A preliminary cervical cancer screening cascade for eight provinces rural Chinese women: a descriptive analysis of cervical cancer screening cases in a 3-stage framework

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Abstract

Background: Cascade analysis is an effective method to analyze the processing data of an event, such as a provided service or a series of examinations. This study aimed to develop a primary cervical cancer screening cascade in China to promote the quality of the screening process.

Methods: We designed a cervical cancer screening cascade in China according to the program flow chart. It had three stages, each with two steps and one result. Data from 117,522 women aged 35 to 64 years in the Rural Cervical Cancer Surveillance Project from January 1, 2014, to December 31, 2014, were collected to analyze the main results of the cascade. The data and proportion are used to describe the follow-up of cervical cancer and pre-cancer detection rate.

Results: In 2014, 117,522 (80.94% of all cases reported by the Rural Cervical Cancer Surveillance Project) women aged 35 to 64 years had not received cervical cytology in the previous 3 years. The pre-cancer and cancer detection rates were 256.12/100,000 and 16.16/100,000, respectively. A total of 3031 cases failed to follow-up through the screening process, and 1189, 1555, and 287 cases were lost at cervical cytology, colposcopy, and histopathological screening stages, respectively. The estimated cases of pre-cancer and cancer cases would have been 544 and 34, respectively, and the estimated detection rates of pre-cancer and cancer would have been 462.89/100,000 and 28.93/100,000, respectively.

Conclusion: In order to increase the detection rate of cervical cancer, cervical cancer screening staff should focus on increasing the rate of follow-up of those who are positive for cervical cancer screening (ie, those with positive cytology results), especially for the 40 to 44 years age range.

Keywords: Uterine cervical neoplasms; Mass screening; China

Introduction

Cervical cancer is the fourth highest incident cancer in the world and a leading cause of cancer death, especially in developing countries. In 2012, 528,000 new cervical cancer cases were diagnosed worldwide, 85% of which occurred in less-developed regions. Each year, 266,000 women die of cervical cancer, most (90%) in low- to middle-income countries.[1] China has a relatively high cervical cancer disease burden. According to the National Cancer Institute of China, in 2011, there were 87,982 new cervical cancer cases and 23,375 cancer deaths in 2011.[2]

There is compelling evidence that cervical cancer is one of the most preventable and treatable forms of cancer if detected early and managed effectively.[3,4] Cervical cancer screening is the most effective intervention for early detection and prevention of the disease.[5] Research on the economic burden of cervical cancer has shown that screening can reduce both the medical resources required and the economic costs associated with the disease.[6] A study by Zhao *et al*[7] found that all screening strategies decrease cervical cancer mortality and effectively increase lifespans.

According to the Comprehensive Cervical Cancer Control guideline edited by the World Health Organization (WHO), national cervical cancer prevention and control programs should be implemented in accordance with the WHO framework, which describes six components or building blocks that constitute a strong health care system.[8]

In China, the National Rural Cervical Cancer Screening Project, supported by the National Health and Family Planning Commission of the People's Republic of China,

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has been operating nationwide since 2009. By the end of 2014, nearly 43 million rural women had received cervical cancer screening, this number, 60,057 cervical pre-cancer and cancer cases were detected.[9] Early-stage cervical cancer was detected in 90% of the women diagnosed.

This project has been welcomed in the target areas and has led to some socioeconomic benefits. However, during the field research in some areas, some women who should have attended for screening did not, and missing data during the reporting process biased the project's final analysis. There is a gap between the actual detection rate and the estimated detection rate during the cervical cancer screening process. This gap is caused by the missing data during screening and weakens the effect of the screening.

Cascade analysis is an effective method to analyze the processing of data from an event, such as a provided service or a series of examinations.[10] Stringer *et al*[11] established the following prevention of mother-to-child transmission (pMTCT) cascade. Gimbel *et al*[12] established a pMTCT cascade analysis tool to support health facility managers to assess facility performance. Based on a comprehensive review and meta-analysis, Zeng *et al*[13] mapped out a pMTCT cascade that reflects the continuum of service provisions for both pregnant women and infants born to human immunodeficiency virus-positive mothers since 2003 in China.

