REVIEW OUTCOMES OF LAPAROSCOPIC ASSISTED COLECTOMY COMPARED WITH OPEN COLECTOMY IN COLORECTAL SURGERY AT HOSPITAL UNIVERSITI SAINS MALAYSIA

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2. DISCLAIMER

I hereby certify that all the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

Dated: ……

Dr Nik Mohd Nurhafizi B. Nik Anuar

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7. ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ASR	Age – Standardized Incidence Rate
HUSM	Hospital Universiti Sains Malaysia
LAC	Laparoscopic Assisted Colectomy
MOH	Ministry Of Health
OC	Open Colectomy
TNM	Tumour Node Metastases
TME	Total Mesorectal Excision

8. ABSTRAK

PENGENALAN

Kanser kolon dan rectum adalah salah satu ketumbuhan malignan yang utama di Negara ini. Pembedahan laparoskopik di kalangan pesakit yang menghidap kanser kolorektal telah memberikan kualiti hidup yang lebih baik. Walaubagaimanapun perkembangan ini tidak dikaji sepenuhnya dalam populasi pesakit di HUSM, Kelantan.

OBJEKTIF KAJIAN

Tujuan kajian adalah untuk mengetahui epidemiologi penyakit kanser kolorektal di kawasan HUSM, Kelantan. Objektif utama kajian ini ialah untuk melihat hasil jangka masa pendek dan jangka masa panjang di antara pesakit-pesakit kanser kolorektal yang menjalani pembedahan laparoskopik dan pembedahan kovensi/terbuka yang dijalankan di Hospital ini.

TATACARA

Kajian ini adalah retrospektif dari 1st Januari 2007 sehingga 31st Disember 2013, melibatkan seramai 124 orang pesakit. Semua pesakit yang menghidap kanser kolorektal dan memerlukan pembedahan telah disenaraikan dalam kajian ini. Faktor umur, Seks dan etnik dikaji sebagai sebahagian daripada kajian epidemiologi . Jenis pembedahan, tempoh pembedahan, tempoh masa tinggal di hospital selepas pembedahan, komplikasi jangka masa pendek dan jangka masa panjang selepas pembedahan telah dikaji dan dibandingkan

antara kumpulan pembedahan melalui bantuan laparoskopik (LAC) dan pembedahan kovensi (OC). Semua data telah dikumpul dari nota-nota pesakit dan laporan histopatologi. Maklumat-maklumat tersebut kemudian dianalisa dengan perisian komputer SPSS, versi 21.0.

KEPUTUSAN

124 Pesakit telah dikaji selama tempoh 7 tahun meliputi dari Januari 2007 sehingga Disember 2013. Nisbah pesakit yang menjalani pembedahan secara konvensi (OC) 80 orang berbanding dengan pembedahan bantuan laparoskopik (LAC) 44 orang ialah 2:1. Terdapat hampir sama taburan jantina dalam setiap kumpulan. Majoriti pesakit ialah Melayu. Purata usia pada penyampaian ialah 59 dalam kumpulan pembedahan konvensi dan 58 dalam kumpulan pembedahan bantuan laparoskopik. Tiada perbezaan penting dalam tempoh pembedahan antara kaedah laparoskopik dengan pembedahan konvensi. Tempoh tinggal di hospital selepas pembedahan dalam kumpulan laparoskopik nyata sekali lebih pendek berbanding dengan kumpulan konvensi ($p<0.05$). Morbiditi selepas pembedahan tidak mempunyai kaitan antara kaedah-kaedah pembedahan.

KESIMPULAN

Pembedahan dengan bantuan laparoskopik untuk kanser kolorektal merupakan alternatif kepada pembedahan konvensi yang terbukti lebih berkesan dari segi kesan jangka masa pendek.

9. ABSTRACT

INTRODUCTION

Colorectal carcinoma is one of the common malignant neoplasms in this country (Rashid et al. 2009). Minimally invasive surgery in colorectal cancer patients has improved quality of life, however the impact of this development has not been studied in HUSM population.

OBJECTIVES

To study the epidemiology of colorectal carcinoma in patient admitted to HUSM from January 2007 till December 2013. The primary objective was to evaluate outcomes of laparoscopic assisted colectomy and open colectomy in colorectal cancer in HUSM

METHODOLOGY

This is a study of retrospective record review of 124 patients diagnosed from 1st January 2007 to 31st December 20013. All patients diagnosed with colorectal malignancy requiring surgery were included in this study. Type of surgery, duration of surgery, duration of hospital stays post operative were surgical free margin were compared between laparoscopic assisted colectomy (LAC) group and open colectomy (OC) group. All these data's were traced from operative notes, patient notes and histopathological reports.

RESULTS

124 patients were studied for 7 years period ranging from January 2007 till December 2013. The ratio of patients underwent OC compared to LAC was 2: 1. There was almost equal sex distribution in each group. Majority of patients are Malay. The average age at presentation was 59 in OC and 58 in LAC group. There is no statistically significant difference in duration of operation between LAC and OC method of surgery. The length of hospital stay post operative in LAC group is significantly shorter compared to OC ($p < 0.05$). The post operative complication and surgical free margin and survival rate have no significant association between methods of surgery.

