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Original Research

Are we on path to eliminate cervical cancer? An analysis of National Cancer Registry Data from 2005 to 2019

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Abstract

Introduction: Cervical cancer is the fourth most common cancer affecting women worldwide. The primary cause for cervical cancer is the persistent or chronic infection with one or more of high-risk oncogenic types of human papilloma virus (HPV). The risk factors for cervical cancer are classified as co-factors favouring acquisition of HPV infection and its persistence. Most cervical cancers can be prevented by risk factor reduction, early detection and treatment at precancerous stage.

Objectives: To analyse the trends of incidence rates, age at diagnosis and histological types of cervical cancer in Sri Lanka from 2005 to 2019

Methods: Data of the National Cancer Registry, Sri Lanka (NCR-SL) of the National Cancer Control Programme (NCCP), Ministry of Health, Sri Lanka were used to calculate the incidence trends from 2005 to 2019 by age at diagnosis and histological type. Joinpoint regression analysis was performed to obtain the average annual percentage change (AAPC).

Results: The crude incidence rate (CR) of the cervical cancer in Sri Lanka showed a significant increasing trend with an AAPC of 1.7% (95% CI: 0.5, 2.9). The age at diagnosis for the majority was between 45-64 years. A significant increasing trend of the age specific incidence was observed in the 65-74-year age group with the AAPC being 1.4% (95% CI: 0.0, 2.8). The Age standardized rate (ASR) showed a declining trend which was not statistically significant. Among the histology types, the majority was squamous cell carcinomas but over the study period it showed a declining trend and adenocarcinomas showed an increasing trend. Both the trends were statistically significant. Other histology types showed an insignificant increasing trend.

Conclusions & Recommendations: Sri Lanka shows a significant increasing trend in CR and a declining non-significant trend in ASR in cervical cancer during 2005-2019. Further, the peak age group of diagnosis was 45-64 years, with an increasing trend in incidence in the 65-74-year age group. Squamous cell type cancer showed a significant declining trend in contrast to a significant increasing trend for adenocarcinoma type. Preventive strategies for cervical cancer should be further strengthen with special emphasis on HPV vaccination, screening and increasing awareness among public.

Key words: *cervical cancer, human papilloma virus, age standardized rate, crude incidence rate, average annual percentage change*

Introduction

Cervical cancer is the fourth most common cancer affecting women worldwide, after breast, colorectal, and lung cancers (1). Worldwide in year 2020, there were an estimated 604 127 new cervical cancer cases, which accounted for 6.5% of all cancers among females and 341 831 deaths (1). The ASR for cervical cancer in the world for the year 2020 was 13.3 per 100 000 populations while that for the Southeast Asian region was 17.8 per 100 000 (1). The ASR for cervical cancer for year 2019 in Sri Lanka was 8.3 per 100 000 populations (2). In the same year, it was the third commonest cancer among females following breast and thyroid cancer in Sri Lanka (2). The primary cause for cervical cancer is the persistent or chronic infection with one or more high risk oncogenic types of HPV (3). The risk factors for cervical cancer are classified as co-factors favouring acquisition of HPV infection and co-factors favouring persistence of HPV infection (3). The co-factors favouring acquisition of HPV infection are early sexual debut, multiple sexual partners, poor socioeconomic status (poor nutrition/poor hygiene), immunosuppression, high parity and young age at first childbirth. The co-factors favouring persistence of HPV infection are HPV type, immune status of the person, co-infection with other sexually transmitted infections (STI), high parity, young age at first childbirth, tobacco smoking, poor socio-economic status and long-term use of oral contraceptive pills (3). Most of the HPV infections are transient and resolve spontaneously with only a few of them persisting and even fewer progressing to precancerous lesions which will take 10-20 years to progress into an invasive cancer (3). Therefore, most cervical cancers can be prevented by risk factor reduction, early detection and treatment at precancerous level.

