# MANAGEMENT OF PSYCHOLOGICAL DISTRESS IN CANCER PATIENTS

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FACULTY OF MEDICINE UNIVERSITY OF MALAYA KUALA LUMPUR

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# MANAGEMENT OF PSYCHOLOGICAL DISTRESS IN CANCER PATIENTS



# THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF MEDICINE

FACULTY OF MEDICINE UNIVERSITY OF MALAYA KUALA LUMPUR

2017

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# ABSTRACT

Psychological distress is highly prevalent in cancer patients, yet there is a lack of a brief and effective non-pharmacological intervention to address this distress. The current study involved a series of research projects. It started with a retrospective cohort study using a hospital pharmacy database to examine the psychotropic prescription rates among the cancer patients. A meta-analysis and a systematic review on the efficacy of different types of psychotherapy in cancer patient were also carried out. It was followed by a 1-year prospective study examining the association between perceived distress and factors such as anxiety, depression, perceived social support and quality of life among a cohort of breast cancer patients. Subsequently, a cross-sectional study was conducted to investigate the correlation between religiosity, religious coping with anxiety and depression in cancer patients. For the management of distress in cancer patient, a brief 5-minute mindful breathing therapy was developed. A randomized controlled trial (RCT) was conducted to examine the efficacy of this 5-minute mindful breathing. The results showed that psychotropic prescription was higher in cancer patient than in cardiology patients. The 1-year prospective study demonstrated that perceived distress was associated more with anxiety rather than depression. They were negatively correlated with perceived social support and quality of life. The evidence of meta-analysis indicated that the efficacy of psychotherapy in cancer patients was unsatisfactory where only adjunct psychological therapy (APT) showed short-term improvement in anxiety. The result of the RCT showed that 5-minute mindful breathing was a quick, easy to administer and effective therapy for rapid reduction of distress in palliative setting. The long term efficacy of the brief 5-minute mindful breathing in cancer patients needs to be established in the future studies.

## ABSTRAK

Tekanan psikologikal sangat kerap terjadi di kalangan pesakit kanser, namun terdapat kekangan maklumat kajian mengenai rawatan bukan farmakologikal yang ringkas dan berkesan untuk menangani situasi ini. Kajian ini melibatkan satu siri projek penyelidikan. Ia bermula dengan kajian kohort retrospektif menggunakan pangkalan data farmasi dari satu hospital untuk memeriksa kadar preskripsi ubat psikotropik di antara pesakit kanser. Meta-analisis dan kajian sistematik mengenai keberkesanan kaedah rawatan psikoterapi yang berlainan bagi pesakit kanser juga telah dijalankan. Ini diikuti dengan satu kajian prospektif selama 1 tahun untuk meneliti hubungan di antara persepsi tekanan dengan keresahan, kemurungan, persepsi sokongan sosial dan kualiti hidup di antara kohort pesakit kanser payudara. Seterusnya, satu kajian keratan rentas telah dijalankan untuk menguji hubungan antara keagamaan, menangani tekanan kaedah keagamaan, dengan keresahan dan kemurungan di kalangan pesakit kanser. Untuk tujuan pengurusan tekanan pesakit kanser, terapi pernafasan sedar 5-minit yang ringkas telah direka. Satu percubaan terkawal rawak (RCT) telah dijalankan untuk mengaji keberkesanan pernafasan sedar 5-minit ini. Keputusan kajian menunjukkan bahawa kadar preskripsi ubat psikotropik adalah lebih tinggi di kalangan pesakit kanser berbanding dengan pesakit kardiologi. Kajian prospektif 1 tahun menunjukkan bahawa persepsi tekanan lebih berkait rapat dengan keresahan berbanding dengan kemurungan. Kedua-dua keresahan dan kemurungan dikaitkan negatif dengan persepsi sokongan sosial dan kualiti hidup. Bukti daripada meta-analisis menunjukkan bahawa keberkesanan rawatan psikoterapi terhadap pesakit kanser adalah tidak memuaskan, di mana hanya "adjunct psychological therapy" (APT) menunjukkan kemajuan jangka pendek dari segi kebimbangan. Keputusan daripada RCT menunjukkan bahawa terapi pernafasan sedar 5-minit merupakan satu kaedah yang cepat, mudah untuk dilaksanakan dan berkesan untuk megurangkan tekanan dengan pantas di tetapan paliatif.

Keberkesanan jangka panjang pernafasan sedar 5-minit yang ringkas ini di antara pesakit kanser perlu ditubuhkan dalam kajian masa depan.

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# TABLE OF CONTENTS

Original literary work declaration.	ii
Abstract	iii
Abstrak	iv
Acknowledgments	vi
Table of Contents	vii
List of Figures	xiv
List of Tables	XV
List of Abbreviations	xvii
List of Appendices	XX

СНА	PTER 1: (	GENERAL INTRODUCTION	1		
1.1	Backgro	Background			
1.2	Aims and Objectives				
	1.2.1	Primary Aim and Objective	3		
	1.2.2	Research Objectives	3		
1.3	Research	a Questions	5		
1.4	Hypothe	sis	6		
1.5	Overview	w of the Chapters	7		

СНА	PTER 2: LITERATURE REVIEW	10
2.1	Psychological Distress: Anxiety and Depression	10
2.2	Psychotherapy for Cancer	12
2.3	Quality of Life	13
2.4	Social Support	13

2.5	Religious Coping	14
2.6	Mindfulness-based Interventions	16

# CHAPTER 3: COMPARISON OF PSYCHOTROPIC PRESCRIPTION BETWEEN THE ONCOLOGY AND CARDIOLOGY INPATIENTS: BASED ON A PHARMACY DATABASE IN A TEACHING HOSPITAL IN MALAYSIA

3.1	Introduction			
3.2	Methodology			
	3.2.1	Data	20	
	3.2.2	Oncology and Cardiology Inpatients	21	
	3.2.3	Variables	21	
	3.2.4	Covariates	21	
	3.2.5	Analyses	22	
3.3	Results.		22	
3.4	Discussi	on	26	
3.5	Conclus	ion	28	

# CHAPTER 4: PERCEIVED DISTRESS AND ITS ASSOCIATION WITH DEPRESSION AND ANXIETY IN BREAST CANCER PATIENTS

4.1	Introduction		
4.2	Methodology		
	4.2.1	Procedure and Measures	32
	4.2.2	Hospital Anxiety and Depression Scale	32
	4.2.3	Distress thermometer	33
	4.2.4	Statistical Analysis	33
4.3	Results.		34
4.4	Discussion		
4.5	Conclusion		

# CHAPTER 5: PSYCHOTHERAPY FOR CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

5.1	Introduction			43
5.2	Methodology			44
	5.2.1	Search Str	ategy and Selection Criteria	44
	5.2.2	Data Extra	action and Clasiification	45
	5.2.3	Data Anal	ysis	45
		5.2.3.1	Qualitative	45
		5.2.3.2	Quantitative	45
5.3	Results.			46
5.4	Discussi	on		56
	5.4.1	Limitation	s	60
5.5	Conclusi	ion		61

# CHAPTER 6: ANXIETY, DEPRESSION, PERVEIVED SOCIAL SUPPORT AND QUALITY OF LIFE IN MALAYSIAN BREAST CANCER PATIENTS: A 1-YEAR PROSPECTIVE STUDY

6.1	Introduction			62
6.2	Methodology			65
	6.2.1	Procedure	and Measures	65
	6.2.2	Statistical .	Analysis	67
6.3	Results.			68
	6.3.1 Quality of Life, Perceived Social Support, Depression and Anxiety.			
	6.3.2	Correlation Support, A	Between Quality of Life with Perceived Social	70
		6.3.2.1	At Baseline	70
		6.3.2.2	At 6 Months	71
		6.3.2.3	At 12 Months	72

6.4	Discussion		
6.5	Conclusi	on	80
CHA ASSO	PTER 7: )CIATIO	ANXIETY AND DEPRESSION IN CANCER PATIENTS: N WITH RELIGIOSITY AND RELIGIOUS COPING	THE
7.1	Introduc	tion	82
7.2	Methodo	ology	85
	7.2.1	Study Subjects and Setting	85
		7.2.1.1 Inclusion Criteria	85
		7.2.1.2 Exclusion Criteria	85
	7.2.2	Procedure	86
	7.2.3	Measurement Tools	86
		7.2.3.1 The Duke University Religion Index (DUREL)	86
		7.2.3.2 Brief Religious Coping Scale (RCOPE)	86
		7.2.3.3 Hospital Anxiety and Depression Scale (HAPS)	87
	7.2.4	Statistical Analysis	87
7.3	Results.		88
7.4	Discussi	on	93
7.5	Conclusi	on	99

# CHAPTER 8: REPORT ON THE DEVELOPMENT OF A BRIEF PYCHOLOGICAL INTERVENTION FOR REDUCTION OF THE DISTRESS IN PALLIATIVE CARE: 5-MINUTE MINDFUL BREATHING

8.1	Introduction		
	8.1.1	Rationale	103
8.2	Methodology		105
	8.2.1	Phase 1: The Development of the 5-Minute Mindful Breathing	105

		8.2.1.1	Preparatory Stage	106
		8.2.1.2	The Steps for 5-Minute Mindful Breathing for Palliative Care Patients	107
	8.2.2	Phase 2: Pi	llot Study	108
	8.2.3	Phase 3: R	andomized Controlled Trial	109
8.3	Results.			110
	8.3.1	Phase 2		110
	8.3.2	Phase 3		111
8.4	Discussi	on		111
	8.4.1	Phase 1		111
	8.4.2	Phase 2		112
	8.4.3	Phase 3		114
8.5	Conclus	ion		118

# CHAPTER 9: THE CORRELATION BETWEEN PERCEIVED LEVEL OF DISTRESS AND PHYSIOLOGICAL PARAMETERS IN PALLIATIVE CANCER PATIENTS

9.1	Introduc	tion		119
9.2	Methodo	ology		121
	9.2.1	Distress T	hermometer	122
	9.2.2	Skin Surfa	ace Temperature Measurement	122
	9.2.3	Galvanic S	Skin Response Measurement	123
	9.2.4	Blood Pre	ssure and Heart Beat Measurement	123
	9.2.5	Procedure	······	123
		9.2.5.1	Normal Listening	124
		9.2.5.2	Five Minutes of Mindful Breathing	124
	9.2.6	Statistical	Analysis	125
9.3	Results.			125

	9.3.1	Participants	126
9.4	Discussion		129
	9.4.1	Blood Pressure	129
	9.4.2	Pulse Rate	130
	9.4.3	Breathing Rate	130
	9.4.4	Skin Surface Temperature	131
	9.4.5	Galvanic Skin Response	131
9.5	Conclusi	ion	132

# CHAPTER 10: THE EFFECT OF FIVE MINUTES MINDFUL BREATHING TO THE PERCEPTION OF DISTRESS AND PHYSIOLOGICAL RESPONSES IN PALLIATIVE CARE CANCER PATIENTS: A RANDOMIZED CONTROLLED STUDY

10.1	Introducti	ion	134
10.2	Methodol	logy	137
	10.2.1	Distress Thermometer	138
	10.2.2	Skin Surface Temperature Measurement	138
	10.2.3	Galvanic Skin Measurement	139
	10.2.4	Blood Pressure and Heart Beat Mesurement	139
	10.2.5	Procedure	139
		10.2.5.1 Normal Listening	140
		10.2.5.2Five Minute Mindful Breathing	140
	10.2.6	Statistical Analysis	141
10.3	Results		141
	10.3.1	Participants	141
	10.3.2	Socio-Demographic Characteristics and Cancer Types	142
	10.3.3	Efficacy	145

	10.3.3.1	Perceived Level of Distess	145
	10.3.3.2	Breathing Rate	145
	10.3.3.3	Systolic Blood Pressure	145
	10.3.3.4	Disatolic Blood Pressure	145
	10.3.3.5	Pulse Rate	146
	10.3.3.6	Surface Skin Temperature	146
	10.3.3.7	Galvanic Skin Response	146
10.4	Discussion		147
10.5	Conclusion		151

# **CHAPTER 11: SUMMARY**

10.5	Conclusion	151
CHAP	PTER 11: SUMMARY	
11.1	Summary Overview	152
11.2	Primary Conclusion	155
11.3	Secondary Conclusion	155
11.4	Strengths	157
11.5	Limitations	160
11.6	Implications	163
11.7	Future research	165

REFERENCES	167
LIST OF PUBLICATIONS AND PAPERS PRESENTED	196
APPENDIX	200

# LIST OF FIGURES

Figure 5.1:	Standardized mean differences for APT vs control for all trials combined with HADS-Depression subscale scores as outcome measured at 2, 4 and 12 months using a fixed effects meta- analysis
Figure 5.2:	Standardized mean differences for APT vs control for all trials combined with HADS-Anxiety subscale scores as outcome measured at 2, 4 and 12 months using a fixed effects meta- analysis
Figure 10.1:	Disposition of patients in the randomized controlled trial between 5 minutes mindful breathing and normal listening for cancer patients under palliative care

# LIST OF TABLES

<b>Table 3.1:</b>	Use of psychotropic drugs in oncology and cardiology subjects	24
<b>Table 3.2:</b>	Associated factors for psychotropic drugs use in oncology patients from the logistic model for each of the covariates	25
Table 4.1:	Characteristics of subjects (N=221)	34
Table 4.2:	The comparison of anxiety and depression scores between breast cancer patients with high or low perceived level of distress	35
Table 4.3:	The correlation between changes in perceived distress with the changes in anxiety and depression scores among the breast cancer patients	36
Table 5.1:	Quality assessment of the 10 eligible studies by using "Quality Assessment Tool for Quantitative Studies" Scale	50
Table 5.2:	Qualitative description of the 17 included clinical trials involving any types of psychotherapy in cancer patients	52
Table 6.1:	Characteristics of the subjects	68
Table 6.2:	Quality of Life, Perceived social support, Anxiety and Depression among the study subjects	69
<b>Table 6.3:</b>	Correlation between anxiety, depression and perceived social support with quality of life	73
Table 7.1:	Characteristics of the subjects	88
<b>Table 7.2:</b>	The subscales and total scores of the Hospital Anxiety and Depression Scales (HADS)	90
Table 7.3:	Analysis of the association between clinical and socio- demographic characteristic with depression and anxiety (based on HADS scores) among the study subjects using Chi Square test	90

Table 7.4:	Analysis of the association between religiosity, religious coping with depression and anxiety (based on HADS scores) among the study subjects using Logistic Regression Test	92
Table 9.1:	Socio-demographic characteristics and types of cancer of the study subjects	125
<b>Table 9.2</b> :	Correlation between the changes in perceived level of distress with blood pressure, breathing rate, pulse rate, Galvanic skin response and skin surface temperature	128
<b>Table 10.1:</b>	Socio-demographic characteristics and types of cancer of the study subjects.	143
Table 10.2:	Comparing the changes of the perceived distress and physiological responses between palliative cancer patients with five minutes mindful breathing (n=30) and normal listening (n=30)	144

# LIST OF ABBREVIATIONS

APT	: Adjuvant Psychological Therapy
BDI	: Beck Depression Inventory
BHS	: Beck Hopelessness Scale
BMS	: Brannon masculinity scale
BNF	: British National Formulary
BSI-18	: Brief Symptom Inventory
CAM	: Complementary and Alternative Medicine
CBT	: Cognitive Behavioral Therapy
CCQ	: Cancer Coping Questionnaire
CES-D	: Centre for Epidemiological Studies Depression Scale
CI	: Confidence Interval
DASS	: Depression, Anxiety and Stress Scale
DBT	: Dialectical Behaviour Therapy
DS	: Distress Scale
DSM	: Diagnostic and Statistical Manual of Mental Disorders
DT	: Distress Thermometer
EORTC	: European Organization for Research and Treatment of Cancer quality-
	of-life

QLQ-BR23 : Quality of life: questionnaire –breast cancer module

FACIT-Sp-Ex : Spirituality Subscale of the FACT

FACT	: Functional Assessment	of Cancer	Treatment
11101	. I unetional l'assessment		reatment

- FACT-B : FACT-Breast Symptom Index
- GEQ : Group Experience Questionnaire
- HADS : Hospital Anxiety and Depression Scale
- HRSA : Hamilton Rating Scale for Anxiety
- HRSD : Hamilton Rating Scale for Depression
- HRV : Heart rate variability
- IIS : Insomnia Interview Schedule
- ISI : Insomnia Severity Index
- MAC : Mental Adjustments to Cancer Scale
- MBSR : Mindfulness-Based Stress Reduction
- MBST : Mindful stress reduction therapy
- MBT : Mindfulness-based therapy
- MFI : Multidimensional Fatigue Inventory
- MIMS : Malaysia Index of Medical Specialities
- MSPSS : Multidimensional Scale of Perceived Social Support
- MyBCC : Malaysian Breast Cancer Cohort
- NCCN : National Comprehensive Cancer Network

- PAIS : Psychosocial Adjustment to Illness Scale
- PIL : Purpose in Life Test
- POMS-SF : Profile of Mood States–Short Form
- PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- PSG : Polysomnography
- PSIT : Psycho-spiritual integrative therapy
- PSS : Perceived Social Support
- PST : Problem-solving Therapy
- QoL : Quality of Life
- QoS : Quality of Sleep
- REBT : Rational-Emotive Behavior Therapy
- RSAS : Rieker sexual adjustment scale
- RSC : Rotterdam symptom checklist
- SCID : Structured Clinical Interview for the DSM-IV
- SCL-90\_R : Symptom checklist
- SEGT : Supportive-Expressive Group Therapy
- SICPA : Stanford Index of Cancer Patient Assessment
- STAI : Spielberger State Trait Anxiety Inventory

# LIST OF APPENDICES

Appendix A:	Ethics Approval I	200
Appendix B:	Ethics Approval II	201
Appendix C:	Front Page for "Comparison of psychotropic prescriptions between oncology & cardiology"	202
Appendix D:	Front Page for "Psychotherapy for cancer patients: A systematic review and meta-analysis"	203
Appendix E:	Front Page for "Anxiety, depression, perceived social support and quality of lifw in Malaysian breast cancer patients: a 1-year perspective study"	204
Appendix F:	Font Page for "Anxiety and depression in cancer patients: The association with religiosity and religious coping"	205
Appendix G:	Front Page for "The effect of 5-minutes of mindful breathing to the perception of distress and physiological responses in palliative care cancer patients: A randomized controlled study"	206
Appendix H:	Letter of acceptance for "Perceived distress and its association with depression and anxiety in breast cancer patients"	207

## **CHAPTER 1: INTRODUCTION**

#### 1.1 Background

Cancer, a disease characterized by the uncontrolled and abnormal growth and spread of cells, has been noted to be one of the leading causes of death worldwide (American Cancer Society, 2016). With the advancement in medical knowledge, research and technology, many treatments including surgery, chemotherapy, immune therapy, and targeted therapy have since been devised in an attempt to treat cancer (American Cancer Society, 2016). The psychological aspect of cancer on the other hand may have not received an equal attention until later years. Aside from the physical pain and symptoms, cancer patients also tend to experience psychological distress related to fear of cancer recurrence, sense of vulnerability and loss as well as changes in their role and social support (Adler & Page, 2007; Sahin et al., 2013).

In fact, many studies have shown that cancer patients are likely to suffer from a variety of psychiatric comorbidities such as depression, anxiety and adjustment disorder with the prevalence rate between 7.5% and 44.5% depending on the type and stage of cancer, and nature of study (Dastan & Buzlu, 2011; Grabsch et al., 2006; Maneeton, Maneeton, & Mahathep, 2012; Miovic & Block, 2007; Wilson et al., 2007; Zainal, Nik-Jaafar, Baharudin, Sabki, & Ng, 2013., Mehnert et al., 2014, Walker et al, 2014). Such comorbidities not only complicate the cancer symptoms and treatment, they also require the prescription of psychotropic medications to relieve the associated distress (Caruso, Grassi, Nanni, & Riba, 2013; Grassi, Caruso, Hammelef, Nanni, & Riba, 2014; Muriel et al., 2009; Ng, Boks, Smeets, Zainal, & de Wit, 2013; Ng, Dijkstra, Smeets, Boks, & de Wit, 2013). Thus, there has been an increasing amount of research that looks into the psychological comorbid of cancer.

Evidence showed that religious commitment or religiosity can reduce depression or distress in medical illness (Koenig, Larson & Durham, 1998a; Greeson et al., 2015; Ronneberg et al., 2016), leading to greater life satisfaction and improved psychological health (McCullough, Hoyt, Larson, Koenig, Thoresen, 2000; Aukst-Margetic , Jakovljevic ´& Margetic , 2002) As a result, religious coping has become an area of interest in terms of helping patients adjust with cancer. However, literature showed mixed results on the association between religious coping and cancer distress (Trevinoet al., 2014; Rohani et al., 2015; Zamanian et al., 2015). Positive religious coping is seen as an expression of a secure relationship with a supportive God/higher power whereas negative religious coping (or 'religious struggle') is considered as an expression of a less secure relationship with a God/higher power that is distant and punishing or as a religious struggle in the search for significance (Pargament et al., 1998a). There was no study in Malaysia examining the association between religion and its role in cancer distress.

Recently, the practice of mindfulness is one of the alternatives research has studied to help patients cope with psychological distress. Mindfulness is understood as focusing attention in a purposeful, in-the-present-moment and non-judgmental way. The main principle is that openly and non-judgmentally experiencing the present moment can help to effectively ameliorate stress. This is because when facing stressors, one may feel depressed from too much rumination about the past and anxious if there is too much worry about the future (Kabat-Zinn, 1994). Being mindful by experiencing "right-here-right-now" can hence break the cycle of ruminating and worrying, reducing the level of distress. Therefore in this study, 5-minute breathing exercise was carried out on palliative care patients, while its efficacy was studied.

## **1.2** Aim and Objective

#### 1.2.1 Primary Aim and Objective

To simplify mindfulness-based intervention into a simple, free, quick and easy to administer 5-minute breathing exercise that can rapidly reduce distress in palliative care patients.

# 1.2.2 Research Objectives

- To compare the prescription rates of three common psychotropic drugs: anxiolytic/ hypnotic, antidepressant and antipsychotic between oncology and cardiology inpatients.
- To compare the levels of depression and anxiety with level of psychological distress among cancer patients. The correlation between the changes in distress level with depression and anxiety over 12 months was examined.
- 3. To critically and systematically review all published trials on psychotherapy available for cancer patients.
- 4. To study the correlation between depression, anxiety and quality of life with perceived social support among breast cancer patients over a period of 12 months.
- 5. To examine the association between religiosity and religious coping with anxiety and depression among cancer patients.
- 6. To propose an alternative psychological intervention called 5-minute mindful breathing that can rapidly reduce distress in cancer patients.
- 7. To investigate the correlation of the changes in perceived distress level with the changes in physiological parameters, namely systolic blood pressure, diastolic

blood pressure, pulse rate, breathing rate, skin surface temperature and galvanic skin responses in cancer patients.

