Review Article

Female-Specific Cancers in Malaysia: A Comprehensive Analysis of Three Decades

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Abstract

A comprehensive review was performed for the identification of female-specific cancer from 1st January 1980 up to 31st May 2016. Overall, the risk of breast cancer was noticed to be the highest among Chinese women (RD 0.42, CI 0.41 - 0.43). Malay women were noticed to have a 22.0% higher likelihood of breast cancer than Indian women (RD 0.22, CI 0.21 - 0.22), but 20% lower than Chinese women (RD -0.20, CI -0.21 -0.19). Cervical cancer was ranked second in Malaysia, with an average ASR of 17.3. Indians had the lowest risk of developing cervical cancer as compared to Malays (RD 0.22, CI 0.18 - 0.26) and Chinese (RD 0.46, CI 0.41 - 0.51). Ovarian cancer was ranked fourth among Malaysians with an average ASR of 7.3 over the seven-year cancer registry. Indians had a lower ovarian cancer risk than Chinese (RD 0.29, CI 0.27 - 0.31) and Malays (RD 0.36, CI 0.34 - 0.38). In 2008, endometrial cancer was ranked sixth in the most-occurring cancers among Malaysian females (average ASR 6.5). Malay females were noticed to have a slightly lower risk of corpus uteri carcinoma than Chinese women (RD -0.06, CI -0.09 -0.03), but are at a higher risk than Indian women (RD 0.25, CI 0.23, - 0.28). The age group of 50-59 has the peak incidence for breast cancer and cervical cancer. Endometrial cancer incidence peaked in the age group of 60-69 years while ovarian cancer incidence rose sharply after the age of 40 years.

Keywords: Breast cancer, Ovarian cancer, Cervical cancer, Endometrial cancer, Malaysia

Introduction

Cancer ranks as one of the most common causes of death worldwide, with 8.2 million cancer deaths reported in 2012 [1]. The majority of the deaths were caused by lung, breast, colorectal, stomach, and prostate cancers [2]. However, addressing the cancer context based on gender, there are also a variety of female-specific cancers including female breast, cervical, uterine or corpus uteri or endometrial or placental, ovary, vagina, vulva and fallopian ligament/adnexa cancer. The highest rates of breast cancer in women were observed in European regions and America, where the rates were almost double that of other regions. For cervical cancer, the highest cancer incidence was reported in women from the African region, followed by Southeast Asia, while the lowest rate was observed in the Eastern Mediterranean region [2].

According to GLOBOCAN 2012, the overall cancer incidence rate and overall mortality rate for Asia are lower than developed continents such as North America, Oceania (Australia, New Zealand) and Europe, for both genders [1]. Based on the WHO top five-cancer lists in 2012, the most common female-specific cancers globally are breast and cervical cancer. Breast cancer had the highest mortality rate with 521,000 deaths that year [3]. Southeast Asia ranked second highest for incidences of and mortality from breast cancer of sub-regions in Asia [1]. Epidemiology studies help us to identify the populations that are at the highest risk and to learn about the various genetic and non-genetic risk factors of cancer with the aim of reducing the burden of cancer [3, 4]. It can also assist in early intervention in the form of education, medical care and diagnostics. Some of the interventions include increasing general public awareness, identifying family-based risk for suspected inherited cancer, and providing counseling for high-risk patients [4]. Many cancers have a higher cure rate when detected and reported at an early stage, and cancer treatments are more effective if the cancer is diagnosed early [3, 4].

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Malaysia, an upper-middle-income country in Southeast Asia, has a different cancer pattern from the high-income groups in America and Europe. However, Malaysia showed a similar trend when compared to the same income group in Europe and Asia in which lung and breast cancer are the most common cancers among males and females [5]. Malaysia is a multi-ethnic country with a population of 28.3 million in 2010, consisting of 67.4% Bumiputera, 24.6% Chinese, 7.3% Indians and 0.7% other ethnic groups. Among the Malaysian citizens from Peninsular Malaysia and East Malaysia, the Malays are the predominant ethnic group in Peninsular Malaysia, while the Ibans are predominant in Sarawak and the Kadazan/Dusun are predominant in Sabah [6]. The most common female-specific cancer in Malaysia is breast cancer, which show similar trend among all Asian countries [1, 5]. In addition, due to the vast diversity in ethnic groups in Malaysia, it is crucial to observe the patterns of ethnic variation in female-specific cancers so that cancer prevention interventions such as provision of education and screening can be targeted to high-risk groups. Generally, Malaysian women are more susceptible to cancer than men. Female breast cancer was the most prevalent cancer among females, as it accounted for 30-31% cases reported in two consecutive National Cancer Registries. Among all ethnic groups, Chinese had overall higher cancer rates than Malays and Indians. The age group of 30- to 50-year-olds had the highest prevalence of female-specific cancers [7, 8].

This study aims to review epidemiological studies of female-specific cancers in Malaysia. The objectives of this study are:

1. To study the female-specific cancer patterns in this country
2. To identify subgroups in the population (in terms of ethnicity, age, etc.) that are at higher risk of getting female-specific cancers

Materials and Methods

Study Design

A systematic review of literatures published on databases from 1st January 1980 up to 31st May 2016 was conducted. Studies involving female-specific cancers in Malaysia were identified.