The World Health Organization (WHO) has set global targets to be met by 2030 to eliminate cervical cancer. These targets known as '90-70-90', where 90% of girls are vaccinated against HPV by the age of 15 years, 70% of women are screened with a high-performance test by 35 and 45 years and 90% of women diagnosed with cervical cancer receive treatment are to be met by countries (4). Sri Lanka is on the path of eliminating cervical cancer, by reaching the WHO target of reducing the incidence of cervical cancer to below four per 100 000 women. In 2016, Sri Lanka initiated the HPV vaccination programme through the Expanded Programme of Immunization (EPI) to schoolgirls between the age 9-12 years. Activities such as screening of cervical cancer using Papanicolaou smear test (Pap smear), HPV DNA testing, early detection and treatment, palliative care for invasive cancers are taking place covering the key three pillars of the WHO Global Strategy for Eliminating Cervical Cancer (4). The objective of this study was to analyse the trends of incidence rates, age at diagnosis and histological types of cervical cancer in Sri Lanka from 2005 to 2019 using NCR-SL data.

Methods

Data form the NCR-SL of NCCP, Ministry of Health, Sri Lanka were selected to calculate the incidence and trends of cervical cancer in Sri Lanka for the period 2005-2019 (2). The NCR-SL is a population-based cancer registry, where data from several points being captured including pathology laboratories, cancer treatment centres and death registrars. International Classification of Diseases for Oncology (ICD-O) (version 3) was used to classify the cancer cases and histology types. In this study, the code for cervical cancer is C53. The age groups were divided as 0-44 years, 45-54 years, 55-64 years, 65-74 years and above 75 years as there were less cases in the early stage of life. The two major histology types of cervical cancer, squamous cell carcinoma and adeno carcinoma were selected to identify the trend of histology type. The ICD-O codes for squamous cell carcinoma used for this study were 8070, 8071, 8072 and 8076; and 8140 for adenocarcinoma. Population data were sourced from Department of Census & Statistics of Sri Lanka. The ASR of cervical cancer per 100 000 population was calculated for each year using WHO age standardized populations (5).

In this study, CR, age specific incidence rate (from <44 to 75+, within 10-year groups) and ASR were calculated. Trends of CR, ASR, age specific incidence rate and histology were analysed using

joinpoint regression, which fitted to the best model on a logarithmic scale to the trends in annual rates. Joinpoint Software (version 4.9.0.0) of the US National Cancer Institute, Surveillance Research Program was used for the analysis (6). Best fit of number of joinpoints was selected after reviewing different charts with different numbers of joinpoints retrieved from the software. No maximum number of joinpoints were specified as the analysis included only 15 years of data. For each trend, annual percent change (APC), a measurement of trends in cancer rates over time and AAPC, a summary measure of the trend over a pre-specified fixed interval were calculated (6). Changes in direction or in the rate of increase or decrease were calculated with p values, and $p<0.05$ was considered as statistically significant.

Results

Data of a total of 14 465 cervical cancer patients diagnosed over the 15-year study period were included in the study. The ASR and CR of the cervical cancer in Sri Lanka from year 2005 to 2019 are shown in Figure 1. The ASR shows a slight declining trend where its value was 8.9 per 100 000 females in year 2005 and 8.3 per 100 000 females in year 2019 (2, 7). The CR on the other hand shows a slight increasing trend from year 2005-2019, where the value for 2005 was 8.9 per 100 000 females and 9.9 per 100 000 females in 2019 (2, 7). In the joinpoint regression analysis, the zero joinpoints model was the best fit model for both CR and ASR (Figure 2). The CR showed an overall significant increasing trend with an AAPC of 1.7% (95% CI: 0.5, 2.9; $p<0.05$), while the AAPC of ASR shows a decline at -0.3% (95% CI: -1.5, 1.0; $p>0.05$), which was not statistically significant (Table 1).

