

Cervical cancer in Brunei Darussalam

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INTRODUCTION Cervical cancer caused by the human papilloma virus (HPV) is a common cancer in women. There is no published data on the recent incidence of cervical dysplasia, cervical cancer and genital warts caused by the different types of HPVs in Brunei Darussalam.

METHODS A cross-sectional, retrospective study was conducted utilising data from patients diagnosed with cervical cancer during the period 2005–2009 in Brunei Darussalam. The varying incidences of different types of cervical lesions among various ethnic and age groups, and in the overall population, were determined.

RESULTS The mean age-standardised incidence of invasive cervical cancer during the five-year period was 24.9 per 100,000 women per year (95% confidence interval [CI] 21.7, 28.1). Age-specific invasive cervical cancer incidence peaked in the age group 45–59 years. Chinese females tended to have a higher incidence of invasive cervical cancer (28.2 per 100,000 women per year; 95% CI 17.8, 38.7) than Malay females (20.6 per 100,000 women per year; 95% CI 17.1, 24.2), while other ethnic groups in Brunei Darussalam had a significantly lower incidence (6.5 per 100,000 women per year; 95% CI 3.0, 10.0).

CONCLUSION The results suggest that Brunei Darussalam has a relatively higher incidence of cervical cancer compared to its neighbouring countries. The findings support the need for more comprehensive screening, public education programmes and vaccination against HPV in the country.

Keywords: Brunei Darussalam, cancer epidemiology, cervical cancer, human papilloma virus
Singapore Med J 2012; 53(9): 604–607

INTRODUCTION

Cervical cancer is the second most frequent cancer in women and a rare consequence of infection with the human papilloma virus (HPV).^(1,2) In a worldwide estimate made in 2008, the age-standardised incidence rate (ASR) of cervical cancer and its associated mortality were 15.3 and 7.8 per 100,000 women per year, respectively.⁽²⁾ There are more than 100 strains or types of HPV,⁽³⁾ with HPV 16 and 18 being responsible for 70.9% of invasive cervical cancer cases worldwide.⁽²⁾ Among the other clinical manifestations of HPV infections are cutaneous warts, epidermodysplasia veruciformis, cervical dysplasia, vulvular and penile cancers, dysplasia, hyperplasia, and cancers of the oropharyngeal and respiratory tracts and eyes.⁽⁴⁾ Each of these may be associated with particular HPV types.^(3,4) HPV is most commonly transmitted through sexual contact. Therefore, its prevalence is high among sexually active persons with multiple partners. Co-factors that predispose to malignancy after HPV infection include immunosuppression, smoking, infection with other sexually transmitted diseases, and host genetic factors such as mutations in tumour suppressor genes.

HPV has a double-stranded circular DNA genome enclosed in a non-enveloped icosahedral capsid composed of major (L1) and minor (L2) capsid proteins.⁽³⁾ The HPV genome is approximately 8,000 base pairs long, with coding information in one strand, and the molecular basis for HPV infection-induced carcinogenesis is largely established.⁽⁵⁾ Currently, there is no

published data on the recent incidence or prevalence of the different forms of HPV-induced cancers and precancerous lesions, or the common strains of HPV that cause HPV-induced cancer in Brunei Darussalam. In a cytological screening of 44% of the country's female population aged > 15 years in 1985–1989, cervical cancer was detected in 0.28% of the screened population.⁽⁶⁾ The incidence rate of cervical cancer is estimated to have increased from approximately 12.1 in 2002 to 17.0 per 100,000 women per year in 2006 in Brunei Darussalam.⁽⁷⁾ There is presently no public education or national vaccination programme for HPV-induced cervical cancer in the country; only an incomplete Pap smear screening programme exists. The present study investigated in detail the incidence rates of different types of cervical cancers based on data from the Oncology Clinic of the Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital during the period 2005–2009.