 To study the efficacy of 5-minute mindful breathing for rapid reduction of distress in a palliative setting. Its effect on the physiological changes of the cancer patients was also examined.

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## **1.3** Research Questions

- 1. **Chapter 3:** Which inpatients, oncology or cardiology that would have higher prescription rates of three common psychotropic drugs namely anxiolytic/hypnotic, antidepressant and antipsychotic
- 2. **Chapter 4:** Was anxiety or depression more associated with perceived psychological distress among cancer patients across a 12-month span?
- 3. Chapter 5: What was the psychotherapy available for cancer patients?
- 4. **Chapter 6:** What was the relationship between depression, anxiety, quality of life and perceived social support among cancer patients over a period of 12 months?
- 5. **Chapter 7:** What was the association between religiosity and religious coping with anxiety and depression among cancer patients?
- 6. **Chapter 8:** What could be the alternative psychological intervention based on mindfulness that can rapidly reduce distress in cancer patients?
- 7. **Chapter 9:** What was the relationship between the changes in perceived distress level and the physiological changes?
- 8. **Chapter 10:** What was the effect of 5-minute mindful breathing on the rapid reduction of distress in cancer patients?

# 1.4 Hypotheses

- 1. **Chapter 3:** Oncology inpatients will have higher prescription rates of the three common psychotropic drugs than cardiology inpatient
- 2. **Chapter 4:** Anxiety rather than depression will be more associated with perceived psychological distress among cancer patients across a 12-month span.
- 3. **Chapter 5:** There will be a series of different psychotherapy with varying efficacy proposed for patients with cancer.
- 4. **Chapter 6:** Both depression and anxiety will be negatively correlated with quality of life and perceived social support among cancer patients over a period of 12 months. Perceived social support is expected to have a positive correlation with quality of life.
- Chapter 7: Higher religiosity and more positive religious coping are linked to lower anxiety and depression among cancer patients.
- 6. **Chapter 8:** The 5-minute mindful breathing can be an effective psychological intervention to rapidly reduce distress in cancer patients.
- 7. **Chapter 9:** Lower perceived distress level is associated with lower breathing rate, systolic and diastolic blood pressure, pulse rate and galvanic skin response but higher skin surface temperature.
- 8. **Chapter 10:** There will be a positive effect of 5-minute mindful breathing on the rapid reduction of distress in cancer patients, supported by physiological evidences.

#### **1.5** Overview of Chapters

There are a total of 11 chapters in this thesis, with the current Chapter 1 being the introduction. Chapters 3 to 10 include eight published papers based on the candidate's doctoral project. The last chapter, Chapter 11 contains a summary that looks into the strengths and limitations of the overall study with implications for clinical practice and future research.

**Chapter 1** presents the background of the study, research objectives and questions together with the corresponding hypotheses were discussed. The main goal of this thesis was to develop a psychological intervention that can rapidly reduce psychological distress among palliative care patients.

**Chapter 2** is focused on the literature review related to the current study and recent publications. **Chapter 3** is apaper on a retrospective cohort study that compared the psychotropic prescriptions (anxiolytic/hypnotic, antidepressant and antipsychotic) between oncology and cardiology inpatients using pharmacy database from University Malaya Medical Center (UMMC) in Malaysia. Psychotropic drugs prescription was used as proxy indicator to study the psychiatric morbidity among cncer patients, Psychotropic drugs prescription was found to be more common in cancer patients and anxiolytic/hypnotic prescription rates were significantly higher in non-Malay female patients in Malaysia.

**Chapter 4** is a paper on a 12 months prospective cohort study comparing the level of depression and anxiety with distress level among female breast cancer patients. The relationship between changes in distress level and depression and anxiety over 12 months was also examined. Anxiety was concluded to be a more significant psychological state that contributed to perception of distress in breast cancer patients as compared to depression.

**Chapter 5** is a critical and systematic review of all available published trials on psychotherapy in cancer patients since there was no quantitative analysis on this topic. A total of 17 clinical trials on six types of psychotherapy for cancer patients were identified by searching PubMed and EMBASE. However, the number and quality of clinical trials for each type of psychotherapy were poor. It was concluded that there was a need for more rigorous and well-designed clinical trials on this topic to gain better evidence on the efficacy of psychotherapy in cancer patients.

**Chapter 6** provids an insight into the level of depression, anxiety, quality of life and perceived social support among Malaysian breast cancer women over a period of 12 months. The level of anxiety was significantly reduced whereas there was no change in the level of depression over the study period. Quality of life and perceived social support were positively correlated with each other but both were negatively associated with anxiety and depression. Thus, perceived social support was an important factor for a better quality of life and lower level of psychological distress.

**Chapter 7** is apaper on a cross sectional study that examined the relationship between religiosity, religious coping, anxiety and depression. The findings showed that subjects with anxiety or depression used more negative religious coping and had lower non-organization religiosity. Higher religiosity and more positive religious coping were thus linked to lower anxiety and depression among cancer patients.

**Chapter 8** discusses the development of 5-minute mindful breathing that can rapidly reduce distress in cancer patients. An expert panel of multidisciplinary team was formed to simplify the theory of mindfulness-based intervention into the 5-minute mindful breathing technique. The efficacy of the 5-minute mindful breathing was investigated in a pilot test and again in a randomized controlled trial, where both found positive results

and suggested that the proposed technique was a useful psychological intervention for reducing psychological distress in palliative care patients.

**Chapter 9** presents a study on the correlation of the changes in perceived distress level with the changes in physiological parameters, namely systolic blood pressure, diastolic blood pressure, pulse rate, breathing rate, skin surface temperature and galvanic skin responses in cancer patients. Apart from diastolic blood pressure or galvanic skin response, other physiological indicators were found to share relationship with changes of distress level. To overcome the limitation of subjective assessment, these physiological parameters could be used as proxy indicators in the monitoring of distress in palliative cancer patients.

**Chapter 10** presents a randomized controlled study that examined the effect of 5minute mindful breathing on the perception of distress and physiological responses in palliative care cancer patients. A significant reduction of perceived distress and physiological changes associated with distress reduction were found in subjects that practiced 5-minute mindful breathing. The efficacy of the newly developed 5-minute mindful technique on distress reduction was confirmed in this study.

**Chapter 11** summarizes the findings of all the eight research projects conducted. The strength and limitations of the studies were discussed. The implication based on the results of the studies was indicated and the future research directions were recommend

#### **CHAPTER 2: LITERATURE REVIEW**

#### 2.1 Psychological Distress: Anxiety and Depression

Psychological distress is a broad construct referring to a range of negative emotions that can manifest as multiple psychological symptoms such as depression and anxiety (Carlson et al., 2010). While it has been established that cancer patients are likely to experience psychological distress namely depression and anxiety throughout the course of their illness (Adler & Page, 2007; Sahin et al., 2013), the conclusion as to whether cancer patients are more prone to depression or anxiety still remains vague till this day. To study this discrepancy, it is important to note the definition and distinction between anxiety and depression. Anxiety is characterized by a state of intense yet excessive worry, uncertainty, and fear in response to a triggering stimulus. Its manifestation has physical, cognitive and physiological components. Anxiety has been shown to increase lethargy which contributes to poor treatment result (McGregor & Antoni, 2009). Cancer patients are likely to experience heightened anxiety when facing uncertainty or confusion about their diagnosis and treatment, as well as anticipating any negative outcome about their health in the future (Barlow, 2000). Dastan and Buzlu (2011) found that 35 % of breast cancer patients in their study had anxiety, while a similar Asian study by (Lueboonthavatchai, 2007) reported a lower prevalence of 16 %, with variation attributed to different research design and type of anxiety studied.

Depression on the other hand is associated with a condition of constant low mood, anhedonia, fatigue, hopelessness, excessive guilt and suicidal ideation (Reich, Lesur, & Perdrizet-Chevallier, 2008). Once diagnosed with cancer, a patient may experience a sense of despair and helplessness where they are "paralyzed" by the diagnosis, rendering their future seems pessimistic and meaningless. Depression has been shown to have a negative impact on cancer condition by affecting the patients' quality of life, interpersonal support, self-care and treatment adherence (Reich et al., 2008). The prevalence of depression in breast cancer patients from Western countries was predicted to be up to 56% while the Asian counterpart was estimated to range from 10 to 30%, depending on the different study methodology (Reich et al., 2008; Zainal, Nik-Jaafar, et al., 2013). However, depression is possibly under-diagnosed among patients with cancer due to its overlapping features with the common physical symptoms of cancer (Reich et al., 2008).

It has been a wide belief that depression is the primary psychological comorbid in cancer patients as compared to anxiety (Shapiro et al., 2001). This notion has gained quite some support in the past where depression was found to be more associated with cancer (Colleoni et al., 2000; Hirschfeld, 2001; Walker et al., 1999). However, some studies seemed to suggest otherwise as anxiety was demonstrated as a more predominant psychological distress among cancer patients (Liao et al., 2008; Hassan et al., 2015). In fact, a more recent study using Malaysian sample indicated that the rate of anxiety and depression in breast cancer patients were 31.7% and 22.0% respectively (Hassan et al., 2015). Many justifications have been provided to address these inconclusive findings, from factors like different type of cancer, to non-standardized methodology and measurement of the depression or anxiety constructs.

Nevertheless, both depression and anxiety have detrimental impact on the treatment outcome of cancer (American Cancer Society, 2016). Being unexpectedly diagnosed with cancer can trigger huge shock, confusion and even grief. However, such reactions of psychological distress are processed differently by different people. It would be of clinical interest to investigate how people differ in their experience of psychological distress in relation to cancer, and what are the key factors or mechanisms that determine whether such distress will manifest as depression or anxiety. A better understanding of this psychological comorbid of cancer will definitely yield a more positive prognosis in treatment plan.

## 2.2 Psychotherapy for Cancer

In view of the psychological comorbid, many cancer patients will go through psychotherapy as well to deal with their illness-triggered depression or anxiety other than the pharmacological treatment. Psychotherapy has been shown to be useful to be a part of cancer treatment plan by reducing psychological distress which in return enhances the patients' quality of life and survival chances (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011; Kissane et al., 2007). There are many types of psychotherapy with different theoretical framework available for cancer treatment. These varying forms of psychotherapies have also been documented to show different efficacy in dealing with cancer related psychological issue. Some of the most commonly used psychotherapies include cognitive behavioral therapy (CBT), problem-solving therapy and adjunctive psychological therapy (Newell, Sanson-Fisher, & Savolainen, 2002).

CBT for example is able to decrease depression and anxiety but increase sleep and life qualities (Savard, Simard, Ivers, & Morin, 2005). Adjuvant psychological therapy (APT) is another form of therapy specially designed to suit the nature of cancer patients (Greer et al., 1992). Despite its good efficacy in reducing psychological distress, APT did not show significant improvement in the social functioning of cancer patients (Greer et al., 1992). It is believed that there are still limited meta-analyses that look into the efficacy of different types of psychotherapy to identify the most suitable choice of psychological treatment for cancer patients. Hence, more well-structured meta-analyses may be required to verify the effective use of psychotherapy in dealing with cancer. A meta-analysis was conducted after the completion of this thesis (Faller et al., 2013). 198 studies were included in the systematic review. The authors concluded that various types of psycho-oncologic interventions are associated with significant, small-tomedium effects on emotional distress and quality of life. The authors also advised that the results should be interpreted with caution, however, because of the low quality of reporting in many of the trials.

# 2.3 Quality of Life

Other than the professional pharmacological and psychological treatment, there has been a movement of exploring self-initiated coping methods that may improve condition of patients with cancer. Though those complementary techniques do not target the clinical treatment of cancer, they have been found to share positive correlation with the patients' quality of life which has a huge impact on their recovery process. Quality of life can be understood as the subjective perception of one's own general wellness that encompasses physical, psychological, cognitive and social dimensions (O'Neil et al., 2013). A better quality of life usually leads to a better treatment outcome of an illness such as cardiovascular disease and major depressive disorder (O'Neil et al., 2013). As such, while it is inevitable that a cancer patient's physical functioning is affected by cancer to a certain extent, there is a need to address and optimally maintain the other aspects of wellness. Besides the conventional psychotherapy to restore a cancer patient's general functioning, social support and religious coping are two of the major aspects that many studies have looked into for this matter.

# 2.4 Social Support

Social support is a form of physical or psychological communication between people, which increases their sense of self-control and self-efficacy during difficult times (Albrecht & Adelman, 1987). Interestingly, the impact of social support does not stem

from the actual, objective network of one's social life, but how much they feel or perceive that they are supported by the social network available in their life (Langford, Bowsher, Maloney, & Lillis, 1997; Trevino, Fasciano, Block, & Prigerson, 2013). Perceived social support has been found to be negatively associated with distress and suicidal ideation among cancer patients (Balci Sengul, Kaya, Sen, & Kaya, 2014). It is also linked to more satisfactory adjustment to cancer and family relationship, as well as better adherence to health care treatments (Rizalar, Ozbas, Akyolcu, & Gungor, 2014). In contrast, a lower perception of social support seems to create a higher level of distress (Rizalar et al., 2014).

While social support can be derived from anybody and any domains of one's social circle such as family, friends, peers, work colleagues and religious institution; family and friends driven social support have demonstrated the most efficacy in reducing cancer related distress (Cicero, Lo Coco, Gullo, & Lo Verso, 2009). As mentioned earlier, when first diagnosed with cancer, patients may experience anxiety or/and depression due to fear, uncertainty, confusion and helplessness (Barlow, 2000; Reich et al., 2008). Social support can buffer such negative emotions by providing comfort and reassurance to the patients, and going through the process with them so that they do not feel singled out by the cancer. This can also strengthen their desire and motivation to battle with cancer. Family and friends can also provide a lot of useful information, advices and reminders in helping the patients gain more knowledge and control over the illness. Patients with adequate social support may also feel more hopeful about their condition.

# 2.5 Religious Coping

Since the Malaysian societal structure is made up of multi-ethnic groups such as Malays, Chinese and Indians with rich cultural beliefs, people may turn to spiritual or religious coping during stressful experience like cancer. Religions usually touch on the aspect of life, illness and death which can provide a different perspective and reframe cancer experience in a less distressing way. Religious coping is 'the use of cognitive and behavioural techniques, in the face of stressful life events, that arise out of one's religion or spirituality' (Tix & Fraser, 1998). There are a few ways religion is helpful as a coping for distress. First of all, it provides meaning to an event despite the negative nature of the event. Secondly, it is able to instill a sense of control over a challenging situation. Thirdly, it provides extra comfort and reassurance during difficult times. Also, it closely relates the person with other people of the same religious beliefs, expanding their circle of social support. Last but not least, it helps people move on during significant life transitions like different states of health (Pargament, Koenig, & Perez, 2000).

There has been increasing amount of research suggesting the benefits of religious coping such as lowering depression level and supporting the recovery process of medical illness (Greeson et al., 2015; Koenig, George, & Peterson, 1998; Ronneberg, Miller, Dugan, & Porell, 2016). It was also found to be associated with improved psychological well-being and lower level of distress (Aukst-Margetic, Jakovljevic, Margetic, Biscan, & Samija, 2005; Jang et al., 2013; Trevino, Archambault, Schuster, Richardson, & Moye, 2012). A study using Malaysian sample (Nurasikin et al., 2013) concluded that psychological distress among the psychiatric patients was higher when religious coping was lower. Interestingly, there has also been some literature with mixed results that disputed such beneficial effect of religious (Rohani, Abedi, Omranipour, & Langius-Eklof, 2015; Trevino, Balboni, Zollfrank, Balboni, & Prigerson, 2014; Zamanian et al., 2015), or with totally contradicting findings that religious coping can actually be detrimental (Thune-Boyle, Stygall, Keshtgar, & Newman, 2006). Since studies on religious coping and cancer in Malaysia were rather limited (Nurasikin et al.,
2013), it would be interesting to investigate the role of religions available in Malaysia in dealing with cancer related distress. The richness of religious diversity in Malaysia may be used as a source to further help people cope with their cancer.

## 2.6 Mindfulness-based Interventions

Mindfulness promotes effective emotional regulation by decreasing negative affect, inducing positive emotions, minimizing reactivity and enhancing response flexibility (Davis & Hayes, 2011). Mindfulness reduces stress through several mechanisms. Firstly, attention is paid to interrupt the automatic negative thoughts. Secondly, worries about the future and rumination about the past are minimized by focusing on the present moment. Thirdly, through non-judgmental observation of own feelings and thoughts from a distance, negative appraisals of the situation are reduced. A mindful person can also gain more awareness and respond to a situation more with conscious choice rather than the automatic reactions. These mechanisms could promote the ability to re-evaluate an unpleasant situation and also to improve emotional regulation (Kabat-Zinn, 1994; Brown et al., 2007). The principle of mindfulness has been adopted into psychotherapy such as mindfulness-based stress reduction (MBSR) – an 8-week program which showed positive efficacy of distress reduction among cancer patients (Ando et al., 2009; Cramer, Haller, Lauche, & Dobos, 2012; Zainal, Booth, & Huppert, 2013).

However, just like the previously mentioned pharmacological and psychological treatment for cancer, coupled with social and religious coping, MBSR assumes a prerequisite that the patients have some intact level of functioning, either physically or psychologically in order to receive the treatment or apply the coping methods. Unfortunately for some patients, the stage of their cancer may be too advanced, leaving them with limited life span and very frail physical or mental condition. It would be a luxury for them to go through the conventional lengthy treatments and coping

mechanisms. They may be under palliative care to improve their quality of life by relieving them from the symptoms or distress related to cancer. For some, the palliative care also signifies end of life care which aims to help them live as well as possible in the last few months of their life. Patients in this condition tend to have even higher psychological distress or suffering.

Delivering psychotherapy in palliative care is challenging. Patients with terminal illness may have some fluctuating physical impairment, mental distress and consciousness (Strada & Sourkes, 2009). They are often too lethargic to undergo many sessions of conventional psychotherapy. Their usually inadequate motivation to replace old habitual reactions to stressor with more adaptive ones can also reduce the efficacy of long term psychotherapy. Most palliative care patients struggle to cope with their deteriorating state of health and thus would use various coping strategies to lessen their suffering, depleting their physical and mental resources as a result. They may also still be in denial or trying hard to accept the current condition of their illness, rendering them not so receptive towards help. As such, it is very often an additional burden for them to go through the conventional psychotherapy which requires some level of physical and mental alertness. Hence, a 5-minute of mindful breathing exercise was developed in order to overcome those limitations.

While adopting mindfulness in life has many advantages, the idea can further be devised into a brief exercise with easy guideline such as 5-minute mindful breathing to address the above limitations. Other than the main goal to reduce psychological distress, this simple technique can also offer unique benefits where it is easy and can be practiced by anyone anywhere, anytime, ignoring the common nuisances like level of social support, religiosity, educational level, insight, comprehension ability and many others. The proposed mindful technique shall not involve complex process nor require as much motivation, efforts, and resources as those usually needed in the conventional treatments. It is designed to be effective, practical and convenient yet at no cost at all.

The 5-minute mindful breathing technique for example is presumably able to fulfil all those requirements and provide the desired advantages. It is derived from a variety of mindful practices. Mindful breathing was chosen since patients effortlessly breathe all the time both involuntarily and voluntarily. It is controlled involuntarily from the brainstem but also voluntarily from the motor cortex. Convenient and practical, patients can practice mindful breathing anytime and anywhere at no cost. Mindful breathing also acts as a key practice that anchors the other mindful practices like mindful eating and mindful walking.

Since the 5-minute mindful breathing is developed for distress reduction purpose, it would be even more ideal to show the supporting scientific evidences for this proposed technique. One way to achieve this objective is to look into its efficacy through the subjective verbal report and objective physiological measurement of distress level. Stress triggers a series of physiological changes in humans – a natural and evolutionarily adaptive response named "fight-or-flight" to help us deal with the stressor (Cannon, 1929). There is a strong relationship between physiological changes and stress levels (Cannon, 1929). The effect of mindful breathing would gain stronger support if it is found to be correlated with biological responses associated with distress reduction during a fight-or-flight mode.

# CHAPTER 3: COMPARISON OF PSYCOTROPIC PRESCRIPTION BETWEEN THE ONCOLOGY AND CARDIOLOGY INPATIENTS: BASED ON PHARMACY DATABASE IN A TEACHING HOSPITAL IN MALAYSIA

#### 3.1 Introduction

The experiences of the cancer patients are variable and they may develop fear of recurrence, sense of vulnerability, sense of loss and alterations in their role and social support (Muzzin et al., 1994; Adler and Page, 2007; Şahin et al., 2013). Studies have shown that cancer patients can suffer from a variety of psychiatric disorders which include adjustment disorder, anxiety disorders and major depression where the prevalence rate can range from 7.5% to 44.5% depending on the type of cancer, the stage of the illness and study type (Grabsch eal., 2006; Wilson et al., 2007; Miovic and Block, 2007; Cullivan et al., 1998; Daştan and Buzlu, 2011; Maneeton et al., 2012; Zainal et al., 2013). Psychiatric co-morbidities not only complicate the cancer symptoms and treatment, but may also necessitate the use of various types of psychotropic medications to relieve the cancer patients' psychological distress (Grassi et al., 2014; Muriel et al., 2009; Caruso et al., 2013; Ng et al., 2013a; Ng et al., 2013).

Available data showed that although the evidence on the efficacy of psychotropic use in cancer patients is not robust (Grassi et al., 2014), 31% and 46% of cancer patients were prescribed with psychotropic medications by their general practitioners and oncologists respectively (Muriel et al., 2009). Psychotropic medications are used to relieve the psychological distress such as anxiety, depression, sleep and appetite disturbances and psychosis as well as in the treatment of cancer symptoms and treatment side effects such as fatigue, nausea, pain, hot flushes and hiccups (Grassi et al., 2014; Caruso et al., 2013).

Our previous study using a large insurance database from the Netherlands found that psychotropic drugs prescription is common in cancer patients, starts soon after diagnosis and increases in the terminal stage (Ng et al., 2012). The result is similar with the findings of another study which compared prescription patterns in breast, prostate and colorectal cancer survivors which showed that long-term breast and prostate cancer survivors were more likely to receive at least one prescription for an antidepressant. On further analyses, those nearing the end of life received significantly more doses of antidepressants, and proximity to death also influenced prescribing for anxiolytics in breast cancer survivors (Ng et al., 2012).

Most studies on the psychotropic prescription in cancer patient were based on the western database, there is absence of literature on the topic from the Asian region especially Malaysia. In this study, we aim to examine the prescription pattern of psychotropic medications in cancer patients and to show that the patients diagnosed with cancer are more likely to be prescribed with psychotropic medications.