When considering the age groups of cervical cancer patients during 2005-2019, the highest (30.2%) were in the age group of 55-64 years, followed by 27.2% in the 45-54-year group and 21.6% in the 65-74-year age group. The incidence in the age group 0-44 years 11.9% and only nine percent of the total cervical cancers were diagnosed at the age group of 75 years and above. In the joinpoint regression analysis, the age-specific incidence trend of the age group 0-44 years had a one joinpoint model while all the other age groups had zero joinpoint models. Notably, age group 0-44 years shows two incidence trends. From 2005 to 2007 it has a declining trend with an APC of -15.1% and an increasing trend from 2007-2019 with an APC of 1.5% (Table 1). However, AAPC shows an overall declining trend of -1.1% (95% CI: -4.4, 2.4) which was not statistically significant. Declining incidence trends were seen in both age groups 45-54 years and 55-64 years with an AAPC of -0.5% (95% CI: -1.7, 0.8) and -1.4% (95% CI: -3.2, 0.4) respectively and none of the above trends were statistically significant. It is noteworthy that age group 65-74 years showed an increasing incidence trend with an AAPC of 1.4% (95% CI: 0.0, 2.8) which was statistically significant (p=0.00). An increasing incidence trend was also observed in the age group of above 75 years with an AAPC of 0.6% (95% CI: -1.0, 2.2) but was not statistically significant. Figure 3 shows the graphs of joinpoint analysis of trends in age specific incidence rate of cervical cancer in Sri Lanka from year 2005 to 2019.

The histology type among cervical cancer patients diagnosed during the study period was similar to the global pattern (3). Around 70% were squamous carcinomas while 20% were adenocarcinomas. Trends in all histology types of cervical cancer show a zero joinpoint model. Squamous cell carcinoma shows a significant downward trend with an APC of -0.8% (95% CI: -1.5, -0.1). However, a noteworthy observation was adenocarcinoma type showing a significant increasing trend with an APC of 3.4% (95% CI: 0.6, 6.3) and the other histology types showed statistically insignificant increasing trend with an APC of 3.4% (95% CI: -0.3, 7.3) (Table 1). Figure 4 shows the graphs of joinpoint analysis of trends in histology types of cervical cancer in Sri Lanka from year 2005 to 2019.

Figure 1: Age standardized rate (ASR) and crude rate (CR) of cervical cancer in Sri Lanka, 2005-2019

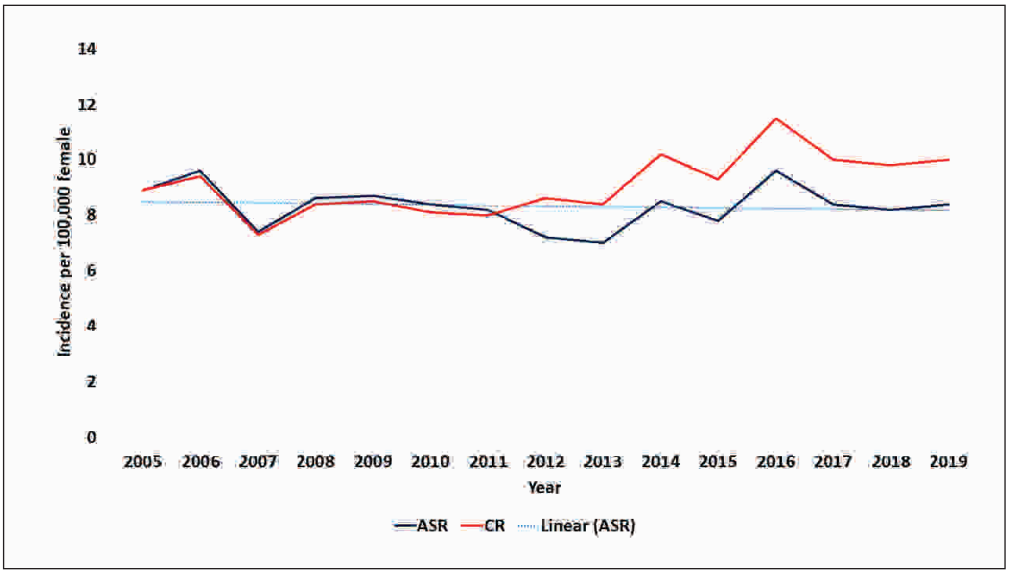

Figure 2: Graphs of joinpoint analysis of trends in crude rates (CR) and age standardized rates (ASR) for cervical cancer in Sri Lanka, 2005-2019

