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Expert Opinion



Towards the elimination of cervical cancer in Japan

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INTRODUCTION

Cervical cancer, caused by persistent infection with one or more high-risk human papillomavirus (HPV) genotype is highly preventable, and if diagnosed and treated early, it is also highly curable. However, despite having both the tools and the knowledge to prevent, diagnose and treat cervical cancer, in 2020, an estimated 12,785 new cases of and 4,213 deaths from cervical cancer occurred in Japan [1]. This is equivalent to an annual age-standardised incidence rate (ASIR) of 15.2 per 100,000 women using the World Standard Population, which is almost double that of other high-income countries in the Asia Pacific such as Australia (6.0 per 100,000), New Zealand (6.0 per 100,000), and the Republic of Korea (7.8 per 100,000) [1] and similar to or higher than some low- and middle-income countries (LMICs) in the region (Fig. 1).

Globally, there are almost 600,000 newly diagnosed cases of cervical cancer annually, with a disproportionate disease burden and death occurring in women of lower socio-economic classes, both within and across countries [2]. This prompted the Director-General of the World Health Organization (WHO), Dr. Tedros Adhanom Ghebreyesus, to issue a global call for action towards the elimination of cervical cancer as a public health problem in May 2018 [3]. In August 2020, despite the challenges of the coronavirus pandemic, the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem was

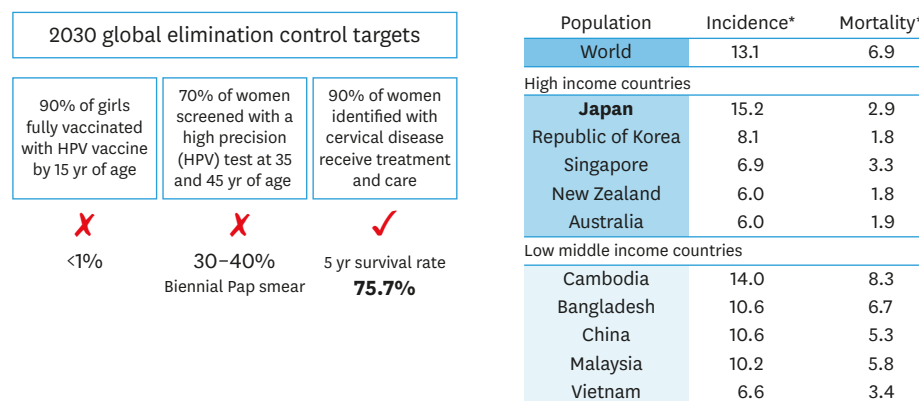


Fig. 1. Overview of cervical cancer control in Japan.
 *World-age standardized.

adopted by the World Health Assembly, which is comprised of 194 Member States, including Japan. Elimination is defined as a threshold of <4/100,000 women diagnosed with cervical cancer annually [3]. To achieve this goal by the end of the 21st century, the global strategy contains three pillars, each with their own associated targets that should be achieved by 2030: 1. Fully vaccinating 90% of girls against HPV by the age of 15 years; 2. Screening 70% of women with a high-performance (HPV) test by the age of 35 years and once again by the age of 45 years; and 3. Treating and managing 90% of women identified with cervical disease [3].

At present, Japan only achieves the third global elimination goal (**Fig. 1**) which raises concerns over the effectiveness of current cervical cancer control measures. Why has this occurred and what needs to be done for Japan to achieve elimination of cervical cancer as a public health problem by the end of the century?

TARGET 1: HPV VACCINATION

The bivalent HPV vaccine was licenced in Japan in October 2009 and the quadrivalent vaccine in July 2011 [4]. From December 2010, special funding was provided for girls aged 12–16 years whereby the national government paid 50% of the vaccine cost, if local government also paid 50%. Uptake was high with three-dose coverage reaching over 70% [4]. From April 1, 2013, both HPV vaccines were included into the Japanese national immunization program (NIP) and were provided free for girls aged 12–16 years. However, soon after the announcement that the vaccine would be included in the national program, unconfirmed reports of adverse events following immunization began to appear in the media and emotive images of girls having difficulty walking or controlling their movements were broadcast extensively in the media [5]. In June 2013, only two months after inclusion in the NIP, the Ministry of Health, Labour, and Welfare announced that, although the vaccine would remain in the NIP and would be free for 12–16-year-old girls, all proactive recommendations for it would be suspended. Over the past eight years, several large-scale epidemiological studies conducted in Japan have shown that the HPV vaccine is effective against both HPV infection [6] and precancerous disease [7,8], and safe [9]. However, as of May 2021, the situation remains unchanged, with the vaccine still available for free to the target age groups but not being proactively recommended. After the suspension of proactive recommendations, vaccination coverage decreased sharply, from >70% to <1% and coverage has remained at less than 1% to date [4,10].