Search Strategy

Relevant studies on female-specific cancers in Malaysia were systematically reviewed by using the Asian Pacific Journal for Cancer Prevention website, and electronic databases including Medline, PubMed, Wiley online library, and ProQuest Central. Included articles were published in any languages and involved all types of trials on patients of all ages between 1980 and 2016 (PRISMA Flow Diagram).

Search Terms

A search was made on PubMed using: ((((((((((((breast cancer) AND Malaysia)) OR ((cervical cancer AND Malaysia)) OR ((uterine cervix cancer) AND Malaysia)) OR ((endometrial cancer) AND Malaysia)) OR ((ovarian cancer) AND Malaysia)) OR ((vagina cancer) AND Malaysia)) OR ((vulva cancer) AND Malaysia)) OR ((placental cancer) AND Malaysia)) OR ((fallopian cancer) AND Malaysia))

Inclusion/Exclusion Criteria

The author included studies that reported the incidences of female-specific cancers in Malaysia, such as cancers of the female breast, cervix uteri, corpus uteri, endometrium, ovary, vagina, vulva, placenta, and fallopian ligament. Studies were excluded if they focused on survival rates, level of awareness, anxiety status of cancer patients, or incidences of cancer screening. The following types of studies were included: reports, prospective studies, retrospective studies, longitudinal studies and record-review studies. However, controlled trials, letters, reviews, opinions, case studies, conference papers, or editorial papers were not included.

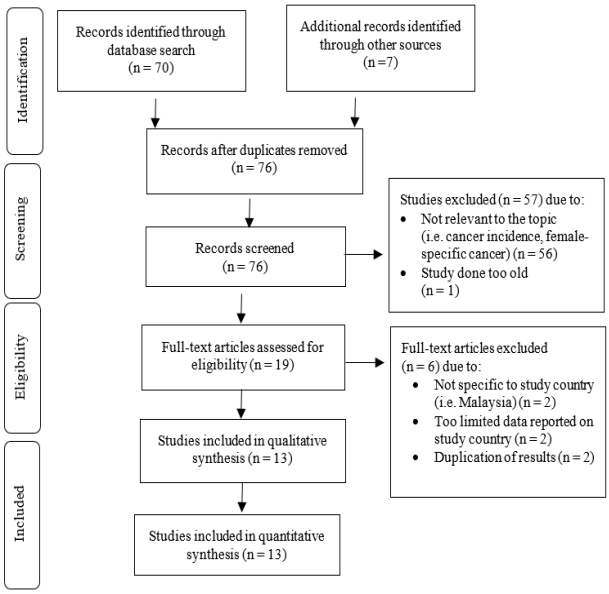

Figure 1. PRISMA 2009 flow diagram

Data Extraction

A data extraction form was developed to collect relevant information for articles that met the inclusion criteria. The data extracted included (1) study author names, (2) year of study, (3) study objectives, (4) study design (e.g. reports, prospective studies, retrospective studies, longitudinal studies, and record-review studies), (5) sample size, (6) study population (age and ethnicity), (7) category of cancers, and (8) main findings. Age-standardized incidence, presentation of cancer, lymph node involvement and relative distribution of tumour subtypes are further divided into subcategories of ethnicities.

Data Analysis

All the quantitative data extracted was further analyzed by estimating the risk difference for the types of cancer among different ethnic groups reported across the selected papers.

Results and Discussion

There were 76 articles identified after the initial screening and 13 studies were included in this review. In total 63 studies were excluded, for the following reasons: study did not report cancer incidences or female-specific cancers (n = 56); study done was too old (n = 1); study done was not specific to the country, which is Malaysia (n = 2); data available was too limited for extraction (n = 2); and duplication of results reported (n = 2) **(Figure 1)**.

Study Characteristics

The characteristics of the included studies are listed in **Table 1**. Among the 13 studies, 11 were conducted specifically in Malaysia, one in the ASEAN region [9], and, one in Singapore-Malaysia [10]. 10 studies took place in hospital-based settings, while three are from cancer registries, specifically two from the National Cancer Registry and one from Penang Cancer Registry.