## 3.2 Methodology

### 3.2.1 Data

This is a retrospective cohort study. The data used in this study were extracted from the University Malaya Medical Centre (UMMC) pharmacy database. The database is the dispensing records of patients stored in the pharmacy's Medication Management and Use System (Ascribe). Data was mined using IBM's Cognos Business Intelligence PowerPlay. A report was generated for all patients dispensed medications from year 2008-2012. The report was limited to patients admitted to the cardiology ward or patients undergoing treatment at the clinical oncology ward. Fields in the report included the gender, date of birth, ethnicity, medications dispensed including quantity, date dispensed and the British National Formulary (BNF) classification for the medication dispensed. Approval from the University Malaya Medical Centre, Medical Ethic Committee was obtained prior to accessing the database.

## 3.2.2 Oncology and Cardiology Inpatients

Study subjects were identified from the database between 1<sup>st</sup> Jan 2008 to 31<sup>st</sup> Dec 2012. All of the patients who were admitted into the oncology and cardiology ward during the study period were identified based on the ward coding (ONCOL and CARDIO). Cardiology patients were chosen as the comparator because of their similar illness chronicity and morbidity. All the prescription data for the selected subjects were extracted from the database. The information on date of birth, gender and ethnicity which were available in the database was also collected. The age of the subjects were taken at 31<sup>st</sup> Dec 2012.

#### 3.2.3 Variables

Drug prescriptions were recorded according to National Formulary (BNF) classification. The central nervous system drug prescription were identified and recoded according to the Malaysia Index of Medical Specialities (MIMS). The following psychotropic prescriptions were included: 4a and 4b (anxiolytic and hypnotic), 4c (antidepressant) and 4c (antipsychotic).

Psychotropic drug use was defined as at least one prescription of any of the psychotropic drugs during the study period. Duplicate or repeat prescriptions were eliminated.

### 3.2.4 Covariates

The following information about the oncology and cardiology patients was gathered: age, gender and ethnicity. The age of the study subjects were taken at December 31<sup>st</sup>,

2012. Ethnicity was dichotomised into Malay and Non-Malay.

#### 3.2.5 Analyses

The prevalence of psychotropic use for the oncology and cardiology inpatients was calculated for the study period (January 1<sup>st</sup>, 2008 to December 31<sup>st</sup>, 2012). The number of psychotropic drugs used in the cancer and the control group was compared. A logistic regression model was used to analyze the determinants of psychotropic drugs use in oncology patients, reported in adjusted odds ratio's. All the tests were two sided at the alpha level of 0.05.

#### 3.3 Results

After removing cases with incomplete dataset and repeated cases, a total of 3345 oncology inpatients and 8980 cardiology inpatients were included in this study. The two groups did not differ in age; the mean age for both groups was 57 years old. There were more female (69%) in the oncology group as compared to the cardiology group.

Co-prescription of one or more psychotropic drugs to oncology patients was more frequent than in the cardiology group. One in twenty oncology patients were 3.94 times more likely to be prescribed with one type of psychotropic as compared to the cardiology patients. Although the percentage of co-prescription of two types of psychotropic drugs was low in oncology patients (2.3%), it was significantly higher than the cardiology patients (OR=5.78, 95% CI= 3.88-8.06). The difference is even bigger for co-prescription of all three types of psychotropic between the two groups. There were significantly more patients in the oncology group with co-prescription of all three types of psychotropic drugs. (OR= 6.13, 95% CI= 4.71-7.98).

As compared to cardiology inpatients, there was a significantly higher percentage of oncology patients being prescribed with any psychotropic drug during the study period.

Anxiolytic was the most commonly prescribed psychotropic drug to the oncology patients (12.3%). This was followed by 7.8% being prescribed with antidepressant drugs, which resulted in an odds of 6.07 when compared to the cardiology group. Although the percentage of oncology patients with antipsychotic drugs prescriptions was relatively low (5.6%), it was significantly higher than in the cardiology group (1.1%) (Table 3.1).

The results demonstrated that Non Malay female oncology used more anxiolytic/hypnotic drugs. There were no significant differences in the use of antidepressant or antipsychotic between gender, age or ethnicity (Table 3.2).

Table 3.1: Use of psychotropic drugs in oncology and cardiology subjects

	Oncology	Cardiology	Crude OR	Adjusted OR
	N=3345	N=8980	(95% CI)	(95% CI)
Any Drug	421 (12.6)	235 (2.6)	5.36 (4.54-6.32)	5.25 (4.41-6.24)
Anxiolytic or Hypnotic (%)	412 (12.3)	217 (2.4)	5.67 (4.79-6.72)	5.55 (4.64-6.63)
Antidepressant (%)	260 (7.8)	123 (1.4)	6.07 (4.88-7.55)	6.08 (4.83-7.64)
Antipsychotic (%)	187 (5.6)	97 (1.1)	5.42 (4.23-6.95)	5.41 (4.17-7.02)

Adjusted OR = Odds ratio adjusted for age, gender and ethnicity. OR = Odds ratio CI = confidence interval The use of psychotropic drugs is defined as at least once prescription during the study period (2008-2010).

...city. C ...e prescription

		Anxiolytic/Hypnotic			Antidep	oressant	Antipsychotic			
	%	Crude OR	Adjusted OR	%	% Crude OR Adjusted OR			Crude OR	Adjusted OR	
		(95% CI)	(95% CI)		(95% CI)	(95% CI)		(95% CI)	(95% CI)	
Age										
<b>≤ 60</b>	5.5	1.19	0.98*	3.5	1.27	1.05*	2.4	1.09	0.90*	
> 60	4.7	(1.01-0.40)	(0.83-1.15)	2.7	(1.04-1.57)	(0.85-1.29)	2.2	(0.86-1.37)	(0.70-1.14)	
Gender										
Female	6.6	1.85	1.21†	3.9	1.63	1.02†	2.9	1.69	1.07†	
Male	3.7	(1.57-2.18)	(1.02-1.45)	2.4	(1.33-2.01)	(0.82-1.26)	1.7	(1.33-2.15)	(0.83-1.38)	
Ethnicity										
Malay	3.6	0.60	0.54‡	2.7	0.60	0.74‡	2.5	1.13	1.06‡	
Non-Malay	5.9	(0.50-0.72)	(0.45-0.65)	3.3	(0.64-1.00)	(0.59-0.93)	2.2	(0.89-1.44)	(0.83-1.35)	

**Table 3.2:** Associated factors for psychotropic drugs use in oncology patients from the logistic model for each of the covariates

\*Adjusted for cardiology group, gender and ethnicity †Adjusted for cardiology group, age and ethnicity

‡Adjusted for cardiology group, age and gender

In this study we compared the prescription pattern of psychotropic drugs in 3345 oncology patients and 8980 cardiology patients extracted from a dispensing record in a teaching hospital in Malaysia between years 2008 to 2012. We found that 12.3% of oncology patients were prescribed with anxiolytic/hypnotic, whilst 7.8% and 5.6% were prescribed with antidepressants and antipsychotics respectively. All classes of psychotropic drugs were more frequently prescribed to the oncology patients as compared to the cardiology patients. Co-prescription of more than one type of psychotropic drugs was also more often among oncology patients.

There was no significant difference of age, gender and ethnicity in the antidepressant or antipsychotic prescription rates. However, interestingly, Non-Malay Female oncology patients had a significantly higher prescription rate for anxiolytic/hypnotic drugs. This probably reflects the higher prevalence of anxiety in Non Malay women with cancer. It may also indicate that Malay female patients turned to their spirituality to counter their psychological distress. Furthermore, the use of complementary and alternative medicines (CAM) is more prevalent in the Malays. One local study found that 64% of the Malay women with breast cancer were CAM users and they believed in the power of prayer and used Malay traditional medicine to assist in healing the body's inner strength, to cure cancer, and to reduce stress (Shaharudin et al., 2011).

Our study showed that the prescription rates of any psychotropic drugs in oncology patients were higher as compared to cardiology patients. It may reflect higher level of psychological distress in the cancer patients. It is consistent with reports of significant increase in distress and decrease in well-being among cancer patients (King et al., 2013). Several studies reported that pain, fatigue, loss of appetite, anxiety and depression are commonly encountered in the terminal cancer patients (Hopwood et al.,

1991; Butler et al., 1999; Ross and Alexender, 2001; Stromgren et al., 2002; Yong et al., 2006). This finding is similar with the reports by Khan et al where benzodiazepine was more often prescribed for breast and prostate cancer patient (Khan et al., 2010).

In this study the prevalence of anxiolytic/hypnotic prescription was 12.3%. Although benzodiazepines are for many decades the most frequently prescribed psychotropic drug in cancer patients, the benzodiazepine prescription in this sample is much lower compared to previous studies in which the rate of benzodiazepine prescription in cancer patients ranged from 24.5% to 28.3% (Cullivan et al., 1998; Derogatis et al., 1979). This could be due to the under-recognition of the anxiety symptoms in the cancer patient or high precaution level among clinician in the local setting to introduce anxiolytic to cancer patients. Furthermore, culturally, Malaysians tend to turn to traditional healers to complement their medical treatment. Study done by Merriam and Muhamad (Merriam and Muhamad, 2013) recently showed that the cancer patients in their study valued the emotional and spiritual benefits derived from traditional healers. Their patients reported that their faith was strengthened with reduction in their anxiety and psychological distress.

Despites the noticeable prevalence of antipsychotic drug prescription (5.6%), it was much lower compared to earlier reports by Derogatis et al in 1979 (13.3%) (Derogatis et al., 1979). In the survey on terminal cancer patients by Goldberg and Mor in 1985, the consumptions of antipsychotic drugs was 7% (Goldberg and Mor, 1985). Antipsychotic drugs are frequently used as antiemetic, which is a highly prevalent symptom in patients with terminal cancer. In the survey conducted by Derogatis et al reported more that 90% of the psychotropic drugs were prescribed because of nausea and vomiting (Derogatis et al., 1979). In addition to the control of gastro-intestinal symptoms it is likely that antipsychotic drugs are being used to control the sudden change in behavior due to

acute brain syndrome or psychosis such as hallucination and delusion during the terminal phase in these patients (Peterson et al., 1987). These symptoms are often related to the progression of cancer, brain metastasis, electrolytes imbalance and effects of cancer treatment.

The prevalence of antidepressant prescription in cancer patients was about 7.8% in this study, which was much lower than the finding of our previous study based on a database from the Netherlands (Ng et al., 2013a). Again, the low prescription rate could attributed to the under-diagnosis of depression and the high caution level in prescribing psychotropic drugs to cancer patients in the local setting. It is known that antidepressants are often prescribed not only for depression but also various other indication such as pain control, insomnia, panic attacks and appetite stimulation.

Limitations of this study include the fact that the study was restricted to the five years of the study period. Patients who received psychotropic prescription prior or after the study period are not identified. This may underestimate the prescription rates in these patients and bias cannot be ruled out. Social and family support which may help the patients to cope with their psychological problem (Liu et al., 2011) was not measured in this study. Lastly, clinical data, such as cancer stage, type of cancer and physical comorbidity were not documented in the database. These factors might confound the result in the analysis of psychotropic drugs prescription rates.

## 3.5 Conclusion

In conclusion, the prescription rates of anxiolytic/hypnotic, antidepressant and antipsychotic among oncology patients were higher that the cardiology patients. Non Malay female cancer patients were more often prescribed with anxiolytic/hypnotic drugs. The highly frequent use of psychotropic drugs seems to be a reflection of the high levels of psychological distress among cancer patients. Further studies are needed to evaluate and to optimize psychotropic drug prescription in cancer patients.

## CHAPTER 4: PERCEIVED DISTRESS AND ITS ASSOCIATION WITH DEPRESSION AND ANXIETY IN BREAST CANCER PATIENTS

#### 4.1 Introduction

Breast cancer is the most common malignancy in women worldwide (Jemal et al., 2008). The diagnosis and treatment for breast cancer in women was well known in leading to significant psychological distress (Linden, Vodermaier, Mackenzie, & Greig, 2012; Massie, 2004; Voorwinden & Jaspers, 2016; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). The prevalence of psychological distress in cancer patients is reported to be above 30% (L. Fallowfield, Ratcliffe, Jenkins, & Saul, 2001; Massie, 2004; Zabora et al., 2001). Despite its impact on the daily functioning, distress in cancer patients is often overlooked and under-treated (Boyes et al., 2013; L. Fallowfield et al., 2001; von Heymann-Horan et al., 2013), which possibly lead to poor treatment compliance and survival (Mols, Husson, Roukema, & van de Poll-Franse, 2013). In 2003, the National Comprehensive Cancer Network (NCCN)he word "distress" to describe the psychiatric problem in cancer patients because it is more accepted and less stigmatizing than other psychological or psychiatric term. Distress is defined as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment" (National Comprehensive Cancer, 2003). Psychological distress is broad in construct, covering a wide continuum of emotions and psychiatric symptoms such as depression and anxiety (Carlson et al., 2010).

Anxiety is one of the most common psychological symptoms in breast cancer patients, with the rates ranging from 10 to 30% (Stark & House, 2000). It is a state of intense apprehension, uncertainty, and excessive fear as a response to unpleasant stimuli.

Anxiety has a multi-dimensional construct which involve cognitive, physiological and physical reactions. Anxiety has been shown to cause fatigue and poor treatment outcome, have impact on the quality of life, and influencing the neuroendocrine and immune systems of the breast cancer patients (McGregor & Antoni, 2009). Breast cancer patient is overwhelmed with anxiety symptoms due to the anticipation of negative outcomes (Barlow, 2000), face extensive uncertainty about the future, concern over recurrence and fear of treatment side effects (Montgomery et al., 2003; Walker et al., 1999). Although it is always believed that anxiety was less frequent in women with breast cancer as compared with depression (Shapiro et al., 2001), there were findings to indicate that anxiety is more prevalent (Saboonchi et al., 2014).

Both anxiety and depression are common and has strong impact in breast cancer patients. Both psychological symptoms cause high level of distress in cancer patients. Previous studies in examining which of these psychological symptoms (either anxiety or depression) were more significantly associated with the distress level in breast cancer patients is lacking. In the current study, we aim to investigate the association of anxiety and depression with perceived level of distress among breast cancer patients in Malaysia in one year prospectively.

## 4.2 Methodology

This study is part of a larger study, the Malaysian Breast Cancer Cohort (MyBCC). MyBCC is a prospective cohort study which aims to identify the association between genetics, lifestyle and nutrition on overall survival and quality of life of Malaysian breast cancer patients. Please refer to the previous literature for further information of MyBCC (Islam et al., 2015). In the current study, we mainly study the association between depression and anxiety and perceived distress among the breast cancer subjects at diagnosis until 12 months of follow up visit. The study subjects of the current study were recruited from University Malaya Medical Centre in Kuala Lumpur, Malaysia. The subjects are those who were diagnosed with breast cancer since 1 May 2011. Inclusion criteria were (i) breast cancer that was confirmed by histological examination, (ii) able to complete the necessary interviews and questionnaires, and (iii) able to understand the objective of the study and provide informed consent. Exclusion criteria were (i) secondary breast cancer (primary cancer of any origin other than the breast, (ii) having confusion or delirium, and (iii) male patients. The purpose and details of the study were explained to all potential subjects. The query from the subjects was addressed. Those patients who agreed to participate and given written informed consent were enrolled. Ethical approval was obtained from the Medical Ethic Committee, University Malaya Medical Centre.

#### 4.2.1 Procedure and Measures

The following scales were used for assessment at the time of diagnosis, 6 months and 12 months follow-up visits thereafter. Information on age and ethnicity were obtained. Breast cancer staging was confirmed by the treating surgeon using the American Joint Committee on Cancer Staging System for breast cancer.

#### 4.2.2 Hospital Anxiety and Depression Scale

Anxiety and depression were assessed using the Malay Version of Hospital Anxiety and Depression Scale (HADS). HADS was the most frequently reported measure in cancer studies and shown to be the best performing measure for each trajectory stage of the disease. It is a self-administered questionnaire that screened for anxiety (7 items) and depressive (7 items) symptoms. It has demonstrated good reliability. The anxiety (HADS-A) and depression (HADS-D) subscales are scored from 0 to 3 (four-point Likert scales), giving maximum scores of 21 for anxiety and depression respectively (Zigmoid & Snaith, 1983). The Malay version of HADS has a good reliability and has been validated among the Malaysian population (Yusoff et al., 2011).

#### 4.2.3 Distress Thermometer

The Distress Thermometer is a validated rapid screening tool for psychological distress and has been endorsed by the NCCN Distress Management Guidelines panel. It serves as an initial single item question screen, which identifies distress from any sources. The word "distress" was chosen because it sounds "normal" and is less embarrassing to patients. It assesses how much distress patients are going through in the past week. The subjects were instructed to circle from a scale of 0 to 10 to indicate their distress level. "0" means no distress and "10" means extremely distress (National Comprehensive Cancer Network., 2013). In the previous literature review, most studies showed that the score of 4 has the maximum sensitivity and specificity relative to established criterion (Donovan et al., 2014).

## 4.2.4 Statistical Analysis

Descriptive statistics for the age, ethnicity and staging of cancer was performed. Study subjects were categorized into moderate to severely distress (distress thermometer score of 4 and above) and low distress (distress thermometer score below 4). The means and standard deviation of HADS-anxiety subscale and HADS-depression subscale scores for both groups were calculated at all three time points (baseline, 6 months and 12 months). The differences between the means of both groups were determined using Independent T test. Logistic regression analysis was further performed to determine the means differences of anxiety scores between the two groups adjusting for the underlying depression scores; or the means differences of the depression scores between the two groups adjusting for the underlying anxiety scores. In the secondary analysis, the changes in distress scores, HADS-anxiety subscale scores and HADS-depression

subscale scores at 12 months from baseline were calculated. The correlation between the changes of distress scores with HADS-anxiety scale scores and HADS-depression subscale scores was tested with Spearman's correlation test. Partial correlation tests were further conducted to examine the correlation between the changes in distress scores with HADS-anxiety subscale scores by adjusting for the changes of HADSdepression scale scores and vice versa. All tests were two-tailed with significant level of 0.05.

#### 4.3 Results

Characteristic	
Age, mean (Terwijn et al.)	55.13 (11.5)
Ethnicity, n (%)	
Malay	71 (32.1)
Chinese	108 (48.9)
Indian	38 (17.2)
Others	2 (0.9)
Staging	
0	26 (11.8)
Ι	60 (27.1)
П	83 (37.6)
Ш	44 (19.9)
IV	8 (3.6)
Surgery, n (%)	211 (95.5)
Chemotherapy, n (%)	132 (59.7)
Radiotherapy, n (%)	151 (68.3)
Hormonal therapy, n (%)	69 (31.2)

 Table 4.1: Characteristics of the subjects (N=221)

At the time of data analysis, 221 female subjects with breast cancer were recruited in MyBCC and had completed the 12 months follow up visit. The average age of the subjects was 55 years old (SD=11.5) with almost half were Chinese, followed by Malay (32.1%) and Indian (17.2%) of ethnicity. Twenty six (11.8%) had non-invasive breast cancer (stage 0), 60 (27.1%) had Stage I, 83 (37.6%) had Stage II, 44 (19.9%) had Stage III and 8 (3.6%) had Stage IV disease. Nearly all (95.5%) had surgery with almost two

third had chemotherapy (59.7%) and radiotherapy (68.3%). Only about 31% had received hormonal therapy (Table 4.1).

 Table 4.2: The comparison of anxiety and depression scores between breast cancer

 patients with high or low perceived level of distress (N=221).

Time point: E	Baseline					
	Distres	s score	Adjusted	95% CI	Р	
	Mean (Ter	wijn et al.)	OR			
	4 and above	Less than 4	-			
Anxiety	6.76 (4.01)	4.06 (2.72)	1.28	1.13 – 1.44	< 0.01	
score						
Depression	4.75 (3.92)	3.05 (2.64)	1.00	0.89 - 1.12	0.96	
score						
Time point: 6	5 months					
	Distres	s score	Adjusted	95% CI	Р	
	Mean (Ter	wijn et al.)	OR			
	4 and above	Less than 4				
Anxiety	5.96 (3.25)	3.38 (3.09)	1.27	1.11 – 1.45	< 0.01	
score						
Depression	4.99 (3.62)	3.14 (2.85)	1.04	0.91 - 1.18	0.60	
score						
Time point: 1	year					
	Distres	s score	Adjusted	95% CI	Р	
	Mean (Ter	wijn et al.)	OR			
	4 and above	Less than 4				
Anxiety	5.44 (3.18)	2.63 (2.50)	1.51	1.29 – 1.76	< 0.01	
score						
Depression	4.55 (2.98)	3.06 (2.93)	0.92	0.80 - 1.06	0.24	
score						

CI = confidence interval, OR = odds ratio, distress = perceived level of distress measured with distress thermometer, anxiety = scores of hospital anxiety and depression scale (HADS) - anxiety subscale, depression = scores of HADS - depression subscale scores.

Breast cancer patients with high perceived level of distress had higher anxiety scores even after adjusted for the underlying depressive scores at all three time points (Adjusted OR at baseline = 1.28, 95% CI = 1.13-1.44; adjusted OR at 6 month = 1.27, 95% CI = 1.11 - 1.45; adjusted OR at 12 months = 1.51, 95% CI = 1.29 - 1.76). There were no significant differences in the depressive scores between the two groups after adjusting for the underlying anxiety scores.

### Table 4.3: The correlation between changes in perceived distress with the changes in anxiety and depression scores among the breast

	Baseline	12 months	Mean difference	95% CI	<i>p</i> value	<i>r'</i>
Distress	3.55 (2.74)	3.06 (2.39)	0.49	0.06, 0.91	0.02	-
Anxiety	5.42 (3.69)	3.78 (3.11)	1.16	1.10, 2.18	< 0.01	0.25*
Depression	3.90 (3.45)	3.60 (3.08)	0.30	-0.27, 0.87	0.03	-0.02

### cancer patients (N=221)

CI = confidence interval, r' = partial correlation with changes of distress after adjusting for the changes of either anxiety or depression scores, distress = perceived level of distress measured with distress thermometer, anxiety = scores of hospital anxiety and depression scale (HADS) - anxiety subscale, depression = scores of HADS - depression subscale scores, \*significance at the level of 0.01

There was reduction in perceived level distress scores, anxiety scores and depression scores at 12 months as compared to the baseline. The

change in anxiety scores was positively correlated with the change in distress scores even after adjustment for the changes in depression

scores (r' = 0.25). There was no significant correlation between the changes in depression scores with the changes in distress scores.

