINs progress to grade 3, we included CIN and CC, as well as VaIN and VaC, in the eight-state model.

Four-state Markov model: For the other diseases, precancerous lesions were not considered and only the cancer stage was considered, including carcinoma in situ, local metastasis, distant metastasis, and death; therefore, a four-state Markov model was established.[25–28] The model comprised VC, PC, AC, OC, OrC, and LC. The structure of the constructed models is shown in Figure 2.

The stage settings of "carcinoma in situ, local metastasis, and distant metastasis" for all the abovementioned cancers were obtained in accordance with studies on the progression of related diseases, clinical guidelines, and previously reported transmission dynamics models for HPV.[29, 30]

Because the follow-up period of patients with GW and RRP in the sample hospital data is less than 1 year and these two diseases can be cured, no model was constructed for the progression of these two diseases and their annual average treatment costs were directly used as the lifetime treatment costs.

For each stage of the target diseases, the population in the start period was set to 1,000 people. The model cycle period was set to 1 year, and the simulation time horizon was lifetime. The model was terminated when the proportion of people alive in the simulation cohort was less than 1%. The annual treatment costs of various diseases per patient were taken as the costs for each period, and the decreasing relationship between the first-diagnosed year and the non–first-diagnosed year was also accounted for. We used health system as the research perspective in this study.

Model inputs and data source

Real-world data

The cost data used in this study were derived from teaching hospitals which met with data quality, completeness,

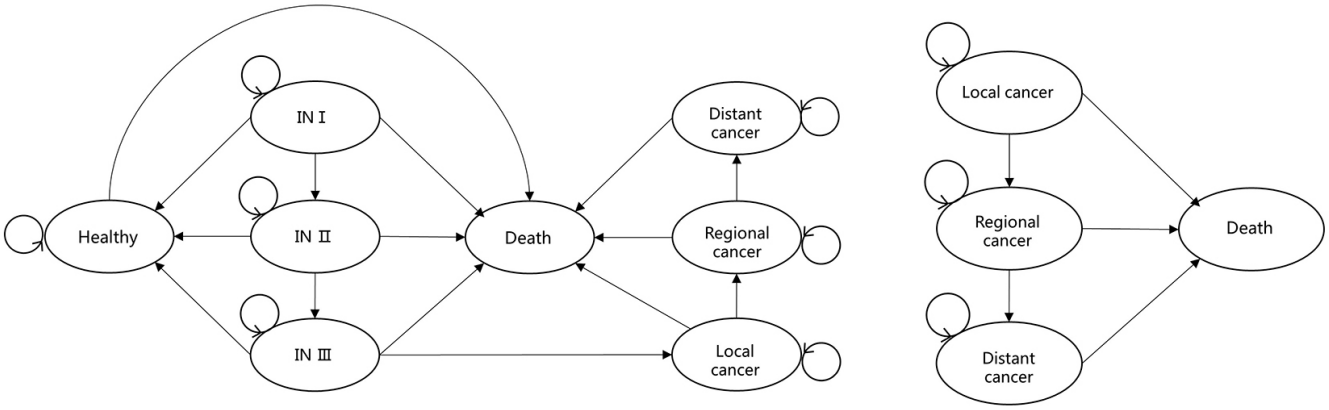

Figure 2: Structure of Markov models. Ovals stand for the health states and arrows stand for the direction of disease progression. Eight-state model involves cervical intraepithelial neoplasia, vaginal intraepithelial neoplasia, cervical cancer and vaginal cancer; four-state model involves vulvar cancer, penile cancer, anal cancer, oral cavity cancer, oropharynx cancer, and larynx cancer. IN1–3: grades 1–3 cervical/vaginal intraepithelial neoplasia. Localized/regional/distant cancer: corresponding to carcinoma in situ/local metastasis/distant metastasis stage for a specific HPV-related cancer.

and availability. The source hospital and time range of the data, sample size together with the corresponding disease stage are listed in Table S1. The specific method of data acquisition was as follows: first, we defined the diagnosis name, English abbreviation, and International Statistical Classification of Diseases and Related Health Problems (ICD) code-10 of the diseases and constructed the rules using logical words; then, we captured patient data for specific stages of the target diseases from the hospital database using artificial intelligence. Descriptive statistics were performed to estimate the cost by disease stage.