CONCLUSION

Laparoscopic assisted colectomy for colorectal cancer is an acceptable alternative to open colectomy and proved to be more effective in term of short terms outcomes.

1. INTRODUCTION

1.1 Background of Study

Breast cancer (BC) is imposing life-threatening issue in the health care of women in this era. From World Health Organization WHO data, BC has increased in incident and has become the highest among the other cancer types in women (National Breast Cancer Foundation, 2015).

Studies in genetic molecular genetic has shown that mutation within genes such as p53, BRCA1 and BRCA2 are the main cause of the development of BC in women, even though the pathophysiology of occurrence of BC still debatable (Schumaker, 2006; Yip *et al.*, 2014). The unhealthy life-style and dietary practice could be the contributing factors towards the observation of increase incidence of BC (Yip *et al.*, 2006).

The prognostic factors of BC are determined by tumour histological grading, nodal and organ involvement and immunohistochemistry (IHC) of the tumour. In northern region of Malaysia most of the BC patients presented at advanced stage of disease (Norsa adah *et al.*, 2005). The management of advanced disease would involve in palliative chemotherapy in the effort of palliation. The chemotherapy imposes risks and unwanted side effects to the patients.

In Malaysia, complementary medicine is widely practiced and favourable among the Malaysian. It does not cure but it provides an improvement to the quality of life where as our conventional chemotherapy prolonging the life expectancy of these advanced BC patients. More emerging studies are required to support the practice of complementary medicine especially in natural products and herbal medicine in oncology patients.

Many studies have shown that complementary medicine has benefits to help in such of patients' condition, thus making such treatment a popular and alternative option to treat illnesses (Mantena *et al.*, 2006). Hence, this study was done to prove that Annona Muricata has cytotoxic effect and anti-metastatic effect on breast cancer cells line.

1.2 Rationale of Study

The management of BC is depending to the TNM staging of the disease. The conventional treatment is surgery followed by adjuvant chemotherapy and radiotherapy. In certain stage of the disease, neoadjuvant chemotherapy may be offered to the patient prior to the definitive surgery. The prognosis is significantly better when treatment is given at the early stage of the disease.

However, the unwanted or unpleasant systemic side effects of the chemotherapy impose a wrong impression to patients which leads them to stigmatize towards chemotherapy.

The reports from previous study shows that the BC patients who uses complementary medicine during and beyond their conventional treatment manage better in terms of their symptoms, prevention of toxicities, pain control and quality of life (Greenlee *et al.,* 2014). The introduction of complementary medicine and herbal medicine gives a new episode in the management of BC.

With more promising study published, complementary medicine should be offered together and adjunct along with the conventional medicine to improve quality of life of these BC patient. It was shown to act synergistically with chemotherapy, increasing the efficacy of chemotherapy (Cheng *et al.,* 2016). Furthermore, it may also act as chemoprevention supplement to prevent from development of cancer (Moghadamtousi *et al.,* 2014b).

This research was designed to study the potential anti-tumour effect of Annona Muricata on MCF-7 and MDA-MB 231 breast cancer cell line. The study will evaluate the apoptotic effects, cell growth arrest and anti-metastatic effects of Annona Muricata on both BC cell lines.

Soursop leaves or Graviola leaves or Annona Muricata has been chosen for this study in view of its potential of anti-tumour effect that was already well-

known world-wide (Moghadamtousi *et al.*, 2014a). These leaves were used as complementary medicine since decades.

Many studied have been done proved that Annona Muricata has good cytotoxic effect on cancer cells (Rachman *et al.*, 2012). It can induce apoptosis and also arrest G1 phase of cell-cycle (Moghadamtousi *et al.*,2014b*)*. Furthermore, Annona Muricata also inhibits cells migration, hence; prevent the metastasis of cancer cells (Moghamtousi *et al.*, 2014b).

All the above properties render the leaves suitable as cancer prevention and for usage in advanced cancer patients.

2. LITERATURE REVIEW

2.1 Breast Cancer

The incidence of cancer is increasing in trend in Malaysia. Based on latest Health Facts 2013, released by Ministry of Health Malaysia, cancer is one of the highest causes of hospitalisation and among the five highest causes of death in Malaysia (Ferlay, 2015). In 2006, breast cancer (BC) was leading cancer in Malaysia and was reported to be the highest among the Malaysian women (Yip *et al.*, 2006).

Figure 1 showed that BC (17.7%) is the highest cancer among other cancers in Malaysian population, followed with colorectal cancer (13.2%) and lungs (10.2%) (National Cancer Registry, 2011). Furthermore, BC is three times higher compared to colorectal and cervical cancer among women in Malaysia, as showed in Figure 2.