Table 1. Characteristics of included studies

#	Author	Year	Study design	Study period	Female Specific Cancers	Ethnic group studied
1	Lim GCC, Yahaya H, Lim TO	2002	Multicentre Report	1st Jan 2002 to 31st Dec 2002	Breast- Cervix Uteri- Ovary- Corpus Uteri Vagina- Vulva Placenta- Fallopian Ligament/ Adnexa	Malay, Chinese, Indian
2	Lim GCC, Rampal S, Yahaya H	2008	Multicenter Report	1st Jan 2003 to 31st Dec 2005	Breast- Cervix Uteri Corpus Uteri-Ovary	Malay, Chinese Indian
3	Azizah Ab M, Devaraj T, Bina Rai S, Norbaiyah Y, Nooraihan M, Noorshila S	2010	Technical Report	1st January 2004 to 31st December 2008	Breast- Cervix Uteri Ovary - Corpus Uteri	Malay, Chinese Indian
4	ACTION Study Group, Kimman M, Jan S, Yip CH, Thabrany H, Peters SA, Bhoo-Pathy N, Woodward M.	2015	Prospective longitudinal study	Between March 2012 and September 2013	Breast - Cervix Uterus - Ovary	Not stated
5	Bhoo-Pathy N, Subramaniam S, Taib NA, Hartman M, Alias Z, Tan GH, Ibrahim RI, Yip CH, Verkooijen HM.	2014	Prospective study	Between 1993 and 2011	Breast	Malay, Chinese Indian, Others
6	Bhoo-Pathy N, Hartman M, Yip CH, Saxena N, Taib NA, Lim SE, Iau P, Adami HO, Bulgiba AM, Lee SC, Verkooijen HM	2012	Prospective study	Between 1990 and 2007	Breast	Malay, Chinese Indian
7	Devi C, Tang TS, Corbex M	2012	Prospective study	Between 1998 and 2009	Breast	Not stated
8	Pathy NB, Verkooijen HM, Taib NA, Hartman M, Yip CH.	2011	Prospective study	Between 1993 and 2008	Breast	Malay, Chinese
9	Cheah PL, Looi LM, Sivanesaratnam V.	1999		January 1, 1991 to December 31, 1992, and January 1, 1996, to December 31, 1997	Cervical	Malay, Chinese Indian, Others
10	Hamzi Abdul Raub S, Isa NM, Zailani HA, Omar B, Abdullah MF, Mohd Amin WA, *et al*.	2014	Multicentre retrospective study	Period of 9 years	Cervical	Malay, Chinese Indian, Others
11	Jalil NA, Zin AA, Othman NH.	2015		From 2000 to 2011	Breast - Cervical Ovary - Endometrial	Malay, Chinese Indian
12	Juhan N, Abd Razak N, Zubairi Y Z, Khattak MN, Naing NN	2013	Retrospective record review study	From 1st July 1995 and 30th June 2007	Cervical	Malay, Non-Malay
13	Razak NA, Khattak MN, Zubairi YZ, Naing NN, Zaki NM	2013	Retrospective record review design	Between 1st July 1995 and 30th June 2007	Cervical	Malay Non-Malay

Overall Female-Specific Cancer Incidence

Incidence

According to the GLOBOCAN 2012 report by the International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO), it is estimated that 25.0% of the cancers in Malaysia (9,363 new cases) are female-specific cancers, which is higher than the overall global incidence (19.7%). The 5-year prevalence for female-specific cancers in Malaysia is 38.4%, compared to 29.5% globally [11]. **Table 2** provides the incidence, 5-year prevalence, and mortality of female-specific cancers as documented by GLOBOCAN 2012.

Table 2. Estimated Incidence, 5-year-prevalence and mortality of female-specific cancers for Malaysia and the World based on GLOBOCAN 2012

Malaysia									
Cancer	**Incidence**			**5-year-prevalence**			**Mortality**		
	Number	(%)	ASR	Number	(%)	Proportions	Number	(%)	ASR
Breast	5,410	14.5	38.7	18,928	23.8	184.4	2,572	11.9	18.9
Cervix uteri	2,145	5.7	15.6	6,130	7.7	59.7	621	2.9	4.7
Corpus uteri	710	1.9	5.3	2,694	3.4	26.3	220	1	1.7
Ovary	1,098	2.9	7.8	2,741	3.5	26.7	645	3	4.9
Total	9,363	25	67.4	30,493	38.4	297.1	4,058	18.8	30.2
Globally									
Breast	1,671,149	11.9	43.1	6,232,108	19.2	239.9	521,907	6.4	12.9
Cervix uteri	527,624	3.8	14	1,547,161	4.8	59.6	265,672	3.2	6.8
Corpus uteri	319,605	2.3	8.2	1,216,504	3.7	46.8	76,160	0.9	1.8
Ovary	238,719	1.7	6.1	586,624	1.8	22.6	151,917	1.9	3.7
Total	2,757,097	19.7	71.4	9,582,397	29.5	368.9	1,015,656	12.4	25.2

The most frequent female-specific cancer among Malaysians was breast cancer (14.5%), followed by cancer of the cervix uteri (5.7%), ovarian cancer (2.9%) and cancer of the corpus uteri (1.9%). When compared with the incidence trend globally, breast cancer (11.9%) and cervical cancer (3.8%) had the same position as Malaysia, namely the top two, but the sequencing for cancer of the corpus uteri (2.3%) and ovarian cancer (1.7%) were slightly different in Malaysia than globally [11].

Stage at Diagnosis and Survival

The survival of patients with breast and cervical cancer is dependent on three main prognostic variables, which are the stage of disease at first diagnosis, the size of the tumor, and the histopathology of cancer [12, 13]. Additionally, breast cancer has another major prognostic variable, which is menstrual status [12]. Breast and cervical cancers are also affected by other underlying factors such as socio-demographic factors (age, ethnicity) and the availability of effective prevention and treatment methods (cancer screening) [12, 13]. Lifestyle factors such as being sexually active tend to reduce the risk of cervical cancer [13].

The overall 5-year survival rates reported for breast and cervical cancers in Malaysia is 49% and 71.1% respectively. Malay women tend to present at the more advanced stage in cancers and have poorer prognosis, which has contributed to them having the lowest survival rate among all three main ethnic groups. Some other factors that may contribute to delayed presentation for cancer treatments are widowers, divorcees, lack of breast self-examination and strong beliefs in traditional medicines [12, 13].

Mortality

The mortality level from female-specific cancers in Malaysia was estimated to be 18.8% of all cancers, comprising 4,058 cases. When compared with the global mortality rate (12.4%), Malaysia has relatively high mortality The top three causes of female cancer deaths both in Malaysia and the world are breast cancer, cervical cancer and ovarian cancer [11].

