

## REVIEW

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# Epidemiology of Uterine Cancer in Sarawak, Borneo, A 20-Year Review

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## Abstract

**Objective:** This study aimed to determine the epidemiology of uterine cancer in Sarawak, Malaysia, using data from a population-based cancer registry. **Methods:** The study population included all women diagnosed with uterine cancer in Sarawak, Malaysia between January 1996 and December 2015. Data on demographic and clinical characteristics were obtained from the Sarawak Cancer Registry. The crude incidence rate, age-standardized incidence rate (ASR), and incidence risk ratios (IRR) were calculated. Joinpoint regression analyses were performed to assess trends in incidence rates. **Results:** A total of 811 women were diagnosed with primary uterine cancer during the study period. The overall crude incidence rate for uterine cancer in Sarawak for the period 1996-2015 was 3.7 per 100,000. The ASR was 4.4 per 100,000 with a 95% CI (4.1-4.8). The ASR in 2011-2015 is 1.6 times higher than the ASR of uterine cancer in 1996-2000. Higher incidence rates were observed in women aged 40-59 years and those aged 60 years and above. Chinese women had the highest ASR, followed by Malay and Iban women. Joinpoint regression analyses showed a significant increase in cases of uterine cancer among all ethnic groups and age groups. **Conclusion:** The incidence of primary uterine cancer in Sarawak, Malaysia, has increased over the past 20 years, with higher incidence rates observed in older age groups and among Chinese women. The findings suggest the need for continued efforts to improve the prevention, early detection, and treatment of uterine cancer in Sarawak.

**Keywords:** Uterine cancer- epidemiology- corpus uteri cancer

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## Introduction

Uterine cancer is one of the most common cancers in women worldwide. According to GLOBOCAN 2020, uterine cancer is the eighth most common cancer worldwide, after breast, prostate, lung and colon cancer, cervical cancer, stomach cancer and liver cancer, with an age-standardised incidence rate of 8.7 per 100,000 population [1]. It is also the sixth most common cancer in women worldwide, after breast, colon, lung, cervix and thyroid. The mortality rate of corpus uteri cancer is 7.3 per 100,000 and the incidence of uterine cancer in Malaysia is expected to double by 2040 (from 1,401 to 2,490 cases) [1].

The incidence of uterine cancer is distributed differently in different regions of the world. It is the most common gynaecological malignancy in developed countries such as America and Europe, and the second most common gynaecological malignancy in developing countries after cervical cancer. After Singapore (most common), Japan, Georgia, Israel, Armenia, Turkey, Korea, Republic of Thailand, Brunei Darussalam, Kazakhstan,

China and Vietnam, Malaysia is ranked eightieth in the world and twelfth in Asia [1-3].

Uterine cancer happens when normal cells proliferate uncontrollably. Non-cancerous conditions of the uterus include fibroids, benign polyps, endometriosis, and endometrial hyperplasia. However, when there is the presence of more atypical cells and complex glands during the endometrium hyperplasia, the risk of developing uterine cancer increases.

There are 2 main types of uterine cancer: adenocarcinoma, which accounts for most uterine cancers, and sarcoma. Adenocarcinoma develops from cells in the lining of the uterus and called endometrial cancer. Other less common subtypes of adenocarcinoma of the uterus include serous, clear cell and carcinosarcoma. Carcinosarcoma is a mixture of adenocarcinoma and sarcoma. Sarcomas account for about 2% to 4% of cancers of the uterus and it develops in the myometrium or supporting tissue of the uterine glands. Subtypes of endometrial sarcoma include leiomyosarcoma, endometrial stromal sarcoma and undifferentiated sarcoma. Endometrial carcinoma arises from the inner layer of the uterus (endometrium) and

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accounts for about 90% of all uterine cancers, followed by uterine sarcoma (8%) and less common cancers (2%). Treatment for uterine cancer depends on the grade of the tumour, how far it has spread into the uterus, and extent of the spread of the disease involving other organs.

Risk factors for uterine cancer are higher in women who are obese, probably due to an increased amount of circulating oestrogen, nulliparous women, early menarche and late menopause [4]. The risk of uterine cancer is also higher in women who have had years of menopausal hormone therapy with oestrogen alone (without progesterone), and women who have taken the drug tamoxifen to prevent or treat breast cancer have an increased risk of uterine cancer [5]. Women in families with an inherited form of bowel cancer (known as Lynch syndrome) have an increased risk of uterine cancer. A history of polycystic ovary syndrome, a condition characterised by infertility, enlarged ovaries and menstrual problems, also increases the risk [6-8].

The most common symptom of uterine cancer is abnormal vaginal bleeding. After menopause, any vaginal bleeding is abnormal. Uterine cancer is often diagnosed in women who are over 51 years old. Other symptoms of uterine cancer include pain or difficulty emptying the bladder, pain during sex and pain in the pelvic area [9, 10].

Malaysia's National Strategic Plan for Cancer Control Programme 2021-2025 serves as the blueprint for fostering collaboration among key stakeholders involved in cancer prevention and management. The primary objective is to mitigate the adverse impact of cancer by reducing its incidence and mortality rates while enhancing the overall well-being of cancer patients and their families. This latest strategic has a holistic approach that encompasses initiatives ranging from prevention, health promotion, screening, and early diagnosis to treatment, survivorship, palliative care, traditional and complementary medicine (T&CM), and research.

Data collected by the Sarawak Cancer Registry was included in this study. We aimed to verify the presumed increasing incidence rate of uterine cancer and to characterise the demographic and clinical profiles of patients residing in Sarawak from 1996-2015.

## Materials and Methods

### *The Study Population*

The study included all primary uterine cancers diagnosed in Sarawak and recorded by the Sarawak Cancer Registry from January 1996 to December 2015. The registry was established in 1996 as a state population-based registry for cancer patients. Data was actively collected from all government and private health centres in Sarawak at diagnosis. The registry also collects data from death reports where cancer is reported as a contributing factor.