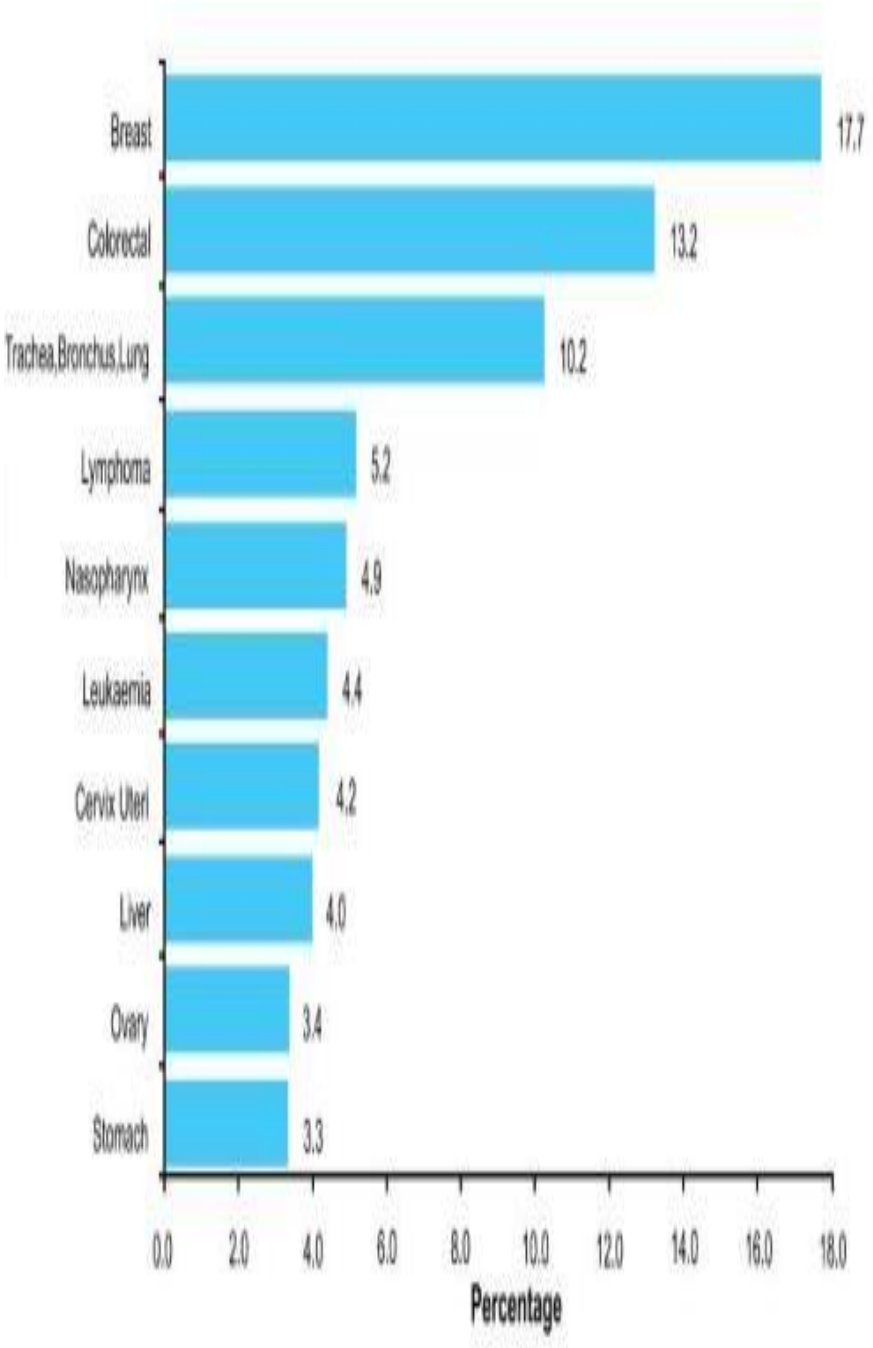

Figure 1: Ten most frequent cancers in Malaysia 2007-2011. (Adapted from; National Cancer Registry Report; Malaysia Cancer Statistic 2007-2011)

Figure 2: Ten most frequent cancers in females, Malaysia 2007-2011. (Adapted from; National Cancer Registry Report; Malaysia Cancer Statistic- Data and Figure; 2007-2011)

Unfortunately, the rate of BC in Malaysia is increasing by years. The report from GLOBOCAN 2012 showed further increment in the incidence of BC in Malaysia to 28% compared to 6 years ago which was 18% as shown in the Figure 3. While, the mortality rate of BC patients is around 24.7% (Figure 4) (Ferlay, 2015).