Four Major Female-Specific Cancers in Malaysia

Breast Cancer

Since 2002, breast cancer has been the most common cancer across all ethnic groups among Malaysian females, and accounted for about 31% of all female-specific cancers [7, 8, 14, 15]. Overall, the lifetime risk for breast cancer among Malaysian women overall was 1 in 20: 1 in 16 for Chinese, 1 in 17 for Indians, and 1 in 32 for Malays [14, 15]. Breast cancer had an average age-standardized rate (ASR) of 48.6 per 100,000 women. Across all studies, Indians had the lowest breast-cancer incidence, then Malays and then the Chinese had the highest incidence. Both Malays and Chinese had more than double the incidence of Indians [7, 8, 14-17]. From 2002 to 2008, the Chinese had the highest ASR with an

average of approximately 62 per 100,000 females, Indians 56 per 100,000, and Malays had the lowest incidence with an ASR of 36 per 100,000 females [7, 8, 14-17]. Overall, 80.0% of females had no familial history of breast cancer and had breastfed. More than 50% of breast cancer patients had three or more children [16, 17]. The most common histologic type for breast cancer was infiltrating duct carcinoma, NOS, comprising 84.5% (4522) of all breast cancer cases [14]. Addressing the Malaysian scenario based on age, the incidence of having breast cancer increases in the age group of 50- to 60-year-olds and then declines gradually in the older age groups **(Table 3)**. This trend is slightly different for Malay and Sarawak females where the peak incidence occurs earlier: between the age of 40 and 50 [7, 8, 16, 18].

Table 3. ASR of female-specific cancers and age sorted according to year of publication

#	Types of Cancer	Incidence	Ethnic Groups			Age								
			Malay	Chinese	Indian	<30	<40	<50	30-50	40-60	45-60	50-65	50-70	>60	>70
1	Breast Cervix Uteri Ovary Corpus Uteri	4337 1715 707 517	1888 542 369 204	1874 887 258 243	450 191 55 52	92 27 99 10	-	-	2176 763 280 132	-	-	-	1827 786 276 314	-	242 139 52 61
2	Breast Cervix Uteri Corpus Uteri Ovary	11952 4057 1253 1627	4969 1205 500 745	5051 1968 528 595	1265 355 161 159	NR	-	-	NR	-	-	-	NR	-	NR
3	Breast Cervix Uteri Ovary Corpus Uteri	1699 418 280 237	392 89 87 65	1115 284 153 124	182 39 39 46	NR	-	-	NR	-	-	-	NR	-	NR
4	Breast Cervix Uterus Ovary	2445 1005 177 242	NR	NR	NR	-	-	2780		2801		2463	-	1467	-
5	Breast	4930	1054	3179	615	-	-	2177		-	-	1961	-	792	-
6	Breast	5624	968	3767	529	NR		-	NR	-	-		NR	-	NR
7	Breast	1034	NR	NR	NR		141	-		356		314		223	
8	Breast	375	132	202	NR	NR		-	NR	-	-	-	NR	-	NR
9	Cervical	266	39	193	29	NR		-	NR	-	-	-	NR	-	NR
10	Cervical	280	135	112	25	-	21	-	-	81			133	-	45
11	Breast Cervical Ovary Endometrial	437 159 143 121	730	110	4	NR		-	NR	-	-	-	NR	-	NR
12	Cervical	120	99	21	-	-	2	-	-	97	-		-	21	-
13	Cervical	120	99	21	NR	-	15	-	-	46	-	38	-	21	-

- = not available, NR = not reported

Age groups are kept as were specified in the original articles, in order to avoid an confusion to the interpreted results.

Quantitative analysis and comparison between the three ethnic groups have further clarified the overall risk difference among the three ethnicities. Comparison between Malays and Chinese revealed that the risk of having breast cancer among Malay women was 20% lower than for Chinese women (-0.20 [-0.21, -0.19]) **(Table 4)**. However, Malay women had a 22.0% higher likelihood of breast cancer than the Indian women (0.22 [0.21, 0.22]) **(Table 5)**. Overall, the risk of breast cancer was noticed to be highest among Chinese women (0.42 [0.41, 0.43]), followed by Malay and Indian women **(Tables 4-6)**.