#### 4.4 Discussion

In the current study, we demonstrated that perceived distress among the breast cancer patients was significantly associated with anxiety but not depression. This finding was reflected at each point of the study - at baseline, 6 months and 12 months; where patients who were moderately to severely distress scored higher in the anxiety scale. There was no difference in the depression scores regardless of the distress level of the breast cancer patients. The association was further shown in the positive correlation between the changes in distress scores with changes in anxiety scores. Over the 12 months period, the reduction of distress was associated with the reduction of anxiety. In contrast, reduction of distress had no association with the changes in the depression scores.

The diagnosis and treatment of breast cancer causes a significant impact on the psychological well—being of the patients (Massie, 2004; Zabora et al., 2001). However, individual breast cancer patients differ in the extent of their psychological reaction to the illness. Psychological distress is a broad construct, covering a wide continuum of symptoms ranging from common normal feeling of vulnerability and fear to mental disabling conditions such as depression, anxiety and adjustment disorder (Jemal et al., 2008; Carlson et al., 2010., National Comprehensive Cancer Network., 2013). The commonest psychological states associated with distress in breast cancer patients are anxiety and depression (Jacobsen, 2007; Pirl, 2004). Up to 50% of the women with breast cancer experience high levels of distress with more than 30% of the women with early breast cancer had depression, anxiety, or both at diagnosis (Burgess et al., 2005). Many studies reported that depression was more common in breast cancer patients. Depressed breast cancer patients were less proactive in seeking treatments, have more severe symptoms, poorer response to systemic therapy, longer recovery times and poor outcomes (Colleoni et al., 2000; Hirscfeld, 2001., Walker et al., 1999). Some other

37

studies argued that anxiety is a more dominant psychological problem in breast cancer patients. Patients with breast cancer face extensive uncertainty about the disease progression, concern over potential recurrence, and fear of physical suffering (Liao, Chen, Chen, & Chen, 2008). All of these feelings contribute to the elevated anxiety levels. Either depression or anxiety has remarkably deleterious effects on the breast cancer patients' quality of life (Hutter et al., 2013).

Anxiety and depressive symptoms frequently co-exist but they can occur and progress independently in breast cancer patients. Anxiety and depression are not synonymous and each has its own distinctive characteristics and forms (Donovan, Gonzalez, Small, Andrykowski, & Jacobsen, 2014; Dunn et al., 2011). Anxiety is one of the most prominent psychological conditions in patients with breast cancer (G. W. Carlson & Wood, 2011; L. E. Carlson & Bultz, 2003). It is believed that anxiety is secondary as compared to depression in the spectrum of psychological distress among breast cancer patients (Shapiro et al., 2001). However, we demonstrated that the perceived level of distress among the breast cancer patients was positively associated with the level of anxiety but not depression in the current study. It was also shown in other studies that anxiety prevails throughout the period of treatment and recovery for patients with breast cancer, even among the disease-free breast cancer survivors (G. W. Carlson & Wood, 2011; L. E. Carlson & Bultz, 2003; Donovan et al., 2014; Dunn et al., 2011; Hutter et al., 2013; Liao et al., 2008; Saboonchi, Petersson, Wennman-Larsen, Alexanderson, & Vaez, 2015). Anxiety occurs when the adaptive response to the diagnosis or treatment of cancer is excessive and impairs the ability to cope with stress. Therefore, among breast cancer patients, uncertainty plays an important role affecting the illness experience, adaptation, and has a detrimental effect on the physical, mental and sexual quality of life (Hirschfeld, 2001).

Psychological response to a stressful event mainly depends on the patients' expectations (Kirsh, McGrew, & Passik, 2004). Breast cancer patients who anticipate more negative effects from the disease and treatment in the beginning experience a higher level of anxiety (Voogt et al., 2005). We have shown that the level of distress and anxiety was higher at diagnosis and significantly reduced over a 12 months period. The reduction of distress was also significantly correlated with the decrease of anxiety in the current study. This could be explained by conceptualizing anxiety as an anticipatory mood state of upcoming negative events (Barlow, 2000). At the early stage, breast cancer patients have heightened sense of vulnerability and high level of anxiety as they face extensive uncertainty about the diagnosis, progress of cancer, effectiveness and outcome of a treatment (Liao et al., 2008). They may have concerns over the possibility of metastasis and fear of treatment side effects. Over a period of time, the breast cancer patients will gradually come to terms with the disease and the treatment proceduces. It renders a progressive decline in the sense of future vulnerability and uncertainty, and consequently, reduces the level of anxiety over time (Millar, Purushotham, McLatchie, George, & Murray, 2005). Uncertainty can be seen as a source of anxiety that lead to psychological distress for breast cancer patients (Liao et al., 2008). A previous study showed that women with breast cancer were severely anxious during the diagnostic period (Burgess et al., 1988; Hall et al., 1999; Iwamitsu et al., 2005). Their anxiety levels before diagnosis were significantly higher than after diagnosis, with the highest level before breast biopsy. The authors concluded that breast cancer patients who chronically feeling anxious were more distressed, compared with those who did not generally feel anxious (Burgess et al., 1988; Hall et al., 1999; Iwamitsu et al., 2005). Their results were similar to the current findings where increasing psychological distress was related to higher level of anxiety. It suggests that a high level of anxiety trait as a personality characteristic could be a key factor in psychological adjustment to

cancer. It also reflects the vulnerability to stress for people with chronically high levels of anxiety (Keyzer-Dekker, de Vries, Mertens, Roukema, & van der Steeg, 2014).

Depression is common in patients with breast cancer (Baumeister, Kriston, Bengel, & Harter, 2010; Harter et al., 2007; Harter et al., 2001). In a study involving 227 advanced breast cancer, it was found that 25.6% had minor depression with 7% had major depression (Grabsch et al., 2006). In another study, it showed that around a quarter of all breast cancer patients have comorbid depression with estimated of 20 to 30% in earlier breast cancer (L. J. Fallowfield, Hall, Maguire, & Baum, 1990) with increased rates during advanced and terminal stages (Fulton, 1997). Despite the high prevalence of major depressive symptoms in breast cancer survivors, they were often misdiagnosed or undertreated in the oncology settings. Depression is associated with a reduced survival time (Watson, Haviland, Greer, Davidson, & Bliss, 1999) and diminished treatment adherence (Ayres et al., 1994), increased health care costs, worsen physical symptom burden, and lower quality of life (L. E. Carlson & Bultz., 2003; Li et al., 2011; Satin et al., 2009) in breast cancer patient. It is commonly believed that co-morbid depression significantly increases the burden of distress and dysfunction for patients with breast cancer (Reich et al., 2008). However, we did not show any association between the levels of depression with perceived distress in the breast cancer patients in the current study. Our results also indicated that there was reduction of depression a year after the cancer diagnosis but it was not correlated with the reduction of distress among the study subjects. This could be explained by the fact that depression in cancer patients is complex and encompasses several aspects. Depression includes a variety of mood disturbances and clinical presentations. Besides the classical depressive symptoms such as low mood, low energy, poor concentration, loss of interests, low selfesteem, guilt feelings, sleep and appetite disturbances and hopelessness, there are features often underrepresented in endogenous depression, such as somatic complaints,

psychic and somatic anxiety. Atypical symptoms such as anger, irritability, and hostility were also often neglected in the assessment of depression (Pasquini & Biondi, 2007; Verhoeven, Booij, Van der Wee, Penninx, & Van der Does, 2011). This gap often leads to the under-diagnosis of depression in breast cancer.

Depression exists on a continuum ranging from normal sadness, to an adjustment disorder, to subclinical depression to major depression. The presence of subclinical depression is higher than clinical depression as one study by Linden et al (2012) found (Linden et al., 2012). In their study the authors found that 12.9% of their patients reported clinical symptoms of depression and an additional 16.5% described subclinical symptoms. In our study the non-association between distress and depression may reflect the fact that the distress level experienced by our cohort of breast cancer patients was subthreshold in nature and did not meet the criteria for depression. Furthermore, culture may influence symptom expression, where individuals of the Asian ethnicity suffering from depression have the tendency to present with somatic symptoms of depression instead of the psychological symptoms (Bailey et al., 2005).

There were some limitations of the study. First, the study subjects were recruited from a single centre which is a teaching hospital at the capital of Malaysia. The generalizability of the samples could be improved in the future by recruiting patients from different sittings and regions of the country. Second, the other associated factors for distress were not included in the current study such as pain, financial support, family background, physical suffering and social support. Third, we only studied the association for the first 12 months after diagnosis. For future analysis, the association between distress with anxiety and depression could be studied for later period of the disease. Lastly, the psychological distress scoring scale used in the study was a single item scale. There are many cancer-specific stresses that may not be detected leading to loss of valuable risk factors for psychological distress.

## 4.5 Conclusion

In conclusion, breast cancer patients experienced high level of distress which including depression and anxiety after the diagnosis. Over time, the level of distress gradually reduced. Although both anxiety and depression were both commonly found in the breast cancer patients, they differ in their impact on the level of distress. Anxiety which could be related to the feeling of uncertainty seems to play a more significant role in the feeling of distress among the breast cancer patients. In contrast, depression which consists of negative emotions had no association with the level of perceived distress in cancer patients. As compared to depression, anxiety was often neglected in the management of psychological well-being among the breast cancer patients. With the current findings, more focus in helping breast cancer patients in relieving their feeling of anxiety in the future is important in reducing their perceived level of distress.

## CHAPTER 5: PSYCHOTHERAPY FOR CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

### 5.1 Introduction

Cancer is a chronic and life-threatening illness. Up to 50% of cancer patients will suffer from some degree of psychological distress (Massie, M. J., 2004; Singer et al., 2010). Researchers (Bultz & Holland, 2006) even suggested that psychological distress is a 'sixth vital sign' in cancer care. Its impact on cancer patients was recognized and endorsed by International Agency for Research on Cancer, World Health Organization (American Cancer Society., 2015). The presence of psychiatric co-morbidities significantly affects the patients' survival rates and associated with a delay in cancer diagnosis (Batty et al., 2012; Giese, D. J., 2011; Sogaard et al., 2013). Furthermore, patients with a psychiatric co-morbidity often do not receive standard cancer treatments such as surgery, chemotherapy, and radiation therapy. Their chances of completing a course of cancer treatment have been found to be lower. There was a higher risk of postoperative complications and mortality in cancer patients with psychiatric morbidities (Batty et al., 2012; Giese, D. J., 2011; Sogaard et al., 2013).

In view of the negative impact that psychiatric co-morbidities have on cancer patients, adequate treatment is vital. There is an increased in popularity on psychological treatments among cancer patients. Studies have shown psychotherapy to be an effective treatment modality where it helps in the reduction of psychological distress and subsequently improvements on overall quality of life and survival chances (Duijts, S. F et al., 2011; Kissane et al., 2007). Previous literature indicated that patients experience high satisfaction levels despite having higher expectations towards psychological therapies (Miller et al., 1998). However, the type of psychotherapies offered or recommended varies. There are many clinical trials addressing and reporting on the

43

efficacy of different forms of psychological treatment for cancer patients. The most commonly applied psychotherapies on cancer patient were cognitive behavioural therapy, problem-solving therapy and adjunctive psychological therapy (Newell et al., 2002).

After more than a decade from the last review on this topic (Newell et al., 2002), the aim of this study is to re-examine the clinical trials involving any types of psychotherapies in cancer patients and conclude on its efficacy in cancer patients. All clinical trials involving the efficacy of psychotherapies in the treatment for psychological morbidities in cancer patients were extracted and reviewed. Each type of psychotherapy and its efficacy in the treatment of cancer patients were discussed. Subsequently, a meta-analysis was conducted on clinical trials involving a specific type of psychotherapy with the same outcome measure.

## 5.2 Methodology

## 5.2.1 Search strategy and selection criteria.

NCG and TKM designed the review protocol and extraction forms in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. NCG and SM conducted a search for the literature in the PubMed and EMBASE databases from inception to Oct 2014, using the search terms: "therapy OR psycho\*" AND "cancer OR oncol\*". We only included clinical trial (randomized (RCTs), quasi-randomized controlled trials (QRCTs), quasi-controlled trials (QCTs), open-labelled trials, observational studies and cohort pre and post-treatment studies that presented original data on psychotherapy intervention on adult (older than 18 years old) cancer (any types) patients. We searched the reference lists of all relevant papers to identify further studies and the conference proceedings likely to contain trials relevant to the review. We excluded case reports, systemic review, case series and duplicate publications where only the first publication was included.

### 5.2.2 Data extraction and classification.

NCG and LKT extracted the primary data independently, which were reviewed systemically. Each of the two reviewers independently assessed the quality of the studies using "Quality Assessment Tool for Quantitative Studies" Scale. The "Quality Assessment Tool for Quantitative Studies" scale was developed by Effective Public Health Practice Project to assess the quality of quantitative studies for interpretation of meta-analysis results (Thomas et al., 2004). This tool assesses outcome evaluations using all types of study design on selection bias, study design, confounders, blinding, data collection methods, and withdrawals and drop-outs. Studies are considered "strong" if they receive no weak ratings on any of these components; "moderate" if they receive one weak rating; and "weak" if they receive two or more weak ratings (Table 5.1). Any disagreement was discussed and resolved by AH and NZZ, acting as mediators.

## 5.2.3 Data Synthesis

#### 5.2.3.1 Qualitative

The information on authors, sample size, type of cancer, types of psychotherapy, primary outcomes and findings of each included trial were summarized and tabulated.

#### 5.2.3.2 Quantitative

Of the 17 included studies, there were more than one RCT conducted on Adjuvant Psychological Therapy (APT) with the same outcome measurement. Four RCTs studied APT on cancer patients using HADS as outcome measurement. Two studies measured the outcomes at 2, 4 and 12 months where one of it measured at 2 and 4 months and the other measured at 12 months. Only these four data were included into quantitative

analysis. The analysis was done with Stats Direct (version 2.7.9). The presence of heterogeneity between the trials was tested using the I-squared (I2) statistic. A p-value of the test less than 0.05 indicates a significant heterogeneity. If the I2 was significant, we pooled the data by using random effects (DerSimonian-Laird), if not, we pooled the data by using fixed effects (Mantel-Haenszel). Data were analyzed with 95% confidence interval by using the effect size (weighted mean difference) meta-analysis if the mean and standard deviation (Terwijn et al.) of endpoint measures were presented. If the SD was not provided in the original article, it was estimated based on the mean, sample size and confidence interval using the formula: confidence interval = mean  $\pm Z\alpha 2^* \sigma/sqrt$  (n).

## 5.3 Results

The initial search strategy identified 5569 titles: 3971 from Pubmed and 1598 from EMBASE. Title screening and elimination of duplicate publications yielded 386 publication; we then excluded 369 publications after reviewing the abstract. Seventeen were eligible for inclusion in this review.

Quality assessment of the included studies showed that only two studies were rated "moderate" and the rest were rated "weak" (Table 5.1). The main limitation of the studies design was no control or adjustment of the confounders. There was no blinding for all the studies which is a common obstacle in psychotherapy study. The information and data of the seventeen studies were extracted and tabulated as shown in Table 5.2. There were eight randomized controlled trials and nine single arm observational studies. Types of psychotherapies included: Adjunctive Psychotherapy (APT) – 5 trials, Cognitive Behavioral Therapy (CBT) – 3 trials, Group Therapy – 3 trials, Supportive-Expressive Group Therapy (SEGT) – 1 trial, Problem-solving Therapy (PST) – 1 trial, Rational-Emotive Behavior Therapy (REBT) – 1 trial, Psycho-Spiritual Integrative Therapy (PSIT) – 1 trial, Dialectical Behaviour Therapy (DBT) – 1 trial and

psychoeducational therapy – 1 trial. Nine studies involved only breast cancer subjects, seven studies included patients with any type of cancer and one study used patients with testicular cancer. Most of the result showed improvement in the psychological well-being, namely anxiety and depression. Only two studies showed no significant changes in anxiety and depression comparing the psychotherapy groups with the control (Table 5.2).

Of the four randomised controlled trials on APT included in quantitative analysis, two studies measured the outcomes at 2, 4 and 12 months. One study measured at 2 and 4 months; and one study measured at 12 months. All studies used HADS as an outcome measure for depression and anxiety. For quantitative analysis of depression at end points of 2, 4 and 12 months, the I2 test was not significant hence the fixed effects (Hedges-Olkin) were used. The standardized mean differences (pooled effect size) were -0.20 (95% CI = -0.41, 0.01) at 2 months, -0.12 (95% CI = -0.33, 0.08) at 4 months and -0.04 (95% CI = -0.26, 0.17) at 12 months. There were no significant differences in depression at all end points of 2, 4 and 12 months, the I2 test was also not significant hence the fixed effects (Hedges-Olkin) were used as well. The standardized mean differences (pooled effect size) were analysis of anxiety at end points of 2, 4 and 12 months, the I2 test was also not significant hence the fixed effects (Hedges-Olkin) were used as well. The standardized mean differences (pooled effect size) were -0.37 (95% CI = -0.57, -0.16) at 2 months, -0.21 (95% CI = -0.42, -0.01) at 4 months and 0.03 (95 % CI = -0.19, 0.24) at 12 months. There was reduction in anxiety in APT treated groups at 2 and 4 months but not at 12 months end point (Figure 5.2).

2 months									
Study	APT			Control			Standard mean difference	Standard mean difference	
	Mean diff	SD	Ν	Mean diff	SD	Ν	Fixed, 95% CI	Fixed, 95% CI	
Moorey et al 1998	-3.80	5.48	25	-2.60	3.71	22	-0.25 (-0.82, 0.33)		
Greer et al., 1992	-1.30	3.60	72	-0.30	3.30	84	-0.29 (-0.61, 0.03)		
Moynihan et al., 1998	-0.51	5.34	73	0.00	5.37	81	-0.09 (-0.41, 0.22)	<b>_</b>	
Total			170			187	-0.20 (-0.41, 0.01)	$\rightarrow$	
Chi <sup>2</sup> =0.76, <u>df</u> = 2, <i>p</i> =0.68, l <sup>2</sup>	² = 0% (95% C	l = 0% to	o 72.9%	5)				la ds o os	
APT = Adjuvant Psychotherapy, HADS = Hospital Anxiety and Depression Scale, SD = standard deviation, CI = confidence interval Mean diff = mean differences of HADS-Depression score at 2 months from baseline									
4 months									
Study		APT		Control			Standard mean difference	Standard mean difference	
	Mean diff	SD	Ν	Mean diff	SD	Ν	Fixed, 95% Cl	Fixed, 95% CI	
Moorey et al 1998	-4.80	6.12	25	-1.90	4.55	22	-0.52 (-1.11, 0.06)		
Greer et al., 1992	-1.70	3.90	72	-1.10	3.30	84	-0.19 (-0.51, 0.12)		
Moynihan et al., 1998	-0.46	5.14	73	-0.80	5.56	81	0.06 (-0.25, 0.38)		
Total			170			187	-0.12 (-0.33, 0.08)		
Chi <sup>2</sup> =3.34, <u>df</u> = 2, <i>p</i> =0.19, I <sup>2</sup>	² = 40.1% (95	% CI = 0%	% to 82	.4%)				15	
APT = Adjuvant Psychotherap Mean diff = mean differences	y, HADS = Hos of HADS-Depr	pital Anxi ession sc	ety and ore at 4	Depression Sca months from I	ale, SD = s baseline	tandard de	eviation, CI = confidence interval		
12 months									
Study		APT		C	ontrol		Standard mean difference	Standard mean difference	
	Mean diff	SD	Ν	Mean diff	SD	Ν	Fixed, 95% Cl	Fixed, 95% CI	
Moorey et al 1998	-4.70	8.67	25	-5.00	7.66	22	0.04 (-0.54, 0.61)		
Moynihan et al., 1998	-0.97	4.29	73	-2.00	10.56	81	0.12 (-0.19, 0.44)		
Moorey et al., 1994	-2.10	4.00	62	-1.10	3.70	72	-0.26 (-0.60, 0.08)		
Total			160			175	-0.04 (-0.26, 0.17)		
Chi <sup>2</sup> =2.69, <u>df</u> = 2, <i>p</i> =0.68, l <sup>2</sup>	² = 25.7% (95	% CI = 0%	% to 79	.2%)				67 · · · · · · · · · · · · · · · · · · ·	
APT = Adjuvant Psychotherap Mean diff = mean differences	APT = Adjuvant Psychotherapy, HADS = Hospital Anxiety and Depression Scale, SD = standard deviation, Cl = confidence interval Mean diff = mean differences of HADS-Depression score at 12 months from baseline								

Figure 5.1: Standardized mean differences for APT vs control for all trials combined

with HADS-Depression subscale scores as outcome measured at 2, 4 and 12 months

using a fixed effects meta-analysis

2 months										
Study	APT			C	ontrol		Standard mean difference	Standard mean difference		
	Mean diff	SD	Ν	Mean diff	SD	Ν	Fixed, 95% Cl	Fixed, 95% CI		
Moorey et al 1998	-3.70	2.81	25	-1.50	5.14	22	-0.53 (-1.11, 0.05)			
Greer et al., 1992	-1.80	4.10	72	-0.20	4.20	84	-0.38 (-0.70, -0.07)			
Moynihan et al., 1998	-1.83	4.10	73	0.42	5.21	81	-0.30 (-0.62, 0.02)			
Total			170			187	-0.37 (-0.57, -0.16)	$\rightarrow$		
Chi <sup>2</sup> =0.50, df = 2, p=0.79, l <sup>2</sup>	² = <mark>0% (</mark> 95% C	l = 0% to	0 72.9%	5)				120 -016 -070 -045 -020 0005		
APT = Adjuvant Psychotherap	y, HADS = Hos	pital Anx	ety and	Depression Sca	ale, SD = s	tandard d	eviation, CI = confidence interval			
wean diff = mean differences	OF HADS-ARXI	ety score	at 2 mo	nths from base	eine					
4 months										
Study		APT		C	ontrol		Standard mean difference	Standard mean difference		
	Mean diff	SD	Ν	Mean diff	SD	Ν	Fixed, 95% Cl	Fixed, 95% Cl		
Moorey et al 1998	-4.20	3.95	25	-2.00	4.19	22	-0.53 (-1.12, 0.05)			
Greer et al., 1992	-2.40	4.30	72	-0.70	4.10	84	-0.04 (-0.72, -0.09)			
Moynihan et al., 1998	-1.34	5.12	73	-1.74	5.44	81	0.08 (-0.24, 0.39)			
Total			170			187	-0.21 (-0.42, -0.01)	$ \rightarrow $		
Chi <sup>2</sup> =5.72, df = 2, p=0.05, l	² = 65% (95%	CI = 0%	to 87.9	%)				15 ds ds		
APT = Adjuvant Psychotherap	y, HADS = Hos	pital Anx	ety and	Depression Sca	ale, SD = s	tandard d	eviation, CI = confidence interval			
Mean diff = mean differences	OI HADS-ANXI	ety score	at 4 mo	nths from base	eine					
12 months		ADT			ontrol		Standard mean difference	Standard mean difference		
Study		AP I	N	Mana aliff	ontroi	N	Standard mean difference	Stanuaru mean unterence		
	iviean dill	SU 0.10	25	Iviean dill	12.04	22	Fixed, 95% CI			
Moorey et al 1998	-4.90	9.18	25	-4.60	13.64	22	-0.03 (-0.60, 0.55)			
Moynihan et al., 1998	-0.97	5.54	/3	-2.63	6.31	81	0.28 (-0.04, 0.60)			
Moorey et al., 1994	-1.70	4.40	62	-0.70	4.00	72	-0.24 (-0.58, 0.10)			
Total			160			175	0.03 (-0.19, 0.24)	$\rightarrow$		
$Chi^2 = 4.73, df = 2, p = 0.09, f$	<sup>2</sup> = 57.7% (95	% CI = 09	% to 86	.2%)				67		
APT = Adjuvant Psychotherap Mean diff = mean differences	APT = Adjuvant Psychotherapy, HADS = Hospital Anxiety and Depression Scale, SD = standard deviation, CI = confidence interval Mean diff = mean differences of HADS-Anxiety score at 12 months from baseline									