Basic parameters and assumptions

The initial cohort number was set as 1,000 for each simulation, and the initial cohort age for each health state was equal to the average age calculated from real-word data of corresponding diseases. In addition, the simulation of each disease was stopped when more than 99% people in the initial cohort were dead.

Average annual treatment cost

The cost parameters of all the remaining health states included the average annual treatment cost for each patient in these states. The average annual treatment cost included outpatient and inpatient costs. To simulate the lifelong costs, we distinguished the costs in the first-diagnosed year and in the subsequent year. Also, we assumed that the costs in the first-diagnosed year were higher than in the follow-up visits. The first-diagnosed cost refers to the treatment cost for a patient in the year of the first medical visit, whereas the non–first-diagnosed cost refers to the average annual treatment cost for a patient in the course of follow-up treatment. For a certain disease stage, the first-diagnosed cost was used for the model to simulate the first cycle of the disease stage and the non–first-diagnosed cost to simulate the remaining cycles.

Owing to the limited sample size, the first-diagnosed cost was calculated from available data only for the following six disease stages: grade 1 CIN, carcinoma in situ of CC, local metastasis of CC, distant metastasis of CC, carcinoma in situ of VC, and carcinoma in situ of LC. For the remaining disease stages with no first-diagnosis data being traced, we performed linear fitting on the first-diagnosed cost and non–first-diagnosed cost of the six disease stages with available data (the fitting function is shown in Figure S1).[31,32] This yielded the proportional coefficient, 1.1567, between first-diagnosed and non–first-diagnosed costs. Assuming that this coefficient applies to all diseases, we inferred the average annual first-diagnosed cost of the disease stages that lacked first-diagnosis data.

Transition probability

The transition probabilities involved in the eight Markov models included the probability of CIN/VaIN transitioning from various grades to the healthy state, the probability of various diseases transitioning from low to high stages, the probability of transitioning from a non-cancerous state to death (background mortality), and the probability of transitioning from a cancerous state to death. Most of these probability parameters were derived from the published literature (see Table 1) and follow the following principles: (1) the same model state setting as in this study; (2) domestic sources are preferred if there are domestic data sources; (3) the mortality rate of certain states is converted from the survival rate of published literature or clinical guidelines; and (4) for diseases with few published studies, the transition probabilities were estimated using similar diseases based on recommendations from key clinical opinion leaders. The parameter sources are