Table 4. Risk difference of cancer among Malay and Chinese women

Type of Cancer	Malay		Chinese		Risk difference
	Events	Total	Events	Total	CI 95%
Breast Cancer					
Lim GC (2002)	1888	4337	1968	4337	0.00 [-0.02, 0.02]
Lim GC *et al.* (2008)	4969	11952	5051	11952	-0.01 [-0.02, 0.01]
Pathy NB *et al.* (2011)	132	375	202	375	-0.19 [-0.26, -0.12]
Azizah Ab M *et al.* (2010)	392	1699	1115	1699	-0.43 [-0.46, -0.40]
Bhoo-Pathy N *et al.* (2014)	1054	4930	3179	4930	-0.43 [-0.45, -0.41]
Bhoo-Pathy N *et al*. (2012)	968	5624	3767	5624	-0.50 [-0.51, -0.48]
Subtotal (95% CI)		**28377**		**28377**	**-0.20 [-0.21, -0.19]**
Total events	**9403**		**15188**		
Cervix Uteri					
Lim GC *et al.* (2008)	1205	4057	1968	4057	-0.19 [-0.21, -0.17]
Lim GC (2002)	542	1715	887	1715	-0.20 [-0.23, -0.17]
Azizah Ab M *et al*. (2010)	89	418	284	418	-0.47 [-0.53, -0.41]
Subtotal (95% CI)		**6190**		**6190**	**-0.21 [-0.23, -0.19]**
Total events	**1836**		**3139**		
Corpus Uteri					
Lim GC *et al.* (2008)	500	1253	528	1253	-0.02 [-0.06, 0.02]
Lim GC (2002)	204	517	243	517	-0.08 [-0.14, -0.02]
Azizah Ab M *et al*. (2010)	65	237	124	237	-0.25 [-0.33, -0.16]
Subtotal (95% CI)		**2007**		**2007**	**-0.06 [-0.09, -0.03]**
Total events	**769**		**895**		
Ovary					
Lim GC (2002)	369	707	258	707	0.16 [0.11, 0.21]
Lim GC *et al.* (2008)	745	1627	595	1627	0.09 [0.06, 0.13]
Azizah Ab M *et al*. (2010)	87	280	153	280	-0.24 [-0.32, -0.16]
Subtotal (95% CI)		**2614**		**2614**	**0.07 [0.05, 0.10]**
Total events	**1201**		**1006**		
Cervical					
Juhan N *et al.* (2013)	99	120	21	120	0.65 [0.55, 0.75]
Hamzi Abdul Raub S *et al*. (2014)	135	280	112	280	0.08 [0.00, 0.16]
Cheah PL *et al.* (1999)	39	266	193	266	-0.58 [-0.65, -0.51]
Subtotal (95% CI)		**666**		**666**	**-0.08 [-0.13, -0.03]**
Total events	**273**		**326**		

Cervical Cancer

In Malaysia, cervical cancer has been ranked second among all female-specific cancers after breast cancer for the past decade [7, 8, 14, 15]. Cervical cancer is also known as the most common cancer of the female reproductive organs [13]. Over 90% of the invasive cervical cancer cases reported were with human papillomavirus (HPV), especially for HPV genotypes 16 and 18 [19]. Overall cervical cancer had an average ASR of 17.3 per 100,000 based on the cancer registry throughout seven years [7, 8, 14, 15]. The Malays had the lowest incidence with an average ASR of 9.8 per 100,000 population from four cancer registry reports, the highest were

the Chinese with an ASR of 25 per 100,000, and Indians were in between, with an ASR of 20 per 100,000 [7, 8, 14, 15]. The three national cancer repositories (NCR) reported the incidence increased after the age of 20, peaked in the age group 50- to 59-years-old, and declined after that [7, 8, 14]. Squamous cell carcinoma was the most common histologic type for cervical cancer [14]. Upon further analysis it is revealed that Indians had the lowest risk of developing cervical cancer when compared to Malays (0.22 [0.18, 0.26]) and Chinese (0.46 [0.41, 0.51]), as shown in **Tables 4-6**. Overall, Chinese women were observed as having the highest risk of cervical cancer.

Ovarian Cancer

In 2002, ovarian cancer was the fourth most-common female-specific cancer in Malaysia, and it dropped to fifth in 2004-2008, making up about 5.0% of all female cancer cases [7, 8, 14, 15]. It reported an average ASR of 7.3 per 100,000 over the seven-year cancer registry. Chinese and Indians reported higher ASRs than Malays, with 8.0, 7.8 and 6.3 respectively. Ovarian cancer was seen in all age groups and the incidence increased sharply after the age of 40 years, and declined at an older age [7, 8, 14]. Serous adenocarcinomas, mucinous cyst adenocarcinoma, and adenocarcinoma, comprising 22.1%, 18.2% and 18.0% of ovarian cases respectively, was the more common morphologic type [14].

Among all three ethnic groups, Indians had the lowest ovarian cancer risk when compared to both Chinese (0.29 [0.27, 0.31]) and Malays (0.36 [0.34, 0.38]) **(Tables 4-6)**. Based on the number of cases reported, the risk difference of ovarian cancer between Chinese and Malay women was 7%. Overall Malay women were at the highest risk of ovarian cancer, followed by Chinese and Indians.

Table 5. Risk difference of cancer among Malay and Indian women

Type of cancer	Malay		Indians		Risk difference
	Event	Total	Event	Total	CI 95%
Breast Cancer					
Lim GC (2002)	1888	4337	450	4337	0.33 [0.31, 0.35]
Lim GC *et al*. (2008)	4969	11952	1265	11952	0.31 [0.30, 0.32]
Azizah Ab M *et al.* (2010)	392	1699	182	1699	0.12 [0.10, 0.15]
Bhoo-Pathy N *et al*. (2014)	1054	4930	615	4930	0.09 [0.07, 0.10]
Bhoo-Pathy N *et al.* (2012)	968	5624	529	5624	0.08 [0.07, 0.09]
Pathy NB *et al.* (2011)	132	375	0	0	Not estimable
Subtotal (95% CI)		**28917**		**28542**	**0.22 [0.21, 0.22]**
Total events	**9403**		**3041**		
Cervix Uteri					
Lim GC *et al.* (2008)	1205	4057	355	4057	0.21 [0.19, 0.23]
Lim GC (2002)	542	1715	191	1715	0.20 [0.18, 0.23]
Azizah Ab M *et al.* (2010)	89	418	39	418	0.12 [0.07, 0.17]
Subtotal (95% CI)		**6190**		**6190**	**0.20 [0.19, 0.22]**
Total events	**1836**		**585**		
Corpus Uteri					
Lim GC *et al.* (2008)	500	1253	161	1253	0.27 [0.24, 0.30]
Lim GC (2002)	204	517	52	517	0.29 [0.24, 0.34]
Azizah Ab M *et al.* (2010)	65	237	46	237	0.08 [0.00, 0.16]
Subtotal (95% CI)		**2007**		**2007**	**0.25 [0.23, 0.28]**
Total events	**769**		**259**		
Ovary					
Lim GC (2002)	369	707	55	707	0.44 [0.40, 0.49]
Lim GC *et al.* (2008)	745	1627	159	1627	0.36 [0.33, 0.39]
Azizah Ab M *et al.* (2010)	87	280	39	280	0.17 [0.10, 0.24]
Subtotal (95% CI)		**2614**		**2614**	**0.36 [0.34, 0.38]**
Total events	**1201**		**253**		