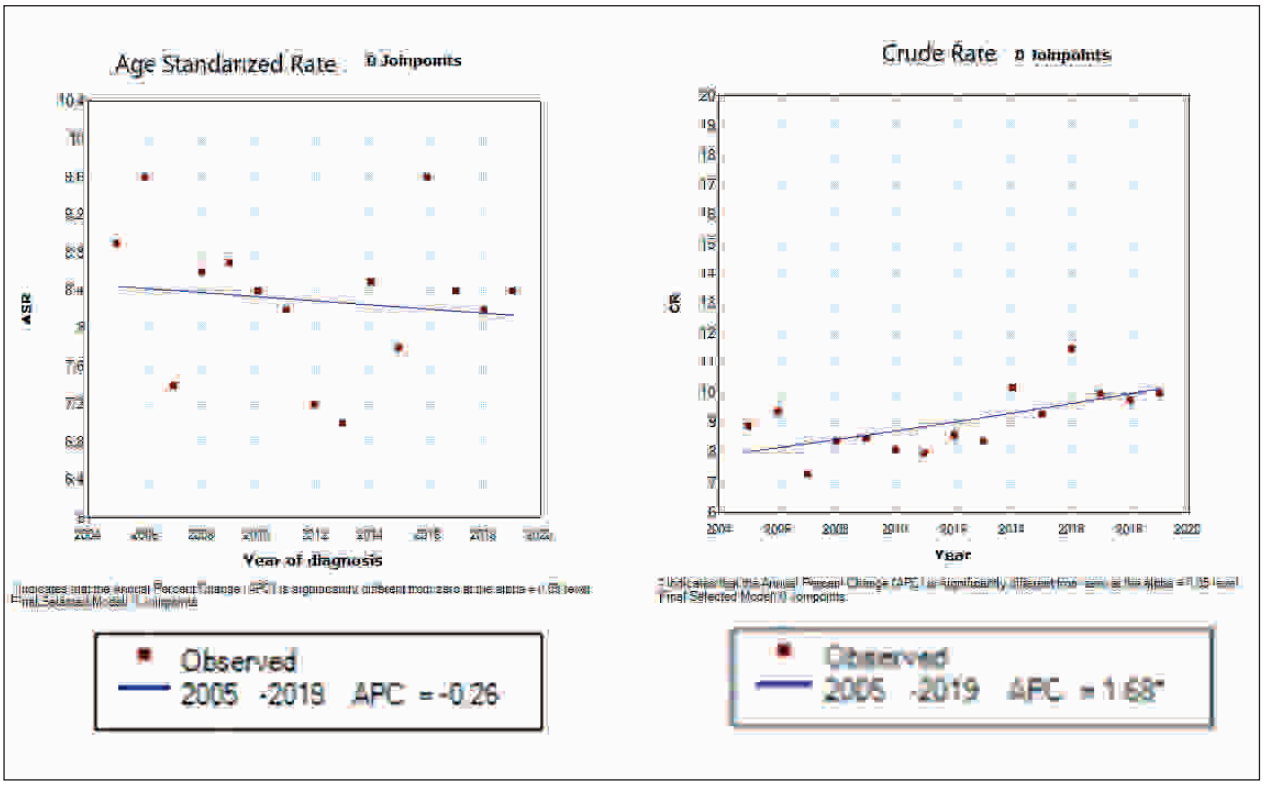

Figure 3: Graphs of joinpoint analysis of trends in age specific incidence rate (ASR) of cervical cancer in Sri Lanka, 2005-2019