Figure 5.2: Standardized mean differences for APT vs control for all trials combined

with HADS-Anxiety subscale scores as outcome measured at 2, 4 and 12 months using

a fixed effects meta-analysis

Study	Year	Selection Bias	n Study Confounders Design		Blinding	Data Collection	Withdrawals	Global Rating
						N		
Cunningham and Tocco.	1989	Moderate	RCT, Strong	Weak	Weak	Strong	Strong	Weak
Greer et al.	1991	Moderate	C, Moderate	Weak	Weak	Strong	Weak	Weak
Greer et al.	1992	Moderate	RCT, Strong	Moderate	Weak	Strong	Strong	Moderate
Moorey et al.	1994	Moderate	RCT, Strong	Weak	Weak	Strong	Moderate	Weak
Moorey et al.	1998	Weak	RCT, Strong	Moderate	Weak	Strong	Strong	Weak
Moynihan et al.	1998	Moderate	RCT, Strong	Weak	Weak	Strong	Strong	Weak
Edmonds et al.	1999	Weak	RCT, Strong	Weak	Weak	Strong	Moderate	Weak
Cunningham.	2005	Weak	C, Moderate	Weak	Weak	Strong	Moderate	Weak
Savard et al.	2005	Moderate	RCT, Strong	Strong	Weak	Strong	Moderate	Moderate
Akechi et al.	2008	Weak	C, Moderate	Weak	Weak	Strong	Strong	Weak
Reuter et al.	2010	Strong	C, Moderate	Weak	Weak	Strong	Moderate	Weak
Garlick et al.,	2011	Moderate	C, Moderate	Weak	Weak	Strong	Weak	Weak
Hassanzad et al.	2012	Weak	RCT, Strong	Weak	Weak	Strong	Weak	Weak
Hirai et al.	2012	Moderate	C, Moderate	Weak	Weak	Strong	Weak	Weak

**Table 5.1:** Quality assessment of the 10 eligible studies by using "Quality Assessment Tool for Quantitative Studies" Scale

Table 5.1,	Continued.
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Study	Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection	Withdrawals	Global Rating
Mahigir et al.	2012	Weak	C, Moderate	Weak	Weak	Strong	Weak	Weak
Yavuzsen et al.	2012	Moderate	C, Moderate	Weak	Weak	Strong	Moderate	Weak
Anderson et al.	2013	Moderate	C, Moderate	Weak	Weak	Strong	Weak	Weak

CS= Cross-sectional, C= Cohort (one group pre + post), RCT= Randomized controlled trial.
Author, year, country	Intervention (No. of subjects)	Types of cancer	Mean age, % female	Measurement	Outcomes
Cunningham and Tocco. 1989, Canada	Support + Psychoeducational Therapy (28) Vs Support therapy (25)	Any types	Mean age for psychoeducationa l group: 48.2 Mean age for support group: 48.7 Female: 73.6%	POMS, SCL-90_R	Both psychoeducational and discussion control groups produced significant improvements. Coping skills training appeared to produce, overall, about a two-fold greater effect than control group.
Greer et al., 1991, UK	Adjuvant psychological therapy, APT (44)	Any types	Mean age: 47.9 Female: 68%	HADS and MAC	APT produced significant improvement in anxiety, depression, fighting spirit, anxious preoccupation and helplessness
Greer et al., 1992, UK	Adjuvant Psychological Therapy, APT (72) vs Control (84)	Any types*	Mean age for therapy group: 51 Mean age for control group: 52 Female: 79.5%	HADS, MAC, Rotterdam symptom checklist, Psychosocial adjustment to illness scale	APT produced significant decrease on anxiety; psychological symptoms; and psychological distress.
Moorey et al., 1994, UK	Adjuvant Psychological Therapy, APT (62) Vs Control (72)	Any types	NA	PAIS, HADS, RSC and MAC	APT group showed improvement in psychological functioning which persists up to 10 months after the end of the intervention.

**Table 5.2:** Qualitative description of the 17 included clinical trials involving any types of psychotherapy in cancer patients

Author, year, country	Intervention (No. of subjects)	Types of cancer	Mean age, % female	Measurement	Outcomes			
Moorey et al., 1998, UK	Adjuvant Psychological Therapy, APT (25) vs Counselling group (22)	Any types	Mean age: 51 Female: 74.5%	HAD, STAI, BDI, MAC, CCQ	APT produced greater change in anxiety, adjustment to cancer and use of coping strategies than a non- directive, supportive intervention.			
Moynihan et al., 1998, UK	Adjuvant psychological therapy, APT (73) Vs Standard care (81)	Testicular	Mean age: NA All males	HADS, MAC, PAIS-SR, RSC, BMS, RSAS.	There were no differences in the outcome.			
Edmonds et al., 1999, Canada.	Long term Group Therapy (30) Vs Control (36)	Breast	Mean age: 50.7 Female: 100%	POMS, FLIC, DUFSS, MAC and RED	In long term intervention, subjects did experience more anxious preoccupation and less helplessness than the controls but no recorded improvements in mood or quality of life.			
Cunningham, 2005, Canada	Group Psychological Therapy Programme (97)	Any types	Mean age: NA Female: 80%	POMS-SF, FACT, SICPA, PIL and FACIT-Sp.	The programmed showed improvement in mood, self-efficacy, quality of life, purpose in life, and spirituality.			
Savard et al., 2005, Canada	Cognitive- Behavioral Therapy, CBT (28) Vs Waiting list control, WLC (30)	Breast	Mean age for CBT group: 54.8 Mean age for WLC group: 53.4 Female: 100%	IIS, SCID, Sleep diary, PSG, ISI, HADS, MFI and QLQ-C30+3	CBT produced significantly better subjective sleep indices, a lower frequency of medicated nights, lower levels of depression and anxiety, and greater global quality of life.			

Table 5.2, Continued.

Author, year, country	Intervention (No. of subjects)	Types of cancer	Mean age, % female	Measurement	Outcomes				
Akechi et al., 2008, Japan	Problem-solving Therapy, PST (4)	Breast	Mean age: 44.5 Female: 100%	BDI-ll and HADS	The PST reduced anxiety and depression.				
Reuter et al., 2010, Germany	Supportive- Expressive Group Therapy, SEGT (49)	Breast	Mean age: 46.8. Female: 100%	HADS-D, EORTC QLQ-C30, EORTC QLQ-BR23, TSK, ZUF-8 and GEQ	SEGT produced no significant improvements in depression or anxiety. Quality of life, tumor-related fatigue and coping strategies				
Garlick et al., 2011, USA	Psycho-Spiritual Integrative Therapy, PSIT (24)	Breast	Mean age: 53.0 Female: 100%	FACT-B, POMS, PTGI, PTG and FACIT-Sp-Ex.	PSIT may improve well-being and stimulate Posttraumatic Growth (PTG) in breast cancer patients.				
Hassanzad et al, 2012, Iran	Cognitive behaviour group therapy (16)	Breast	Mean age: NA Female: 100%	HRSA and HRSD	CBT reduced depression and anxiety levels; and improved physical symptoms.				
Hirai et al., 2012, Japan	Problem-solving Therapy, PST (36)	Breast	Mean age: 50.2 Female: 100%	DIT and HADS	The PST produced significant improvement in anxiety and depression. There were also significant changes in worry, self-				
Mahigir et al., 2012, Iran and Inida.	Rational-Emotive Behavior Therapy, REBT (43) Vs Control (45)	Any types	Mean age: NA Female: NA	MPQ	Results showed that the REBT group in post-test had less pain.				

Table 5.2,	Continued.
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Author, year, country	Intervention (No. of subjects)	Types of cancer	Mean age, % female	Measurement	Outcomes
Yavuzsen et	Group Therapy	Breast	Mean age: 47.8	BDI, BHS, STAI,	Group therapy produced significantly
al., 2012,	Programme (16)			Likert scale for	improvements in anxiety, depression,
Turkey			Female: 100%	distress, QoL and QoS	and distress.
Anderson et al, 2013, USA	Dialectical Behaviour	Breast	Mean age: NA	DS, BSI-18, FACT-B and	Improvements in distress levels with better coping abilities and recognising
	Therapy (14)		Female: 100%	DASS	stress triggers.

HADS = Hospital Anxiety and Depression Scale, STAI = Spielberger State Trait Anxiety Inventory, BDI = Beck Depression Inventory, MAC = Mental Adjustments to Cancer Scale, CCQ = Cancer Coping Questionnaire, RSC = Rotterdam symptom checklist, PAIS = Psychosocial adjustment to illness scale, BHS = Beck Hopelessness Scale, QoL = Quality of Life, QoS = Quality of Sleep, BMS = Brannon masculinity scale, RSAS = Rieker sexual adjustment scale, EORTC QLQ-C30 & EORTC QLQ-BR23 = Quality of life: European Organization for Research and Treatment of Cancer quality-of-life questionnaire – core 30 and breast cancer module, TSK = Trierer Skalen zur Krankheitsbew ätigung, ZUF-8 = Fragebogen zur Messung der allgemeinen Patientenzufriedenheit, GEQ = Group Experience Questionnaire, POMS-SF = Profile of Mood States–Short Form, FACT = Functional Assessment of Cancer Treatment, SICPA = Stanford Index of Cancer Patient Assessment, PIL = Purpose in Life Test, FACIT-Sp-Ex = Spirituality Subscale of the FACT, IIS = Insomnia Interview Schedule, SCID = Structured Clinical Interview for the DSM-IV, PSG = Polysomnography, ISI = Insomnia Severity Index, MFI = Multidimensional Fatigue Inventory, SCL-90\_R = Symptom checklist, DS = Distress Scale, BSI-18 = Brief Symptom Inventory, FACT-B = FACT-Breast Symptom Index , DASS = Depression, Anxiety and Stress Scale, HRSA = Hamilton Rating Scale for Anxiety, HRSD = Hamilton Rating Scale for Depression

#### 5.4 Discussion

In the current review, the efficacy of the following psychotherapeutic methods; adjuvant psychological therapy (APT), supportive-expressive group therapy (SEGT), problemsolving therapy (PST), group therapy, rational-emotive behavior therapy (REBT), cognitive-behavioral therapy (CBT), support and psychoeducational therapy, support discussion group and dialectical behavioural therapy (DBT) were studied in cancer patients. Of all, APT was most commonly studied followed by CBT and group therapy. In the quantitative analysis of four randomised controlled trial of APT, there was no significant improvement in depression. However, there was a reduction in anxiety symptoms with APT at early months but not after a year. Although, the overall literature demonstrated that most types of psychotherapy reduce psychological distress, anxiety and depression; improved quality of life and coping in cancer patients but the evidence appeared to be limited.

Adjuvant psychological therapy (APT) is a therapy specifically designed for cancer patients. APT has proven effective in improving anxiety, coping, fatalism, psychological health and well-being, helplessness, mood and psychological distress by several studies (Greer, S, Moorey, S & Baruch, J., 1991; Greer, S., 1992; Moorey, S et al., 1994; Moorey, S, Greer, S, Bliss, J & Law, M., 2012). APT is more effective in helping with anxiety, depression, fighting spirit, helplessness, anxious preoccupation and fatalism within a period of four weeks and more variables such as self-perceived problems and coping were achieved within a longer period of therapy as compared to counselling. Over time, patients that have undergone counselling also improved but slower than the APT group. This may be due to the differences in methods where APT focuses more on the present while counselling allows the patients to explore the root cause of their problems from the past. Hence, allowing the patients to solve their current situation that may be affecting the patient's current medical conditions (Greer, S,

56

Moorey, S & Baruch, J., 1991; Greer, S., 1992; Moorey, S et al., 1994; Moorey, S, Greer, S, Bliss, J & Law, M., 2012). APT allows patients to explore further on the cognitive behavioural point of their problems and resolves them to allow patients to improve on these elements (Greer, S, Moorey, S & Baruch, J., 1991). Despite the effectiveness of APT on cancer patients, it is unable to provide improvement towards patients socially (Greer, S., 1992). Social interactions and relationships with others are vital in improving their conditions to gain a supportive environment (Cunningham, A. J., 1998).

Group therapy is a process of having a group of patients with similar conditions to conduct interactions through discussion among themselves and peer discussions. This therapy has proven to decrease the anxiety, depression and stress levels among cancer patients. Several more studies have suggested that group therapy helps in reducing irrational thoughts, anxiety, negative emotions, resiliency, stress, tiredness, hopelessness and psychosocial signs (Yavuzsen, T, Karadibak, D, Cehreli, R & Dirioz, M., 2012). In another study done on group psychological therapy has shown that this therapy improves the mood, self-efficacy, quality of life, life purpose and spiritual needs of cancer patients (Cunningham, A. J., 2005). In a similar research (Reuter, K et al., 2010) where the effects of supportive-expressive group psychotherapy (SEGT) on cancer patients were tested, it was stated that there were positive effects on the participants before and after therapy especially prevalent on the quality of life and future perspectives. Other variables that also showed positive signs were emotional functions, fatigue and search for affiliation. This therapy helps patients improve their well-being by creating a supportive environment and allowing them to express their experiences with their peers (Cunningham, A. J., 1998; Reuter, K, Scholl, I, Sillem, M et al., 2010).

Problem-solving therapy (PST) is a therapy that concentrates on the problems faced by cancer patients. Patients are allowed to explore their problems and focus on solving them. The researcher suggested that PST brings beneficial results in terms of depression and anxiety whereby the primary focus of this therapy is in solving the current problems that may be affecting the patient's current condition (Akechil, T et al., 2008). In another similar study (Hirai, K et al., 2012), it supports the results of the previous research (Hirai, K et al., 2012), it supports the results of the previous research (Akechil, T, Hirai, K, Motooka, H et al., 2008) where the results obtained were the same in terms of improving depression and anxiety levels comparing from before therapy and after. This therapy may help to expand the patient's social circle such as family and friends which may have contributed to the effectiveness of this therapy.

Rational-emotive behavior therapy (REBT) is a therapy that helps the patients in pain to understand and accept the problems that they are facing. REBT focuses on how an individual can control pain through how they perceive their pain. The results showed that REBT is highly effective for cancer patients in reducing their pain. This is because the patient can avoid clinical pain through acceptance and understanding their pain. In other words, REBT helped the subjects to change their perception towards their pain (Mahighir, F, Khanehkeshi, A & Karimi, A., 2012).

Psycho-spiritual integrative therapy (PSIT) is a therapy that allows the patient to spiritually connect with their existence and purpose of life. Basically, understanding and accepting their true meaning of life. This will help the patients in the regulation of their emotions, self-control, mindfulness and life quality. Studies have shown that patients with PSIT were experiencing improvement in emotional, physical and functional well-being and stimulates posttraumatic growth (Garlick, M, Wall, K, Corwin, D et al., 2011). The participants were taught to use relaxation techniques such as meditation, yoga and how to be mindful of what they are feeling, thinking and acting. These techniques allow

the participants to view their emotion on a more neutral ground, be more aware of their negative side to make changes in the way they live and reduce the stress relating to physical dissatisfactions (Garlick, M, Wall, K, Corwin, D et al., 2011).

Cognitive behavioural therapy is a type of therapy focussing on the thought that is affecting the emotion and behaviour. Researcher focused on revealing the effects of CBT on insomnia problems among cancer patients in a prior study. The results showed a decrease in depression, anxiety and frequency of sleep medication while improving sleep and life quality which revealed that sleeping problems can be addressed through other strategies other than medication (Savard, J., 2005). In another similar research done on proving the effectiveness of group therapy with the influence of CBT on decreasing cancer symptoms, it is shown that CBT lowers the depression and anxiety levels while improving physical symptoms. According to this study, CBT improves the condition of the cancer patient because of the techniques applied in the therapy such as relaxation and imagination skills. These skills help participants to regulate their emotion which will then lead to an improvement in depression and anxiety levels (Hassanzade, R et al., 2012).

Psychoeducational therapy is a therapy that has a combination of supportive conversations, learning on coping, relaxation and imagination skills and healthy lifestyles. The therapy focuses on living a healthy life holistically by practicing healthy communication, coping and healthy physical work. This type of therapy mainly focuses on the negative stress and emotions that the patient is facing. The researchers divided the participants into two groups where the first group received only supportive discussions while the other group received psychoeducational therapy. The study showed that both therapies were effective. However, the psychoeducational therapy group received better scorings than the first group. Overall, psychoeducational therapy improved the conditions of the patients in term of anxiety, depression, hostility,

59

somatisation, psychotisism, phobia, anger, vigor, fatigue and confusion. The effectiveness of the therapy remained effective after three months of completing the therapy. The factors taken into consideration for the results obtained are that the patients were segregated according to their preferences on the type of therapy received. Also, the therapist's methods in conducting the therapies play a role in the effectiveness of the both the therapies (Cunningham, A. J & Tocco, E. K, 1989).

Dialectical behaviour skills (DBT) is a type of therapy where the main focus is to teach the patients cognitive-behavioral skills. In this form of therapy, the patients are asked to practice on understanding how the way they think may affect how they behave. It will eventuallty helps them cope with their situation better. In a recent study (Anderson, R. C, Jensik, K & Peloza, D, 2013), the results obtained showed that DBT helps cancer patients both psychologically and physically. Psychologically, the patients improved in terms of their coping with stress, recognising the causes of their stress and also the motivation to educate other patients on these methods. Physically, they showed signs of decrease in pulse rates, stress levels, somatization symptoms and changes in biothermal indicators. The main method that was found to be most effective was the mindfulness method.

# 5.4.1 Limitations

There were insufficient numbers of research on specific type of psychotherapy to identify the best method for improving cancer patients' conditions. Most of the studies on the different types of psychotherapy were limited and lacked variation. Hence, there were barriers in proving the effectiveness of psychotherapy in cancer patients.

Furthermore, biases exist in the studies reviewed. The participants were allocated to specific therapy by the clinical psychologists. The clinician may unconsciously divide the participants with the influence of their prior clinical knowledge and judgements

towards the patients. Participants also may withdraw from the study during the study after selection processes. Researchers also faced problems in getting some of the participants to cooperate in commenting on the results of the therapy. Next, some of the cancer patients may have attended the therapy right after their medication or treatments which may affect their bodily function and lead to biases in the results. The gender distribution of participants were unequal as most of them were female. As such, some of the participants may not be able to complete the research on time due to their conditions. Hence, this may cause a bias in evaluating the true effectiveness of psychotherapy in cancer patients.

A significant number of studies did not have a control group, therefore, making the effectiveness of the therapy on cancer patients harder to interpret. Furthermore, blinding is a challenge is conducting trials on psychotherapy as the subjects will know the type of treatment received.

#### 5.5 Conclusion

Various kinds of psychotherapy were introduced for the treatment of psychological distress in cancer patients. These include adjuvant psychological therapy (APT), group counselling, problem-solving therapy (PST), rational-emotive behavior therapy (REBT), psycho-spiritual integrative therapy (PSIT), cognitive-behavioral therapy (CBT) psychoeducational therapy and Dialectical behaviour skills (DBT). Individual study examining each type of psychotherapy showed some promising results. However, more rigorously and well-designed trials are needed to confirm the efficacy. Among all, APT and CBT were most commonly studied. The combined results showed the benefit of APT in anxiety at early months but not depression. Hence, future work to determine the specific type of psychotherapy with a significant positive result for cancer patients is profoundly crucial.

# CHAPTER 6: ANXIETY, DEPRESSION, QUALITY OF LIFE AND PERCEIVED SOCIAL SUPPORT IN MALAYSIAN BREAST CANCER PATIENTS: A 1- YEAR PROSPECTIVE STUDY

#### 6.1 Introduction

Breast cancer is the most common cancer diagnosed among the female in Malaysia (National Cancer Registry Malaysia., 2006). Over the decades, the survival rate in breast cancer improved with the early detection and advances in cancer treatment (Ries, L. A. G et al., 2007). As such, the current focus in the cancer treatment is not only about illness control but also the general wellbeing of the patients. Quality of life (QoL) is the measure of the patient's perception of self-wellbeing. QoL encompasses several aspects of functioning such as psychological, physical, cognitive and social functioning (O'Neil, A et al., 2013). Of the limited number of studies on QoL among breast cancer patients in Malaysia, a descriptive study involved 58 Malays and 15 Chinese women newly diagnosed with breast cancer found that the QoL was satisfactory based on the Malay version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). There was no different in the QoL between the two ethnic groups (Yusuf et al., 2013). Complementary and alternative medicine (CAM) is popular among cancer patients in Malaysia. In a cross-sectional study on OoL among breast cancer patients under chemotherapy, it was found that the level of QoL was similar between CAM user and non-users (Chui, P. L., Abdullah, K. L., Wong, L. P & Taib, N, 2015). In general, studies showed that the scores of general health status among breast cancer patients in Malaysia based on EORTC QLQ-C30 is about 60 to 65 which were considered satisfactory (Yusuf et al., 2013; Chui, P. L., Abdullah, K. L., Wong, L. P & Taib, N, 2015).

Depression and anxiety are the two most common psychiatric comorbidities encountered in breast cancer patients (Baumiester, H et al., 2010). Depression and/or anxiety may occur to a patient with breast cancer at any stage of their illness from prediagnosis to the terminal phase of the illness. Studies from the Western countries have shown that the prevalence of depression ranges from 1% to 56% whereas the prevalence of depression from the Asian studies ranges between 12.5% and 31% (Zainal, N. Z et al., 2013). The prevalence rate of anxiety disorders differs greatly depending on the type of anxiety disorder being measured. A study by Dastan and Buzlu (Dastan, N. B & Buzlu, A, 2011) reported that 35% of their breast cancer patients had anxiety, while an Asian study reported a lower prevalence of 16% (Lueboonthavatchai, P., 2007). According to Burgess et al. (Burgess, C et al., 2005), it seems that the prevalence of depression and anxiety among women with breast cancer declined from the first year of diagnosis to the fifth year after diagnosis from 48% to 15%. In a study on depression and anxiety among Malaysian breast cancer patients, the rate of anxiety was 31.7% and depression was 22.0%. Younger age, financial burden, and being single were the associated factors for anxiety or depression among Malaysian breast cancer patients (Hassan, M. R et al., 2015).