Sarawak is a state in Malaysia. Sarawak is the largest of the 13 states and has an area of 124,450 km<sup>2</sup>, which is almost equal to the area of Peninsular Malaysia. Sarawak is located in the northwest of the island of Borneo, bordering the Malaysian state of Sabah to the northeast, Kalimantan (the Indonesian part of Borneo) to the south

and Brunei to the north. The capital Kuching is the largest city in Sarawak, the economic centre of the state and the seat of the Sarawak state government. In 2021, the population of Sarawak was estimated at 2.45 million. It is ethnically, culturally, and linguistically diverse. Major ethnic groups include Iban (28.6%), Malay (22.9%), Chinese (22.4%), Bidayuh (5.1%) and Melanau (5.1%).

### *Data Sources*

Cases were coded in the registry based on the 10th revision of the International Classification of Diseases (ICD-10) according to the location of the tumour. Cases included are C54.0–C54.9 (corpus uteri cancer) and C55.9 (uterus, NOS cancer). The data were organised using CanReg software, an open-source tool from the International Association of Cancer Registries, with the latest version being CanReg5. There were 811 cases of uterine cancer reported in Sarawak from 1996 to 2015. Patient demographic and clinical characteristics recorded included patient registration number, age, place of residence, tumour topography, tumour morphology, tumour stage, tumour grade and treatment. Population data was obtained from the Department of Statistics Malaysia based on a census conducted every 10 years.

### *Data Management and Statistical Analysis*

The histopathological types of tumours were classified into 4 types based on the histopathologic grouping of the International Agency for Research on Cancer (WHO) used in Cancer Incidence in Five Continents Volume IX (C15).

The morphology codes for uterine cancer have been divided into 4 main subgroups. These are carcinoma (8010-8574 and 8576), sarcoma (8800-8811, 8830, 8840-8921, 8990-8991, 9040-9044, 9120-9133, 9150 and 9540-9581) and other specified malignant neoplasms and unspecified malignant neoplasms (8000-8005). Carcinomas were divided into adenocarcinomas (8140-8141, 8190-8211, 8230-8231, 8260- 8263, 8310, 8380, 8382-8384, 8430, 8440-8490, 8510, 8560, 8570-8574 and 8576) and other specified carcinomas and unspecified carcinomas (8010-8035).

The incidence rate (IR) was calculated by dividing the number of events (E) by the total number of risk populations (P) per 100,000 women. The 95% confidence interval (CI) was calculated using the following formula:  $CI = IR \pm 1.96 \times IR / \sqrt{E}$  and the 95% CI of the rate ratio was calculated by using  $CI = \exp(\ln(IR1/IR2)) \pm 1.96 \times \sqrt{(1/E1 + 1/E2)}$ . The Sarawak Census of 1996 - 2005 was used to determine the number of women at risk.

Due to the small number of cases, incidence rates were compared over the 3 periods 1996 to 2002, 2003 to 2006 and 2007 to 2010. The crude incidence rate was used to compare the incidence of uterine cancer over the entire time frame of the study with the initial incidence in the period 1996 to 2015. The world standard population (WHO, 2000) was used to calculate the age-standardised rate expressed per 100,00 population. A two-sided p-value of  $\leq 0.05$  was considered statistically significant for all analyses. Differences between groups were analysed with negative binomial regression against reference groups. SPSS version 25 and STATA were used for all statistical

analyses.

Trend analysis was performed using the National Cancer Institute's Joinpoint Regression Programme version 4.9.10 to analyse changes in trends by age group and ethnic group. This research was approved by the Malaysia Medical Research and Ethics Committee.

## Results

In Sarawak, 811 women were diagnosed with primary uterine cancer between January 1996 and December 2015. Table 1 and Table 2 show the distribution of demographic and clinical characteristics of the patients. Most of them were diagnosed in the age group of 40-59 years (65.5%), followed by those aged 60 years and above (28%) and those aged 40 years and below (9.5%). The average age at diagnosis is 53.3 years (Table 1). The average age at diagnosis is 59.8 years in 1996, compared to 52.7 years in 2015 (Figure 1). Mainly Chinese were affected, followed by Iban, Malay and Bidayuh. Most uterine cancer cases were diagnosed in Kuching (31.1%), Sibü (14.7%) and Miri (12.6%) divisions.

Table 1. Demographic Characteristics of 811 Uterine Cancer Patients in Sarawak between 1996 and 2015. (n=811)

Variables	Frequency	Per cent	Mean (SD)
Year			
1996-2000	138	17.02	
2001-2005	188	23.18	
2006-2010	196	24.17	
2011-2015	289	35.64	
Age groups (years)			
20-39	77	9.5	53.3 ( $\pm$ 10.99)
40-59	507	65.5	
$\geq$ 60	227	28	
Ethnic			
Malay	149	18.4	
Chinese	350	43.2	
Iban	192	23.7	
Bidayuh	51	6.3	
Melanau	29	3.6	
Others	40	4.9	
Division			
Kuching	252	31.1	
Samarahan	53	6.5	
Sri Aman	27	3.3	
Betong	25	3.1	
Sarikei	35	4.3	
Sibü	119	14.7	
Kapit	18	2.2	
Mukah	15	1.8	
Bintulu	29	3.6	
Miri	102	12.6	
Limbang	18	2.2	

The overall crude incidence rate for uterine cancer in Sarawak for the period 1996-2015 was 3.7 per 100,000. The age-standardised incidence rate (ASR) was 4.4 per 100,000 with a 95% CI (4.1-4.8). The ASR in 2011-2015 is 1.6 times higher than the ASR of uterine cancer in 1996-2000 (Table 2). The age-standardised incidence rate (ASR) was higher among the Chinese, followed by the Malays and the Iban (Table 3). Over the 20 years, an increasing ASR was observed in all races. Although the incidence is higher among the Chinese, with a 1.2-fold increase in ASR among Chinese women in 2011-2015 compared to 1996-2000, the ASR for uterine cancer among Melanau's has increased significantly over the 20 years (approximately 4-fold, from 2.3 to 8.7) (Table 4).

