The Natural History of Cervical Cancer in Chinese Women: Results from an 11-Year Follow-Up Study in China Using a Multistate Model

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Abstract

**Background:** It is important to understand the natural history of cervical cancer, which has implications for cancer prevention and management. However, a dearth of studies on the long-term development of cervical cancer exists in China.

**Methods:** We investigated the natural history of cervical cancer in Chinese women by creating a multistate model using 11 years of follow-up data from the Shanxi Province Cervical Cancer Screening Study I conducted from 1999 to 2010. In 1999, a total of 1,997 eligible women, ages 35 to 45 years, were enrolled in Xiangyuan County, Shanxi Province. Participants were followed up in 2005 and 2010, respectively.

**Results:** The average time a subject spent in CIN1 before transiting into another state was 1.4693 years (95% confidence interval [CI]: 1.1215–1.9251) and the average time a subject spent in CIN2 was 2.9822 years (95% CI: 1.9790–4.4938). A subject’s transition probability from CIN1 to normal increased with time. However, the transition probability from CIN1 to CIN2 was relatively lower, with 3-, 5-, and 10-year transition probabilities of 0.1415, 0.1066, and 0.0437. Comparison of 5-year transition probabilities between CIN2 to normal/CIN1 and CIN2 to CIN3+ yielded a ratio of 2.74.

**Conclusions:** Women with CIN1 had a substantial tendency for regression. Similarly, women with CIN2 had a higher probability of regression to normal/CIN1 than progression to CIN3+. Findings in this study may have significant implications for the development and evaluation of formal cervical cancer preventive strategies in China.

**Impact:** This study may serve as a valuable reference to future research on other multistate cancer processes.

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Introduction

Cervical cancer is the third most common cancer in women worldwide (1, 2). As the most populous country in the world, China has an especially high burden of disease, accounting for 14% of the annual global incidence (75,500 new cases) and 12% of the annual global mortality (34,000 deaths) from cervical cancer (3).

While the incidence and mortality of cervical cancer have been effectively lowered in many countries due to preventive screening, no national screening program exists to curb this malignancy in China. To address this problem, the Chinese government launched a cervical cancer prevention program in 2009 which aims to screen 10 million rural Chinese women over 3 years using either Pap smear or visual inspection with acetic acid (4). Although the coverage of the program is limited, it is a promising first step towards providing cervical cancer screening for Chinese women.

It is important to understand the natural history of cervical cancer which has implications for cancer prevention and management (5). However, a dearth of studies on the natural development of cervical cancer exists in China. As the progression of cervical cancer is a long-term, multistate process, multistate model can be applied to describe the effect of carcinogenesis over time, which has been used in various fields (6–11). At any given time during follow-up, the model classifies a subject into one of a finite number of distinct states and estimates the instantaneous rate of transition between states, probability of transition from one state to another within a specific time period, and mean sojourn time, defined as the average time spent in a state during a single stay. The...
information derived from multistate modeling is invaluable in helping us understand the natural history of cervical cancer.

The purpose of this article is to describe the natural history of cervical cancer in Chinese women by creating a multistate model using 11 years of follow-up data from the Shanxi Province Cervical Cancer Screening Study I (SPOCSS-I).

Materials and Methods

Study population

A total of 1,997 eligible women ages 35 to 45 years were enrolled at the local Maternal and Children’s Hospital in Xiangyuan County, Shanxi Province in 1999. All participants underwent a minimum of 4 small biopsies and an endocervical curettage to determine final histologic diagnosis, as previously described (12). All women were invited to participate in follow-up studies in 2005 and 2010. Study procedures were similar at follow-up, and women reporting cervical therapy after the previous study visit completed a questionnaire on detailed treatment information including the date, hospital, and type of therapy received. Women with abnormal results from any test received colposcopic evaluation with biopsies as necessary, and no biopsies were taken for the screen-negative women (13).