Social support is defined as any types of communication in the form of physical or psychological assistance for someone to feel of more self-control during a difficult situation (Albrecht, T. L & Adelman, M. B, 1987). Studies showed that the positive impact of social support does not derive from the people or institutions that form the social networking. In contrast, they may cause negative impact or stress for the individual. Instead, research showed that the social support felt or perceived by the individual that produce the positive impact (Langford, C. P et al., 1997; Trevino, K. M et al., 2013; Pietras, T et al., 2011). Perceived social support was negatively correlated with psychological distress and suicidal thought in cancer patients (Ceyhan, M et al.,

2014). It is also associated with better orientation to health care services and adjustment to family relationship. Cancer patients with higher level of perceived social support had a better psychosocial adjustment to the illness (Rizalar, S et al., 2014). Among the different domains, support from family and friends were shown to be associated with less breast cancer related distress (Cicero, V., 2009). There was no study on the association of perceived social support with QoL or distress among breast cancer patients in Malaysia. However, there was a study which indicated that emotional/informational support was associated with a better quality of life among the elderly in the rural community in Malaysia (Ibrahim, N et al., 2013).

Cancer patients experience a fluctuating course of anxiety throughout the diagnosis and treatment phases (So, W. K. W et al., 2014; Reich, M & Lesur, A., 2008). From the time of diagnosis, the cancer patients experience different types of mental distress and adaptation to the process of cancer treatment including investigation, waiting for results, planning for surgery, chemotherapy, hormonal therapy, radiotherapy and recovery (Pandey, M et al., 2006; Zainal, N. Z & Ng, C. G., 2010). Interestingly, the result of a study by Kristin et al in post-surgery breast cancer patients showed that QoL improved over the first 6 months. Anxiety remained unchanged after a year but is influenced by the cancer diagnosis and treatment (Hartl, K et al., 2010).

Little is known about the course of depression and anxiety in women with breast cancer in Malaysia. There is also no prospective study examining the changes in QoL of breast cancer patients and its relationship with depression, anxiety and perceived social support in Malaysia. In the current study, we aim to study the changes of QoL, depression and anxiety among Malaysian breast cancer patients from the time of diagnosis till one year follow up. We also examine the association between the changes of QoL with depression, anxiety and perceived social support in the subjects.

## 6.2 Methodology

This study is part of a larger study, the Malaysian Breast Cancer Cohort (MyBCC) which is a prospective cohort study which aims to identify the association between genetics, lifestyle and nutrition on overall survival and quality of life of Malaysian Breast Cancer patients. For further detail of the cohort, please refer to the previous published report (Mohd, T. N. A et al., 2013). In our study, we mainly focused on the natural course of anxiety depression and quality of life among the female patients at diagnosis till 12 months of follow up visit. The association between the quality of life with anxiety, depression and perceived social support of the subjects were also examined in this study.

Patients at University Malaya Medical Centre in Kuala Lumpur, Malaysia who were diagnosed with breast cancer were consecutively enrolled since 1 May 2011. Inclusion criteria were (i) breast cancer that was confirmed by histological examination, (ii) able to complete the necessary interviews and questionnaires, and (iii) able to understand the objective of the study and provide informed consent. Exclusion criteria were (i) secondary breast cancer (primary cancer of any origin other than breast), (ii) having confusion or delirium, and (iii) male patients. The purpose and details of the study were explained to all potential subjects, and participants who gave written informed consent were enrolled. This study was approved by the Medical Ethic Committee, University Malaya Medical Centre.

#### 6.2.1 Procedure and Measures

All questionnaires and psychiatric measures were administered to patients by trained clinical research coordinators when patients were first diagnosed with breast cancer (baseline). The psychiatric measures were administered again at 6 months and 12 months follow-up visits thereafter. Information on age and ethnicity were obtained.

Breast cancer staging was confirmed by the treating surgeon using the American Joint Committee on Cancer Staging System for breast cancer.

Anxiety and depression were assessed using the Malay Version of Hospital Anxiety and Depression Scale (HADS). HADS was the most frequently reported measure in cancer studies and shown to be the best performing measure for each trajectory stage of the disease. It is a self-administered questionnaire that screened for anxiety (7 items) and depressive (7 items) symptoms. It has demonstrated good reliability. The anxiety (HADS-A) and depression (HADS-D) subscales are scored from 0 to 3 (four-point Likert scales), giving maximum scores of 21 for anxiety and depression respectively (Zigmoid, A. S & Snaith, R. P., 1983). The Malay version of HADS has a good reliability and has been validated among the Malaysian population (Yusoff, N., Low, W. Y & Yip, C. H., 2011).

Quality of life was measured using the Quality of Life Questionnaire QLQ–C30, Version 3.0 of the EORTC Study Group on Quality of Life (Aaronson, N. K et al., 1993). The QLQ-C30 is composed of both multi-item scales and single-item measures. These include a global health status/QoL scale and five functional scales evaluate physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. The symptom scales and items were not included in this study. All the measures range in score from 0 to 100. Higher mean scores on these scales represent better functioning and QoL. The additional module QLQ–BR23 contains breast-cancer–specific scales. Similar with previous study, we only used three most relevant subscales: body image, arm symptoms, and breast symptoms (Hartl, K et al., 2010). Higher mean values on the arm- and breast-symptom scales indicate an increased extent of symptoms. Higher mean scores on the Body Image scale of the QLQ–BR23 represent better functioning (McLachlan, S. A., Devins, G. M & Goodwin, P. J., 1998). Perceived social support was measured with Multidimensional Scale of Perceived Social Support (MSPSS). MSPSS is one of the self-administered scales. It is simple to be administered and scored. The scale consists of 12 questions and uses a 7-point Likert scale The scoring ranges from "strongly disagree" to "strongly agree". The scale has three subscales consisting of four questions to measure namely, family, friend, and significant other support. A high score represents high perceived social support (Zimet, G. D et al., 1988). It was translated into Malay language and its psychometric properties have been established. The Malay version of MSPSS was shown to have high internal consistency of the total and each subscale with excellent factorial validity (Ng, C. G et al., 2010).

## 6.2.2 Statistical Analysis

Descriptive statistics for the age, ethnicity and staging of cancer was performed. Mean and standard deviation for all items in the QLQ-C30, HADS depression subscale and anxiety subscale scores, MSPSS total and each domain subscale scores were calculated for the baseline, 6 months and at the 12 months visits. The normality of the data was tested with Kolmogorov-Smirnov test. As the data was non-normally distributed, the QLQ-C30, MSPSS total and domain scores, HADS depression and anxiety subscale scores at 6 and 12 months were compared with baseline using the Wilcoxan test.

The correlation between QLQ-C30 with HADS and MSPSS at baseline, 6 months and 12 months were examined using Spearman test. Partial correlation between QLQ-C30 with HADS was further tested by controlling of MSPSS scores. Likewise, the partial correlation between QLQ-C30 and MSPSS was tested by controlling the HADS scores. All the tests were two-tailed with alpha level of 0.05.

Up till May 2015, 221 female subjects with breast cancer were recruited in MyBCC and had completed the 12 months follow up visit. The mean age of the subjects was 55.1 years old (SD=11.5) with almost half were Chinese, followed by Malay (32.1%) and Indian (17.2%). Twenty six (11.8%) had non-invasive breast cancer (stage 0), 60 (27.1%) had Stage I, 83 (37.6%) had Stage II, 44 (19.9%) had Stage III and 8 (3.6%) had Stage IV disease. Almost all (95.5%) had surgery with more than half had chemotherapy (59.7%) and radiotherapy (68.3%). Only about one third had hormonal therapy (Table 6.1).

Characteristic	
Age, mean (Terwijn et al.)	55.13 (11.5)
Ethnicity, n (%)	
Malay	71 (32.1)
Chinese	108 (48.9)
Indian	38 (17.2)
Others	2 (0.9)
Staging	
0	26 (11.8)
Ι	60 (27.1)
П	83 (37.6)
ш	44 (19.9)
IV	8 (3.6)
Surgery, n (%)	211 (95.5)
Chemotherapy, n (%)	132 (59.7)
Radiotherapy, n (%)	151 (68.3)
Hormonal therapy, n (%)	69 (31.2)

 Table 6.1: Characteristics of the subjects (N=221)

#### 6.3.1 Quality of life, perceived social support, depression and anxiety

Quality of life of the 221 subjects was measured using QLQ-C30 and QLQ-BR 23 at three time points; baseline, 6 months and 12 months were showed in Table 6.2. There was improvement in the global health status/QoL at 12 months as compared to baseline (Baseline – 12 months, p = 0.015) with no significant change at 6 month (Baseline – 6

months, p > 0.05). Among the five functional scales, physical functioning showed significant improvement at 6 months (Baseline – 6 months, p = 0.001) and social functioning improved at 12 months (Baseline – 12 months, p = 0.03). There was significant improvement in emotional functioning at both 6 and 12 months (Baseline – 6 months, p = 0.002; Baseline - 12 months, p < 0.001). There was no significant changes in other two functioning scales, namely, role and cognitive.

The mean scores of perceived social support of the subjects were relatively high. The mean score for the total scale was 71.50 (SD=10.37), significant others subscale was 24.53 (SD=3.35), family subscale was 24.90 (SD=3.10) and friends subscale was 22.08 (SD=5.37). There were no significant changes for the scores of the perceived social support from baseline at 6 months or 12 months.

Anxiety and depression were measured with HADS and reported at three time points. Depression was relatively low and had no significant changes at both 6 months and 12 months' time point (Baseline – 6 months, p = 0.932; Baseline - 12 months, p = 0.428). There was significant reduction in anxiety at 6 and 12 months as compared to baseline (Baseline – 6 months, p = 0.002; Baseline - 12 months, p < 0.001) (Table 6.2).

Table 6.2: Quality of Life, Perceived social support, Anxiety and Depression among the

	Baseline mean (Terwijn et al.)	6 months mean (Terwijn et al.)	1 year mean (Terwijn et al.)	Baseline – 6 months <i>p</i> value <sup>a</sup>	Baseline – 12 months <i>p</i> value <sup>a</sup>	
QLQ-C30						
Global health	69.83	70.56	72.48	0.557	0.015	
status/QoL	(17.23)	(16.61)	(15.68)			
<b>Functional Sca</b>	les					
Physical	91.58	87.77	72.48	0.001	0.236	
functioning	(13.87)	(15.02)	(15.68)			

study subjects (N=221)

	Baseline	6 months	1 year	Baseline –	Baseline –
	mean	mean	mean	6 months	12 months
	(Terwijn et	(Terwijn et	(Terwijn et	p value <sup>a</sup>	p value <sup>a</sup>
	al.)	al.)	al.)	_	-
Role	93.21	90.11	91.59	0.066	0.280
functioning	(14.18)	(19.03)	(15.65)		
Emotional	78.17	83.70	86.89	0.002	0.000
functioning	(20.44)	(21.53)	(16.99)		
Cognitive	89.44	86.26	89.44	0.060	1.000
functioning	(15.70)	(18.47)	(15.70)		
Social	91.18	92.49	94.47	0.448	0.029
functioning	(18.64)	(15.72)	(12.98)		
QLQ-BR 23					
Functional					
scales					
Body image	92.61	91.39	94.85	0.575	0.151
	(16.27)	(17.39)	(13.21)		
Symptoms					
scales					
Breast	10.06	9.80 (14.53)	9.09 (12.92)	0.940	0.579
symptoms	(14.39)				
Arms	10.56	11.48	10.96	0.396	0.593
symptoms	(18.30)	(18.09)	(16.70)		
HADS					
Anxiety	5.42 (3.68)	4.45 (3.39)	3.75 (3.11)	0.002	0.000
subscale	•				
Depression	3.90 (3.44)	3.91 (3.31)	3.60 (3.07)	0.932	0.428
subscale	6				
MSPSS					
Significant	24.53 (3.35)	24.10 (4.19)	23.95 (3.71)	0.510	0.104
others					
Family	24.90 (3.10)	24.37 (3.93)	24.14 (3.34)	0.297	0.012
Friends	22.08 (5.37)	22.23 (4.91)	22.37 (4.76)	0.965	0.797
Total	71.50	70.70	70.46	0.666	0.404
	(10.37)	(11.49)	(10.54)		

QLQ–C30= Quality-of-Life Questionnaire (QLQ–C30), Version 3.0 of the EORTC Study Group on Quality of Life; QLQ–BR23 Questionnaire= a breast cancer-specific module for the QLQ; HADS= Hospital Anxiety and Depression Scale, sd = standard deviation; <sup>a</sup>Wilcoxan test

# 6.3.2 Correlation between quality of life with perceived social support, anxiety

# and depression

#### 6.3.2.1 At Baseline

There was negative correlation between global health status, all functional scales (physical, role, emotional, cognitive and social functioning) and body image with anxiety or depression (r = -0.22 to -0.50). The correlations remained significant in partial correlation analysis after controlling for perceived social support scores. In contrast, breast and arm symptoms based on QLQ-BR23 were positively correlated with anxiety and depression. The correlation was also significant after controlling for the perceived social support scores.

Only global health status was significant positively correlated with the MSPSS total and domain subscales scores. The functioning (physical, role, emotional, cognitive and social functioning), body image, breast and arm symptoms were not significantly correlated with perceived social support as measured with MSPSS after controlling for anxiety and depression (Table 6.3).

#### 6.3.2.2 At 6 months

There was negative correlation between global health status, all functioning (physical, role, emotional, cognitive and social functioning) and body image with anxiety or depression (r = -0.22 to -0.50). The correlations with depression were no more significant in partial correlation analysis after controlling for perceived social support scores. Breast symptoms based on QLQ-BR23 were positively correlated with anxiety and depression. The correlation with depression was also not significant after controlling for the perceived social support scores.

Similar to the finding at baseline, only global health status was significant positively correlated with the MSPSS total and domain subscales scores. The functioning (physical, role, emotional, cognitive and social functioning), body image, breast and arm symptoms were not significantly correlated with perceived social support as measured with MSPSS (Table 6.3).

#### 6.3.2.3 At 12 months

Although there were still negative partial correlation between global health status, most functioning (except role functioning) and body image with anxiety or depression, the correlation were lower as compared to baseline (pr = -0.15 to -0.38). The correlations were remained significant in partial correlation analysis after controlling for perceived social support scores. Arm but not breast symptoms based on QLQ-BR23 were positively correlated with anxiety and depression. The correlation was also significant after controlling for the perceived social support scores (pr = -0.15) (Table 6.3).

At baseline and 6months, global health status was positively correlated with the MSPSS total and domain subscales scores. Emotional and social functioning was positively correlated with total MSPSS, family and significant others subscale scores after controlling for anxiety and depression (Table 6.3).

Time point: Bas	eline											
		HA	DS			MSPSS						
	Anxiety	Subscale	Depre Subs	Depression Subscale		Significant other		nily	Friends		Total	
	R	$pr^{l}$	r	$pr^{l}$	r	$pr^2$	R	$pr^2$	r	$pr^2$	r	$pr^2$
QLQ-C30												
Global health	-	-	-	-	$0.27^{**}$	0.29	$0.26^{**}$	$0.24^{**}$	$0.28^{**}$	$0.25^{**}$	0.31**	0.30**
status/QoL	0.28**	0.29**	$0.22^{**}$	0.21**								
HADS												
Anxiety	-	-	-	-	-0.08	C - \	-0.074	-	-0.15*	-	-0.12	-
Subscale												
Depression	-	-	-	-	-0.13*	_	-0.09	-	-0.19*	-	$-0.17^{*}$	-
Subscale												
Time point: 6 months												
QLQ-C30						14 54	1919			M 12		
Global health	- **	-	<b>-</b> **	-0.28	0.31**	$0.24^{**}$	$0.28^{**}$	0.21**	0.35**	$0.27^{**}$	0.36**	$0.27^{**}$
status/QoL	.286**	0.24**	0.32**									
HADS									v			
Anxiety	-	-	-	-	-0.13	-	-0.11	-	-0.19*	-	-0.16*	-
Subscale												
Depression	-	-	-	-	-0.17*	-	-0.12	-	-0.20*	-	-018*	-
Subscale												
Time point: 12 n	nonths											
QLQ-C30												
Global health	-	-	-	-	0.29**	0.23**	$0.27^{**}$	$0.17^{*}$	0.25**	$0.17^{*}$	0.31**	$0.22^{**}$
status/QoL	0.38**	0.31**	0.38	0.27								
Global health status/QoL HADS Anxiety Subscale Depression Subscale Time point: 12 m QLQ-C30 Global health status/QoL	.286** - - nonths 0.38**	0.24**	0.32**	-0.28 - - 0.27**	0.31 -0.13 -0.17 <sup>*</sup> 0.29 <sup>**</sup>	0.24	0.28 -0.11 -0.12 0.27 <sup>**</sup>	0.21	0.35 -0.19 <sup>*</sup> -0.20 <sup>*</sup> 0.25 <sup>**</sup>	0.27 - - 0.17 <sup>*</sup>	0.36 -0.16 <sup>*</sup> -018 <sup>*</sup> 0.31 <sup>**</sup>	0.27

**Table 6.3:** Correlation between anxiety, depression and perceived social support with quality of life (N = 221)

Table 6.3, Continued.

HADS												
Anxiety	-	-	-	-	-	-	-0.35**	-	-	-	-0.35***	-
Subscale					$0.32^{**}$				0.30**			
Depression	-	-	-	-	-	-	-0.41**		-	-	-0.40***	-
Subscale					$0.38^{**}$				$0.35^{**}$			

HADS = Hospital Anxiety and Depression Scale, MSPSS = Multidimensional Scale of Perceived Social Support, QLQ–C30= Quality-of-Life Questionnaire (QLQ–C30), Version 3.0 of the EORTC Study Group on Quality of Life; QLQ–BR23 Questionnaire = a breast cancer-specific module for the QLQ, r = Spearman correlation coefficient,  $pr^{l}$  = partial correlation controlling for MSPSS scores,  $pr^{2}$  = partial correlation controlling for HADS scores; \*\* p < 0.01; \* p < 0.05

#### 6.4 Discussion

This prospective study showed that Malaysian breast cancer patients had relatively low levels of depression and anxiety and high QoL at the time of diagnosis. There were no changes in the level of depression at 6 months and 1 year. In contrast, the level of anxiety reduced at 6 months and 1 year. The global health status, functioning, image status, breast and arm symptoms are all correlated with anxiety and depression. The correlation with depression became insignificant at one year. The global health status was significant positively correlated with perceived social support. The level of perceived social support remained high throughout the 12 months period of study.

Breast cancer patients were known to suffer from high level of psychological distress at the beginning of the illness (Burgess, C et al., 2005). This was related to the fear and uncertainties toward the illness and its treatment. The reported prevalence of distress in breast cancer patients varies depending on the study design, settings and assessment tools. On average, the prevalence of depression and anxiety among cancer patients ranged from 20 to 30% (Burgess, C et al., 2005; Fann, J. R et al., 2008; Zainal, N. Z et al., 2013). In our study, the level of depression and anxiety was found to be comparable with previous studies. The average scores for both HADS depression subscale and anxiety subscale for the subjects in this study were lower than the threshold score for HADS defined anxiety or depressive disorder (Zigmoid, A. S & Snaith, R. P., 1983). A striking finding was that the level of anxiety and depression did not change throughout the 12 months of follow up. This finding is different from a previous study. In the study by Stafford et al, the course of anxiety and depression of the breast cancer and gynaecological cancer patients were measured using HADS - Anxiety Subscale and Centre for Epidemiological Studies Depression Scale (CES-D) at diagnosis and again every 8 weeks for 56 weeks (Stafford, L et al., 2013). The authors found that anxiety and depression symptoms were highest at diagnosis with significant improvements observed by 8 and 24 weeks, respectively and maintained thereafter. The authors argued that the depressive symptoms was not significantly decreased in the beginning of the cancer was due to the inclusion of physical symptoms in the assessment tool like CES-D, in which they were frequently encountered during the early treatment stage of cancer like surgery and chemotherapy (Stafford, L et al., 2013). However, in our study, we studied the depressive symptoms using the HADS depression subscale which does not contain somatic symptoms in the assessment (Zigmoid, A. S & Snaith, R. P., 1983). In other words, our finding demonstrated the persistence of depression for 12 months after the diagnosis in Malaysian breast cancer patients. This was in concordance with the finding by Ferrandina et al. Their study examined the quality of life and psychological distress among early stage cervical cancer patients and found no changes in the depressive symptoms after 12 months. In contrast to our findings, the anxiety symptoms in the study by Ferrandina et al decreased over time starting from 3 months after surgery (Ferrandina, G et al., 2012). The illness and treatment related sequelae were recognized as possible risk factors for psychological distress. For instance, lymphoedema which is a common consequence of breast cancer surgery/ radiotherapy had negative impact on patients' body image, ability to carry daily activities and social interaction.

QoL has become one of the main outcome measures in cancer treatment (So, W. K. W et al., 2014; Pandey, M et al., 2006). QoL is a multi-dimensional measure of psychological, physical, role, cognitive and social well-being (O'Neil, A et al., 2013). It is shown to be closely related to the illness progress, cancer treatment, underlying psychological condition, coping strategies and social support (Burgess, C et al., 2005; Hartl, K et al., 2010; Reich, M & Lesur, A., 2008; Schleife, H et al., 2014; So, W. K. W et al., 2014). The scores of global health status of the study subjects were slightly higher than the Western studies (Hartl, K et al., 2010; Schleife, H et al., 2014). In other words, the general QoL was better in our study subjects which was comparable with the

findings of other studies in Asia (Abu-Helalah, M et al., 2014). We also demonstrated that the global health status of the breast cancer subjects improved after 12 months together with social and emotional functioning. This was similar to the result of previous study by Kristin et al (Hartl, K et al., 2010). The improvement in QoL was expected at 6 months to a year as most patients should have completed and recovered from the initial surgery, hospitalization, chemotherapy or radiotherapy (Hartl, K et al., 2010). At this time points, the patients were expected to have recovered from the initial emotional reaction. This was reflected in the result of our study where the emotional functioning improved at 6 and 12 months. Another interesting finding of our study was the improvement of social functioning. This was never reported in the previous studies. In contrast, there was a reduction in social, emotion and cognitive functioning which was still apparent at 12 months after cancer diagnosis especially in the younger subjects. The authors argued that older women have developed adequate strategies to cope with disease and impairment (Jones, S. M. W et al., 2015).