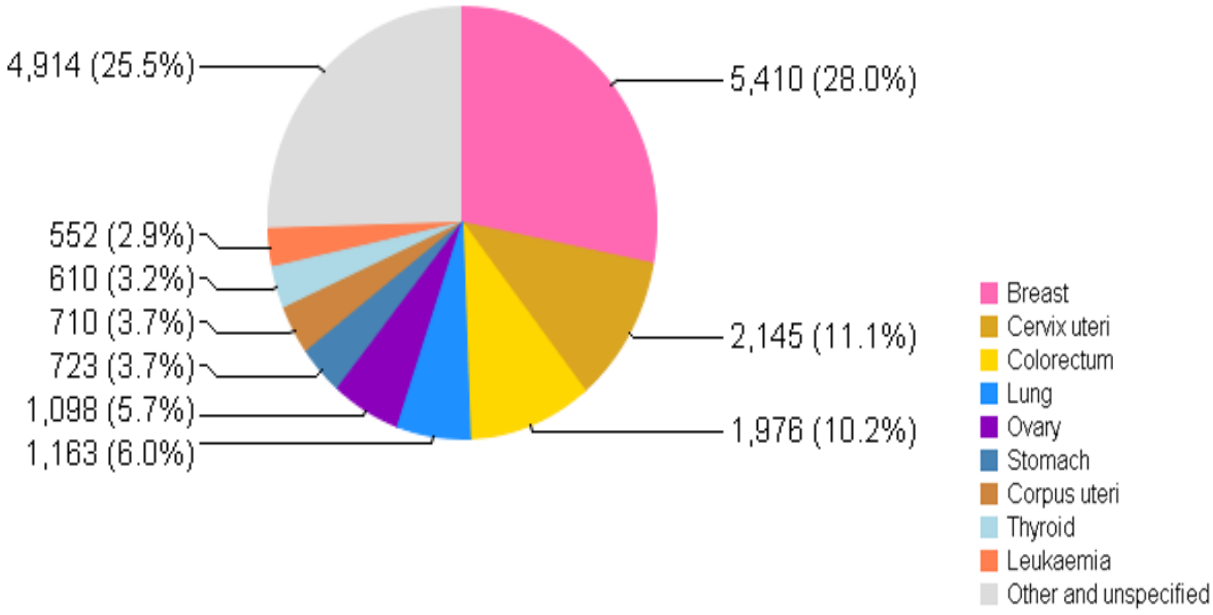

Figure 3: The incidence of cancers in Malaysia in 2012. (Adapted from; International Agency for Research in Cancer (GLOBOCAN, 2012)

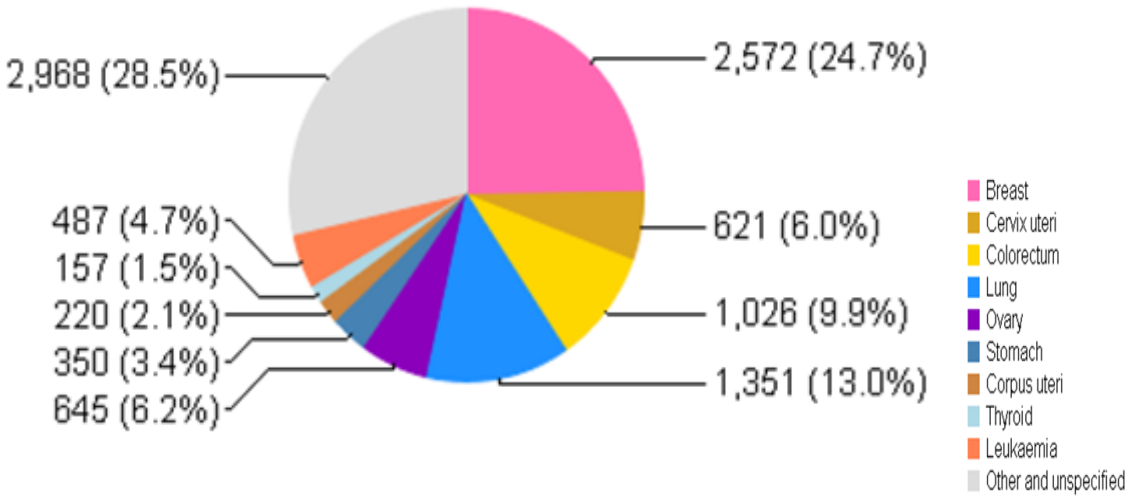

Figure 4: The percentage of mortality case of cancers in Malaysia in 2012. (Adapted from; International Agency for Research in Cancer (GLOBOCAN, 2012)

The National Cancer registry (NCR) 2003-2005 reported as Age-Standardised Rate (ASR) of 47.3 per 100,000 (Malaysia Cancer Statistics, 2006). The International Agency for Research in Cancer (GLOBOCAN) 2012 estimated the ASR of BC in Malaysia as 38.7 per 100000 with 5410 new cases in 2012 (Yip *et al.*, 2014) (Figure 5).