Table 1: Input parameters used in Markov models

Input parameters	Mean	Stand error‡	Source
Cost			
CIN1*	366	85.6	Hospital databases
CIN2*	819	40.2	Hospital databases + estimated increase
CIN3*	1,096	37.9	
CCI*	10,051	649.5	Hospital databases
CCr*	11,251	889.2	
CCd*	11,813	1,180.9	
CIN1†	422	33.3	Hospital databases + estimated increase
CIN2†	708	34.8	
CIN3†	947	32.8	
CCI†	6,952	618.6	
CCr†	6,960	899.3	
CCd†	11,348	2,002.1	
VaIN1*	3,262	423.7	
VaIN2*	3,038	391.5	
VaIN3*	1,555	139.8	
VaCI*	4,576	387.4	
VaCr*	5,940	628.1	
VaCd*	7,749	1,306.5	
VaIN1†	2,820	366.3	
VaIN2†	2,626	338.5	
VaIN3†	1,344	120.9	
VaCI†	3,956	334.9	
VaCr†	5,135	543.0	
VaCd†	6,700	1,129.5	
VuCI*	5,236	517.4	Hospital databases
VuCr*	6,944	532.5	Hospital databases + estimated increase
VuCd*	8,296	1,058.3	
VuCI†	3,402	508.7	
VuCr†	6,004	460.3	
VuCd†	7,172	914.9	
PCI*	7,040	487.4	
PCr*	10,385	680.2	
PCd*	13,189	1,604.8	
PCI†	6,087	421.4	
PCr†	8,978	588.1	
PCd†	11,402	1,387.4	
ACI*	7,846	760.7	
ACr*	10,324	973.4	
ACd*	14,076	1,646.2	
ACI†	6,783	657.6	
ACr†	8,925	841.5	
ACd†	12,169	1,423.2	
OcCI*	5,526	361.6	
OcCr*	7,918	527.9	
OcCd*	10,653	1,141.1	
OcCI†	4,777	312.6	
OcCr†	6,845	456.4	
OcCd†	9,210	986.5	
OrCI*	6,644	589.8	
OrCr*	9,188	783.0	
OrCd*	12,162	1,394.5	
OrCI†	5,744	509.9	
OrCr†	7,943	676.9	
OrCd†	10,514	1,205.6	
LCI*	17,426	4,033.5	Hospital databases
LCr*	8,702	435.3	Hospital databases + estimated increase
LCd*	10,301	716.2	
LCI†	12,696	1,705.4	
LCr†	7,523	376.4	
LCd†	8,905	619.2	

Table 1: Input parameters used in Markov models

Input parameters	Mean	Stand error‡	Source
Transition probabilities			
CIN1 to health	0.230	0.057	[33]
CIN2 to health	0.315	0.061	
CIN3 to health	0.004	0.027	[34]
CIN1 to CIN2	0.031	0.012	[33]
CIN2 to CIN3	0.193	0.058	
CIN3 to CCl	0.152	0.027	[34]
CCl to CCr	0.239	0.062	
CCr to CCd	0.547	0.113	
CCl to death	0.223	0.062	[35]
CCr to death	0.453	0.110	
CCd to death	0.588	0.113	
VaIN1 to health	0.230	0.057	[33]
VaIN2 to health	0.315	0.061	
VaIN3 to health	0.004	0.027	[34]
VaIN1 to VaIN2	0.031	0.012	[33]
VaIN2 to VaIN3	0.193	0.058	
VaIN3 to VaCl	0.070	0.015	[36]
VaCl to VaCr	0.239	0.062	[34]
VaCr to VaCd	0.496	0.113	
VaCl to death	0.288	0.059	[37]
VaCr to death	0.504	0.109	
VaCd to death	0.632	0.056	
VuCl to VuCr	0.239	0.062	[34]
VuCr to VuCd	0.547	0.113	
VuCl to death	0.223	0.062	[35]
VuCr to death	0.453	0.110	
VuCd to death	0.588	0.113	
PCl to PCr	0.210	0.061	[38]
PCr to PCd	0.547	0.113	[34]
PCl to death	0.223	0.062	[35]
PCr to death	0.453	0.110	
PCd to death	0.588	0.113	
ACl to ACr	0.239	0.062	[34]
ACr to ACd	0.500	0.090	[39]
ACl to death	0.181	0.060	[40]
ACr to death	0.330	0.080	
ACd to death	0.501	0.087	
OcCl to OcCr	0.239	0.062	[34]
OcCr to OcCd	0.547	0.113	
OcCl to death	0.307	0.055	[41]
OcCr to death	0.453	0.110	[35]
OcCd to death	0.588	0.113	
OrCl to OrCr	0.239	0.062	[34]
OrCr to OrCd	0.547	0.113	
OrCl to death	0.163	0.084	[42]
OrCr to death	0.163	0.084	
OrCd to death	0.408	0.108	
LCl to LCr	0.239	0.062	[34]
LCr to LCd	0.547	0.113	
LCl to death	0.223	0.062	[35]
LCr to death	0.453	0.110	
LCd to death	0.588	0.113	
Background mortality	0.056	0.023	[43]

AC: anal cancer; CC: cervical cancer; CIN: cervical intraepithelial neoplasia; d: distant; l: localized; LC: larynx cancer; OcC: oral cavity cancer; OrC: oropharynx cancer; PC: penile cancer; r: regional; VaC: vaginal cancer; VaIN: vaginal intraepithelial neoplasia; VuC: vulvar cancer.