In 2006, an effective quadrivalent vaccine, Gardasil® (Merck, Whitehouse Station, NJ, USA), which protects against the four HPV types (6, 11, 16, 18) that are responsible for 70% of cervical cancers and 90% of genital warts, became available.⁽⁸⁾ In 2007, Cervarix® (Glaxo-Smith-Kline, Brentford, Middlesex, UK), a bivalent vaccine that protects against HPV types 16 and 18 (both types confer a high risk of cervical cancer), was produced.⁽⁹⁾ Both vaccines are composed of recombinant HPV surface proteins that are made in yeast cells. The protein assembles spontaneously

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Table I. Cervical cancer CR and ASR per 100,000 women per year for the period 2005–2009.

Year	No. of new cases (%)	Female population	CR; 95% CI	ASR; 95% CI
2005	25 (14.9)	174,800	14.3; 8.7–19.9	19.5; 12.9–26.0
2006	30 (17.9)	179,700	16.7; 10.7–22.7	29.0; 21.1–36.8
2007	40 (23.8)	183,100	21.9; 15.1–28.6	30.6; 22.6–38.6
2008	33 (19.6)	187,000	17.7; 11.6–23.7	21.9; 15.2–28.6
2009	40 (23.8)	191,200	20.9; 14.4–27.4	26.7; 19.4–34.0
2005–2009	168 (100.0)	915,800	18.3; 15.6–21.1	24.9; 21.7–28.1*

*Average incidence rate for the five years.

CR: crude incidence rate; ASR: age-standardised incidence rate; CI: confidence interval

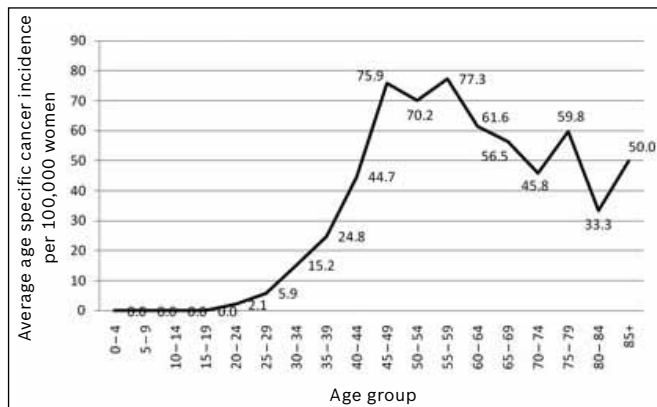


Fig. 1 Age-specific cervical cancer incidence per 100,000 women per year in the period 2005–2009 in Brunei Darussalam.

into virus-like particles (VLPs) in a manner similar to Hepatitis B surface antigen VLPs, which have successfully been used as a vaccine. The two HPV vaccines are similarly effective, and they are being considered for introduction into the public health immunisation programme of the country. Currently, the vaccine is available only through the private sector. The present study was carried out with the aim of generating data relevant to considering vaccination against HPV in Brunei Darussalam.

METHODS

This cross-sectional, retrospective study utilised anonymised data from all patients diagnosed with cervical cancer in the period 2005–2009 from the Cancer Registry of the Oncology Clinic, RIPAS Hospital, Bandar Seri Begawan, Brunei Darussalam. Tumour staging was done routinely, but the data was not available for analysis. Data for breast, colorectal and lung cancers for the same period was also obtained from the Cancer Registry. For all other cancers,⁽¹⁰⁾ RIPAS Hospital was the first point of detection and investigation for gynaecological cancers and precancerous lesions for most Bruneians and resident foreigners in the whole country. Treatment was later provided to some patients at the National Cancer Centre, Jerudong Park Medical Centre when it was established in 2010. Some patients opted for treatment abroad after the initial diagnosis at RIPAS Hospital. Although a national registry of cancer data has since been created at the National Cancer Centre, data for the period 2005–2009 from the Cancer Registry at RIPAS hospital would show the incidence of cancer for this period in the whole population (comprised Bruneians and resident foreigners). Population statistics were

obtained from the Department of Economic Planning and Development, Prime Minister's Office, Brunei Darussalam.