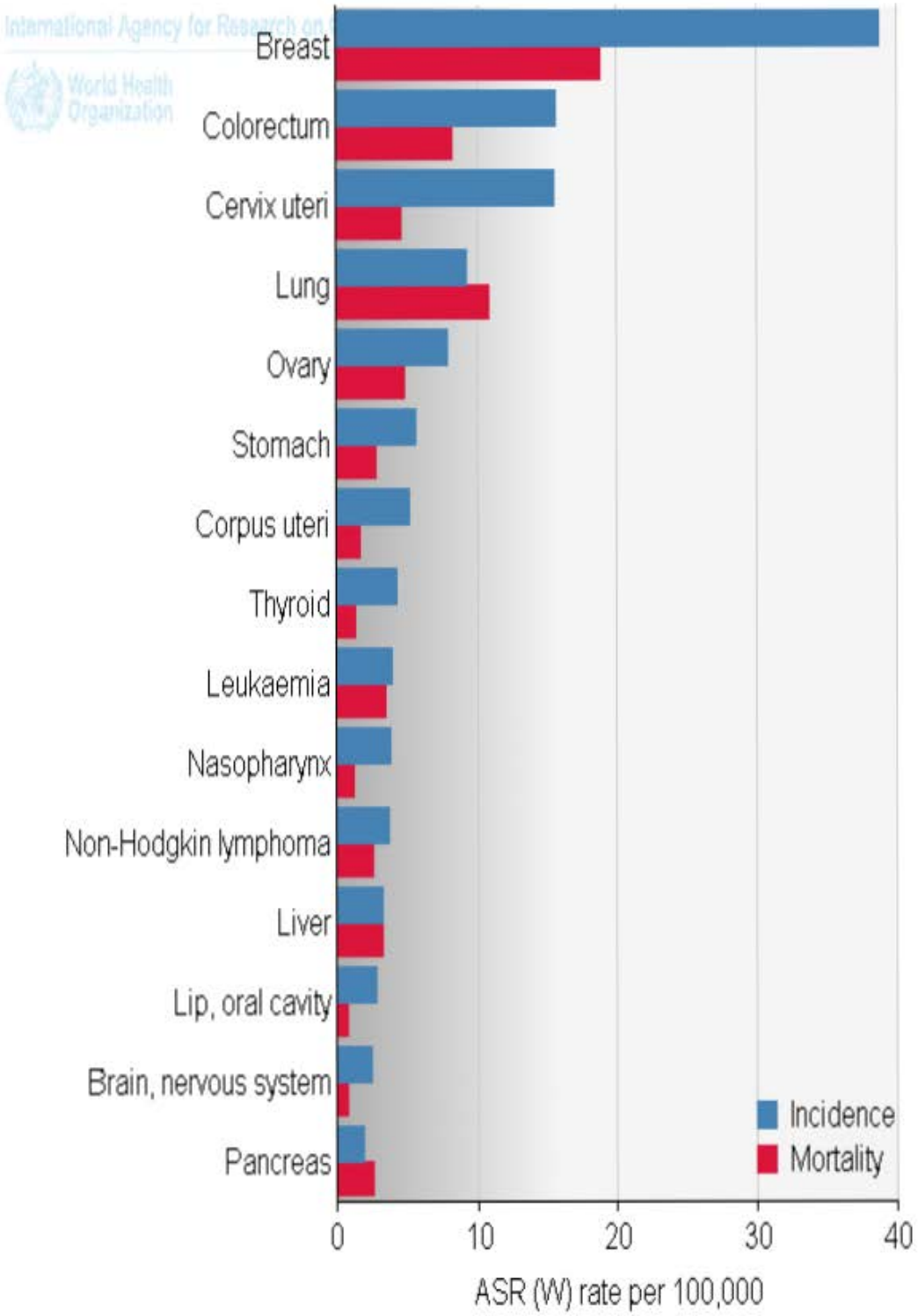

Figure 5: Estimated age-standardised rate and mortality in Malaysia. (Adapted from;

International Agency for Research in Cancer (GLOBOCAN, 2012)

BC is more common found in the Chinese population in comparison to the Indian and Malay population. According to Clinical Practice Guidelines of management of breast cancer, Chinese women had the highest incidence with an ASR of 46.4 per 100 000 populations followed by Indian women with an ASR 38.1 per 100 000 populations and Malay women with an ASR 30.0 per 100 000 populations (Khatcheressian *et al.*, 2013). This is probably due to genetic predisposition among the Chinese. Furthermore, it was known that Chinese has better awareness about BC compared to Malay.

Table 1: Incidence of breast cancer per 100 000 populations (CR) and Age-Standardised Incidence (ASR), by Ethnicity and Sex, Peninsular Malaysia 2006 (Khatcheressian *et al.*, 2013).

	Incidence			
Ethnic Group	No	%	CR	ASR
Malay	1,539	47.6	25.3	30.4
Chinese	1,375	42.5	53.2	46.4
Indian	320	9.9	34.9	38.1

Most of Malaysian women have poor survival from BC and it is estimated that half of the death due to BC could be prevented (Yip and Taib, 2012). Table 2 showed the list of study that had been done by various researches concerning the risk factors of BC among Malaysian.