The study aimed to develop a primary cervical cancer screening cascade in China based on the cervical cancer screening process and to describe the gap between the actual and estimated cervical cancer and pre-cancer detection rates in 2014 in the surveillance regions.

Methods

Ethical approval

This study was approved by the National Center for Women and Children's Health, Chinese Center for Disease Control and Prevention Ethical Review Committee (No. FY2016-009), and all participants provided written informed consent.

The cervical cancer screening cascade

The process of cervical cancer screening comprises three steps established in 2015 by the NCWCH [Figure 1].[14] In the present study, the first step involved cervical cytology screening using the Traian Bethesda system (TBS) for classification and reporting. Women who had a positive result in the cytology examination received a colposcopy examination. Women who had a positive colposcopy result received a histopathological examination. As the human papillomavirus test was not used until 2015, it was excluded from this study. Pre-cancer includes cervical intra-epithelial neoplasia 2 and cervical intra-epithelial neoplasia 3. The abnormal and suspected cases in the cervical cancer screening included atypical squamous cells (ASC) of undetermined significance or above in the cervical cytology examination, abnormal, and suspected results in the colposcopy examination, and high-grade squamous intra-epithelial lesion or above in the histopathological examination.

We designed the cervical cancer screening cascade according to the program flow chart. The cascade has three stages, each of which contains two steps and one result [Table 1].

The cascade result comprises four parts:

(1) Number and rate of follow-up cases in steps 1 to 6 and results 1 to 3.
(2) Number and rate of lost cases in steps 1 to 6.
(3) Number and rate of cervical cancer and pre-cancer cases of missed screening and reporting at each step.
(4) Estimated cancer and pre-cancer detection rate.

From the cascade, we established the assumption that the rates of positive cervical cytology, colposcopy, and histopathology results in the lost cases at each stage are identical to the actual detection situation. Therefore, we could calculate the estimated number and rate of lost cases of pre-cancer and cancer to obtain a full picture of the number of pre-cancer and cancer cases in all women receiving screening as well as the extent of lost pre-cancer and cancer cases.

Data sources

According to the administrative district division and the implementation of cervical cancer screening, two to three provinces were randomly selected from eastern, western and internal areas of China, respectively, and two counties were randomly selected from each province as survey areas. A total of 16 counties from eight provinces (Hebei, Liaoning, Hubei, Hunan, Guangdong, Guizhou, Yunnan, and Shaanxi) were included in the study.

Women aged 35 to 64 years from the above rural areas volunteered for cervical cancer screening from January 1, 2014 to December 31, 2014. Women who had duplicate records in the system were excluded from the study. The following demographic characteristics and clinical data were collected, including medical history, gynecological examinations, cervical cytology examinations, colposcopy examinations, and histopathological examinations. The study outcomes were number and proportion of cervical cancer and pre-cancer cases.

All data in this study were collected in the National Rural Cervical Cancer Screening Project using an electronic system established in 2013. This real-time data-monitoring and error-correction system collects case-based data from all women who had received cervical cancer screening in the surveillance regions. In addition to the number of women screened and diagnosed, the system also collects processing data such as cytology, colposcopy, and histopathological examinations results. The system is equipped with quality control measures, such as logical verification. Data verification was carried out monthly and quarterly.