Tissues were stained with haematoxylin and eosin, and examined under 400 times magnification for routine microscopy, as described previously.⁽⁶⁾ The Statistical Package for the Social Sciences version 16.0 (IBM Corporation, Armonk, NY, USA) and Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, WA, USA) were used to determine the incidence of malignant cervical lesions in different ethnic and age groups as well as in the overall population during the study period. The 95% confidence intervals (CIs) of incidence rates and the significance of variations in incidence rates between different cancers were calculated based on a Poisson distribution. ASR was determined using the direct method,⁽¹¹⁾ based on the World Health Organization world standard population.⁽¹²⁾ The study was approved by the ethics committees of Universiti Brunei Darussalam, Institute of Health Sciences and the Ministry of Health.

RESULTS

Data of 168 cases of invasive cervical cancer was used for analysis. Table I shows the cervical cancer crude incidence rate (CR) and ASR per 100,000 women per year in Brunei Darussalam in 2005–2009. There was a steady increase in the number of new cases during the study period, except for a drop in 2008. The CRs of colorectal and lung cancers among Bruneian women for the same period were significantly lower, at 12.2 and 7.9 per 100,000 women per year, respectively ($p < 0.001$). When compared to other female-specific cancers, only breast cancer had a significantly higher CR of 33.0 per 100,000 women per year ($p < 0.001$) during the same period. Fig. 1 shows the characteristics of age-specific cervical cancer incidence per 100,000 women per year in Brunei Darussalam in 2005–2009. Overall, the age-specific cervical cancer incidence increased with age until it peaked at age 45–59 years, after which it tended to fall, with smaller peaks in later years.

Table II shows the CR per 100,000 women per year among different ethnic groups in the period 2005–2009. The category 'Others' includes persons of European and South Asian origin, Ibans, Nepalese, Indonesians, Filipinos and Thais. Although Dusuns are regarded as a separate race in the Cancer Registry, they were included in the 'Malay' category in this study in order to be consistent with the population ethnicity grouping in

Brunei Darussalam. The incidence among ethnic Chinese was higher than among Malays, although the difference was not statistically significant. However, the overall incidence among the other ethnic groups was significantly lower than that in the Chinese and Malays. Table III shows the CR and ASR of the six types of invasive cervical cancer that were identified histologically during the study. Among these, squamous cell carcinoma was the most common (ASR = 18.9), followed by adenocarcinoma (ASR = 4.1), and this is consistent with that seen in other countries. The other four types, namely adenosquamous carcinoma, metastatic carcinoma, small cell carcinoma and undifferentiated carcinoma, were less common (with ASRs \leq 1.0).

DISCUSSION

The results of this study show that the average ASR of cervical cancer per 100,000 women per year over the five-year study period (2005–2009) in Brunei Darussalam was 24.9 (95% CI 21.7, 28.1), which was considerably higher than the previously estimated value (95% CI 12.1, 17.0) in the period 2002–2006.⁽⁷⁾ It is also higher than the ASR reported in 2007 for the neighbouring countries of Indonesia (15.7) and Malaysia (15.7),⁽¹³⁾ and for Singapore in the period 2005–2009 (7.8).⁽¹⁴⁾ The reported values for ASRs in 2007 are, however, comparatively lower in developed countries (USA 7.7, Japan 8) but higher in some less developed countries (Haiti 87.3, India 30.7).⁽¹³⁾ Compared with other common cancers among women, the incidence of cervical cancer among Bruneian women in 2005–2009 was significantly higher than that for colorectal or lung cancer but lower than that for breast cancer. In contrast, the incidence of cervical cancer was lower than colorectal or lung cancer among Singaporean females.⁽¹⁴⁾ Therefore, additional steps to reduce the incidence of cervical cancer through public education, more comprehensive screening and the introduction of vaccination can make a significant contribution to reducing the overall morbidity and mortality from cancer in Bruneian women.