Based on Divisions in Sarawak, Kuching had the highest age-standardised incidence rate for uterine cancer at 4.8 per 100,000 population, followed by Sibü (4.4 per 100,000 population) and Miri (3.9 per 100,000 population) (Figure 2). Uterine cancer in the endometrium (C541) was the commonest, which comprises 87.1% of all uterine cancer diagnoses in Sarawak, followed by malignant neoplasm of the uterus, part unspecified (C55) (12.5%), the body of uterus (0.4%) and the myometrium (0.1%). Uterine cancer diagnosed was mainly adenocarcinoma (90.9%) compared to just 9.1% were sarcoma (Table 5).

A negative binomial regression model was used to predict the relationship of year of diagnosis, division, ethnic group, and age group (Table 6). Women diagnosed in the year 2011 to 2015 have an Incidence Risk Ratio (IRR) of 1.52 (SE=0.31, 95% CI= 1.02-2.28, p=0.040) compared to those women diagnosed in 1996 to 2000. Higher ages show a significant increase in Incidence Risk Ratio (IRR), with those aged 40 to 59 years has 10.73 times higher chances of getting uterine cancer compared to those 40 years and below (SE=2.09, 95% CI= 7.33-15.71, p<0.000). Those aged 60 years and above have an IRR of 10.7 (SE=2.21, 95% CI= 7.13-16.06, p<0.000) of getting uterine cancer compared to

Table 2. Annual Incidence of Corpus Uteri per 100,000 in Sarawak 1996-2015

Year	NO.	CR	ASR	(ASR 95%CL)
1996-2015	811	3.7	4.4	4.1, 4.8
1996-2000	138	2.9	3.9	3.2, 4.5
2001-2005	188	3.6	4.4	3.7, 5.0
2006-2010	196	3.4	3.9	3.3, 4.5
2011-2015	289	4.7	5	4.4, 5.5

Table 3. Annual Incidence of Corpus Uteri per 100,000 by Ethnicity, Sarawak 1996-2015

1996-2015	NO.	CR	CR74	ASR	(ASR (95%CL))
All Residents	811	3.7	0.5	4.4	4.1, 4.8
Iban	192	2.9	0.4	3.4	2.9, 3.8
Chinese	350	6.3	0.8	6.5	5.8, 7.2
Malay	149	2.9	0.5	4.1	3.4, 4.7
Bidayuh	51	2.8	0.4	3.3	2.3, 4.2
Melanau	29	2.4	0.3	2.8	1.7, 3.8

Table 4. Trends in the ASRs of Uterine Cancer by Race and Period of Diagnosis

RACE	1996-2000	2001-2005	2006-2010	2011-2015
Iban	3 (1.9, 4.0)	3.4 (2.4, 4.4)	3.3 (2.4, 4.2)	3.4 (2.5, 4.3)
Chinese	6 (4.5, 7.5)	5.9 (4.5, 7.2)	6.1 (4.8, 7.5)	7.4 (6.1, 8.8)
Malay	3.4 (2.0, 4.9)	4.3 (2.8, 5.7)	3.2 (2.1, 4.3)	4.5 (3.2, 5.7)
Bidayuh	2.3 (0.4, 4.2)	3.3 (1.5, 5.2)	2 (0.7, 3.4)	4.3 (2.4, 5.9)
Melanau	2.3 (0.2, 4.3)	3.9 (1.4, 6.4)	1.4 (0.0, 2.9)	8.7 (5.4, 12.0)