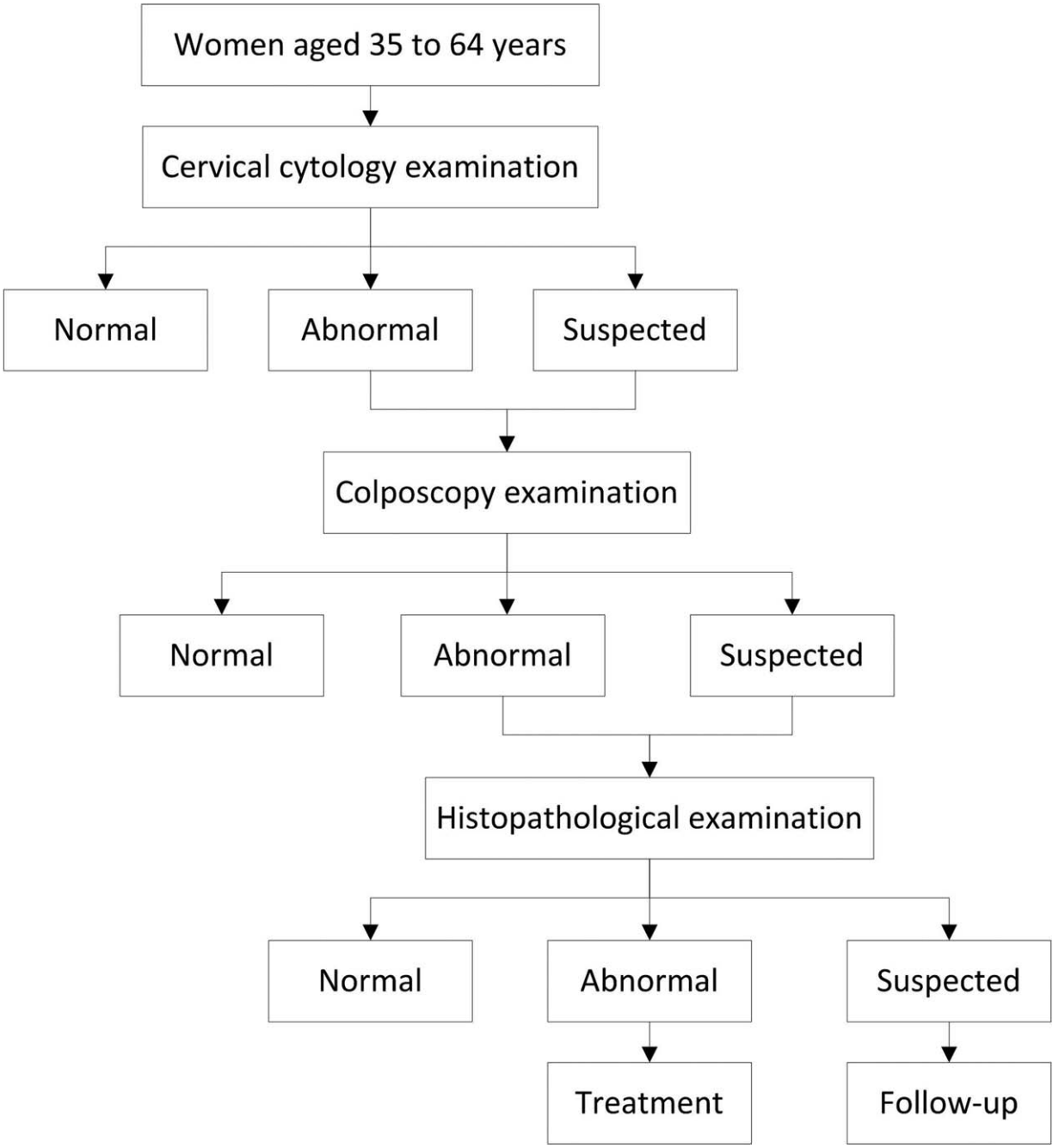

Figure 1: The process of cervical cancer screening in China.

Statistical analysis

All data were exported from the data collection system and imported into SPSS 13.0 (SPSS, Chicago, IL, USA) for statistical description and analysis. The socio-demographic data are described using the mean and standard deviation (SD) or median for continuous variables and frequencies (%) for categorical variables. The data describe the total loss to follow-up, the number of lost patients with positive cytology results, the actual number of cases of pre-cancer and cancer detected, the estimated number of lost patients with pre-cancer and cancer, and the estimated number of cases of pre-cancer and cancer detected. The proportions describe the crude loss rate (%), the loss rates of positive cytology results (%), the actual detection rates of pre-cancer and cancer (100,000), the estimated loss rates of pre-cancer and cancer (100,000), the estimated detection rates of pre-cancer and cancer (100,000), and the estimated loss numbers/estimated detection numbers of pre-cancer and cancer cases. As a person is a whole part, the result of the calculation took the integer part.

Results

General data

In this study, 145,194 cases were reported by the National Rural Cervical Cancer Surveillance Project, 117,522

Table 1: The preliminary cervical cancer screening cascade in rural Chinese women.