Table 2: Risk factor of breast cancer in Malaysia. (Adapted from; Yip, C. H., Bhoo Pathy, N. & Teo, S. H. (2014). A review of breast cancer research in Malaysia. Med J Malaysia)

Author (year)	**Controls (n)**	**Cases (n)**	**Recruitment**	**Factors that reduce risk**	**Factors that increase risk**	**Factors that are not significant**
Matalqah et al (2011)	150	150	Penang General Hospital	Low fat diet, education >11 years, breast feeding, being employed	Family history, benign breast disease, menstrual irregularity, use of oral contraceptive (OCP)	
Razif et al (2011)	216	216	HKL and UKMMC	Higher number of life births	Family history	Age at first child birth and menarche not signficant
Norsa'adah et al (2005)	147	147	Kelantan	Breast feeding	Nulliparity, overweight, family history, use of OCP	
Hejar et al (2004)	89	89	Chinese, HKL and UMMC	Breast feeding		
Kamarudin et al (2006)	203	203	HKL	Exercise, low fat diet, longer duration of breast feeding		
Rejali (2007)	62	62	Malayan Hospital	Higher intake of selenium	Nulliparity, exposure to cigarette smoke, use of OCP	
Shahar et al (2010)	70	138	Klang Valley	Higher intake of selenium	Abdominal obesity, physical inactivity, low serum adiponectin	
Sulaiman et al (2011)	382	382	Kuala Lumpur			Total fat and fat subtypes not associated
Suzana et al (2009)	64	127	Klang Valley	Higher intake of selenium, vit A, Vit E		

CON'T

Author (year)	Controls (n)	Cases (n)	Recruitment	Factors that reduce risk	Factors that increase risk	Factors that are not significant
Sharhar et al (2008)	57	139	Klang Valley		Poor antioxidant status and oxidative stress measured by higher levels of malondialdehyde (MDA)	
Shahril et al (2013)	382	382	Kuala Lumpur	Higher Healthy Eating Index-2005 (HEI-2005)		
Ho et al (2009)	37pre-menopausal 68 post-menopausal	36pre-menopausal 66 post-menopausal	Kuala Lumpur		Higher serum progesterone and testosterone levels in postmenopausal women	

Table 3: Risk factor for breast cancer in Malaysia (Modified from; Yip, C. H., Taib, N. A. & Mohamed, I. (2006). Epidemiology of breast cancer in Malaysia. Asian Pac J Cancer Prev)

Increasing age
Geographic location
Family history
Reproductive factors
Early menarche less than 11 years
Late Menopause more than 55 years
Nulliparous
Late first child-b irth more than 30 years
Carcinoma of uterus
Carcinoma of ovary
dietary factors – diet rich in animal fat
Exogenous hormones – oral contraceptives
Hormonal replacement therapy
Alcohol – more than 2 drinks per day
Postmenopausal obesity
Higher socioeconomic group
Limited breast feeding (for long periods is a protective factor)

2.2 Management of breast cancer

The common practice for diagnosis of BC is via triple assessment, which consist of clinical history and physical examination, tissue biopsy and radiological assessment.

Table 4: TNM staging for breast cancer (7th Edition) (Adapted from American joint Committee of Cancer, (Giuliano *et al.*, 2017).

Staging	Description
Tx	Primary cannot be ruled out
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget)	Paget disease of nipple NOT associated with invasive carcinoma and (DCIS and or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the site and characteristic of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor ≤20mm in greatest dimension
T1mi	Tumor ≤ 1mm in greatest dimension
T1a	Tumor > 1mm but < 5mm in greatest dimension
T1b	Tumor > 5mm but < 10mm in greatest dimension

Cont. Table 4

T1c	Tumor > 10mm but < 20mm in greatest dimension
T2	Tumor > 20mm but < 50mm in greatest dimension

T3	Tumor >50mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, NOT including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for the inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Nx	Regional LN cannot be assessed (e.g.: previously removed)
N0	No regional LN
N1	Metastases to movable ipsilateral level I, II axillary LN
N2	Metastases in ipsilateral level I, II axillary LN that are clinically fixed or matted OR metastases in clinically detected ipsilateral internal mammary in the absence of clinically evident axillary LN
N2a	Metastases in ipsilateral level I,II axillary LN fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary node and in the absence of clinically evident level I, II axillary LN
N3	Metastases in ipsilateral infraclavicular (level III axillary) LN with or without level I, II axillary LN involvement OR metastases in clinically detected ipsilateral metastases OR metastass in ipsilateral supraclavicular LN with or without axillary or internal mammary LN involvement
N3a	Metastases in ipsilateral infraclavicular LN
N3b	Metastases in ipsilateral internal mammary LN and axillary LN
N3c	Metastases in ipsilateral supraclavicular L
Mx	Metastases cannot be assessed (e.g.: previously removed)
M0	No metastases
M1	Metastases

The management of BC involves the commitment from multidisciplinary team approach depending on the stage of the disease. Surgery is considered the mainstay of treatment for BC, with chemotherapy, radiotherapy and hormonal therapy utilised as adjunctive therapy (Yip *et al.*, 2014).