The improvement of functioning and QoL was much related to coping strategies. Spiritual coping is an important strategy during stressful situation such as having cancer. Malaysia is a multi-ethnic country which mainly composed of Malay, Chinese and Indian. The better level of QoL in our subjects with breast cancer could probably reflect that Malaysian female patients turned to spiritual coping to counter their psychological distress. Furthermore, the use of complementary and alternative medicines (CAM) is common in the Malays. One local study found that 64% of the Malay women with breast cancer were CAM users and they believed in the power of prayer and used Malay traditional medicine to assist in healing the body's inner strength, to cure cancer, and to reduce stress (Shaharudin et al., 2011). Religious coping were also showed to be positively correlated with lower risk of psychological distress in other Asian study (Jang, J. E et al., 2013). There were qualitative studies which shown that women with

breast cancer of different cultural background did have different psycho-social- cultural concerns.

Many studies have shown that QoL of cancer patients were negatively correlated with depression and anxiety (Ho, S. S. M et al., 2013; Huttera, N et al., 2013; Reich, M & Lesur, A., 2008; So, W. K. W et al., 2014). This was also reflected in the result of our study. The negative relationship between QoL with depression and anxiety was observed at all three time points of the current study at baseline, 6 months and 12 months. There were two previous Chinese studies which reported correlation between anxiety and depression with poorer quality of life in breast cancer patient under chemotherapy or even post therapy (Ho, S. S. M et al., 2013; So, W. K. W et al., 2014). In a German study, it highlighted that anxiety and depression were associated not only with the psychosocial but also the somatic aspects of QoL of breast cancer patients (Schleife, H et al., 2014). An integrative review to explore the factors contributing to the QoL of African American breast cancer survivor was conducted by Mollica et al (Mollica, M et al., 2015). The result showed that psychological domains were most highly represented QoL domain among the included studies. In another literature review, the findings demonstrate that depression diminishes quality of life, affects compliance with medical therapies and reduces survival (Reich, M & Lesur, A., 2008). It suggests that depression impairs interpersonal relationships, occupational performance, stress and perceptions of health and physical symptoms. Therefore, depression has a detrimental impact on patients' overall quality of life.

In our study, we demonstrated that QoL was positively correlated to perceived social support. The higher level of perceived social support among the breast cancer subjects was associated with better QoL. This finding is similar to several previous studies (Ceychen, M et al., 2014; Cicero, V., 2009; Rizalar, S et al., 2014). In general, the level of perceived social support measured using MSPSS was relatively good among our

78

study subjects in comparison with other studies (Ceychen, M et al., 2014; Aaronson, N. K et al., 1993). This could the relatively better QoL among the Malaysian breast cancer patients in this study. The result of a Turkish study showed that perceived social support was lower for family and friends especially in the advanced stage (Rizalar, S et al., 2014). This could be due to expectation of the patients from family and friends, physical dependency and increased discomfort. The study also showed that low level of perceived social support was associated with higher suicidal ideation among the cancer patients. In another Turkish study on breast cancer patients, the results demonstrated that social support was a detrimental factor of adjustment to the illness (Ozpolat, A. G. Y et al., 2014). Social support particularly from the family affects the adaptation to the illness process. Patients seem to be more hopeful with better social support. In a German study, social support was also shown to be strongly associated with QoL (Schleife, H et al., 2014). The authors believed that social support encompasses various aspects such as emotional support which include caring and concern; instrumental support which includes provision of goods and services; and information assistance. Social support was assumed to be the mediator or a buffer between psychological distress and QoL in cancer patients (buffering hypothesis) (Cohen, S & Wells, T, A., 2015). Not only in cancer patient, but social support seem to be associated with better coping among women with high risk of hereditary breast cancer. In a Dutch study, it showed that family communication, perceived social support from family and friends are important factors for long-term adaptation and reduced psychological distress among women with high risk of hereditary breast cancer (Heijer, M. D et al., 2011).

In most studies, anxiety and depression was shown to be negatively correlated with perceived social support in cancer patients (Ceyhan, M et al., 2014). OSocial support buffer or mediate between psychological distress and QoL (Cohen, S & Wells, T. A, 2015). Interestingly, our result showed that this negative relationship was not significant

in the beginning but became most significant after 12 months. This was similar to other reports about the decline of social support and increases of psychological distress as disease progresses (Ceyhan, M et al., 2014; Cicero, V., 2009; Ozpolot, A. G. Y et al., 2014; Rizalar, S et al., 2014). It reflects the breakdown of contact with social circle and exhaustion of social support when disease progresses. At the same time, there is increased expectation for social support due to physical pain and more suffering at the later stage of cancer. Studies showed that social support gradually drifted away during advancement of disease (Ceyhan, M et al., 2014). Social support particularly from family is an important factor for the adjustment to social environment, adaptation to the disease progress and domestic environment (Cicero, V., 2009; Rizalar, S et al., 2014; Ozpolot, A. G. Y et al., 2014). As such, social support is an important protective factor for the emotional and physical well-being of the cancer patients.

There were several limitations of our study. First, the study was conducted in a tertiary hospital setting located in the capital city of the country. The group of study subjects may not be representative of the general population in the country. Second, other factors potentioally associated with depression, anxiety and QoL such as type of anti-cancer treatment, religiosity, understanding and knowledge of the illness and its treatment were not measured in the study. Lastly, the observational period of a year may be insufficient to demonstrate the changes of psychological distress in breast cancer patients. We should take into account of the long term impact of the illness and treatment on the psychological well-being of breast cancer patients. The changes of the psychological suffering may require a longer period of monitoring and assessment.

#### 6.5 Conclusion

In conclusion, Malaysian breast cancer patients have relatively low levels of depression and anxiety which are associated with better QoL for the first 12 months after the diagnosis. The higher level of QoL among breast cancer women in Malaysia was also associated with the relatively high level of perceived social support. Cancer is becoming a major cause of morbidities and morbidities across the globe. With the advancement in cancer treatment, there is increased attention in improving the QoL among the cancer patients. The reported level of distress and QoL among breast cancer patients varies depending on the coping strategies and level of acceptance in concordance to the local culture, belief and health care support. The current findings reflected the importance of improving the caregiver system for breast cancer patients. Care giver support group, educational program, and other activities that will enhance the social support system are likely to benefit the care giver and indirectly improve the QoL among the breast cancer patients. Prevention or reduction of psychological suffering among the breast cancer patients such as depression and anxiety could be achieved by improving of perceived social support.

# CHAPTER 7: ANXIETY AND DEPRESSION IN CANCER PATIENTS: THE ASSOCIATION WITH RELIGIOSITY AND RELIGIOUS COPING.

# 7.1 Introduction

It is estimated that 20% to 40% of the cancer patients have significant distress (Derogatis et al., 1983; Jørgensen et al., 2016). The cause is often multifactorial where issues relating to the physical symptoms, psychosocial and practical concerns. The distress levels may depend on the type and stage of cancer. Its severity tend to fluctuate over the course of the cancer duration and often peak at initial diagnosis, recurrence, development of treatment related side effects, having uncontrolled pain and fatigue as well as while experiencing psychosocial stressors. How well cancer patients cope with their distress depends on their interpersonal and intrapersonal resources and the medical context of the disease itself as discussed by (Rowland & Julia, 1989)

Religion refers to an organized system of beliefs, practices, and ways of worship (Emblen, 1992).There is a growing body of evidence that religious commitment or religiosity can buffer depression, support the healing process in medical illness (Koenig , Larson & Durham, 1998a; Greeson et al., 2015; Ronneberg et al., 2016) leading to greater life satisfaction and improved psychological health (McCullough, Hoyt, Larson, Koenig, Thoresen, 2000; Aukst-Margetic , Jakovljevic , Margetic , 2002) Religiosity is a multidimensional sociological term. It covers different aspects such as involvement in religious activities, intrinsic faith, belief, religious attitudes and practices, and religious identification and affiliation (Musick, Koeing, Larson & Matthews, 1998; Garssen & de Jager Meezenbroek, 2007; Hood, Spilka, Hunsberger & Gorsuch, 1996). Various studies have shown that cancer patients turned to religion during distress and depression. There is strong association between religiosity and religious coping.

However, it should be clear that 'having a strong religious identification' and 'engaging in religious types of coping' are by no means identical to each other (Block, 2006)

Religious coping has increasingly become an area of much interest in terms of helping patients adjust with cancer. Tix and Fraser (1998) defined religious coping as 'the use of cognitive and behavioural techniques, in the face of stressful life events, that arise out of one's religion or spirituality'. Positive religious coping is seen as an expression of a secure relationship with a supportive God/higher power whereas negative religious coping (or 'religious struggle') is considered as an expression of a less secure relationship with a God/higher power that is distant and punishing or as a religious struggle in the search for significance (Pargament et al., 1998a). The authors further elaborated the 5 main functions of religion in coping: (i) to give meaning to an event; (ii) to provide a framework to achieve a sense of control over a difficult situation; (iii) to provide comfort during times of difficulty; (iv) to provide intimacy with other likeminded people; and (v) to assist people in making major life transformations (Pargament, Koenig & Perez, 2000)

Growing literature showed mixed results on the association between religious coping and cancer distress (Trevinoet al., 2014; Rohani et al., 2015; Zamanian et al., 2015). In a systematic review of 17 studies examining religious/spiritual coping strategies in cancer adjustment, Thune-Boyle, Stygall, Keshtgar, and Newman (2006) found 7 of the studies showed some evidence for the beneficial effect of religious coping, with 1 study showing religious coping to be detrimental in a sub-group of their population. Three studies found religious coping to be harmful, and seven did not find any significant results. However, many studies in the review had methodological problems, and the studies failed to control for possible influential variables such as stage of illness and perceived social support. Therefore, the authors concluded that any firm conclusions about the possible beneficial or harmful effects of religious coping with cancer could not be made.

A recent study by Trevino, Archambault, Schuster, Richardson and Moye (2012) found showed that among the 48 veteran cancer survivors, those with negative religious coping was associated with greater distress and poorer posttraumatic growth whereas positive religious coping was associated with greater posttraumatic growth (Trevino et all., 2012). Other studies confirmed that better emotional adjustment, interpersonal functioning and quality of life in cancer patients were associated with positive religious coping (Gall, 2004; Stanton, Danoff-burg, & Huggins, 2002; Tarakeshwar et all., 2006; Rand et all., 2011). On the other hand, negative religious coping has been consistently associated with greater psychological distress, lower levels of life satisfaction and quality of life in people with cancer.( Tarakeshwar et al., 2006 ; Hebert, Zdaniuk, Schulz & Scheier,2009). The similar findings were shown in a study conducted in Malaysia which involved 228 psychiatric patients. The authors concluded that negative religious coping or lower religious commitment were associated with higher psychological distress among the patients with any psychiatric diagnoses (Nurasikin et al., 2012).

Malaysia has a multi-ethnic population comprising of Malay, Chinese and Indian with Islam being the predominant religion. Other religions such as Christianity, Buddhism and Hinduism are widely practiced by other races. There were limited studies on religiousity or religious coping in Malaysia (Nurasikin et al., 2012). An Islamic Religiosity Scale was previously introduced for measuring Islamic knowledge and practice among the Muslims in Malaysia (Salleh et al., 1999). However, to date, there has been no study in Malaysia examining the association between religion and its role in cancer distress. Furthermore, religious coping is not routinely asked in cancer patients in Malaysia. Therefore, the aim of this study is to examine the association between religiosity, religious coping methods with depression and anxiety in cancer patients.

# 7.2 Methodology

#### 7.2.1 Study Subjects and Setting

This was a cross-sectional study conducted at, University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. The subjects were recruited from the surgical and oncology units of the medical centre. During the study period (Jan 2014 to Dec 2014), both in- and out-patients with known diagnosis of cancer at the surgical/oncology units were approached and explained regarding the study details. Those who consented to participate were screened for the inclusion and exclusion criteria as follows:

#### 7.2.1.1 Inclusion Criteria

- Age 18 years and above.
- Confirmed diagnosis of cancer (any types)
- Able to understand and read Malay or English.

#### 7.2.1.2 Exclusion Criteria

- Diagnosed with dementia or mental retardation.
- Acutely psychotic or disturbed
- Having a delusion of religiosity based on Yangarber-Hicks (2004) criteria.

Ethical approval was obtained from the Medical Ethical Committee, University Malaya Medical Centre prior to the commencement of the study. Patient who screened positive for either depression or anxiety during the study, were referred to the psychiatric unit for further assessment and management.

#### 7.2.2 Procedure

All questionnaires and psychiatric measures were administered to patients by trained clinical research coordinators. Information on age, gender, marital status, employment, religion and ethnicity were obtained. Clinical data such as type of cancer and duration of illness were collected.

#### 7.2.3 Measurement Tools

# 7.2.3.1 The Duke University Religion Index (DUREL)

This instrument was used to measure religiousness of the respondent. It consists of five items covering three major dimensions of religious commitment: organizational religious activity (ORA, one item); non-organizational religious activity (NORA, one item); and intrinsic religiosity (IR, three items). ORA consists of public religious activities, such as frequency of attending religious services or participation in other group-related religious activities. NORA consists of religious activities performed in private, such as prayer or Bible reading. IR is the degree of personal religious commitment or motivation. The DUREL has an overall score range from 5 to 27 (Koenig & Büssing, 2010). It was translated into the Malay language and has been validated (Nurasikin, Aini, Aida Syarinaz & Ng, 2010). Cronbach's  $\alpha$  was good (0.80) in this study.

#### 7.2.3.2 Brief Religious Coping Scale (RCOPE)

This scale consists of 14 items to measure the religious coping methods of the respondent. It was designed to offer an efficient, theoretically meaningful way to integrate religious dimensions into models and studies of stress, coping and health. The

scale consists of seven positive coping items (P COPE) and seven negative coping items (N COPE). The score of each item ranges from 0 ('not at all') to 3 ('a great deal'). The total score ranges from 0 to 21 for the subscale of positive and negative items (Pargament et al., 2000). The reliability and validity of the translated Malay version of Brief RCOPE was established in a previous study (Yusoff, Low & Yip, 2009). P COPE and N COPE had high internal consistency in this study (Cronbach's  $\alpha$  for P COPE = .87, N COPE = .88).

#### 7.2.3.3 Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression was assessed using the Malay Version of Hospital Anxiety and Depression Scale (HADS). HADS was the most frequently reported measure in cancer studies and shown to be the best performing measure for each trajectory stage of the disease. It is a self-administered questionnaire that screened for anxiety (7 items) and depressive (7 items) symptoms. It has demonstrated good reliability. The anxiety (HADS-A) and depression (HADS-D) subscales are scored from 0 to 3 (four-point Likert scales), giving maximum scores of 21 for anxiety and depression respectively (Zigmond & Snaith, 1983). The Malay version of HADS has a good reliability and has been validated among the Malaysian population (Yusoff, Low, Yip, 2011).

# 7.2.4 Statistical Analysis

All data were analysed using Statistical Package Social Science (SPSS) version 16.0. Descriptive statistics were performed for the characteristics of the subjects. The number of subjects with depression (HADS–depression subscale scores  $\geq$  5) and anxiety (HADS-anxiety subscale scores  $\geq$  7) were calculated (Singer et all., 2009). The association between the clinical and socio-demographic characteristics of the subjects (age, gender, ethnic, marital status, employment and duration of illness) with depression and anxiety were examined using Chi Square test. The association between the three
most common types of cancer, namely breast cancer, gastrointestinal cancer and haematological cancer with depression and anxiety were examined by creating three dummy variables and tested using Chi Square analysis. The normality of the data of DUREL and RCOPE were tested with Kolmogorov-Smirnov test. As the data were non-normality, logistic regression analysis was used to examine the relationship between religiosity (DUREL) and religious coping (positive coping and negative coping in RCOPE) with anxiety and depression (The presence of anxiety or depression was used as the reference category). Subsequently, the significant associated characteristic variables were included in the multiple logistic regression analysis. All analyses were two sided with a significant value of p < 0.05.

# 7.3 Results

A total of 200 cancer patients were included into the study with the mean age of 53.6 years old. They were predominantly female (81.5%) and of Malay (53.0%) ethnic. The commonest religion was Muslim (54.5%) followed by Buddhist and Christian. Most of the subjects were married (83.5%) and unemployed (63.5%).

The average of the duration of cancer for the study subjects was 38 months. The commonest type of cancer in the study group was breast cancer (57%) followed by hematological and gastrointestinal cancer (Table 7.1).

# Table 7.1: Characteristics of study subjects

Variable		
Age, mean (Terwijn et al.)	53.63 (13.29)	

Variable	
Gender, n (%)	
Male	37 (18.5)
Female	163 (81.5)
Ethnicity, n (%)	
Malay	106 (53.0)
Chinese	65 (32.5)
Indian	25 (12.5)
Others	4 (2.0)
Religion, n (%)	
Muslim	109 (54.5)
Buddhist	43 (21.5)
Christian	25 (12.5)
Hindu	15 (7.5)
Others	8 (4.0)
Marital Status, n (%)	
Single	24 (12.1)
Married	167 (83.5)
Divorced	4 (2.0)
Separated	1 (0.5)
Widowed	3 (1.5)
Employment	
Yes	73 (36.5)
No	127 (63.5)
Duration of Illness, mean (Terwijn et al.)	38.14 (45.73)
Type of Cancer, n (%)	
Breast	114 (57.0)
Genito-urinary	9 (4.5)
Gastro-intestinal	20 (10.0)
Hematological	23 (11.5)
Hepatobiliary-pancreatic	4 (2.0)
Others	30 (15.0)

# Table 7.1, Continued.

sd = standard deviation

The means of the total HADS scores for the study subjects was about 9.0. Of the 200 subjects, 26% were possible cases based on the cut off scores of more than 13 (Singer et

al. 2009). For the depression subscale, the mean score was about 3.8 with 35.5% of the total subjects with depression based the cut off score above 5 (Singer et al. 2009). For the anxiety subscales, the mean score of the study subjects was 5.1. Based on the cut off score of 7 (Singer et al. 2009), 36% of the study subjects were having anxiety (Table 7.2).

**Table 7.2**: The subscales and total scores of the Hospital Anxiety and Depression

#### Scales (HADS)

HADS-Depression	n Subscale		HADS-Anxiety Subscale		
Mean (Terwijn et	Depression	$(\text{scores} \ge 5)^*$	Mean	Anxiety (score	$s \ge 7)^*$
al.)	n (%)		(Terwijn		
	Yes	No	et al.)	Yes	No
3.82 (3.20)	71 (35.5)	129 (64.5)	5.12 (3.72)	72 (36.0)	128 (64.0)
1 . 1 1 1 .					

sd = standard deviation

\*Cut off scores based on study by Singer et al. 2009

In the analysis of the association of socio-demographic characteristic with HADS, it showed that depression or anxiety were significantly more common in Non-Malay and those who were unemployed. The odds having depression or anxiety were less than 0.5 in subjects of Malay ethnic as compared to the Non-Malay. The odds of being employed were also less than 0.5 in subjects with depression or anxiety (Table 7.3).

 Table 7.3: Analysis of the association between clinical and socio-demographic

characteristic with depression and anxiety (based on HADS scores) among the study

subjects using Chi Square test

# Variable

Age, mean (Terwijn et al.)

53.63 (13.29)

Variable	
Gender, n (%)	
Male	37 (18.5)
Female	163 (81.5)
Ethnicity, n (%)	
Malay	106 (53.0)
Chinese	65 (32.5)
Indian	25 (12.5)
Others	4 (2.0)
Religion, n (%)	
Muslim	109 (54.5)
Buddhist	43 (21.5)
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Others	8 (4.0)
Marital Status, n (%)	
Single	24 (12.1)
Married	167 (83.5)
Divorced	4 (2.0)
Separated	1 (0.5)
Widowed	3 (1.5)
Employment	
Yes	73 (36.5)
No	127 (63.5)
Duration of Illness, mean (Terwijn et al.)	38.14 (45.73)
Type of Cancer, n (%)	
Breast	114 (57.0)
Genito-urinary	9 (4.5)
Gastro-intestinal	20 (10.0)
Hematological	23 (11.5)
Hepatobiliary-pancreatic	4 (2.0)
Others	30 (15.0)
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<b>T</b> . 1.1.	<b>F</b> 1	$\alpha + 1$
I able	7 <b>.1</b> ,	Continued.

OR = odds ratio CI = confidence interval  $Depression = HADS - Depression Subscale scores \ge 5$   $Anxiety = HADS - Anxiety Subscale scores \ge 7$ 

In the analysis of clinical characteristic with HADS, the duration of illness was not associated with depression. However, the shorter duration of illness (less than 38 months) was significant associated with anxiety. The types of cancer (breast, gastrointestinal and hematological cancer) were not associated with either depression or anxiety (Table 7.3).

The results of single regression analysis showed that subjects with depression used more negative religious coping and had lower non-organization religiosity. The results were remained significant even after adjusted for the significant associated characteristics (ethnicity and employment status) in the multiple logistic regression analysis. For anxiety, it was associated with negative coping and lower non organizational religiosity in single regression analysis. After adjusted for ethnicity, employment status and duration of illness, anxiety was only significantly associated with negative coping (Table 7.4).

**Table 7.4**: Analysis of the association between religiosity, religious coping with

 depression and anxiety (based on HADS scores) among the study subjects using

Depression						
	SLR			MLR		
	<b>OR</b> <sup>a</sup>	95% CI	<i>p</i> value	OR <sup>b</sup>	95% CI	<i>p</i> value
RCOPE positive	1.03	0.98-1.09	0.20	1.00	0.94-1.06	0.87
<b>RCOPE</b> negative	0.88	0.82-0.96	< 0.01	0.89	0.82-0.97	0.01
Organizational religiosity	1.19	0.97-1.46	0.09	1.16	0.94-1.43	0.18
Non-organizational	1.27	1.08-1.49	0.04	2.47	1.26-4.84	0.01
Religiosity						
Intrinsic religiosity	1.07	0.97-1.18	0.16	1.00	0.88-1.12	0.93
Anxiety						
	SLR			MLR		
	<b>O</b> R <sup>a</sup>	95% CI	<i>p</i> value	OR <sup>c</sup>	95% CI	<i>p</i> value
RCOPE positive	1.04	0.99-1.09	0.12	0.98	0.88-1.07	0.61
RCOPE negative	0.88	0.82-0.96	< 0.01	0.87	0.80-0.96	< 0.01

Logistic Regression Test

Anxiety						
	SLR			MLR		
	<b>O</b> R <sup>a</sup>	95% CI	<i>p</i> value	OR <sup>c</sup>	95% CI	p value
Organizational religiosity	1.08	0.89-1.32	0.43	1.02	0.76-1.37	0.89
Non-organizational	1.23	1.05-1.45	0.01	1.13	0.88-1.46	0.34
Religiosity						
Intrinsic religiosity	1.10	1.00-1.21	0.06	1.01	0.84-1.23	0.89

#### Table 7.4, Continued.

SLR = single logistic regression

MLR = multiple logistic regression

 $OR^{a}_{L}$  = crude odds ratio

OR<sup>b</sup> = adjusted odds ratio (adjusted for employment status and ethnicity)

 $OR^{c}$  = adjusted odds ratio (adjusted for employment status, ethnicity and duration of illness) CI = confident interval

Depression = HADS -Depression Subscale scores  $\geq 5$ 

Anxiety = HADS-Anxiety Subscale scores  $\geq 7$ 

#### 7.4 Discussion

This study involved 200 patients with different types of cancer. Anxiety and depression were highly prevalent among the study subjects. More than 35% of the subjects were having either anxiety or depression. These comorbid psychological conditions were more common in Non Malay subjects. Negative religious coping and unemployment were common in cancer patients with anxiety or depression. Non-organizational religiosity was also low in patient with comorbid anxiety or depression.