*First diagnosis. †Non-first diagnosis; estimated increases in progressed stage were simulated using linear fitted model. Refer to Figure S1 for model information. ‡Standard errors were calculated from 1,000 times random sampling from ±20% around the mean values.

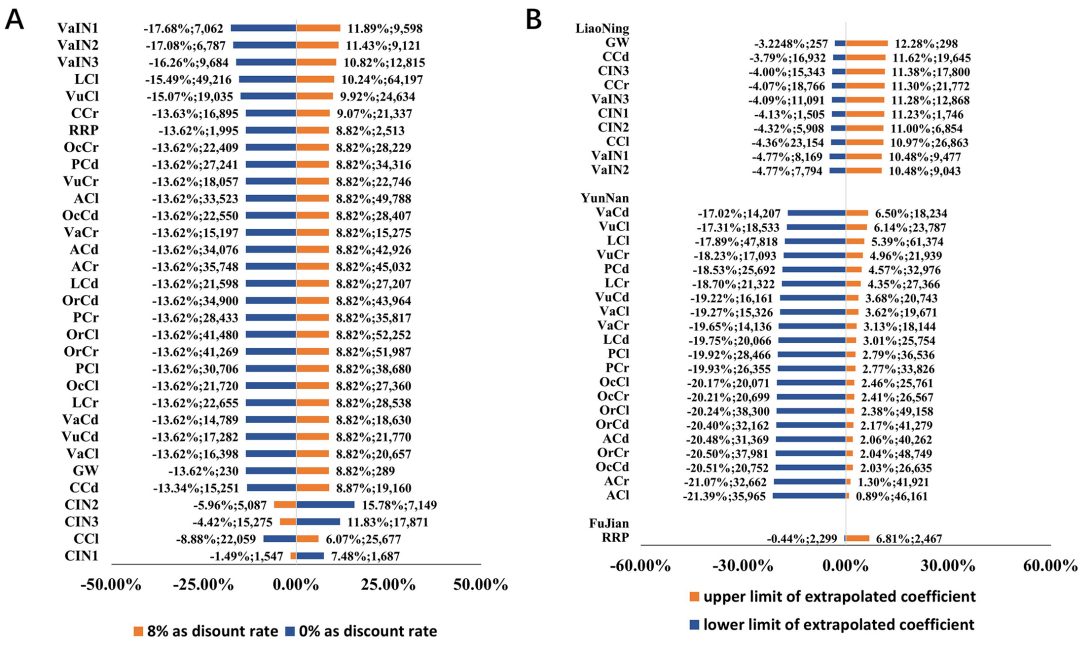

Figure 3: Results of univariate uncertainty analysis. AC: anal cancer; CC: cervical cancer; CIN: cervical intraepithelial neoplasia; d: distant; GW: genital warts; l: localized; LC: larynx cancer; OcC: oral cavity cancer; OrC: oropharynx cancer; PC: penile cancer; r: regional; RRP: recurrent respiratory papillomatosis; VaIN: Vaginal intraepithelial neoplasia; VaC: vaginal cancer; VuC: vulvar cancer.

summarized in Table 1. The cost parameters and standard errors are listed in Table 1.

Cost extrapolation

Because the micro-treatment costs for diseases were only derived from hospitals in a single province and city, we extrapolated them to the national-level adjusted per person cost. According to the method published by Liu *et al.*[44] for calculating the national average cost using regional data, we assumed that the difference in the medical cost of all diseases between regions is also applicable to single diseases and constructed a regional coefficient for linear extrapolation. Further details are available in Table S2.