Cervical					
Hamzi Abdul Raub S *et al*. (2014)	135	280	25	280	0.39 [0.33, 0.46]
Cheah PL *et al*. (1999)	39	266	29	266	0.04 [-0.02, 0.09]
Juhan N *et al*. (2013)	99	120	0	0	Not estimable
Subtotal (95% CI)		**666**		**546**	**0.22 [0.18, 0.26]**
Total events	**273**		**54**		

Endometrial Cancer

For the most frequent cancer among Malaysian females, endometrial cancer was ranked seventh in 2002, and then rose to sixth in 2008 [7, 8, 14, 15] from 2002 to 2005, the average ASR for endometrial cancer was 6.5. Among the three main ethnic groups, Indians had the highest seven-year average ASR of 10.0 per 100,000, the Chinese had an ASR of 7.7, and the Malays had the lowest ASR of 3.7. The incidence for endometrial cancer was fairly low before the age of 30 years and increases with age. The incidence peaked between the ages of 60 and 69 and declined thereafter [7, 8, 14]. The most frequent histologic type of endometrial cancer was adenocarcinoma, NOS, comprising 55.3% (390) cases [14].

Further analysis reveales that risk difference for corpus uteri among Malay and Chinese women was (-0.06 [-0.09, -0.03]) **(Table 4)**. Malay women were at least 6% less at risk of carcinoma of corpus uteri. In comparison with Indian women, Malay women were at a higher risk (0.25 [0.23, 0.28]) of having carcinoma of corpus uteri. Like other types of cancer, Chinese women remained at the highest risk of having carcinoma of corpus uteri. Details are shown in **Tables 4-6**.

Table 6. Risk difference of cancer among Chinese and Indian women

Type of cancer	Chinese		Indians		Risk difference
	Event	Total	Event	Total	CI 95%
Breast Cancer					
Bhoo-Pathy N *et al.* (2012)	3767	5624	529	5624	0.58 [0.56, 0.59]
Azizah Ab M *et al.* (2010)	1115	1699	182	1699	0.55 [0.52, 0.58]
Pathy NB *et al*. (2011)	202	375	0	0	Not estimable
Bhoo-Pathy N *et al.* (2014)	3179	4930	615	4930	0.52 [0.50, 0.54]
Lim GC (2002)	1874	4337	450	4337	0.33 [0.31, 0.35]
Lim GC *et al.* (2008)	5051	11952	1265	11952	0.32 [0.31, 0.33]
Subtotal (95% CI)		**28917**		**28542**	**0.42 [0.41, 0.43]**
Total events	**15188**		**3041**		
Cervix Uteri					
Azizah Ab M *et al.* (2010)	284	418	39	418	0.59 [0.53, 0.64]
Lim GC (2002)	887	1715	191	1715	0.41 [0.38, 0.43]
Lim GC *et al.* (2008)	1968	4057	355	4057	0.40 [0.38, 0.42]
Subtotal (95% CI)		**6190**		**6190**	**0.41 [0.40, 0.43]**
Total events	**3139**		**585**		
Corpus Uteri					
Lim GC (2002)	243	517	52	517	0.37 [0.32, 0.42]
Lim GC *et al*. (2008)	528	1253	161	1253	0.29 [0.26, 0.33]
Azizah Ab M *et al.* (2010)	153	237	46	237	0.45 [0.37, 0.53]
Subtotal (95% CI)		**2007**		**2007**	**0.33 [0.31, 0.36]**
Total events	**924**		**259**		
Ovary					
Lim GC (2002)	258	707	55	707	0.29 [0.25, 0.33]

Lim GC *et al.* (2008)	595	1627	159	1627	0.27 [0.24, 0.30]
Azizah Ab M *et al.* (2010)	153	280	39	280	0.41 [0.34, 0.48]
Subtotal (95% CI)		**2614**		**2614**	**0.29 [0.27, 0.31]**
Total events	**1006**		**253**		
Cervical					
Juhan N *et al.* (2013)	21	120	0	0	Not estimable
Hamzi Abdul Raub S *et al.* (2014)	112	280	25	280	0.31 [0.24, 0.38]
Cheah PL *et al.* (1999)	193	266	29	266	0.62 [0.55, 0.68]
Subtotal (95% CI)		**666**		**546**	**0.46 [0.41, 0.51]**
Total events	**326**		**54**		

Risk Factors for Female-Specific Cancers

Tobacco

Smoking had been attributed to increasing the risk of cancers. Being a current cigarette smoker was shown to raise the risk of squamous cell carcinoma in cervical cancer by up to 60%, or two- to four-fold [13]. In addition, a meta-analysis reported current smoking increased the risk of mucinous cancer in ovarian cancers two- to three-fold, and the risk increased with the amount of smoking. The risk of cancers returns to baseline risk within 20 to 30 years of smoking cessation [20].