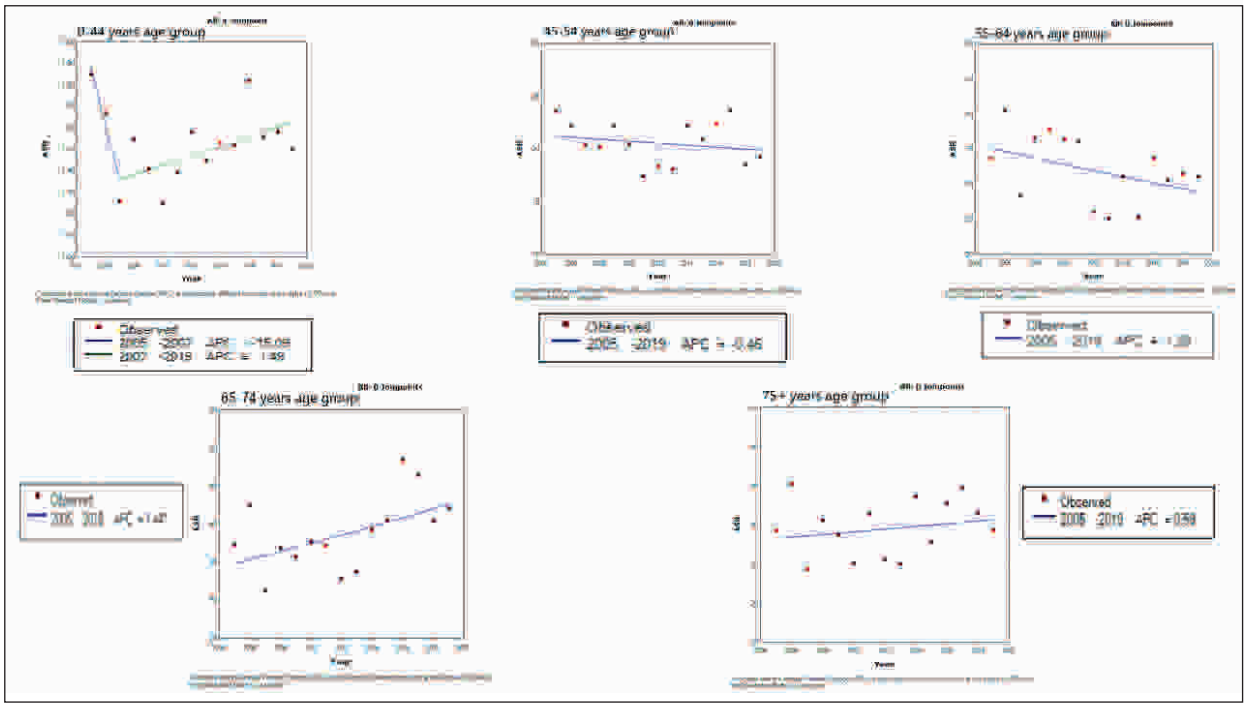

Figure 4: Graphs of joinpoint analysis of trends in histology types of cervical cancer in Sri Lanka from year 2005 to 2019

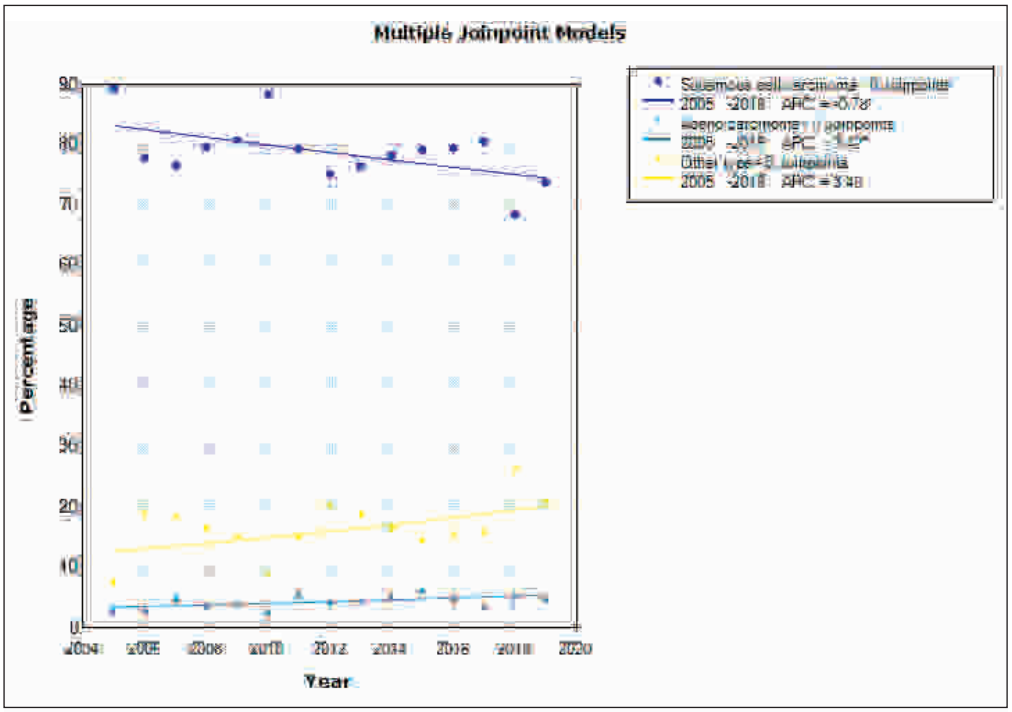

Table 1: Trends in crude rate, age standardized rate, age specific incidence rate and histology type for cervical cancer in Sri Lanka, 2005-2019