Discounting and currency conversion

In this study, we first adjusted the historical data (2017–2019) in the hospital database to the year 2021 (baseline year of the Markov model) and then discounted future costs to 2021 using a discount rate of 5%. All costs were converted into USD using the current exchange rate in 2020: 1 Chinese yuan (CNY) = US $0.1524.[45]

Uncertainty analysis

Monte Carlo simulation

The second-order Monte Carlo simulation with 10,000 iterations was used to simulate the influence of randomly distributed parameters that included costs, transition probabilities, and mortality rates. We assumed that the costs conformed to the gamma distribution, and the transition probability and mortality rates conformed to the beta distribution. The standard errors of cost parameters came from the results of hospital data analysis. For some inputs, including transition probabilities and mortality estimates, there was no standard error available; thus, we randomly sampled 1,000 times from ±20% around the mean values and obtained the standard error from simulation. Standard errors for cost, transition probabilities, and mortality rates are shown in Table 1.

Univariate sensitivity analysis

We used univariate sensitivity analysis to explore the influences on non-randomly distributed uncertain parameters. Discount rate was assumed to be varied in the range of 0%–8%.[46] Extrapolation coefficients were assumed to be varied according to the upper and lower limits of model estimates. Results of univariate sensitivity analysis are presented in Figure 3.

RESULTS

Base-case results

Table 2 summarizes the life expectancies, disease-related lifetime costs simulated based on the Markov model, and the disease-related lifetime costs extrapolated to the whole country.

The lifetime costs per patient for carcinoma in situ, local metastasis, and distant metastasis CC are $26,174, $21,214, and $19,141, respectively. For carcinoma in situ,

Table 2: Calculation results of lifetime treatment costs of HPV-related diseases

Diseases	Base-case analysis			Uncertainty analysis*					
	Life years†	Markov model	National-level adjusted per person cost	MC simulation			National-level adjusted per person cost		
				Mean	95%CI lower	95%CI upper	Mean	95%CI lower	95%CI upper
Long-term diseases									
CIN1	>60	1,702	1,570	1,765	956	2,575	1,629	882	2,376
CIN2	56	6,679	6,175	6,857	3,723	9,992	6,340	3,442	9,238
CIN3	56	17,344	15,981	17,831	12,423	23,239	16,430	11,447	21,413
CCl	14	26,174	24,208	26,863	20,320	33,406	24,845	18,793	30,897
CCr	8	21,214	19,562	21,702	15,677	27,726	20,012	14,456	25,567
CCd	7	19,141	17,599	19,801	11,533	28,069	18,206	10,604	25,807
VaIN1	>60	9,234	8,578	9,504	5,968	13,040	8,828	5,543	12,113
VaIN2	>60	8,811	8,185	8,993	6,263	11,722	8,354	5,818	10,889
VaIN3	41	12,538	11,564	12,913	9,023	16,802	11,909	8,322	15,496
VaCl	8	12,260	18,984	12,451	9,663	15,238	19,279	14,962	23,596
VaCr	8	11,308	17,593	11,451	8,494	14,409	17,816	13,215	22,417
VaCd	7	11,364	17,120	11,424	8,080	14,768	17,210	12,172	22,249
VuCl	10	14,825	22,411	14,821	12,645	16,997	22,405	19,116	25,694
VuCr	9	13,673	20,902	13,674	10,740	16,609	20,905	16,418	25,391
VuCd	6	12,928	20,006	12,921	9,534	16,308	19,995	14,754	25,237
PCl	10	22,771	35,546	23,346	17,119	29,573	36,444	26,723	46,164
PCr	9	21,082	32,915	21,597	15,478	27,715	33,718	24,165	43,271
PCd	8	20,552	31,535	21,146	12,866	29,427	32,447	19,741	45,153
ACl	12	28,770	45,754	29,410	21,540	37,280	46,771	34,255	59,288
ACr	11	26,127	41,382	26,641	19,730	33,551	42,195	31,250	53,140
ACd	10	25,093	39,447	25,620	16,943	34,297	40,276	26,635	53,917
OcCl	11	16,055	25,143	16,332	12,675	19,988	25,576	19,850	31,302
OcCr	9	16,558	25,941	16,982	12,170	21,794	26,605	19,066	34,144
OcCd	8	16,600	26,104	17,173	10,587	23,760	27,006	16,648	37,363
OrCl	13	30,638	48,018	32,060	19,891	44,228	50,247	31,175	69,318
OrCr	10	30,382	47,773	31,627	20,397	42,856	49,731	32,073	67,388
OrCd	9	25,727	40,401	26,926	14,013	39,839	42,284	22,006	62,562
LCl	10	38,251	58,236	39,145	26,393	51,897	59,597	40,183	79,012
LCr	9	17,056	26,226	17,493	12,855	22,131	26,898	19,767	34,030
LCd	8	16,051	25,002	16,531	10,501	22,560	25,750	16,358	35,142
Short-term diseases									
GW	/	291	266	/	/	/	266	235	296
RRP	/	2,292	2,309	/	/	/	2,309	2,001	2,618

