Potential impact on cervical carcinoma-in-situ incidence after classifying CIN 2 as CIS under ICD 11

David Lu, Asia Chief Medical Officer, Swiss Re

Introduction

The concept of cervical cancer precursors and its terminology has evolved during the past decades. The use of mild to severe dysplasia and carcinoma-in-situ (CIS) to define cervical cancer precursors was started in 1950s [1], and the term cervical intraepithelial neoplasia (CIN) was introduced in 1968 [2], which is divided into grades 1, 2 and 3, and CIN 3 corresponded to both severe dysplasia and CIS. In the tenth version of International Classification of Diseases (ICD-10), CIN 3 is considered as comparable to CIS whether severe dysplasia is mentioned or not.

In the 1980s, the pathological changes associated with human papillomavirus (HPV) infection were increasingly recognized. This led to a modified CIN terminology [3] for histology which combined CIN 2 and 3 as high-grade CIN and considered to be true precursors of invasive cancer. In 1991, the two grades Bethesda system terminology[4,5] for cytology was proposed, while the high grade squamous intraepithelial lesion (HSIL) encompasses both CIN 2 and 3. The newly released ICD-11 reflected these developments and reclassify CIN 2 from benign neoplasm to CIS, same as CIN 3.

In most of Asia markets, CIS is covered under critical illness with partial payment. Classifying CIN 2 as CIS will increase the incidence of CIS and affect insurance risk assumption. This essay is trying to understand the magnitude of this impact.

Review

In 2014, Ting et al. did a systematic review [6] on the worldwide incidence of cervical lesions, which includes 54 studies from different countries. Within the 54 studies, only one from Norway recorded CIN 2 incidence independently, all others recorded combined CIN 2 and 3 incidence either as HSIL or as CIN2/3.

In Norway, CIN 2 is registered separately at national level since 1997. As cervical cancer screening coverage in Norway has held steady around 65–68% after 1995, CIN 2 data from Norway could be a good reference to observe the incidence, prevalence of CIN2 and its trends at a population level.

A recent published study from Norway [7] reviewed nation-wide data of CIN2, CIN3 from 1992 to 2016, and found both CIN 2 and CIN 3 showed steady increase during this period, while the age-standardised Incidence Rate (ASIR) of CIN2 increased by 4.7% per year, higher than the 1.6%

annual increase of CIN3. In 2016, the age-standardised incidence of CIN2 was 50.1/100,000, while CIN 3 was 171.0/100,000, means adding CIN 2 into the same category of CIN 3 will increase CIS incidence by 29.3% in Norway.

They also found CIN 2 is more prevalent in younger ages, with the highest incidence rate at age 22. A pooled analysis [8] of studies published from 1950 to 1993 showed that regression happened in 43% of CIN2. This supports that screening at younger ages may cause over-diagnosis without bring additional benefit in preventing cervical cancer.

Another interesting finding is that women born in 1996 had a fivefold higher IR for CIN2 than women born in 1970. It is thought this age group have not been vaccinated against HPV, but sexual lifestyle is more open, leading to higher exposure to sexually transmitted infections, including HPV.

Future impact in insurance industry

Reclassifying CIN 2 from benign to CIS will change the assumption on CIS incidence. In Norway, it will increase cervical CIS incidence for 29.3% in 2016.

The impact might be different in other countries / regions. A higher HPV vaccination rate helps minimize the impact, while higher screening rate, especially in younger ages, may exaggerate the impact, and vice versa. We have discussed with insurance doctors in Japan, they think the nearly zero HPV vaccination rate in Japan may result in increased incidence of cervical cancer, but not CIN 2 as screening rate in young age group is also very low.

It is very unlikely to exclude CIN 2 from CIS benefit without objections from medical professionals, public and regulators. Insurers should make individual assumption for each market based on its own affecting factors.

Reference:

1. Reagan, J.W., Seidermann, I.L., & Saracusa, Y. (1953) The cellular morphology of carcinoma in situ and dysplasia or atypical hyperplasia of the uterine cervix. Cancer, 6, 224-235.

2. Richart, R.M. (1968) Natural history of cervical intraepithelial neoplasia. Clin. Obstet. Gynecol., 5, 748-784.

3. Richart, R.M. (1990) A modified terminology for cervical intraepithelial neoplasia. Obstet. Gynecol., 75, 131-133.

4. National Cancer Institute Workshop. (1989) The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. JAMA, 262, 931-934.

5. National Cancer Institute Workshop. (1993) The Bethesda System for reporting cervical/vaginal cytologic diagnoses: revised after the second National Cancer Institute Workshop, April 29-30, 1991. Acta Cytol., 37, 115-124.

6. Ting, J., Rositch, A. F., Taylor, S. M., et al. (2014) Worldwide incidence of cervical lesions: a systematic review. Epidemiol. Infect., 1-17.

7. Orumaa, M., Leinonen, M. K., Campbell S., et al. (2019) Recent increase in incidence of cervical precancerous lesions in Norway: Nationwide study from 1992 to 2016. Int. J. Cancer. DOI: 10.1002/ijc.32195

8. Ostör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993 Apr;12(2):186-92.