Stages	Steps	Indexes
Stage 1: cervical cytology	Step 1	Number of cases receiving cervical cytology
	Step 2	Number/proportion of cases with reported cervical cytology result
Result1		Number/proportion of cases who should receive colposcopy examination
Stage2: colposcopy	Step 3	Number/proportion of cases receiving colposcopy examination
	Step 4	Number/proportion of cases with reported colposcopy examination result
Result 2		Number/proportion of cases who should receive a histopathological examination
Stage 3: histopathological	Step 5	Number/proportion of cases receiving a histopathological examination
	Step 6	Number/proportion of cases with reported histopathological examination result
Result 3		Number/proportion of cases who had pre-cancer and cancer

(80.94%) of whom were aged between 35 and 64 years and had not undergone cervical cytology in the previous 3 years.

The mean age was 48.41 years (SD 7.78), and the range was 35 to 64 years. Overall, 2034 (1.7%) had a college degree and above, 5554 (4.7%) had a senior high school education, 40,423 (34.4%) had a junior high school education, and 69,511 (59.1%) had a primary school education. A total of 46,542 (39.60%) had reached menopause. The median numbers of pregnancies and deliveries were 3 (range 0–17) and 2 (range 0–10), respectively.

Number and rate of patient follow-ups in steps 1 to 6 and results 1 to 3

Cervical cytology results were reported for all 117,522 patients (100.00%) in this study, and TBS classification results reported for 116,333 (98.99%). Overall, 4830 (4.15%) patients had results that were above ASC or atypical glandular cells requiring colposcopy, and 3407 (70.54%) received this procedure. The results of colposcopy examinations were reported for 3275 patients (96.13%), and 1631 (49.80%) had abnormal colposcopy results necessitating further histopathological examination. The results of histopathological exams were reported for 1344 patients (82.40%); 301 (22.40%) were pre-cancer and 19 (1.41%) were cancer requiring further treatment [Figure 2]. Therefore, the pre-cancer and cancer detection rates were 256.12/100,000 and 16.16/100,000, respectively.

Women who received cervical cancer screening were divided into six age groups: 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, and 60 to 64 years. According to the established cervical cancer screening cascade, we calculated the number and proportion in each step and result [Table 2].

Number and rate of missing cases in steps 1 to 6

According to the cervical cancer screening data analysis, 3031 patients failed to follow-up on the whole screening process, and 1189, 1555, and 287 patients were lost at the cervical cytology, colposcopy, and histopathological screening stages, respectively. In addition, we computed the number lost to follow-up in the groups aged 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, and 60 to 64 years [Table 3 and Figure 3].

Number and rate of missed cervical cancer and pre-cancer screenings and reporting at each step

Of the 117,522 women in this study, 1189 (1.01%) lacked reports on the results of cervical cytology, 49 reported patients had abnormal cervical cytology results, and 24 had abnormal colposcopy results; pre-cancer was detected in five patients and no cancer was detected. A total of 1423 (29.46%) women should have undergone colposcopies but did not, and 709 women that did have colposcopies had abnormal results; 159 pre-cancers and ten cancers were detected. The results of 132 (3.87%) colposcopies were not reported, and when they were reported, 66 women had abnormal results; 15 pre-cancers and one cancer were detected. Overall, 287 (17.60%) women should have undergone histopathological examination but did not, and 64 pre-cancers and four cancers were detected.

Estimated cancer and pre-cancer detection rate

The numbers of women with pre-cancer or cancer, respectively, who did not receive examinations or whose results were not reported were 243 and 15. If there had been no failures of examination and reporting in the course of the screenings, the estimated cases of pre-cancer and cancer would have been 544 and 34, respectively, and the estimated detection rates of pre-cancer and cancer would have been 462.89/100,000 and 28.93/100,000, respectively.

Discussion

There is a gap between the estimated and the actual detection rates in the cervical cancer screening process. Some possible causes of this are poor technical abilities of local health care workers, missing data, diagnostic errors, and sub-standard quality control and data checks at each level. In this study, we focused on the failure to follow-up and report data during the screening process.