AC: anal cancer; CC: cervical cancer; CIN: cervical intraepithelial neoplasia; d: distant; GW: genital warts; l, localized; LC: larynx cancer; OcC: oral cavity cancer; OrC: oropharynx cancer; PC: penile cancer; r: regional; RRP: recurrent respiratory papillomatosis; VaIN: vaginal intraepithelial neoplasia; VaC: vaginal cancer; VuC: vulvar cancer.

*Uncertain parameters include costs from sampled hospital data, transition probabilities, and mortality rates.

†Number of model cycles when simulated cohorts dead more than 99%; /: no simulation.

local metastasis, and distant metastasis VaC, the lifetime costs are $12,260, $11,308, and $11,364, respectively. The base-case lifetime cost per patient for carcinoma in situ, local metastasis, and distant metastasis VuC/PC/AC/OcC/OrC/LC are $14,825, $13,673, $12,928/$22,771, $21,082, $20,552; $28,770, $26,127, $25,093/$16,055, $16,558, $16,600; and $30,638, $30,382, $25,727/$38,251, $17,056, and $16,051, respectively. For CIN1–3 and VaIN1–3, the lifetime costs are $1,702, $6,679, $17,344 and $9,234, $8,811, $12,538, respectively. The base-case lifetime cost per patient for GW and RRP are $291 and $2,292, respectively.

After extrapolating the above results to national-level adjusted per person cost, the lifetime costs per patient for carcinoma in situ, local metastasis, and distant metastasis CC are $24,208, $19,562, and $17,599, respectively. For carcinoma in situ, local metastasis, and distant metastasis VaC, the lifetime costs are $18,984, $17,593, and $17,120, respectively. The base-case lifetime cost per patient for

carcinoma in situ, local metastasis, and distant metastasis VuC/PC/AC/OcC/OrC/LC are $22,411, $20,902, $20,006/$35,546, $32,915, $31,535; $45,754, $41,382, $39,447/$25,143, $25,941, $26,104; and $48,018, $47,773, $40,401/$58,236, $26,226, and $25,002, respectively. For CIN1-3 and VaIN1-3, the lifetime costs are $1,570, $6,175, $15,981 and $8,578, $8,185, $11,564, respectively. The base-case lifetime costs per patient for GW and RRP are $266 and $2,309, respectively.

Uncertainty analysis

Results from Monte Carlo simulation are also presented in Table 2. The median, maximum, and minimum values of the extrapolated costs are summarized in Table S3.

Results from univariate sensitivity analysis are shown in Figure 3. Lifetime cost of VaIN1 is most sensitive to the change of discount rate and that of CIN1 the least sensitive. Lifetime costs of diseases extrapolated from Yunnan province are majorly more uncertain from other two provinces.