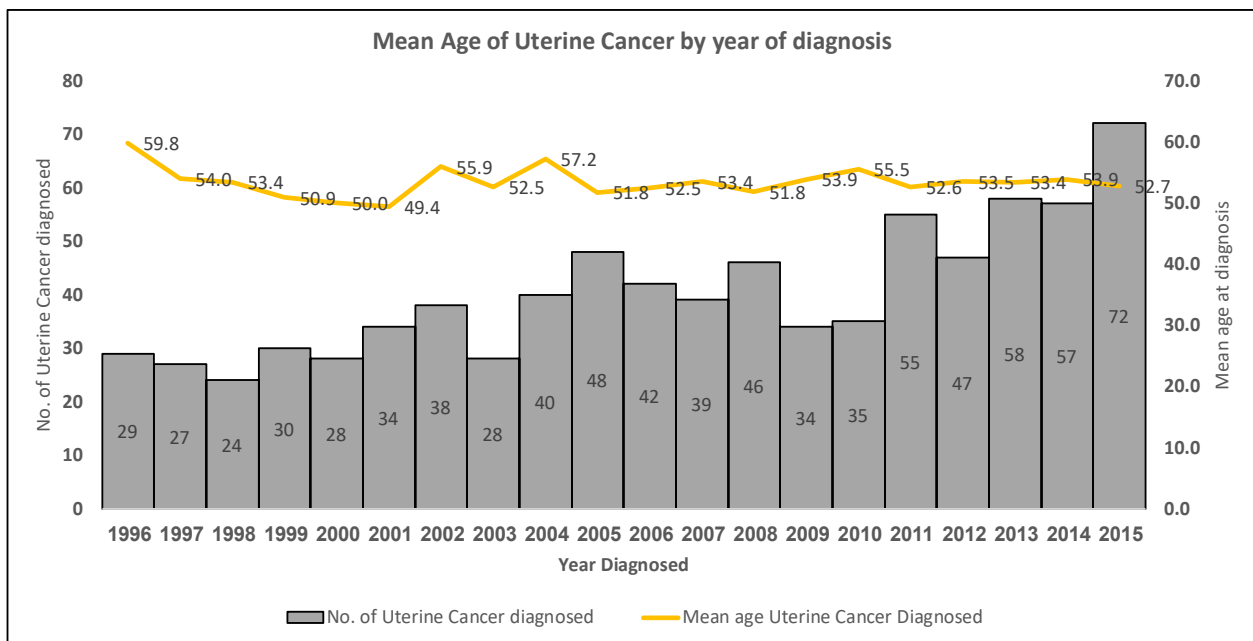


Figure 1. Mean Age of Uterine Cancer by Year of Diagnosis in Sarawak, 1996-2015

those below 40 years old. Chinese has the highest IRR (IRR=1.92, SE=0.58, 95% CI= 1.06-3.46, p=0.031), among other ethnic groups of getting uterine cancer in Sarawak. Kuching, Sibuh and Miri had a higher IRR compared to the Kapit division, however, there is no

significant difference.

Joinpoint regression analyses for ethnicity and gender are shown in Table 7 and Figures 3 to 6. Overall, there was a significant increase in cases from 1995 to 2015, with an annual increase of 2.99 per cent. Analysis of individual

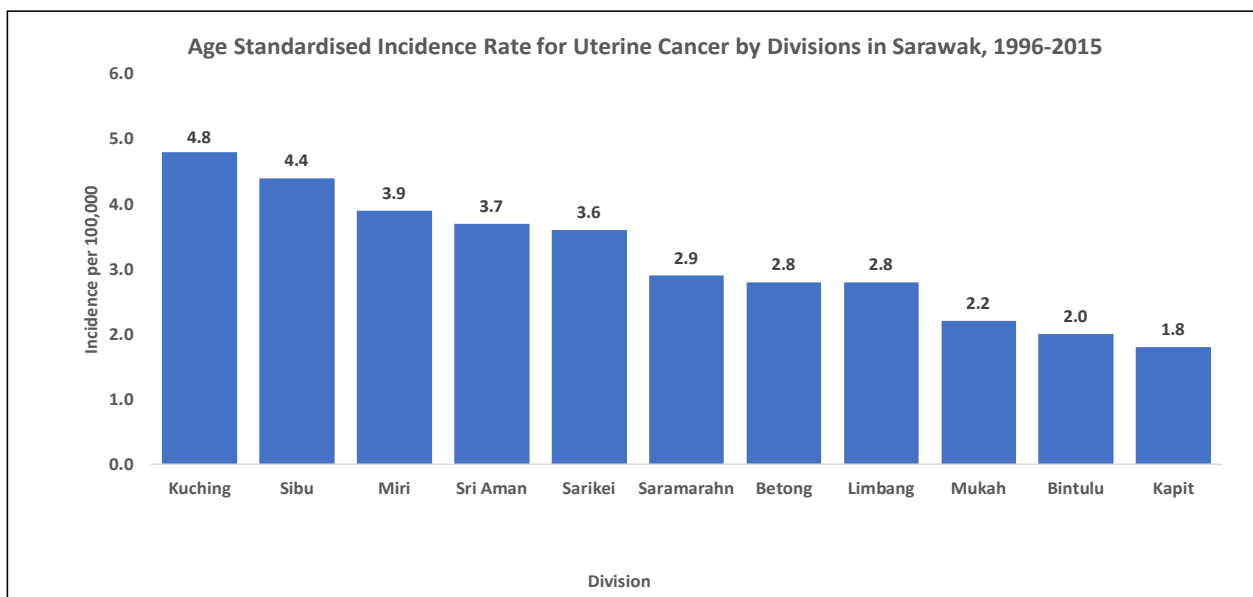


Figure 2. Age-Standardised Incidence Rate for Uterine Cancer by Divisions in Sarawak, 1996-2015

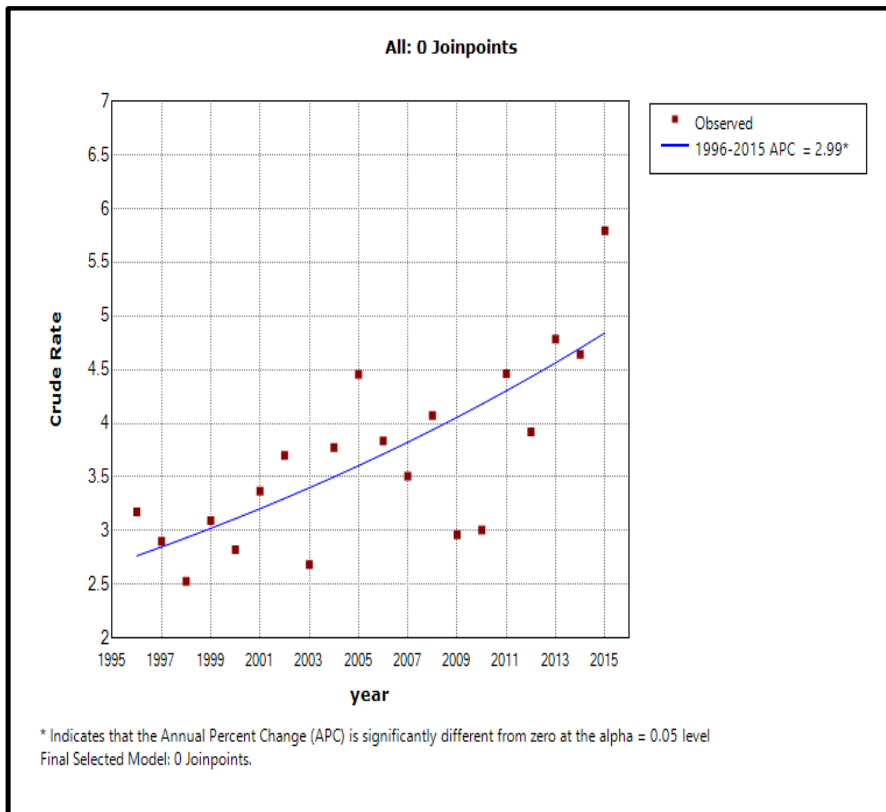


Figure 3. Joinpoint Regression Chart for Uterine Cancer Crude Rate from 1995-2015

ethnic groups also showed a significant increase in uterine cancer cases among the Chinese, Malay and other races with an annual increase of 2.77 per cent, 2.71 per cent and 5.38 per cent respectively. There was also a significant

annual increase of 5.19 per cent among those aged 20-39 years old.