The Surgical Guidelines for the Management of BC stated that there are two teams that should be involved in the management of BC patient. First team is the diagnostic team; consist of breast specialist clinician (a consultant surgeon), radiologist, and pathologist breast care nurse. Second team is the cancer treatment team, which include the diagnostic team, oncologist, plastic and reconstructive surgeon and/or onco-plastic breast surgeon, medical prosthetist, psychologist and palliative care team (BASO, 2009).

After staging the disease, the patients are categorised into two categories, operable or inoperable. For inoperable disease, the option is neoadjuvant chemotherapy to downstage the tumour followed by surgery. For operable disease, surgery is the gold standard followed by adjuvant radiotherapy, chemotherapy, hormonal therapy and targeted therapy.

2.3 Tumorigenicity

Tumour literally means “new growth”. It is defined as an abnormal mass of tissue growth which exceeds and is coordinated with that of the normal tissues. The tissue growth persists in the same excessive manner after the cessation of the stimuli that lead to tumour development. As we know, tumour can be benign or malignant. Benign tumours are composed of well differentiated cells that closely resemble their normal counterparts, slow growth and have no invasion or metastasis characteristic. In the other hand, malignant tumours are opposite characteristics where they are usually undifferentiated cells, rapid growth and has characteristic of invasiveness and metastasis (Kamb, 1995).

Tumorigenicity is a process of a cells/tissues becoming tumour. This process happens on the intracellular level due to faulty to repair or error in growth signalling in the genetic level. According to study done by Astirin, O.P et al (2013), incidence of cancer is associated with the increase in the expression or mutation of gene that trigger cancer and the decrease in expression of cancer suppressor gene (Astirin *et al.*, 2013). The absence of DNA-repair enzymes also plays an important role in the raise of cancer incidence. As we know, cancer suppressor gene has a crucial function in cell homeostasis to prevent tumour occurrence (Astirin *et al.*, 2013). Deregulation of cancer suppressor gene can lead to cancer progression.

P53 is a tumour suppressor gene that regulates the normal cell cycle. It is an essential protein to suppress cancer. The function is to arrest cell growth by arresting the cell cycle at the G1/S regulation point upon DNA damage recognition. This allows the cell to have time to fix the damage. In addition, p53 also can initiate the apoptosis, if DNA damage proves to be irreversible (Sheikh *et al.*, 1998). Thus, the incidence of cancer also associated with the abnormal process of apoptosis.

Hence, literally, anti-tumorigenicity is a reversible process to prevent or counteract the formation of tumour. Mode of cell death can be implemented through necrosis, apoptosis and aging. Necrosis and apoptosis have different entity and mechanism of action, even though there is certain characteristic of overlap properties.

2.3.1 Necrosis

Necrosis is an irreversible process of cell death that triggered by external factor such as hypoxic, acidic environment, toxic and injury. There will be changes in morphology of the cell, where the cells become swollen with formation of cytoplasmic vacuoles, blebbed cytoplasm and also condense and swollen mitochondria (Cotran, 2010).

2.3.2 Apoptosis

Apoptosis is defined as programmed cell death that is important to maintain equilibrium in tissue (Peter, 2011). Apoptosis is a crucial process in the human body. If the process fails, the tissue will continuously proliferate and will result in the formation of tumour. The characteristics of cells during apoptosis are similar to necrosis, except, the cells shrunk rather than swollen. There is presence of apoptotic body with condensation of chromatin and DNA fragmentation in the cytoplasm and nucleus (Cotran, 2010).

Table 5: The differences between apoptosis and necrosis (Adapted from Robin and Contran, Pathology Basis Of Disease, 8th Edition, 2010)

Differential features of apoptosis and necrosis	
Apoptosis	Necrosis
Affects single cells	Affects groups of neighbouring cells
No inflammatory response	Significant inflammatory response
Cell shrinkage	Cell swelling
Membrane blebbing but integrity maintained	Loss of cell integrity
Increased mitochondria membrane permeability, release of proapoptotic proteins and formation of apoptotic bodies	Organelle swelling and lysosomal leakage
Chromatin condensation and non-random DNA fragmentation	Random degradation of DNA
Apoptotic bodies ingested by neighbouring cells	Lysed cells ingested by macrophages

2.4 Cell Cycle

The proliferation of a cell is a regulated process that involves a large number of molecules and interrelated pathways. The replication of cells is stimulated by growth factors by signalling extracellular membrane components through integrin (Cotran, 2010). The proliferation process of cell cycle is to achieve DNA replication and division.

Cell cycle consists of presynthetic (G1), DNA synthesis (S), Premitotic (G2) and mitotic (M) phases. G0 phase is the phase where the quiescent cells that have not entered the cell cycle reside. Each of the transition is important step in cell cycle. The first transition in the process is from G0 to G1. This is where the activation of transcription genes, including various proto-oncogenes and genes required for ribosome synthesis and protein translation. The critical transition is at the G1 to S transition called restriction point, which is a rate-limiting step for replication (Cotran, 2010).