Figure 1 illustrates the flowchart of this study. Forty-three women at baseline and 4 women at the first follow-up diagnosis as CIN3+ were excluded. In the follow-up visit in 2005, 168 women were lost to follow-up, and 167 women were excluded, including 113 women who received any type of treatment on the cervix (i.e., physiotherapy or surgery) between 1999 and 2005; and 54 women with inconclusive diagnoses [i.e., unsatisfied or missing cytology, low-grade squamous intraepithelial lesion (LSIL)+, and atypical squamous cells of undetermined significance (ASC-US) with human papillomavirus (HPV)-positive]. In the follow-up visit in 2010, 315 of the eligible 1,837 women were lost to follow-up, 53 women were treated during 2006 to 2010, and 24 women had inconclusive diagnoses. As multistate model asks for at least two visits (i.e., the baseline visit and at least one follow-up visit), another 231 women at baseline were excluded due to lacking of two follow-up results by any reason. In total, 4,787 visits were included in our analysis with 1,723 women at baseline, 1,619 at the follow-up in 2005, and 1,445 at the follow-up in 2010.

Institutional Review Board (IRB) approval was obtained from the Cancer Institute/Hospital, Chinese Academy of Medical Sciences (Beijing, China), the Cleveland Clinic (Cleveland, OH), and the University of North Carolina (Chapel Hill, NC).

Multistate model

We used multistate model to analyze 11 years of follow-up data. A multistate model describes how an individual...
transits between a series of states in continuous time. Suppose an individual is in state $S(t)$ at time $t$. The movement on the discrete state space $1; \ldots; R$ is governed by transition intensities $q_{rs}$; $r, s = 1; \ldots; R$ (14, 15). The intensity represents the instantaneous risk of moving from state $r$ to state $s \neq r$:

$$q_{rs}(t) = \lim_{\Delta t \to 0} P(S(t + \Delta t) = s | S(t) = r)/\Delta t$$  \hspace{1cm} (1)

The $q_{rs}$ forms a $R \times R$ matrix $Q$ whose rows sum to zero, so that the diagonal entries are defined as $q_{rr} = - \sum_{s \neq r} q_{rs}$. If a particular instantaneous state-to-state transition is not permitted in the underlying multistate model, then the corresponding transition intensity has a value of 0. Multistate models are often based on first-order Markov processes, which means that future evolution of the disease process depends only on the current state (16). Specifically, the state occupied at time $t + \Delta t$ is conditional on the state occupied at time $t$.

The transition intensities matrix $Q$ can be used to compute the transition probability matrix $P(u; t + u)$. The $(r; s)$ entry of $P(u; t + u)$ is the probability of being in state $s$ at a time $t + u$, given the state at time $u$ is $r$. $P(u; t + u)$ is calculated in terms of $Q$ using the Kolmogorov differential equations. The sum of each row of the transition probabilities matrix is 1.

The full likelihood is then the product of probabilities of transitions observed, over all individuals $i$ and observation times $j$:

$$L(Q) = \prod_i L_i = \prod_i \prod_j L_{i,j} = \prod_i \prod_j p(S(t_i) | S(t_{i-1}))(t_{i,j+1} - t_{i,j})$$  \hspace{1cm} (2)

Each component $L_{i,j}$ is the entry of the transition matrix $P(t)$ at the $S(t_i)$th row and $S(t_{i,j})$th column, evaluated at $t = t_{i,j+1} - t_{i,j}$. The likelihood $L(Q)$ is maximized in terms of $\log(q_{rs})$ to compute the estimates of $q_{rs}$ using standard optimization algorithms. The likelihood assumes that the sampling times are ignorable, which means that a particular observation made at a certain time does not implicitly give information about the value of that observation. Sampling times are ignorable if they are fixed in advance or chosen independently of the outcome, which is in line with our follow-up process.

**Statistical analysis**

In our study, we took into account four states of cervical carcinogenesis depicted in Fig. 2. At each visit, a subject was categorized into one of the following four states:

1. Normal: Subjects who were pathologically diagnosed as normal or were negative on all screening tests.
2. CIN1: Subjects who were pathologically diagnosed as CIN1.
3. CIN2: Subjects who were pathologically diagnosed as CIN2.
4. CIN3*: Subjects who were pathologically diagnosed as CIN3 or cervical cancer.