The detection rate of pre-cancer and cancer

The actual cervical cancer detection rate was 16.16/100,000 in 2014 according to the National Rural Cervical Cancer Surveillance Project. According to GLOBOCAN2012, the estimated crude incidence of cervical cancer in China was 9.4/100,000,[1] which is much lower than our study findings. The estimated crude incidence worldwide, in more-developed regions, and in

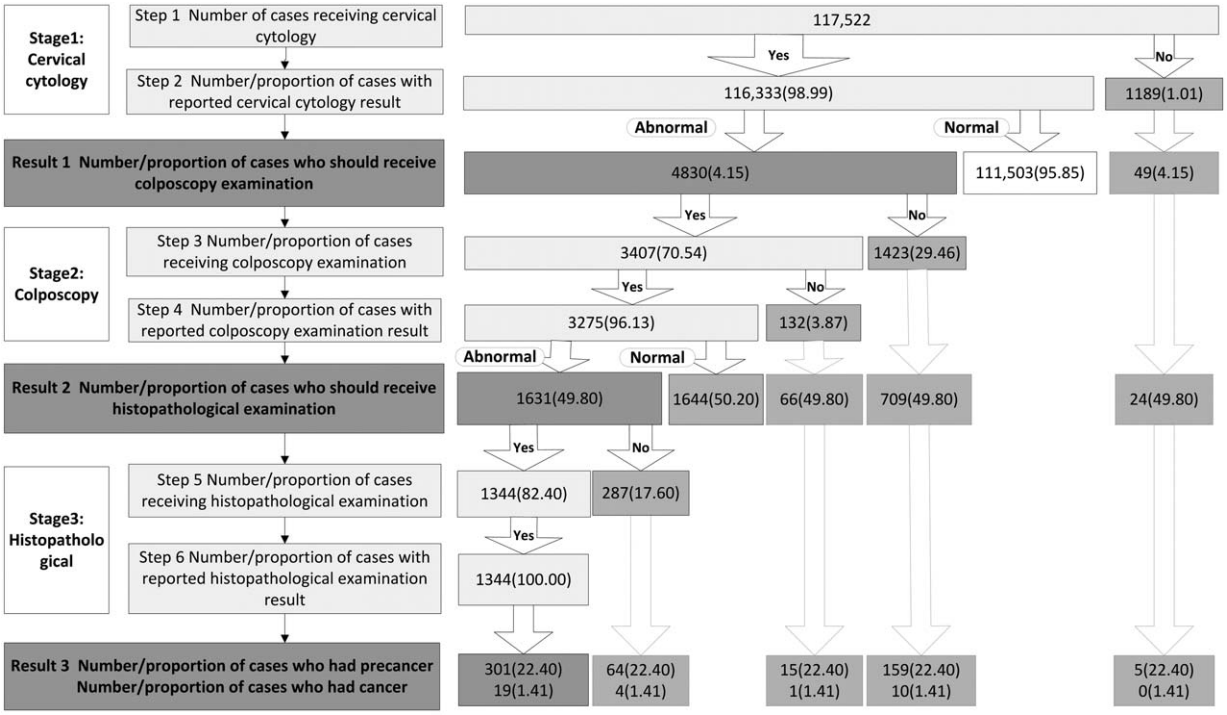

Figure 2: The cervical cancer screening cascade among rural Chinese women in 2014. Data are presented as *n* or *n* (%). Dotted lines indicate the estimated lost cases. From the cascade, we established the assumption that the rates of positive cervical cytology, colposcopy, and histopathology results in the lost cases at each stage are identical to the actual detection situation. As a person is a whole part, the result of the calculation took the integer part.

Table 2: The stages and results of cervical cancer screening cascade among different age of Chinese rural women in 2014.