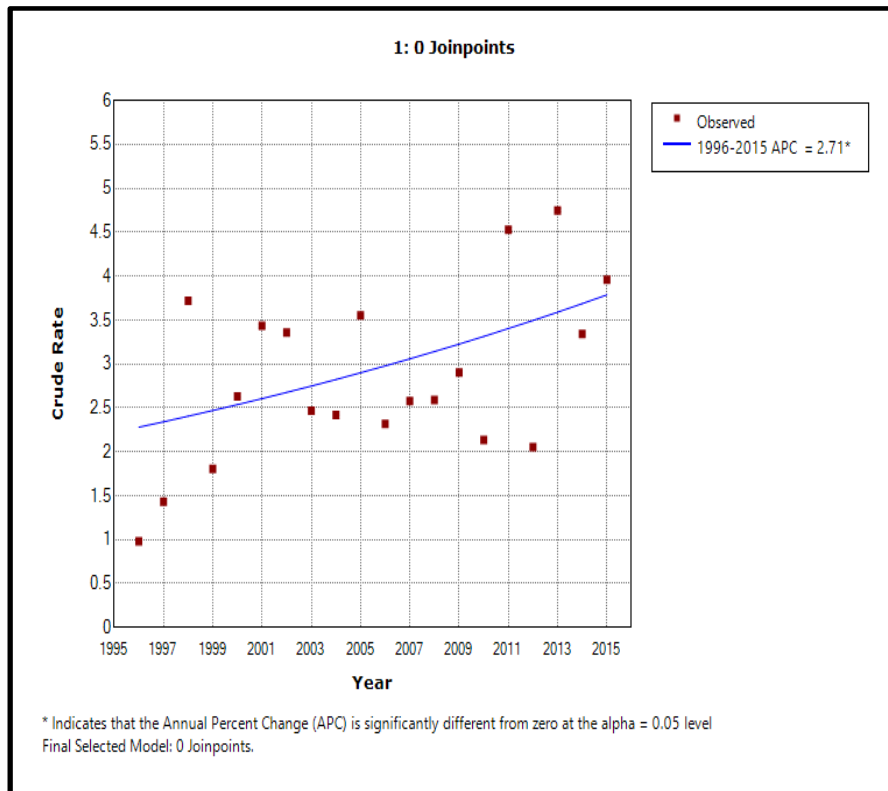


Figure 4. Joinpoint Regression Chart for Malay from 1995-2015



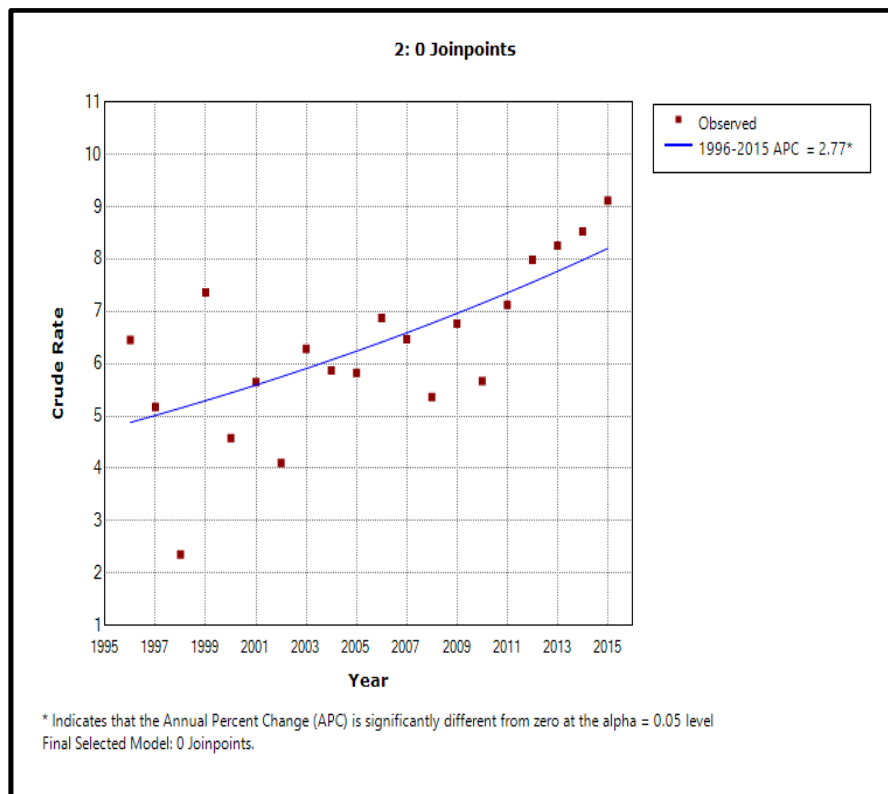


Figure 5. Joinpoint Regression Chart for Chinese from 1995-2015

### Discussion

The results of this study on uterine cancer in Sarawak provide valuable insights into the distribution of demographic and clinical characteristics of patients for the past 20 years. The study also used a negative binomial regression model to predict the relationship between the year of diagnosis, division, ethnic group, and age group. The study found that the overall incidence rate of uterine cancer in Sarawak was 3.7 per 100,000, with an age-standardized incidence rate (ASR) of 4.4 per 100,000. Based on the Sarawak Cancer Registry Report, uterine cancer is the ninth most common cancer among women in Sarawak with an age-standardised incidence rate (ASR) of 4.4 per 100,000 woman-years (95% CI:4.1, 4.8) after breast, cervical, colorectal, tracheal, bronchus, lung,

ovarian, NPC, lymphoma, and stomach cancers.