The variation of the ASR for cervical cancer in Brunei Darussalam is not very different from that seen globally, where there is a broad peak between the ages of 45 and 65.⁽²⁾ Brunei Darussalam's population comprises approximately 70% Malay, 10% Chinese and 20% other ethnic groups. The lower incidence of cervical cancer among other ethnic groups in Brunei Darussalam compared to the Chinese and Malays may be due to cultural and social factors resulting in under-detection, differences in sexual mores or population genetic variations. Migrant workers comprise a large proportion of the other ethnic groups in Brunei Darussalam, and some of them may prefer to undergo medical investigations in their home countries.

The Papanicolaou test, or Pap smear, is the mainstay for detecting cervical dysplasia or cancer, and its widespread use has had a significant impact on the incidence of cervical cancer and its associated mortality.⁽¹⁵⁾ There was no national Pap smear screening programme prior to 2010 in Brunei Darussalam.

Table II. Average cervical cancer CR per 100,000 women per year by ethnicity for the period 2005–2009.

Ethnicity	No. of cases (%)	Female population	CR; 95% CI
Malay	127 (75.6)	615,300	20.6; 17.1–24.2
Chinese	28 (16.7)	99,200	28.2; 17.8–38.7
Others	13 (7.7)	201,300	6.5; 3.0–10.0

CR: crude incidence rate; CI: confidence interval

Table III. Cervical cancer frequency and average CR and ASR per 100,000 women per year by cancer type for the period 2005–2009.

Type of cancer	No. of new cases (%)	CR; 95% CI	ASR; 95% CI
Squamous cell carcinoma	130 (77.3)	142; 11.8–16.6	18.9; 16.1–21.7
Adenocarcinoma	27 (16.1)	3.0; 1.8–4.1	4.1; 2.8–5.4
Adenosquamous carcinoma	7 (4.2)	0.8; 0.2–1.3	1.0; 0.4–1.7
Metastatic carcinoma	1 (0.6)	0.1; 0.0–0.3	0.1; 0.0–0.3
Small cell carcinoma	2 (1.2)	0.2; 0.0–0.5	0.4; 0.0–0.8
Undifferentiated carcinoma	1 (0.6)	0.1; 0.0–0.3	0.1; 0.0–0.3

CR: crude incidence rate; ASR: age-standardised incidence rate; CI: confidence interval

Instead, Pap smears were done on demand and in women after childbirth. Since 2010, all women aged 22–65 years attending health clinics have been screened using the Pap smear test every three years. Experience in culturally similar Malaysia suggests that even when Pap smears were offered free of charge, only 47.3% of women had been screened.⁽¹⁶⁾ Furthermore, there is currently no planned public education programme on HPV and cervical cancer in Brunei Darussalam. The present findings suggest that Pap smear screening for all women in the relevant age group and raising awareness on cervical cancer among the female population would be helpful.

High-risk HPV types 16, 18, 31, 51, 52, 56, 58 and 66 were detected in abnormal cervical smears in neighbouring Malaysia, with HPV 16 and 52 being the commonest and accounting for 23.7% of infections in each case.⁽¹⁷⁾ Types 16 and 18 are common in Indonesia, Philippines, Thailand and Vietnam.⁽¹⁸⁾ HPV typing by DNA probe hybridisation is presently being established in Brunei Darussalam, and our preliminary findings are compatible with the presence of high-risk HPV types as well as HPV 6/11 in the country (unpublished observations). Detailed investigations on the prevalence of the different HPV types with specific DNA probes required before vaccination can be recommended for preventing HPV infection, which is a likely cause of most cases of cervical cancer in Brunei Darussalam.

ACKNOWLEDGEMENT

We are grateful to Dr L Naing of Universiti Brunei Darussalam for providing statistical advice.

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