DISCUSSION

Main findings

In this study, the lifetime treatment costs of LC, OrC, AC, CC, VC, PC, and VaC were higher (from $17,120 to $58,236) as compared to the costs of CIN/VaIN, RRP, and GW (from $266 to $15,981). This result is consistent with the logic that the greater the disease severity and the longer the disease course, the higher the treatment cost. It should be pointed out that although the lifetime treatment cost of CC was not at the highest level, the incidence of CC was the highest compared with the other diseases.[47] Moreover, according to the physiological and pathological processes of cervical malignant tumor progression, nearly all CCs are related to HPV.[48–50] Therefore, overall, the economic burden of CC was heaviest among the HPV-related diseases evaluated in this study. We also compared the above result with those of existing studies.

From the limited studies evaluating the burden of HPV-related diseases in China, we found that only Hu and Goldie[51] reported both point estimates and ranges for primary HPV-related conditions. Although it was published in 2008, the rank order of expenditures for various conditions is similar to our study. For example, their study findings showed that OrC has the highest lifetime treatment cost, followed by AC, VaC, VC, and PC; the lifetime treatment cost of GW is the lowest.

Our results also showed that the average annual treatment costs per patient of CIN/VaIN caused by HPV exhibited an increasing trend with increasing lesion grade; that is, the more serious the intraepithelial neoplasia, the higher the lifetime treatment cost. In contrast, the costs of HPV-related cancers exhibited a decreasing trend with increasing disease stage; the treatment cost of carcinoma in situ was the highest, whereas the treatment costs of local and distant metastases decreased successively. This trend is relatively in line with the real-world cancer treatment model. Patients with early carcinoma in situ have a long survival period and require long-term maintenance treatment, resulting in relatively high lifetime costs. In contrast, patients with advanced metastatic cancer have a short survival period and even more complex treatment methods, such as surgery combined with chemoradiotherapy, which will lead to relatively low lifetime treatment costs. This trend of lifetime costs is similar to that in previously reported studies on disease burden. For instance, in a study involving older patients with AC in the USA, Deshmukh *et al.*[52] found that the average lifetime treatment costs of AC stages III and IV were US $93,291 and US $73,178 for male patients and US $78,039 and US $63,276 for female patients, respectively. This result indicates that as disease severity becomes greater, the lifetime treatment cost first increases and then decreases.

Among the lifetime treatment costs of the diseases simulated in this study, although grade 1 CIN/VaIN belongs to the same grade as precancerous lesions, the lifetime treatment cost of the former disease (US $1,629) was considerably lower than that of the latter disease (US $8,828). Combined with the data of individual patients, we found that patients with VaIN grade 1 had a lower average annual number of outpatient visits, but a higher number of inpatient visits; in other words, most patients with VaIN grade 1 must be hospitalized owing to severe symptoms. Accordingly, we speculate that this result may be related to implementation of the CC screening program in China.[53,54] This program targets Chinese women of the appropriate age to detect patients with early CIN in a timely manner and prompt patients with mild disease to seek medical treatment as early as possible; as a result, patients consume fewer medical resources and bear lower treatment costs.[55]

Applications of lifetime treatment costs

There have been four kinds of HPV vaccines approved in China against two, four, or nine kinds of viruses from HPV-6, 11, 18, 31, 33, 45, 52, and 58 with different efficacies and costs of protecting HPV-related diseases mentioned in our study. So, how to choose the most cost-effective HPV vaccination strategy and make relevant public health policies is an important question that cannot be ignored by health policy makers in China. Accordingly, we provide a comprehensive estimate of the lifetime costs of HPV-related diseases in China, which are very necessary

for the dynamic transmission model used for economic evaluation of HPV vaccination strategies. The results of these economic evaluations will be supportive evidences to support HPV vaccination strategies. And finally, the allocation of health resources in China will be optimized.