Rate	Year	APC (95% CI)	AAPC (95% CI)	p
Crude incidence rate	2005-2019	*1.7 (0.5, 2.9)	*1.7 (0.5, 2.9)	<0.01
Age standardized rate	2005-2019	-0.3 (-1.5, 1.0)	-0.3 (-1.5, 1.0)	0.6
Age specific incidence rate				
• 0-44 years	2005-2007	-15.1 (-34.6, 10.2)		
	2007-2019	1.5 (-0.1, 3.1)	-1.1 (-4.4, 2.4)	0.5
• 45-54 years	2005-2019	-0.5 (-1.7, 0.8)	-0.5 (-1.7, 0.8)	0.4
• 55-64 years	2005-2019	-1.4 (-3.2, 0.4)	-1.4 (-3.2, 0.4)	0.1
• 65-74 years	2005-2019	*1.4 (0.0, 2.8)	*1.4 (0.0, 2.8)	<0.01
• Above 75 years	2005-2019	0.6 (-1.0, 2.2)	0.6 (-1.0, 2.2)	0.4
Histology type				
• Squamous cell carcinoma	2005-2019	*-0.8 (-1.5, -0.1)	*-0.8 (-1.5, -0.1)	0.035
• Adeno carcinoma	2005-2019	*3.4 (0.6, 6.3)	*3.4 (0.6, 6.3)	0.021
• Other histology types	2005-2019	3.4 (-0.3, 7.3)	3.4 (-0.3, 7.3)	0.071

APC=annual percent change; 95% CI=95% confidence interval; AAPC=average annual percent change

*APC and AAPC are significantly different from zero (p<0.05)

Discussion

The ASR of cervical cancer in Sri Lanka from 2005 to 2019 has an insignificant decreasing trend (AAPC=-0.3%; p>0.05) but this decrease was not statistically significant. This finding is similar to most of the countries in the European and American region and Asian region like Singapore, Japan, Philippines and India (8). This decreasing trend of ASR in Sri Lanka could be due to improvement of nutrition, socio-economic status, proper treatment of co-infections with other sexually transmitted infections, having a national condom promotion programme targeting high risk groups, and cervical cytology screening targeting 35 and 45 year old cohorts, despite these improvements a substantial decline of incidence of cervical cancer was not seen in Sri Lanka as the declining trend of ASR did not gain statistical significance and on top of that having a significant increasing trend in CR of cervical cancer in Sri Lanka over the years from 2005 to 2019 (AAPC=1.7%), should be a concern to policy makers and clinicians. Similar pattern of increasing CR of cervical cancer has been observed in China, Zimbabwe, Uganda, Netherland and some countries of Central and Eastern Europe (8-10). This increase in the CR in Sri Lanka could be due to the growing prevalence of high-risk HPV and lack of screening programme using high performance test for early detection of pre-cancerous lesions (9).

The CR of cervical cancer in Sri Lanka could be reduced in the future due to the HPV vaccination programme for 9-12-year age female cohort. The best indicator to evaluate the cancer burden in a country is the CR as ASR is calculated using the world standardized population. Therefore, the current situation of the cervical cancer in Sri Lanka should be described using the CR, which suggests an increase in cervical cancer burden within the country.

The age at diagnosis was 45-64 years in most of the cases during the study period which was closer to India (55-59 years) and China (49-54 years) (9, 11). The age at diagnosis was much less in United States of America (47-48 years) (11). This finding could be

influenced by the population structure of Sri Lanka, where the population is getting older and could also be due to the inefficiencies in screening and access to early treatment. In Sri Lanka the Pap smear screening for cervical cancer was introduced in 1996 for females above 35 years and screening of cohorts of 35 and 45 years was commenced in year 2007 (12). Therefore, females born in the age cohort of 1950 or 1960 would not have been covered by the screening programmes which leaves them at an increase in risk of diagnosing with cervical cancer in their later stages of life. These trends would be changed in future in Sri Lanka with the HPV vaccination programme and routine screening of 35- and 45-year age cohorts.