The incidence of uterine cancer varies widely from country to country, being higher in Western countries and lower in countries such as Africa and Asia, including Sarawak. The ASR in this study was lower than in the US, UK and Germany, and even than in our neighbouring country Thailand, where it was 25.8, 22.3, 21 and 16 per 100,000 women respectively, but higher than in Sri Lanka, Egypt and Cambodia (4.2, 3.9 and 3.3 respectively). The ASR for uterine cancer in Sarawak was also lower than the ASR in Malaysia (2012-2016) at 8.3 per 100,000 women [11]. From 1996 to 2015, there was a significant increase in uterine cancer cases in Sarawak with an annual increase of 2.99 per cent over this 20-year period. A negative binomial regression model in this study showed that women diagnosed with cancer from 2011 to 2015 had an incidence risk ratio (IRR) of 1.52 (SE =0.31, 95% CI= 1.02-2.28, p=0.040) compared to women diagnosed with cancer from 1996 to 2000. A dramatic increase in the incidence of uterine cancer has also been observed in countries such as Japan and China [1]. In general, uterine cancer is a disease that occurs in countries with Western lifestyles and is increasing in populations with urbanisation and economic growth, in parallel with rising rates of obesity and sedentary lifestyles. Recent epidemiological studies have shown that the incidence rate of uterine cancer in Asia is steadily increasing with the influence of Western culture [12-16].

Furthermore, the study found that Kuching division had the highest age-standardized incidence rate for uterine cancer, followed by Sibul and Miri. This may be attributed to differences in lifestyle factors, such as diet and physical

Table 5. Clinical Characteristics of uterine cancer patients in Sarawak between 1996 and 2015 (n=811)

Variables	Frequency	Per cent
Cancer topography		
C541 (Endometrium)	706	87.1
C542 (Myometrium)	1	0.1
C549 (Corpus Uteri, Body of Uterus)	3	0.4
C55 (Malignant neoplasm of uterus, Part unspecified)	101	12.5
Cancer Morphology		
Adenocarcinoma	737	90.9
Sarcoma	74	9.1

Table 6. Negative Binomial Multivariate Regression Analysis to Compare Crude Incidence Rates of Uterine Cancer in Sarawak to Demographic Groups.

Variables	Crude Incidence Rate	Univariate Analysis, IRR (95% CI)	p	Multivariate analysis, IRR (95% CI)	p
<b>Year</b>					
1996-2000 (RC)	2.9				
2001-2005	3.6	1.40(0.84-2.33)	0.192	1.44 (0.95-2.17)	0.086
2006-2010	3.4	1.30 (0.79-2.16)	0.302	1.33 (0.88-1.99)	0.176
2011-2015	4.7	1.47 (0.89-2.42)	0.125	1.52 (1.02-2.28)	0.040*
<b>Age groups (years)</b>					
20-39 (RC)	1.2				
40-59	11.9	10.28 (7.09-14.91)	0.000*	10.73 (7.33-15.71)	0.000*
≥60	12.8	10.99 (7.41-16.32)	0.000*	10.70 (7.13-16.06)	0.000*
<b>Ethnic</b>					
Malay	2.9	1.43 (0.70-2.92)	0.325	1.58 (0.86-2.89)	0.138
Chinese	6.3	2.05 (1.03-4.09)	0.041*	1.92 (1.06-3.46)	0.031*
Iban	2.9	1.33 (0.67-2.64)	0.411	1.42 (0.78-2.57)	0.249
Bidayuh (RC)	2.8				
Melanau	2.4	1.06 (0.46-2.48)	0.882	1.29 (0.60-2.76)	0.517
Others	2.7	0.97 (0.43-2.20)	0.939	1.26 (0.60-2.66)	0.542
<b>Division</b>					
Kuching	4.1	2.80 (1.18-6.66)	0.020*	1.99 (0.96-4.17)	0.065
Samarahan	2.5	1.67 (0.66-4.21)	0.275	1.49 (0.68-3.27)	0.323
Sri Aman	2.9	1.75 (0.64-4.80)	0.271	1.40 (0.60-3.26)	0.433
Betong	2.3	1.52 (0.55-4.24)	0.423	1.30 (0.55-3.05)	0.552
Sarikei	3.8	2.22 (0.86-5.80)	0.101	1.63 (0.72-3.68)	0.239
Sibu	4	2.67 (1.09-6.52)	0.031*	1.98 (0.93-4.21)	0.077
Kapit (RC)	1.7				
Mukah	0.9	1.30 (0.47-3.62)	0.609	1.23 (0.51-2.99)	0.647
Bintulu	2.6	1.30 (0.50-3.40)	0.588	1.14 (0.51-2.57)	0.752
Miri	3.3	2.54 (1.05-6.11)	0.038*	1.92 (0.92-4.02)	0.082
Limbang	2.3	1.18 (0.42-3.31)	0.749	1.06 (0.43-2.58)	0.901

\*, Statistically significant difference when compared to the comparator group.