Stages	Steps	Total population	Age (years)					
			35–39	40–44	45–49	50–54	55–59	60–64
Stage 1: cervical cytology	Step 1	117,522	17,178	23,266	25,632	22,923	16,080	12,443
	Step 2	116,333 (98.99)	16,991 (98.91)	23,012 (98.91)	25,363 (98.95)	22,700 (99.03)	15,952 (99.20)	12,315 (98.97)
Result 1		4830 (4.15)	628 (3.70)	923 (4.01)	1145 (4.51)	998 (4.40)	664 (4.16)	472 (3.83)
Stage 2: colposcopy	Step 3	3407 (70.54)	459 (73.09)	694 (75.19)	807 (70.48)	689 (69.04)	444 (66.87)	314 (66.53)
	Step 4	3275 (96.13)	451 (98.26)	675 (97.26)	782 (96.90)	657 (95.36)	419 (94.37)	291 (92.68)
Result 2		1631 (49.80)	252 (55.88)	390 (57.78)	405 (51.79)	312 (47.49)	165 (39.38)	107 (36.77)
Stage 3: histopathology	Step 5	1344 (82.40)	219 (86.90)	321 (82.31)	340 (83.95)	266 (85.26)	124 (75.15)	74 (69.16)
	Step 6	1344 (100.00)	219 (100.00)	321 (100.00)	340 (100.00)	266 (100.00)	124 (100.00)	74 (100.00)
Result 3	Pre-cancer	301 (22.40)	41 (18.72)	87 (27.10)	78 (22.94)	50 (18.80)	26 (20.97)	19 (25.68)
	Cancer	19 (1.41)	2 (0.91)	2 (0.62)	5 (1.47)	5 (1.88)	2 (1.61)	3 (4.05)

Data are presented as *n* or *n* (%).

less-developed regions was 15.1/100,000, 13.0/100,000, and 15.6/100,000, respectively. The results of our study of rural women receiving cervical screening are similar to findings from less-developed regions. The prevalence of cervical cancer reported in the China Health Statistical Yearbook was 13.3/100,000 in 2012,[15] a figure lower than reported here.

The actual cervical pre-cancer detection rate was 256.12/100,000 in 2014. According to data from the National Rural Cervical Cancer Screening Project, the cervical pre-cancer detection rates were 106.85/100,000 in 2012 and 119.26/100,000 in 2013,[16] much lower than reported here. The substantial differences in pre-cancer detection rates between 2013 and 2014 may be because the 2013 results were based on aggregate data, whereas the 2014 results were based on individual participants, and are thus more reliable.

There were differences in the estimated and actual detection rates of cervical cancer as a result of the failure to follow-up in every step. Assuming that cervical cancer and pre-cancer detection rates for women lost to follow-up were approximately equal to rates for women who were followed-up, 578 cases of cervical cancer and pre-cancer should have been detected, of which 258 cases of cancer and pre-cancer were lost to follow-up. That is, almost 44.64% of cancers and pre-cancers were not detected because of patient failure to follow-up with colposcopy and histopathological examinations. In addition, 169 of 258 (65.50%) cases of cancer and pre-cancer were not detected because of failure to follow-up with a colposcopy (step 3).

Table 3: The key indexes during the cervical cancer screening cascade among Chinese rural women in 2014.

Index	Total population	Age (years)					
		35–39	40–44	45–49	50–54	55–59	60–64
Total number lost to follow-up and crude loss rate	3031 (2.58)	397 (2.31)	571 (2.45)	697 (2.72)	610 (2.66)	414 (2.57)	342 (2.75)
Patients with positive cytology results lost and loss rate	1423 (29.46)	169 (26.91)	229 (24.81)	338 (29.52)	309 (30.96)	220 (33.13)	158 (33.47)
Actual detection number of pre-cancer and cancer and actual detection rate (100,000)	320 (272.29)	43 (250.32)	89 (382.53)	83 (323.81)	55 (239.93)	28 (174.13)	22 (176.81)
Estimated lost number of patients with pre-cancer and cancer and estimated loss rate (100,000)	258 (219.53)	24 (139.71)	72 (309.46)	62 (241.89)	42 (183.22)	30 (186.57)	28 (225.03)
Estimated detection number of pre-cancer and cancer and estimated detection rate (100,000)	578 (491.82)	67 (390.03)	161 (692.00)	145 (565.70)	97 (432.16)	58 (360.70)	50 (401.83)
Estimated loss number/estimated detection number of pre-cancer and cancer	44.64	35.82	44.72	42.76	43.30	51.72	56.00

Data are presented as *n* or *n* (%).