The assessment for damaged DNA occurs twice and there is often referred to checkpoint. First checkpoint is at the G1/S checkpoint that ensures that the damaged DNA or chromosomes do not complete the replication and to monitor the integrity of DNA before replication (Mantena *et al.*, 2006). The second checkpoint is the G2/M checkpoint where it checks the DNA after replication and monitors whether the cell can safely enter mitosis or not (Cotran, 2010). If there is DNA damaged,

checkpoint activation delays the cell cycle and trigger DNA repair. However, if the damaged is too severe, they are eradicated by the process of apoptosis. On the other hand, if the checkpoint is defective, the cell will continuously be replicating and dividing, which is the basis of tumour formation (Kamb, 1995). Figure 6 summarized the process of cell cycle.

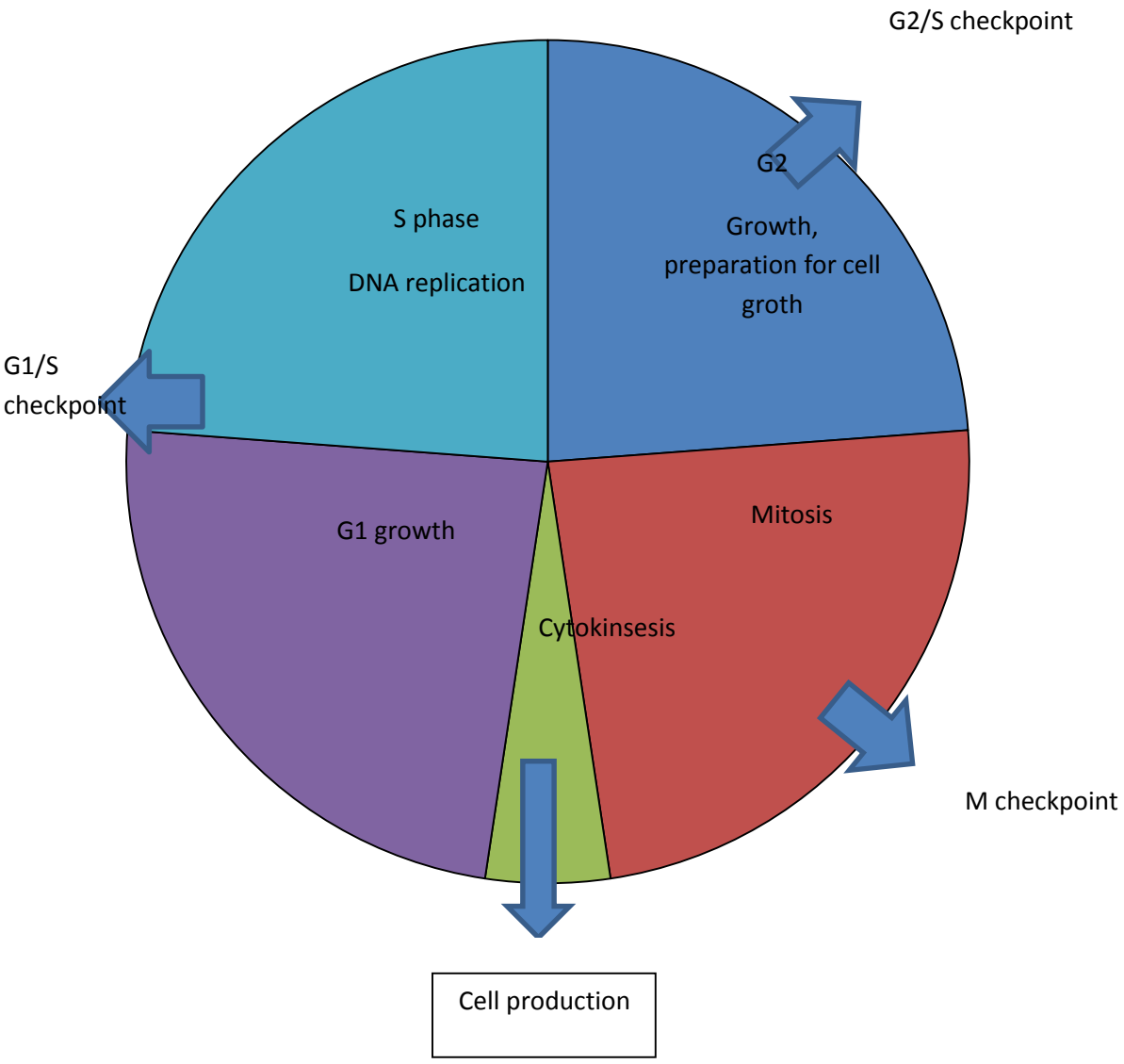

Figure 6: The image above shows the schematic diagram of cell cycle (Adapted from Robin and Contran, Pathology Basis of Disease, 8th Edition, 2010)