There was inconsistent evidence on the relationship between smoking and breast cancer. In a large study in the United States, current smokers had an increased risk of getting breast cancer and the risk increased with smoking intensity in both pre- and postmenopausal women [21, 22]. One article from Malaysia associated the increasing number of female smokers with the increase in breast cancer incidences. It also stated that young female smokers or being a long-term second-hand smoker increased the risk of premenopausal breast cancer [20, 23].

Diet

Malaysian studies have found that red meat and high-fat food such as pork increases the risk of breast cancer [20]. This was researched and was suggested that high-fat foods (e.g. meat, dairy products, and fried foods) increased the amount of oestrogen that encouraged cancer cell growth. High-fat food intake and consumption during premenopausal years was associated with an almost 20% higher risk of breast cancer [20]. The World Cancer Research Fund reported increased consumption in fruits and vegetable, especially green vegetables, may contribute to a lower risk of breast cancer. Additionally, the Shanghai Women's Health Study found that high soy food intake during adolescence and as an adult protected against premenopausal breast cancer [24].

Alcohol

The risk of developing breast cancer proportionally increases with alcohol consumption. In a meta-analysis, a modest increase in risk was associated with drinking from one to three or more alcoholic drinks per day [20, 25]. Epidemiological studies found that every additional 10g increase in consumption of alcohol per day was associated with an increased breast cancer risk of 7.1%. Also, the risk was the same for female smokers and non-smokers but it is uncertain whether there is any difference in risk between pre- and post-menopausal women. On the other hand, no significant risk was found between alcohol intake and endometrial cancer; rather, an inverse relationship was observed between endometrial cancer and light alcohol consumption [26]. Alcohol may offer possible protection from ovarian cancer, though further studies are required to confirm this [25].

Breastfeeding

A Malaysian study claimed that breastfeeding among the Malay ethnic group was linked with a reduced risk of breast cancer [20]. Studies reported that the duration of breastfeeding played a crucial role; it was found that breastfeeding for at least one year decreased the risk among BRCA1 mutation carriers by 32% and the reduction was even stronger for those who breastfed for two or more years [20, 27, 28]. This is likely to be due to the cumulative exposure to estrogen and decrease in the regulating role of progesterone for breast cancer. Interestingly, there was no association discovered between BRCA2 mutation carriers and breastfeeding despite the duration of breastfeeding being one or more years [27, 28].

Studies have also shown a slightly decreased risk of ovarian and endometrial cancer is associated with breastfeeding, particularly with a longer duration of breastfeeding [29]. However, a study found that the inverse relationship between breastfeeding and ovarian cancer was only confined to pre-menopausal women [30]. Although there were studies that reported inconsistent results on the decreased risk of endometrial cancer, a study suggested long-term lactation which took place in developing countries may make the risk of endometrial cancer lower than in developed countries [30].

Cancer Screening

Cervical Cancer Screening

Cervical cancer screening or conventional Pap-smear screening started in Malaysia in 1969. In 1995, cervical

cancer screening was provided by various parties as part of a cancer campaign and was available once every 3 years for all women aged between 20 and 65 [31]. The current 2003 Clinical Practice Guidelines on management of cervix cancer recommended all sexually active women aged between 20 and 65 to have a Pap smear screening for two consecutive years. If both results shown are negative, then the guidelines recommended to have a screening once every 3 years [32].

Malaysia reported 26% coverage of Pap-smear screening in 1996, which increased to 47.3% in 2006, which is considered low compared to developed countries such as Finland and United Kingdom, where the coverage is 70% and above. Various factors could lead to the poor practice in Pap-smear screening in Malaysia, such as an insufficient average doctor-to-population ratio, and a lack of cytoscreeners or smear-readers. Among well-educated women, 36% were unfamiliar with Pap-smear screening, 13% were afraid to do the test, 10% were embarrassed and 3% did not manage to find a female physician. Furthermore, a Pap smear is a culturally taboo subject in Malaysia and many Malaysians still believe in traditional health care [33, 34].

Cervical cancer screening has a strong impact in decreasing the incidence of cervix cancer. Studies reported the screening to be very effective in decreasing cervical cancer incidence and mortality when done on sexually active women once yearly or once every two to five years [32]. For instance, a European study found that screening among the 35-64 age group every 1 to 3 years reduced the cervix cancer incidence rate by more than 90%. The efficacy of cervical cancer screening had shown to decrease with decreasing frequency, with 83% for a screening every 5 years, and 64.1% for a screening every decade [35].

However, due to the high sensitivity and specificity of the conventional cervical cytology test, the results obtained may vary a lot, which could be possibly due to both sampling and detection errors. Besides, in developing countries like Malaysia, there is limited budget allocated to health care and limited resources; hence the screening approach in developing countries was less successful in reducing cervical cancer than developed countries. Malaysia, a middle-income developing country, may consider focusing on reorganizing the screening program with good quality and a highly sensitive test as well as wide coverage (>80%) of the targeted population [32]. More cost-effective alternatives that have been used in low-income developing countries, such as visual inspection with acetic acid (VIA) and HPV DNA testing, may be considered only if reorganizing Pap-smear screening fails. This is because researchers are still evaluating the accuracy and effectiveness of the alternatives that have been used in developing countries [32].