The basis of our multistate model describes the underlying progression of cervical cancer, rather than the observed progression. For example, if a subject diagnosed as CIN2 at baseline but normal at follow-up does not imply that instantaneous regression from CIN2 to normal is clinically possible. Rather, at some time point between baseline and follow-up, the subject transited through CIN1 before arriving at normal. On the basis of existing literature and clinical expertise on the progression of cervical cancer, transitions between states 1 and 2 and states 2 and 3 are considered to be bidirectional. However, subjects may not reach state 1 from state 3 without experiencing state 2. Once state 4 has been reached, no further transitions can be made, as CIN3* is considered as an absorbing state. The corresponding transition intensity matrix $Q$ is expressed below based on the underlying four-state model:

$$Q = \begin{pmatrix}
-q_{12} & q_{12} & 0 & 0 \\
q_{21} & -(q_{21} + q_{23}) & q_{23} & 0 \\
0 & q_{32} & -(q_{32} + q_{34}) & q_{34} \\
0 & 0 & 0 & 0 
\end{pmatrix}$$  \hspace{1cm} (3)

All data were analyzed using R version 2.14.0. The multistate model was formulated and fitted using the msm package (17). The Broyden–Fletcher–Goldfarb–Shanno optimization method was used to maximize the likelihood for the multistate models. The robustness of our parameter estimates was tested by running the models from two different sets of starting values.

![Figure 2. Underlying four states model for the progression of cervical cancer. Bidirectional transitions could only appear between normal and CIN1, CIN1 and CIN2, rather than directly between normal and CIN2. CIN3* is considered an absorbing state with no further transitions to other states.](image-url)
Results

Table 1 shows the number of times state \( r \) followed by state \( s \) from simple observation. At baseline, 1,580 subjects had normal pathology, 111 had CIN1, and 32 had CIN2. During the 11 years of follow-up, there were 54 transitions from normal to CIN1, 10 transitions from CIN1 to CIN2, and 11 transitions from CIN2 to CIN3. Conversely, there were 7 transitions from CIN2 to CIN1 and 114 transitions from CIN1 to normal. Also, there were transitions from normal to CIN2 or CIN3, and transitions from CIN2 to normal. Table 1 showed the observed frequencies and did not reflect the underlying pathologic progression of cervical cancer.

Table 2 shows the estimated parameters of transition intensity with 95% confidence intervals (CI). Despite beginning at different sets of initial values, our multistate model yielded convergent transition intensity parameters, assuring that the global maximum estimate had been attained. For subjects in the normal state, the transition intensity to CIN1 was 0.0129 (95% CI: 0.0095–0.0174). For subjects in the state of CIN1, the transition intensity to normal (0.4903; 95% CI: 0.3619–0.6641) was 2.57 times higher than to CIN2 (0.1903; 95% CI: 0.1163–0.3116). For subjects with CIN2, the transition intensity to CIN1 (0.2614; 95% CI: 0.1565–0.4365) was 3.53 times higher than from CIN2 to CIN3 (0.0740; 95% CI: 0.0484–0.1133). Moreover, the transition intensity from CIN1 to normal was 1.88 times higher than from CIN2 to CIN1. Meanwhile, the transition intensity from CIN1 to CIN2 was 2.57 times higher than from CIN2 to CIN3.

The multistate model could also estimate the mean sojourn time with 95% CIs in each non-absorbing state. The average time that a subject spent in CIN1 before transiting into another state was 1.4693 years (95% CI: 1.1215–1.9251). However, the average time a subject spent in CIN2 was 2.9822 years (95% CI: 1.9790–4.4938) before making a transition, which was higher than the time spent in CIN1.