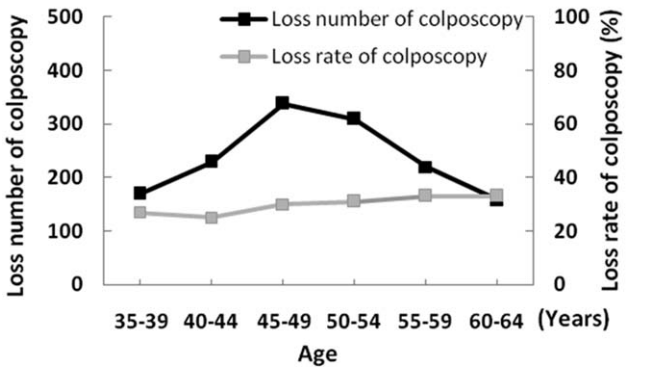

Figure 3: The loss number and rate of colposcopy examinations in different age groups.

Analysis of missing cases in the cascade

Losses existed in almost every step of the cervical cancer screening cascade. The most common loss was in step 3, failure to receive a colposcopy. Some 1423 (29.46%) women who should have undergone colposcopies did not. If these colposcopies had been performed, 159 pre-cancers and ten cancers would have been detected, accounting for 65% and 67%, respectively, of the cascade. In addition, 64 pre-cancers and four cancers would have been detected in the women who should have received colposcopies but did not, accounting for 25% and 27% of the cascade.

The key step is the colposcopy; this tends to be ignored, which results in a higher loss rate. Therefore, we should strengthen the follow-up for colposcopy to ensure the procedure is performed after histopathological examination [Figure 2].

The loss rate in the different age groups

The greatest estimated cancer and pre-cancer loss rate was in the 40 to 44 years age range. The loss rate of failure to receive a follow-up colposcopy after an abnormal cervical cytology result was greatest in the 60 to 64 years age range. This may be because of the physical limitations of aging and/or inadequate knowledge of the importance of colposcopy results. The smallest loss rate was in the 40 to 44 years age range. In addition, the prolonged wait time for the cervical cytology report makes follow-ups more difficult. Many women in the 40 to 44 years range had to migrate to other cities for work, increasing the difficulty of follow-up.

The actual detection rate and the estimated detection rate differed across these age groups. The difference between the actual detection rate and the estimated detection rate was greatest in the 40 to 44 years age range, which was characterized by a high detection rate. Therefore, the highest loss ratio and estimated detection rate were for the 40 to 44 years age range.

Many studies have identified possible positive and negative biomarkers for cervical pre-cancer, which could help to identify cancer earlier.[17-19] The biomarkers are more sensitive to increase the early detection rate and reduce the false negative rate. However, the examination of biomarkers is more expensive than screening by cervical cytology, but taking shorter to process. For these reasons, biomarkers are not yet used in nationwide screening and need further research to explore the reasonable framework. Fertility-sparing approaches play an important role in improving the quality of life of women with cervical cancer earlier.[20-22] Therefore, increase the early detection rate and reduce failing in follow-up rate are more important.

In recent years, artificial intelligence is widely used in disease diagnosis and screening, such as cervical cancer screening, which can more effectively enhance follow-up.[23,24] However, studies on the sensitivity and specificity of artificial intelligence should be done in the future.

Limitations

The calculations of the estimated cervical cancer and pre-cancer detection rates in this study were based on the assumption that cervical cancer and pre-cancer detection rate in women lost to follow-up was approximately equal to the rates for those who were followed-up. Further research is necessary to assess whether the incidence of cervical cancer was similar between women followed-up and those not followed-up.

The 16 counties included in this study have relatively low economic development compared with other counties in China. Therefore, they may not be representative of the economic situation in urban areas or in the whole country.

In conclusion, failure in examination and reporting is common in the course of cervical cancer screening and can be attributed not only to the level of screening skills but also to the quality of follow-up at each step. Loss of follow-up would reduce the detection rate of cervical cancer and precancerous lesions directly. In order to increase the detection rate of cervical cancer, cervical cancer screening staff should focus on increasing the rate of follow-up of those who are positive for cervical cancer screening (ie, those with positive cytology results), especially for an age range of 40 to 44 years.

Conflicts of interest

None.

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