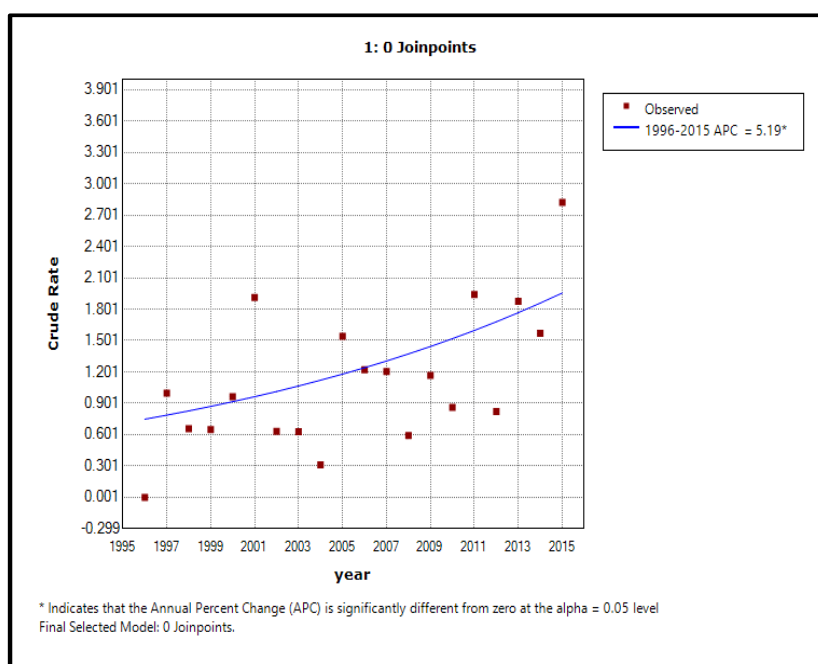


Figure 6. Joinpoint Regression Chart for Age Group 20-39 Years Old

Table 7. The Trends of Crude Rate of Uterine Cancer in Sarawak by Joinpoint Analysis, 1996-2015

Groups	Trend 1 years	APC
Ethnic		
All	1995-2015	2.99*
Malay	1995-2015	2.71*
Chinese	1995-2015	2.77*
Bidayuh	1995-2015	2.59
Iban	1995-2015	1.76
Melanau	1995-2015	2.06
Others	1995-2015	5.38*
Age Group (years)		
20-39	1995-2015	5.19*
40-59	1995-2015	0.86
≥ 60	1995-2015	0.28

\*Indicates Annual Percent Change (APC) is significantly different from zero at the  $\alpha=0.05$  level

activity, or variations in access to healthcare services. The commonest type of uterine cancer in Sarawak was endometrial cancer, and the majority of cases were adenocarcinoma.

Although the specific cause of uterine cancer is still ambiguous, the increased incidence may be due to certain factors. The increased life expectancy of the population, better nutrition, consumption of foods high in animal fats, improved health care and better living conditions have resulted in most women living long enough to develop uterine cancer. Other risk factors for developing uterine cancer include early menarche, late menopause, obesity, diabetes mellitus, hypertension, family history, tamoxifen therapy and uncontrolled oestrogen therapy.

The majority of patients were diagnosed in the age group of 40-59 years, followed by those aged 60 years and above and those aged 40 years and below. This is consistent with the literature, which suggests that uterine cancer is more common in postmenopausal women [17, 6]. The average age at diagnosis in this study is 53.9 years. The older the women, the higher and more significant the incidence risk ratio (IRR) in those aged 40-59 and those aged 60 and older, with a 10.73 and 10.70-fold risk of developing uterine cancer, respectively, compared to those aged 40 and older. Uterine cancer is not common in people under 40. However, it is interesting to note that this study found a significant annual increase of 5.19 per cent in women aged 20-39 years diagnosed with uterine cancer over the last 20 years. These trend changes can be attributed to risk reduction through health education and awareness of the positive impact of early detection among the younger generation. Since obesity plays an important role in increasing the risk of uterine cancer, this could also be due to the dramatic increase in obesity prevalence among 20-39-year-olds over the years. The 2006 and 2015 Malaysia's National Health and Morbidity Survey (NHMS) showed that adults aged 20-24 years were 20.8% (18.7-23.2) obese, compared with only 9.1% (8.1-10.2) of adults of similar age in 2006, an increase of 2.3-fold [18, 19]. Obesity prevalence also increased 2.2-fold in the

25-29-year age group between 2006 and 2015. In both surveys, the prevalence of obesity was higher in women than in men [18, 19].

Studies had shown that early menarche increases the risk of developing uterine cancer. In Asia, the average menarche age was reported to be 12.4 years in Hong Kong, 12.6 years in Japan and 12.5 years in Thailand (Parent et al., 2003). In Malaysia, studies had shown that the mean ( $\pm$ SD) menarche age was 11.97 ( $\pm$ 1.11) years, ranging from 9 to 16 years [20].

The fast pace of modern life and work pressures can lead to early menopause, as early as age 40, compared to earlier when it occurred at ages 45 and 46. The earlier women reach menopause, the earlier they use hormone replacement therapy. Women taking hormone replacement therapy (HRT) after menopause, especially if taking oestrogen alone, have a fourfold increased risk of uterine cancer compared to 1.4-fold in women using combined oestrogen and cyclic progestogen therapy [5]. Taking these oestrogens for 5 or more years was associated with a 3.7 risk of developing uterine cancer. Studies had also shown that a positive association became significant when the age at menopause was above 46.5 years. The RRs (95% CIs) of uterine cancer risk were 1.04 (1.03-1.06), 1.17 (1.14-1.20), 1.57 (1.45-1.71) and 2.08 (1.80-2.39) for ages 47, 50, 54 and 57 years at menopause, respectively [21]. Studies have shown an increasing usage of HRT over the years. A 2009 study in Sarawak found that 8.1% of women were taking HRT, and that they had been taking HRT for less than 3 years. The main reason they did not take HRT was that it was not recommended by their doctors [22]. A 2010 study in Asian countries found that 19% menopausal women used HRT, with very few Chinese women reporting previous use of HRT (9%) but high usage among Taiwanese and Thai women (33% and 25%, respectively) [23]. In 2017, 20.3% of Malaysian women used hormone replacement therapy (HRT) [24].