The estimated 1-, 3-, 5-, and 10-year transition probabilities are shown in Table 3. The transition probability of a subject from CIN1 to normal increased with time, where 1-, 3- and 5-year transition probabilities were 0.3561, 0.6502, and 0.7576, respectively. The transition probability from CIN1 to CIN2 was relatively lower, with 3-, 5-, and 10-year transition probabilities of 0.1415, 0.1066, and 0.0437. With increasing time, the transition probability from CIN1 to CIN3 also increased. Although the 5-year transition probability was only 0.0443, it was 8.69 times higher than 1-year transition probability. The probability of transition from CIN2 to CIN3 was much higher than CIN1 to CIN3. At a peak of 0.0633, the 1-year probability of transition from CIN2 to CIN3 was higher than even the 5-year transition probability from CIN1 to CIN3. The 3- and 5-year transition probabilities of CIN2 to CIN3 were 0.1464 and 0.1966, which corresponded with a 15% and 20% chance of developing CIN3 after 3 and 5 years, respectively. The probability of CIN2 subjects regressing to normal pathology also increased with time, with 3- and 5-year transition probabilities of 0.2316 and 0.3916, respectively.

Discussion

To our knowledge, this is the first study in China to evaluate the long-term natural history of cervical cancer using a multistate model. Given the heavy burden of cervical cancer in China, formal preventive strategies are urgently needed for Chinese women and government policy makers. Our study can serve as a useful reference to address this pressing need.

As a useful method to fit the multistate process of diseases, multistate model has been developed over many years. The valuable information provided by this method has been increasingly incorporated by health care providers into their clinical decision-making process (7, 8). As the progression of cervical cancer is also a multistate process, it is well suited for the application of multistate modeling. However, to date there have been no studies on the natural history of cervical cancer using this model. The reasons behind the dearth of research in this aspect in China are two-fold. First, long-term studies on the progression of cervical cancer are difficult to perform in China and other developing countries due to the loss of study participants to follow-up. Second, researchers may not clearly understand the basic theories behind multistate modeling and how to implement it in actual disease processes. The multistate analysis presented in this article overcomes these two obstacles and provides insight into the natural progression of cervical cancer states over time.

This is important for countries where the routine cervical cancer screening system has not been available. In those countries, women have a limited chance to get the screening during a long period. The multistate model provides an alternative in those areas to investigate the natural history of cervical cancer year by year. Our study may also serve as a valuable reference to future studies on other multistate cancer processes.

On the basis of our study, the 1-year transition probability for a subject with CIN2 to normal/CIN1 was 0.2056. The probability of progressing to CIN3 or remaining in CIN2 in one year was 0.0633 and 0.7311, respectively. However, after 5 years, the transition probability changed.

Table 1. Number of times from an observation of state \( r \) followed by state \( s \)

<table>
<thead>
<tr>
<th>Current state</th>
<th>Normal</th>
<th>CIN1</th>
<th>CIN2</th>
<th>CIN3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2,795</td>
<td>54</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>CIN1</td>
<td>114</td>
<td>11</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>CIN2</td>
<td>21</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviation: CIN3+, CIN grade 3 or worse.
53.79% of women with CIN2 will regress to normal/CIN1, significantly increased. This means that after 5 years, normal/CIN1 in 3 to 5 years without any intervention at all (18–20). Invasive treatment for all women with CIN2 may cause unnecessary mental and physical risks. Furthermore, indiscriminate treatment of all CIN2 cases may deplete the limited medical resources in China, which could have been diverted to other urgent health sectors. Therefore, screening with additional confirmatory tests such as biomarkers that can distinguish women with CIN2 at higher risk of progression to invasive cervical cancer from those with high probability of spontaneous regression should be considered. Treatment would then be restricted to the high-risk CIN2 group as indicated by biomarkers. Recent developments in biomarker technology have identified several such potential biomarkers. In the HPV-Pathogen ISS study, Branca and colleagues found that topoisomerase II alpha (TOP2A) expression correlated with the progression of CIN2 to CIN3(21). Murphy and colleagues demonstrated that the CDC6 protein was preferentially expressed in high grade lesions and in invasive squamous cell carcinoma (22). In addition,