The joinpoint analysis showed an increasing trend in the age specific incidence among the 65-74 years age group from 2005 to 2019, which was statistically significant. Similar pattern was observed in India and Singapore among the age group 50-74 years (1971-1993) (13). However, Finland, France and Italy showed a decreasing incidence trend in the age group 50-74 years (13). This increasing trend in Sri Lanka could well be due to the age cohort effect where the age cohorts of 1950 and 1960 had not been covered by the screening programme in Sri Lanka (12). It needs to be mentioned that the impact of vaccination against HPV has not yet had a measurable impact as the age cohort who received the vaccination has not yet entered the age category of screening for the cervical cancer.

Squamous cell carcinoma was the leading histological type (>70%) in the cervical cancer during 2005 to 2019 in Sri Lanka. This finding was similar to the global findings as globally among the cervical cancers almost 90% are in the histological type of squamous cell carcinoma (3). When considering the trends of the histological types, squamous cell carcinoma shows a significant decreasing trend (APC=-0.8%) while the adenocarcinoma (APC=3.4%) showed significant increasing trend and other histological types (APC=3.4%) showed an insignificant increasing trend over the years 2005 to 2019. A similar pattern was observed in the cervical cancer trends in United States, where squamous cell carcinoma has an insignificant declining trend (APC=-9.2%) from year 2001-2007, while adenocarcinoma (APC=4.2%) from year 1981-1998 and other histological types (APC=16.9%) from year 2001-2005 show an insignificant upward trend (14). Difference in the statistical significance in trends of histological types in two studies might me caused by the difference in total study time period and difference in study time windows. Several studies have attributed the increasing incidence of adenocarcinomas to an increase in the detection of lesions that were previously undiagnosed or were not categorized as adenocarcinomas (15-17). Other studies suggest that cytology-based screening may be more effective for squamous cell cervical cancer screening than for adenocarcinoma screening (18-20).

There are few limitations to the current study. The data of the current study was dependent on NCR-SL reporting. Although the NCCP has made significant efforts to ensure the completeness and accuracy of data, there may be differences in cancer incidence reporting due to duplication of the entries. Moreover, NCR-SL data on cervical cancer staging were incomplete and mortality data was not available and could not be analysed.

Conclusions & Recommendations

Main findings of this study on cervical cancer include the following: CR has a significant increasing trend and ASR a declining trend which is not statistically significant; the majority are diagnosed among the age group 45-64 years, while age specific incidence in the age group 65-74 years shows a significant increasing trend; and squamous cell carcinoma shows a significant declining trend, adenocarcinoma a significant increasing trend, and other histology types an insignificant increasing trend.

Preventive strategies for cervical cancer should be strengthen with continuation of HPV vaccination with a high coverage and shifting to a high-performance screening test (HPV DNA test) for HPV for early detection of precancerous lesions to prevent invasive cervical cancer. The health seeking

behaviour of women should be improved to increase coverage of screening at WWC and a proper referral pathway should be established for women with precancerous lesions to prevent loss to follow up. In future, trend analysis should be carried out once in five years to find out the effectiveness of the preventive strategies adopted for cervical cancer in Sri Lanka. Further, more research on survival rates, mortality rates, cervical cancer staging at diagnosis and prediction of crude rates in future will shed more light to identifying the direction of the strategies opted for elimination of cervical cancer in Sri Lanka.

Public Health Implications

- This trend analysis indicates the need of implementing the strategies identified in the National Strategic Plan (2020-2024) in cancer control and prevention to reduce risk factors, promote early detection of cervical cancer in Sri Lanka and women diagnosed with invasive cancer are offered the best current treatment options available to achieve the WHO of 2030 to eliminate the cervical cancer as a public health problem.

Author Declarations

Competing interests: Author declares that there is no conflict of interest.

Ethics approval and consent to participate: The article was written using the secondary data from the NCR-SL. Ethical approval for NCR-SL was obtained from the Ethics Review Committee of Faculty of Medicine, University of Colombo on 22.11.2010 (EC-10-106).

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Author contributions: All authors planned the study. AS and JV extracted the data, SN and TW compiled and analysed the data. AS wrote the article. All authors proofread the article.

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