Based on these lifetime treatment costs, researchers can also estimate the disease burden of HPV-related diseases in China, even in other developing countries, combined with corresponding epidemiological data. The disease burden can be used to compare with average per capita income of China to explore the extent of burden of HPV-related diseases in the Chinese society and to support HPV-related vaccination strategy and the policy controlling these diseases.

Strengths and limitations

First, this study systematically estimated the lifetime treatment costs of patients with HPV-related diseases in China using quantitative analysis. Other studies have not reported the results of all HPV-related diseases[56] or considered the stages.[50] Second, based on real-world data, we simulated long-term lifetime treatment costs instead of replacing them with short-term ones, which may lead to underestimation of the lifetime treatment cost for economic evaluations using a transmission dynamics model. For example, Karen *et al.*[57] and Zou *et al.*[58] only reported the costs of various items and total cost, but not the lifetime treatment cost of CC when evaluating the cost-effectiveness of HPV vaccination strategies in China. Third, real-world data can also represent the treatment costs of Chinese patients, and thereby better support decision-making in China, corresponding to the recommendations of the Chinese Pharmacoeconomics Evaluation Guide 2020 and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[46,59] for priority use of local data in decision-affected regions. Therefore, the economic evaluations of HPV vaccination strategies in China by Song *et al.*[60] and Ma *et al.*[61] based on data from other counties are unsuitable. Finally, we considered the differences in economic level among various regions of China[44] and obtained the national-level adjusted per person lifetime treatment costs of HPV-related diseases, which can strongly support national-level decision-making.[62,63]

Inevitably, this study still has certain limitations. With regard to the methods, for the transmission probabilities and their standard errors or deviations and the first-diagnosed treatment costs which cannot be obtained from the published literature or existing data, we referred to similar diseases, fitting, or assumptions; for the extrapolation costs of the whole country, we used a simple linear extrapolation method. These references and assumptions increase the uncertainty of the study results to a certain extent. With regard to the sample data, they were all from hospital databases lacking channels to trace the out-of-hospital treatment costs of patients, and not all target diseases correspond to the samples are caused by HPV, which may lead to bias of the results. Hu *et al.*[51] only assumed the proportion of HPV-caused diseases of the overall patients when estimating the lifetime costs of HPV-related diseases. The possible reason is that for the same disease, whether or not caused by HPV, the treatment methods are similar and have little influence on the differences in treatment costs.

In recent years, the health care system in China has attached increasing importance to the construction of data platforms and has also paid increasing attention to real-world evidence.[64,65] If researchers can collect more comprehensive treatment cost data with HPV-related diseases in China, the results of our study can be externally verified to ensure that the bias is within an acceptable range.

CONCLUSIONS

The lifetime costs per patient for carcinoma in situ, local metastasis, and distant metastasis CC are $24,208, $19,562, and $17,599, respectively. Lifetime costs for other HPV-related diseases in China vary from $266 (GW) to $58,236 (carcinoma in situ LC). Based on real-world data from the public hospitals in China, the findings of this study fill in the gap in the literature regarding the life treatment costs of patients with HPV-related diseases in the country using data analysis, model simulation, and linear extrapolation. The results provide a reference for multiple types of research, including but not limited to: (1) estimating the economic burden of HPV-related diseases combined with the prevalence of these diseases; (2) conducting economic evaluation of HPV vaccination strategies in China or neighboring countries, combined with a transmission dynamics model; (3) evaluating the cost and affordability of combination strategies for the prevention and control of CC in China or neighboring countries; and (4) providing evidence to support the development of other related health policies.

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Conflict of Interest

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Author disclosures

We confirm that this manuscript has not been published elsewhere and is not under consideration in whole or in part by another journal. All authors have approved the manuscript and agree with this submission.

Author contributions

WT takes responsibility for the integrity of the data and accuracy of the data analysis. Study design: YM, WD, and WT. Data analysis: YM and WD. Drafting of manuscript: YM and WD. Critical revision of the manuscript: CM, LS, AM, and DM.

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