<table>
<thead>
<tr>
<th>Estimation</th>
<th>95% CI</th>
<th>Estimation</th>
<th>95% CI</th>
<th>Estimation</th>
<th>95% CI</th>
<th>Estimation</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-0.0129</td>
<td>(−0.01744—−0.0095)</td>
<td>0.0129</td>
<td>(0.00955—0.0174)</td>
<td>0.0</td>
<td>—</td>
<td>0.0</td>
</tr>
<tr>
<td>CIN1</td>
<td>0.4903</td>
<td>(0.36196—0.6641)</td>
<td>-0.6806</td>
<td>(−0.89173—−0.5195)</td>
<td>0.1903</td>
<td>(0.11635—0.3116)</td>
<td>0.0</td>
</tr>
<tr>
<td>CIN2</td>
<td>0.0</td>
<td>—</td>
<td>0.2614</td>
<td>(0.15655—0.4365)</td>
<td>-0.3353</td>
<td>(−0.50534—−0.2225)</td>
<td>0.0740</td>
</tr>
<tr>
<td>CIN3+</td>
<td>0.0</td>
<td>—</td>
<td>0.0</td>
<td>—</td>
<td>0.0</td>
<td>—</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Abbreviation: CIN3+, CIN grade 3 or worse.

Table 2. Transition intensity of the multistate model with 95% CI

Table 3. Transition probability between states at 1, 3, 5, and 10 years with 95% CI
HPV E6 oncoprotein may also be a useful biomarker (23). However, additional long-term studies are needed to further verify these effects.

We found that the mean sojourn time of CIN1 was only 1.5 years, indicating that CIN1 is a state of instability. Studies showed that mild cervical abnormalities (e.g., CIN1) could be observed during productive HPV infection (24). However, CIN1 is not sensitive for HPV infection, and is not precancer (25). Our study supports the observation that women with CIN1 have a substantial tendency for regression, as described in other studies (26, 27). There are several studies about the natural history of HPV infection that reported the HPV clearance by types (28, 29). Women who regressed from CIN1 to normal state included a subgroup of clearing the productive HPV infection. This could be partly reflected by the fact that the mean sojourn time of CIN1 was about 1.5 years, whereas most HPV infection cleared at 1 to 2 years (30, 31). The 3-year transition probabilities from CIN1 to CIN2 and CIN3þ in our study were only 14.1% and 2.59%, respectively. This is in line with study conducted by Gage and colleagues which reported that the short term (12–24 months) CIN3þ risk for CIN1 was 2.0% (32). In their study, when stratifying by referral cytology, although the short-term risk of CIN2þ increased for CIN1 women with high-grade squamous intraepithelial lesion or worse, it was still relatively low. Castle and colleagues reported the risk of different HPV types for progressing to CIN3þ in CIN1 women and showed low risk except HPV16 and HPV18 (33). On the basis of the low risk of development of cervical cancer and higher regression, lengthening the follow-up interval after cytology predictive of CIN1 (e.g., ASC-US or LSIL) to more than one year in lower resource settings, or alternatively using HPV testing in this group to triage women who are HPV positive to colposcopy, could be considered in some settings, to minimize unnecessary referrals and biopsies. This could alleviate the burden of screening on limited resources and pathologists in underserved regions, as well as lessen anxiety of the patients. Although it may be possible that additional CIN2þ are missed during this period, they can be detected in subsequent years and saved medical resource will mobilize more women for free screening service in China. A recent meta-analysis of HPV testing to triage ASC-US and low-grade cytology suggested that the specificity trade-offs compared with repeat cytology are different for ASC-US versus LSIL, with no loss of specificity for ASC-US cytology but with a lower specificity for LSIL (34). Therefore, the decision to use HPV triage testing for LSIL should be based on local cost-effectiveness analyses, local prevalence of HPV in LSIL, and compliance of women with follow-up recommendations.