TARGET 2: CERVICAL SCREENING

Cytology-based cervical screening began in Japan in the late 1950s. Before 1998, the national government was responsible for cancer control activities [11]. From 1998, due to economic reasons, the financial burden of cancer control was moved to prefectural governments. As a result, the Health and Medical Services for the Elderly Act, transferred responsibility from the central level to prefectural and municipal levels [11,12]. Preventative medicine is not included in the National Health Insurance System, so screening activity and vaccination are funded directly by each municipality [13]. Japanese women have multiple opportunities to be screened for cervical cancer, these include: screening organized by municipalities (free or for a small charge); individual screening at a gynecologist's clinic (around 70% of fee covered by the national health insurance system); screening as part of a workplace health check-up (cervical

screening is an add-on option for a small fee) or screening as part of a comprehensive health check-up (ningen-dock, not covered by national health insurance but may be subsidized by the workplace) [11,13] However, cervical screening is predominantly opportunistic, and since there is no national screening program, accurate estimates of coverage are difficult to ascertain. Data from the Comprehensive Survey of Living Conditions, which randomly samples 290,000 households from 5,410 districts nationwide, is normally cited for biennial cervical screening coverage. Data from the 2019 survey suggests that only 43% of women aged between 20–69 years underwent cervical screening in the past 2 years [14,15].

TARGET 3: TREATMENT AND MANAGEMENT OF CERVICAL DISEASE

Due to the absence of a systematic monitoring system, treatment rates for cervical cancer are also difficult to estimate in Japan. However, while the ASIR of cervical cancer in Japan is higher than the global ASIR, as well as many LMICs in the Asia Pacific region [1], universal access to health care means mortality rates are much lower: 8.3 and 6.7 per 100,000 in Cambodia and Bangladesh, respectively, compared to 2.9 per 100,000 in Japan (Fig. 1) [1]. Five-year survival rates for cervical cancer are also comparable or better than other high-income countries: 75.7% in Japan [16], compared to 73.5%, 66.0%, and 61.4% in Australia [17], the US [18] and England [19] respectively, suggesting women who do need follow-up are adequately treated and managed.

ACHIEVING ELIMINATION OF CERVICAL CANCER AS A PUBLIC HEALTH PROBLEM IN JAPAN- WHAT SHOULD CHANGE?

Because of the wide-ranging influence of the Internet and social media, suspension of proactive recommendations for the HPV vaccine not only resulted in a decrease in vaccine uptake in Japan, but also likely contributed to a decrease in coverage in other countries such as Denmark and Ireland [20,21]. However, despite the negative media coverage, the Danish and Irish governments and medical professionals continued to proactively promote HPV vaccination and as a result, uptake recovered to previous levels [20,22]. One Japanese study investigating correlates of HPV vaccine acceptance in mothers with adolescent daughters found that recommendation from a physician or the local health board were strong motivators for mothers to get their daughter vaccinated [23]. Therefore, immediate resumption of proactive recommendations for the HPV vaccine by the Ministry of Health, Labour and Welfare is essential to increase public confidence in the HPV vaccine and increase coverage. However, vaccination alone is not enough, a recent modelling study found that even if coverage could recover to previous rates, even using the 9 valent vaccine, Japan would still not achieve the elimination threshold of >4 cases per 100,000 women by the end of the century. Increase in screening coverage is also essential [14].

Screening guidelines are developed by the Japanese Advisory Committee on Cancer Screening and implemented by local government [12]. Currently, biennial cervical cancer screening using the Pap smear with reflex HPV testing for atypical squamous cells of undetermined significance in women aged >20 years is recommended [13]. The guidelines

were updated in 2020 and now also recommend 5 yearly physician-led primary HPV testing [24]. As well as the extended screening intervals, one advantage of HPV testing is that it can also be performed on self-collected samples with similar accuracy to a clinician led sample [25]. HPV self-sampling has been found to be highly acceptable by women across a range of cultural settings, including Japan [26,27]. Empowering women to take their own samples may be one way to increase cervical screening coverage in Japan.

CONCLUSION

Despite having the tools, knowledge and wealth to prevent, diagnose and treat cervical cancer, Japan is not on track to eliminate cervical cancer as a public health problem by the end of the century. To rectify this, high level political support is also necessary. During his call to eliminate cervical cancer, Dr. Tedros Adhanom Ghebreyesus declared ‘When we have the weapons at hand, failure should not be an option’. Sadly, the present lack of resolution by the Japanese government, particularly towards the HPV vaccine, will result in a high number of preventable cervical cancers. The Japanese government must act now so that failure is not an option.

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