Of these risk factors, obesity may play the biggest role. A recent study shows that almost 57% of cases of uterine cancer are due to obesity [4]. The fatty tissue of people who are overweight produces extra oestrogen. Among developing Southeast Asian countries, Malaysia records the highest adult obesity rate [25-27]. Between 1996 and 2015, the prevalence of adult obesity in Malaysia quadrupled, increasing from 4.4% to 17.7% [12, 13]. In 2011 and 2015, obesity accounted for 15.1% and 17.7% of the population respectively [28].

Uncontrolled diabetes may also increase the risk of uterine cancer. National studies from 1996-2015 show that the prevalence of diabetes in Malaysia was 17.5% in 2015, more than doubling since 1996. The prevalence of diabetes in Sarawak was 10% in 1996 and had increased to 14.8% in 2015. Women, older age groups, Indians and urban dwellers were at the highest risk of diabetes [18, 19]. At the same time, adults consumed too few fruits and vegetables compared to the recommended intakes of the food groups in the Malaysian food pyramid. Physical activity among adults was also moderate, which could also lead to an increase in obesity. The increasing trend of obesity over the past 20 years could also contribute to the increased risk of uterine cancer in Sarawak [14].



History of hypertension has been investigated as a risk factor for developing uterine cancer in several case-control studies [29-32]. Hypertension is a strong risk factor for uterine cancer with a 61% increase in relative risk [33]. These findings are consistent with a large cohort study of women in Austria, Norway and Sweden, which found an increased risk of uterine cancer with rising levels of diastolic and especially systolic blood pressure [25].

Tamoxifen, an anti-oestrogen, is an effective drug for the treatment and prevention of hormone-dependent breast cancer. An important side effect of tamoxifen is an increase in the risk of cancer of the uterus. The benefits of tamoxifen usually outweigh the risk of getting uterine cancer. This happens after long-term (more than 2 years) use, especially in postmenopausal women with pre-existing pathologies in the uterus. From 2006 to 2015, a study in Sarawak showed that incidence rates for hormone receptor (HR)-positive breast cancer increased by 4.46% per year (95% CI = 2.19-6.78) and decreased by 2.29% per year (95% CI = -4.31 to -0.24) for HR -negative breast cancer [34]. With the increasing trend of hormone receptor (HR)-positive breast cancer in Sarawak, the use of tamoxifen may increase, putting women at higher risk for uterine cancer.

The ASR in this study was higher among Chinese, followed by Malays and Iban, and an increasing ASR was observed in all races over the 20 years. The Chinese had the highest incidence rate, with a 1.2-fold increase in ASR among Chinese women in 2011-2015 compared to 1996-2000. Interestingly, the ASR for uterine cancer among Melanau's increased significantly over the 20 years, approximately 4-fold. These findings suggest that race may be a significant risk factor for uterine cancer in Sarawak. The National Cancer Registry of Malaysia 2012-2016 report shows that uterine cancer is most prevalent among Indians, followed by Chinese and Malays with ASRs of 5.5, 5.1 and 4.4 per 100,000 population respectively [35, 36]. As there is a minimal number of Indians in Sarawak, the incidence of uterine cancer was highest among Chinese women and Malay women compared to other ethnic groups with an ASR of 6.5 and 4.1 per 100,000 population respectively. Analysis of each ethnic group also showed a significant increase in uterine cancer cases over the past 20 years among Chinese and Malays, with an annual increase of 2.77 per cent each. There are many different ethnic groups in Singapore; the incidence of uterine cancer was higher in the Chinese population, as in this study [23]. The age-adjusted incidence of uterine cancer is lower in Asians than in whites, which was 16.8 compared to 26.1 per 100,000. However, Asians occurred at a younger age (mean 58.4 years compared to 65.1 years;  $P < 0.01$ ) and with a more advanced stage of disease than whites (21.5% compared to 15.4%;  $P < 0.01$ ) [22].

In conclusion, this study highlights the significance of race as a risk factor for uterine cancer in Sarawak. The findings suggest the need for targeted interventions and screening programs to address the increasing incidence of uterine cancer, especially among older age groups and Chinese women. Further research is warranted to explore the underlying factors contributing to the differences in incidence rates among ethnic groups and divisions

in Sarawak. Finally, avoiding risk factors, maintaining a healthy weight, ideally, a body mass index (BMI) of less than 25, tight diabetes control and strengthening protective factors can reduce the risk of uterine cancer in both younger and older women.

The limitation of this study is that the information in this study was lacking on demographic data and risk factors for uterine cancer for each individual, such as actual ethnicity, income status, parity, contraception or hormone replacement therapy, BMI, presence of diabetes mellitus and hypertension, early symptoms and duration to diagnosis, and staging at diagnosis. The data were also insufficient to determine overall survival.

### Author Contribution Statement

The authors contribution to the paper as follows: study conception and design: Ooi Choo Huck, Diana Jawa, Johnny Pangkas; data collection: Wong Kung Yee, Mastulu Binti Wahab; analysis and interpretation of results: Diana Jawa, Wong Kung Yee, Azizah Azhar, Emmanuel Joseph Foong; draft manuscript preparation: Diana Jawa. Eunice Melissa Joseph. All authors reviewed the results and approved the final version of the manuscript.

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#### Approval

The study was conducted according to the guidelines and approved by the Malaysia Medical Research and Ethics Committee (NMRR ID-22-01151-6KI; MREC Reference: 22-01151-6KI (2) approved on 22nd June 2022).

#### Ethical Declaration

This research was approved by the Malaysia Medical Research and Ethics Committee. (NMRR ID-22-01151-6KI; MREC Reference: 22-01151-6KI (2) approved on 22nd June 2022).

#### Conflict of Interest

There is no conflict of interest. No involvement in any commercial trials for anti-cancer or any commercial ventures.

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