Large variations in economic development and health resource management exist among different countries, especially between developed and developing regions. Countries should choose the most appropriate cervical cancer screening method based on independent evaluation of their own health economics (35–38). In most cases, this health economics evaluation relies on transition probability calculations (39–42). However, the lack of such data in China prevents the comparison of the economics of different screening technologies. Results from our study serve as a good platform to address this knowledge gap. Uniquely, in this modeling study, we have had access to direct data from a cohort of patients with extensive 4-quadrant biopsy information, and with longitudinal follow-up. This has allowed us to directly estimate transitions between CIN states in the cohort. In contrast, prior modeling studies have tended to use large scale or national-level datasets to estimate these transitions using population modeling approaches, taking a fitting approach (43, 44). In the most comprehensive models, an underlying natural history model is fit to the data after taking into account screening compliance and accuracy, referral to treatment, and posttreatment follow-up management protocols. Using these methods, age-specific or time-in-state-based transition rates at every stage from HPV infection to cervical cancer and death can be estimated, particularly if accurate cancer registry data are available. Our study is complementary to this population modeling approach and should provide more direct information on some key transitions between low- and high-grade CIN which are likely to be of value in defining the range of feasible parameters for these CIN transitions in future models of cervical cancer.

Our study has certain limitations that must be addressed. First, some state transitions in our data are limited, such as transition from CIN2 to CIN1, which can affect the estimation of parameters. However, we tested the robustness of parameter estimates by running the models from two different sets of starting values and got nearly the same results, indicating adequate performance of our estimation of parameters. In the future, we plan to expand the number of states transitions by analyzing the next 14 years of follow-up data. Second, we did not apply the use of covariates in the current study to understand how risk factors may affect transition between states. Further studies may examine the association between covariates and transition between states in our multistate model. Third, our multistate model did not completely comply with the established model of natural history of cervical cancer. There are usually four major steps in cervical cancer development: infection of metaplastic epithelium, viral persistence, cervical precancer, and cancer (25). In our model, we combined CIN3 and cervical cancer as the absorbing state, which defines CIN3 as a terminal state that cannot regress to CIN2 or less. However, we acknowledged that CIN3 is somewhat different from cervical cancer and previous study demonstrated that less than half of CIN3 lesions progressed to cancer if untreated after 30 years (45). We made the combination (i.e., CIN3þ as the terminal state) because there were few CIN3 and cervical cancer cases at follow-up. With this combination, we cannot observe the transition probability from CIN3 to cervical cancer when compared with other models in the literature. At present, CIN3 is the best proxy...
for cervical cancer and once CIN3 was detected, it would be treated immediately as women with CIN3 are at high risk of cervical cancer. In addition, little evidence showed that women with CIN3 had a relatively higher probability to regress. Therefore, our combination is acceptable. With greater numbers of CIN3 and cervical cancer cases at subsequent follow-up studies, we could modify our multistate model accordingly. Fourth, in our model, women with normal pathology may not adequately reflect the true “health states”. To analyze this implication, we redefined women with non-HPV infection as normal state, and combined the normal women with HPV infection and women with CINI together, defined as “productive HPV infection” state. As expected, the modified model had a lower transition probability from productive HPV infection state to normal and from productive HPV infection state to CIN2 and a higher transition probability from normal state to productive HPV infection state (Supplementary Table S1).

Moreover, to rule out the impact of treatment in our model, we excluded women with either physiotherapy or surgery on the cervix in this study, which may affect the estimations of the model. However, most of the treated women were <CIN2 and they consisted of a small proportion of the total <CIN2 women. Of the CIN2 women who were followed up in the year 2005 and 2010, only 13.9% (5/36) and 8.8% (3/34) got treated, respectively. So we believe treatment would have little influence on the estimates in our model. Actually, we had analyzed the data including women who were treated, and observed similar results as we reported in this manuscript. Besides, given that 4-quadrant biopsies were not performed on screen-negative women at follow-up as dictated by IRBs, there would be some inaccurate CIN classifications in our study. On the basis of the data from baseline study, which did 4-quadrant biopsies on all participants, none of the screen-negative women had CIN2+ lesions. We consider that with the multiple screening methods, we could get a relatively accurate cervical intraepithelial neoplasia (CIN) classification.

In conclusion, we applied multistate model to 11 years of follow-up data to study the natural history of cervical cancer. The results we obtained, including transition intensity, the mean sojourn time, and transition probability may have significant implications for setting up of formal cervical cancer screening program in China. Further studies will focus on the association between risk factors and transitions between states of cervical cancer in Chinese women.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions

Acknowledgments
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