Breast Cancer Screening

In Malaysia, breast cancer screening consists of Breast Self-Awareness (BSA), Clinical Breast Examination (CBE) and mammography screening. In 2006, BSA had a prevalence rate of 57.14 %, CBE had a rate of 51.77 % and mammography 7.57 %. The age group with the highest percentage of women doing breast examinations was 30- to 34-year-olds (82.04%). The current screening policy recommends all women between 20 and 39 years old to have a CBE once every 3 years and women above 40 years or high-risk groups to have an annual CBE [36]. The low percentage of population who underwent mammography could possibly be due to the various reasons. Mammograms were only provided for free at government facilities for those considered 'high risk' according to the Clinical Practice Guidelines. Otherwise, Malaysian women had to have their mammography done in private centers at their expenses.

This is perhaps the first systematic review aiming to scrutinise the overall risk of female-specific cancers in Malaysia. Based on the four most common female-specific cancers in the country, Chinese women had the highest risk of breast, cervical, and endometrial cancer whereas Malay women had the highest risk of ovarian cancer. The peak incidence of breast cancer and cervical cancer was in the 50-59-year-old age group. Endometrial cancer incidence peaked between 60 and 69, whereas the incidence rose sharply after the age of 40 for ovarian cancer.

Breast cancer was the most common cancer and had the highest ASR among all female-specific cancers in Malaysia, and it seems to require more attention than other cancers. Among all Southeast Asian countries, Malaysia and Thailand had the largest increase in breast cancer mortality rates whereas Hong Kong and Singapore had stabilised trends. Malaysia was reported to have a 6% increase per year between 1997 and 2008, while Thailand had a 7% increase per year between 2000 and 2006, with an average annual increase of 9% from 1985 onwards. The mortality trend for Malaysia is similar to the Philippines and South Korea, where breast cancer mortality rates increased in groups both under and above 50 years old [37]. Some possible risk factors have been associated with developing female-specific cancers in a Malaysian setting, such as obesity, diet (especially a diet high in fat), a sedentary lifestyle, and consumption of oral contraceptive pills. These factors affect the risk of developing female-specific cancers.

Although cervical cancer was not the most common cancer, the National Cancer Society Malaysia has focussed heavily on cervical cancer screening and prevention such as HPV vaccination and pap smear test [38]. This is because cervical cancer caused by HPV through sexual contact can be more easily prevented or reduced by screening than breast cancer. One-fifth of the malignancies in developing countries are caused by infectious agents, including HPV, which leads to cervical cancer. In contract, these cause only 8% of all malignancies in developed countries, as most malignancies in these countries are caused by chronic infections only. Developed countries are equipped with better public health infrastructure, have higher compliance among women, and have better coverage for Pap-smear testing leading to early

detection of cervical cancer, thus successfully reducing the mortality rate in developed countries. According to the WHO, the main reason for this may be vaccines. The WHO predicts that the HPV vaccination will be able to prevent cervical cancer in the near future [39].

Limitations

This systematic review has several limitations. Firstly, Malaysia consists of various multi-ethnic populations with different genotypes or genetic factors, cultures, socioeconomic status, lifestyle behaviours and cancer risks. Chinese population in particular presented very different cancer rates and cancer risks compared to other ethnic groups. So, studies that classified all of the ethnic groups together may be unreliable. For instance, when studies just categorise Malays and non-Malays, non-Malays may consist of many ethnic groups. Next, most of the studies done in Malaysia focused on the two or three main ethnic groups and do not report any data on the minority ethnic groups. Also, there were papers and national registry reports that only studied Peninsular Malaysia or certain states. This may lead to potential bias of over-reporting of certain ethnic groups because the ethnic distribution for all states are slightly different; for example, the predominant ethnic group for Sarawak is Ibans, and for Penang is Chinese. Therefore these studies do not show the complete report for the whole Malaysian population.

Conclusion

Overall, cancer incidence is expected to rise due to an aging population, and the cancer burden will continue to grow. This report has shown that the Chinese have a generally higher risk of developing female-specific cancers than Indians or Malays, with the exception of ovarian cancer that was dominated by the Malay population. Cancer screening and prevention programmes should be done with the most cost-effective method as the country only has a limited budget for its healthcare system, for instance putting more focus on the Chinese population. However, it is essential to provide good quality training to yield more qualified personnel to ensure these programmes will be carried out effectively.

Directions for Future Research

There are very few studies done on cancers among Asians, specifically in Malaysian setting. Most studies performed in Malaysia were questionnaires studies on knowledge of the public and most of the studies were done on cervical cancers, with little research into breast, ovarian and endometrial cancers. Data on geographical coverage and efficacy of cancer screenings is lacking. There is a need to explore more cost-effective cancer screening methods to have better screening coverage which could potentially improve the prognosis because Malaysians are generally more inclined to traditional complementary medicines or treatments, meaning cancer patients tend to be diagnosed at more advanced stages. However, there are some significant barriers to be overcome, which include Malaysians having negative perception towards and fear of cancer, as the disease has been linked to end of life, limited access to treatment, poverty and poorer education. Finally, the Chinese population in Malaysia should be compared with the Chinese population from other countries (e.g. China, Singapore, Indonesia) to identify any possible genetic or lifestyle factors that could contribute to such a high incidence of female-specific cancers.

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