There were various studies on the associated factors for psychological distress in cancer patients. Cancer patients with lower education or income, younger age, widower/divorcee was found to have higher risk of depression or anxiety (Ell et all., 2005; Lueboonthavatchai, 2007). In the current study, we did not find any significant association of depression or anxiety with age, gender or marital status. This is similar with the findings of a few previous studies (Soo, Byung & Sook, 2008; Vahdaninia, Omidvari & Montazeri, 2009). In contrast, a study on the risk factors for depression in Chinese cancer patients showed that advanced age was linked with depression. The authors explained that elderly may have reduced ability to ask and communicate with

others. They are more likely to feel worry about treatment cost and family financial burden (Jin & Jun, 2014).

Interestingly, depression and anxiety were found to be less common among Malay cancer patients in the current study. Malaysia is a multi-ethnic country which mainly composed of Malay, Chinese and Indian. Each ethnicity has different cultural belief, religious practices and languages. The lower level of anxiety or depression in Malay subjects is in concordance to our previous study which demonstrated that Malay cancer patients were less prescribed with anxiolytic/hypnotic drugs (Ng, 2014). This could probably reflect that Malay patients turned to their spiritual coping to counter their psychological distress. Furthermore, the use of complementary and alternative medicines (CAM) is more prevalent in the Malays. One local study found that 64% of the Malay women with breast cancer were CAM users and they believed in the power of prayer and used Malay traditional medicine to assist in healing the body's inner strength, to cure cancer, and to reduce stress (Merriam & Muhamad, 2013).

Depression and anxiety were found to be more common among unemployed subjects in the current study. Advances in cancer treatment have allowed cancer patients to live longer and overcome the illness. In comparison to management of physical needs, attention on social rehabilitation in cancer survivors is lacking. As a result, there was previous study observed cancer survivors have higher risk for unemployment than the general population or patients with other morbidities (Mols et all., 2009). Employment is not only a key indicator of social restoration but also known to maintain emotional function and self-esteem of cancer subjects. Alternatively, psychological distress such as depression or anxiety could be the cause of unemployment.

Surprisingly, we did not find the association between duration of illness with depression. The similar finding was found in other studies where the longer duration of

cancer was not associated with depression (Friedman, Lehane, Webb, Weinberg & Cooper, 1994; Jadoon, Munir, Shahzad & Choudhry, 2010). This is in contrast to the finding of the study by Sahin, Tan and Polat (2013) where it showed that hopelessness and depression were associated with longer duration of cancer. With the advancement of cancer, there was increased risk of coexistence of physical conditions and frequency of treatment including surgery, chemotherapy and radiotherapy. These added on to the physical and psychological burden of the cancer patients. The current study is a crosssectional study, the duration of illness is the measure of the period of time the patient was having the illness at the point of data collection. The current finding demonstrated that shorter duration of illness was associated with higher level of anxiety. In other words, anxiety is more significant at the early phase of the cancer. This was reflected in the results of another study on gastrointestinal cancer patients (Nordin, Glimelius, Påhlman & Sjödén, 1996). Anxiety level was shown to be high in whom less than one year was passed after the diagnosis of cancer. Most literatures showed that psychological distress were prominent at the diagnosis of cancer and slowly improved over time (Nordin et all., 1996; Bergerot et al., 2015). The uncertainty and unpreparedness for acceptance are most likely contributed to the high level of anxiety at the beginning of the illness.

We did not find any significant association of anxiety or depression with the types of cancer. In the current study, we only examined the three common types of cancer, namely breast cancer, gastrointestinal and hematological cancer. There were previous studies looking into psychological distress, anxiety or depression of each individual cancer types (Nordin et al., 1996; Bergerot et al., 2015; Mausbach, Schwab & Irwin, 2015). However, there were no comparison studies on the psychological impacts between types of cancer. Many studies were conducted and demonstrated that depression and anxiety were highly prevalent in breast cancer patients (Mausbach et all.,

2015; Zainal, Nik-Jaafarm, Baharudin, Ahmad Sabki, & Ng, 2013). In our previous systematic review, we found that the prevalence of depression was about 20% among the breast cancer patients depending on the assessment tolls used (Zainal et all., 2013). Study by Nordin et al. (1996) found that anxiety was generally low in patients with gastrointestinal cancer. Female patients reported higher level of anxiety. Frequent schedule visits or tests also posed threat for the psychological well-being among the gastrointestinal cancer patient (Nordin, 1996). In another study on patients with hematological cancer under chemotherapy, it showed that 50% of the patients were having significant distress at the beginning and reduced in the subsequent visits (Bergerot et al., 2015). Fatique was foud to be closely related to depression and reduced performance status in hematological cancer patients (Dimeo et al., 2004).

Religiosity is often described as being a multi-dimensional concept, of which have been measured in different ways by researchers (Hackney & Sanders, 2003). In the current study, we measured religiosity based on three dimensions, namely the organizational activities, non-organizational activities and intrinsic faith. We found that depression and anxiety were inversely related to the practices of private religious activities. The result was similar with the findings of most of the previous research, where they found significant associations between higher religiosity and lower distress level in cancer patient (McBride, Arthur, Brooks & Pilkington, 1998; Koenig, George, Peterson, 1998b; Koenig, 1992; Braam et all., 2011). Cancer patients may use religious beliefs to cope with the diagnosis and consequences of living with cancer (Bowie, Curbo, Laveist, Fitzgerald & Pargament, 2001; Gall, 2000; Jenkins & Pargament, 1995). Religion may buffer stress for those coping with illness and, may provide an interpretive framework, aiding in coping (Siegel, Anderman & Scrimshaw, 2001). Many cancer patients draw meaning from their suffering (Kappeli, 2000) and find prayer to be helpful (Taylor, Outlaw, Bernardo & Roy, 1999). In the review article, Aukst-Margetić and Margetić

(2005) mentioned that religion help patients to prevent pessimistic thought; influence the stress-vulnerability equilibrium by decreasing hopelessness. Religiosity may also reduce psychological distress by increase self-esteem or the constructive attributional perspectives that help a person find his sense of meaning. Generally, the interpretation of consequences or outcomes related to life events may be influenced by religious beliefs (Pargament et all., 1998b; Pargament et all., 1990). It is suggested that religious practice is effective in emotion regulation, behavioral inhibition, and self-control. It also helps in enabling the suppression of distressing thoughts and disorganized behaviors; and acts as a defense against unpleasant feelings (Spilka, Hood, Hunsberger & Gorsuch, 2003). Religious activity such as prayer or meditation helps to reduce distress and promote relaxation (Dull & Skokan, 1995). Surprisingly, in the current study, we do not find association between organizational religious activities with depression and anxiety. It is believed that contact with religious practitioners, who provide emotional, and informational support, may buffer the psychological distress. Moreover, religion activities can promote social support and social networks conducive to mental health. In other words, the interpretation of consequences or outcomes related to life events may be influenced by religious beliefs (Pargament, 1998b; Pargament, 1990).

Coping is a dynamic, progressive and life-preserving process of responding to a perceived threat to the self like cancer (Carver, Scheier & Weintraub, 1989; Lazarus & Folkman, 1984). The common coping strategies include problem focused strategies which intervene on the stressful situation and emotion-focused strategies which target the emotional distress associated with the situation (Carver, 1989). Both of these coping responses are generally associated with positive outcomes in cancer patients (Lutgendorf et al., 2002; Al-Azri, Al-Awisi, & Al-Moundhri, 2009; Low, Stanton, Thompson, Kwan & Ganz, 2006) . In the recent years, there was increased attention on religious coping among cancer patients in the scientific research. According to Koenig

et al. (1997) religious coping is the use of religious beliefs or practices to reduce distress and deal with problems in life. Religious coping methods can be further classified into positive and negative religious coping (Pargament, 1998a). In general, positive religious coping strategies reflect an adaptive, confident and constructive turning to religion for support (Koenig et al., 1997; Ano & Vasconcelles, 2005). In contrast, negative religious coping strategies reflect an engaging in religious struggle and doubt, are generally more maladaptive for patients undergoing stressful events (Ano & Vasconcelles, 2005; Exline & Rose, 2005). In a study by Olson, Trevino, Geske & Vanderpool (2012), the use of positive religious coping was reported as a predictor of better mental health and conversely, negative religious coping as a disturbing factor for mental health. In the current study, we found that negative religious coping was associated with higher level of depression and anxiety. This is in concordance with the previous literature showing that negative religious coping is associated with higher levels of distress in cancer patients (Tarakeshwar, 2006; Zwingmann, Wirtz, Mu"ller, Ko"rber, & Murken, 2006; Sherman, Simonton, Latif, Spohn & Tricot, 2005; Fitchett, 2004). It is hypothesized that patients who struggle with their faith may become unable to use their faith as a resource for coping where religious belief may be seen as weak, distant or uncaring leading to an existential crisis. Pargament and colleagues, proposed a comprehensive theory on the role of religion in coping with stressors. They suggested three possible mechanisms for religion to deal with distress. Firstly, patients may consider religion as a part evaluation of the threatening factor and its severity; Secondly, religion may interfere with the coping process by helping the patients to re-define the stressor as a solvable challenge. Lastly, religion can affect the outcomes of stressor factors (Pargament, 1998b; Pargament, 1990).

This study is limited by a cross-sectional design. As such we do not able to establish the causality. It was a single centred study with relatively small sample size, which limited

its generalizability. However, the study was conducted at a tertiary referral centre. It made the sample composed of subjects originated from various parts of the country and contributed to the diversity of the samples. The information of some potential confounding factors was not collected in the current study. These include the severity of illness, cancer staging, comorbid physical condition, current treatment and its response. Although cancer staging was not analysed in the current study, the duration of illness was included into the association analysis. It could be used as a proxy indicator for the phases (early or late) of the illness. The presence of physical suffering or adverse events such as pain, nausea and lethargy which either related to the illness or treatment were also potentially cause depression or anxiety in cancer patients. The measurement of social support, financial statues and family background were not included in the study. Social factors play a major role in the maintenance of mental health in patients undergoing stressful events such as cancer. Strong family support and conducive environment are important protective factors for mental health in cancer patients. Lastly, we must be awared that religiousness and religious coping varies in patients of different religious background. Although, the psychometric properties of the measurement scales in the current study was established but they are limited in their brevity and practicality. Religion is neither simplistic nor conceptual but encompasses many aspects of living. There is a need for more future research looking into improvement of the assessment in these aspects.

#### 7.5 Conclusion

In conclusion, religiosity is associated with the level of psychological distress in cancer patients. Depression and anxiety are more common in cancer patients with low level of intrinsic faith and less practices of non-organizational (private) religious activities. The current study also showed that cancer patients with depression or cancer were using more negative coping methods. A prospective longitudinal study is helpful in

99

establishing the causal relationship and answering whether psychological distress in cancer patients that suppresses the level of belief in Gods and use more negative religious coping methods or vice-verse.

# CHAPTER 8: REPORT ON THE DEVELOPMENT OF A BRIEF PSYCHOLOGICAL INTERVENTION FOR REDUCTION OF DISTRESS IN PALLIATIVE CARE: 5-MINUTE MINDFUL BREATHING

# 8.1 Introduction

Suffering, or psychological distress, is common among terminally ill patients. According to Cassell (1982, 1991), there are four essential ideas of suffering. First, it is experienced by a person both mentally and physically. Second, it occurs as there is an impending threat of destruction to the person and it continues until either the threat has passed or the person has restored their integrity. Third, acute distress arises as a person's sense of intactness becomes greatly vulnerable during suffering experience. Lastly, suffering can happen in any aspect of a person (Cassell, 1982; Cassell, 1991). Among existing psychosocial interventions, mindfulness-based treatment or interventions have demonstrated effectiveness in reducing psychological stress and promoting relaxation (Ando et al., 2009; Bohlmeijer et al., 2010; Foley et al., 2010; Shennan et al., 2011; Whitebird et al., 2013; Zainal et al., 2013).

The principle of mindfulness has been adopted into psychotherapy such as mindfulnessbased stress reduction (MBSR) and its efficacy in cancer patients have been studied by a number of meta-analyses. Ledesma and Kumano's meta-analysis that suggested a Cohen's effect of 0.48 concluded that the mental health of their cancer subjects was improved by MBSR (Ando et al., 2009). Cramer et al (2012) later confirmed this result in their meta-analysis. More recently, Zainal et al (2013) suggested that MBSR was efficacious in cancer patients for a year. MBSR is a rather long-term program across 8 weeks where 2.5 hours is allocated to each therapy session (Zainal et al., 2013).

Although MBSR is useful in reducing psychological stress, applying it in the palliative setting can be challenging. First of all, patients with terminal illness usually have weak

determination to break their habitual yet unhealthy responses to distressing situations, restricting the practical application of MBSR. Besides, they tend to have limited life span and ability to focus due to the nature of their illness. Also, the lethargy associated with their condition means that they are often reluctant or simply too tired to take part in the long MBSR sessions (Shennan et al., 2011). Hence, 5-minute mindful breathing was developed to overcome these setbacks of MBSR. In our previous study, we demonstrated that 5-minute mindful breathing was effective in rapidly reducing distress among palliative care patients and their caregivers (Tan et al., 2015).

Jon Kabat-Zinn (1994) - the pioneer of MBSR defined mindfulness as focusing attention in a purposeful, in-the-present-moment and non-judgmental way. The main principle is that openly and non-judgmentally experiencing the present moment can help to effectively ameliorate stress. This is because when facing stressors, one may feel depressed and anxious if there is too much attention on the past or future (Kabat-Zinn, 1994).

Mindfulness has received much attention since the 20th Century. There have been many literatures that show a great deal of success of mindfulness in stress reduction (Ando et al., 2009; Bohlmeijer et al., 2010; Foley et al., 2010; Shennan et al., 2011, Whitebird et al., 2013; ; Zainal et al., 2013). In recent years, the concept of mindfulness has been incorporated into mainstream psychotherapy (Shapiro et al., 2006). MBSR and mindfulness-based cognitive therapy (MBCT) for example have been shown to reduce psychological distress, pain and anxiety (Yook et al., 2008; Ando et al., 2009; Bohlmeijer et al., 2010; Foley et al., 2010; Shennan et al., 2011; Cramer et al., 2012; Whitebird et al., 2013; Zainal et al., 2013). A meta-analysis conducted by Hoffman et al (2010) based on 39 studies which involved 1,140 patients with medical or psychiatric conditions, reported that mindfulness-based therapy (MBT) was efficient in reducing depression and anxiety symptoms. Through MBT might not be diagnosis-specific, it 102

addressed suffering processes present in different disorders by altering multiple evaluative dimensions and emotions that underlie the general aspect of wellbeing (Hoffman et al., 2010)

A review by Davis & Hayes (2011) categorized three dimensional benefits of mindfulness, namely: affective, interpersonal, and intrapersonal benefits. Research shows that mindfulness helps to cultivate effective emotional regulation in the brain, hence the affective benefits (Davis & Hayes, 2011). Research also indicates that mindfulness may allow effective emotional regulation through decreasing negative affect or rumination but inducing positive emotions. Mindfulness can also minimize reactivity and enhance response flexibility (Davis & Hayes, 2011). It is not surprising that these positive effects will then positively impact the person's relationship with others as well.

The practice of mindfulness reduces stress through several mechanisms. Firstly, attention is purposefully paid to automatic negative thoughts which are interrupted as a result. Secondly, worries about the future and rumination about the past are minimized by focusing on the present moment. Thirdly, by paying attention non-judgmentally, negative appraisals of the situation are reduced. When someone is mindful, it allows the person to observe own feelings and thoughts from a distance, without attaching meaning to them. Though mindfulness, a person can gain more awareness and thus respond to a situation with conscious choice rather than the usual automatic reactions. These mechanisms could promote the ability to re-evaluate an unpleasant situation and also to improve emotional regulation (Kabat-Zinn, 1994; Brown et al., 2007).

# 8.1.1 Rationale

Delivering psychotherapy in palliative care is challenging. Patients with terminal illness may have some physical impairment, high mental distress and unstable levels of awareness (Strada & Sourkes, 2009). They often have too low of energy to undergo many sessions of conventional psychotherapy. Their motivation to change the old habitual reactions and adopt more adaptive responses to stressors can also directly impact the efficacy of long term psychotherapy. Most palliative care patients struggle to cope with their deteriorating state of health and thus would use various coping strategies to lessen their suffering, depleting their physical and mental resources as a result. They may also still be in denial or trying hard to accept the current condition of their illness, rendering them not so receptive towards help. As such, it is very often an additional burden for them to go through the conventional psychotherapy which requires some level of physical and mental alertness. Hence, 5-minute of mindful breathing exercise was developed in order to overcome those limitations.

The 5-minute mindful breathing technique is derived from a variety of mindful practices. Mindful breathing was chosen since patients effortlessly breathe all the time both involuntarily and voluntarily. It is controlled involuntarily from the brainstem but also voluntarily from the motor cortex. Convenient and practical, patients can practice mindful breathing anytime and anywhere at no cost. Mindful breathing also acts as a key practice that anchors the other mindful practices like mindful eating and mindful walking.

When patients rest their attention on their breathing, they experience each breath in and out that follows one after another. Breathing serves as an anchor that brings the patients back into the present moment and helps them enter a state of awareness. Worrying about the future or ruminating about the past will hence be interrupted. Breathing is thus used to improve the ability to focus and enhance calmness.

Patients are required to pay full attention during mindfulness sessions. In such instance, a patient's motivation to pay attention is one of the prerequisites before instituting the 5-

minute mindful breathing technique. They need to pay full attention with an open, nonjudgmental mind. Besides, the attitude toward mindful therapy is also a crucial factor where they should be receptive and not resistant. It is important to inform the patients that the exercise is suitable for anyone regardless of ethnicity, religious beliefs or cultural background. It purely aims at teaching them to be aware of and stay focused on their own breathing process in order to disconnect them from their old typical reactions to suffering. These maladaptive habits may include ruminating about the past or worrying about the future which only makes them helpless and paralyzed. Besides, the rapport between the therapist and the patient has to be well established. The therapist should spend some time introducing and explaining the concept, rationale and benefits of 5-minute mindful breathing prior to the sessions. This would in return let the patients be more at ease and open to learning the technique.

#### 8.2 Methodology

# 8.2.1 Phase 1: The development of the 5-minute mindful breathing

This present study was conducted at the University Malaya Medical Centre (UMMC) in 3 phases. The 5-minute mindful breathing was developed with the objective to be highly feasible and efficient, by taking into account factors such as poor physical fitness, limited life span, inadequate attention and mental alertness, and fluctuation of consciousness etc that are commonly associated with patients in palliative setting. The 5-minute mindful breathing was developed and devised through a series of discussion among a panel of experts in palliative medicine, psychiatry and clinical psychology. The proposed intervention must fulfil the requirement criteria as these: 1. Easy to administer; 2. Easy to learn; 3. Quick; 4. Rapid efficacy; 5. No cost incurred. A series of focus group discussions with patients, palliative caregivers and staffs in palliative setting was done to obtain feedback on the suitability of the instructions and their reception by the subjects.

The concept of 5-minute mindful breathing is summarized into the following stages and steps:

# 8.2.1.1 Preparatory Stage

Before the start of 5-minute mindful breathing, it is useful to help the patients to understand and practise their breathing processes. We encourage the therapist to assist the patients to do so in the following five stages:

- Stage 1.-The subject is asked to slowly breathe in and out. The word "In" is repeated silently in their mind during inhalation and "Out" during exhalation, ie., In-Out-In-Out. This helps the subject to capture the moments of both inhalation and exhalation.
- Stage 2.–In this stage, the word "In" is repeated twice silently during inhalation and "Out" is repeated twice during exhalation, ie., In-In-Out-Out. This helps the subject to remember two anchor points at both inhalation and exhalation.
- Stage 3.–The subject is asked to repeat thrice the word "In" silently at the beginning, middle and end of inhalation respectively. This will enable the subject to be fully aware of the whole process of breathing in. It is followed by asking the subject to repeat the word "Out" silently three times at the beginning, middle and end of exhalation, ie., In-In-In-Out-Out.
- Stage 4.-This time, the subject repeats the word "In" continuously throughout the whole process of breathing in followed by the word "Out" throughout the whole process of breathing out, ie., "I....n-Ou.....t". This stage is to create awareness

and help the subject to pay attention to the whole process of both of breathing in and out.

*Stage 5.*—The subject is asked to pay attention to the whole "breath body" without the need to mention either the word "In" or "Out". The subject needs to be aware of the whole process of breathing. There are several reference points to help the subject to attend to their breathing. The subject is advised to feel and concentrate on the sensations on their nostril and upper lip while breathing in and out. They can also focus on the movement of their chest or stomach during the breathing cycle. After the subject is able to master their focus on the breathing, they are then asked to continue with stage 5 for five minutes.

# 8.2.1.2 The Steps for 5-Minute Mindful Breathing for Palliative Care Patients

- 1. Do it either in a sitting or lying position, whichever you are most comfortable in. Make sure the position does not cause pain or discomfort.
- 2. Relax all the muscles of your body.
- 3. Close your eyes gently and try to feel all that is happening in the environment.
- 4. Notice the noise, feel the temperature in the room, scan your body for sensations such as pain or itchiness.
- 5. Then, bring your attention to your breathing.
- 6. Take in deep breaths twice, naturally and slowly.
- 7. Notice air flow through your nostrils and mouth.
- 8. Feel the movement of your chest and abdomen when you are breathing.
- 9. Gently rest your attention on your breath.
- 10. During the breathing exercise, thoughts may enter your mind. You need only acknowledge the presence of the thoughts and bring your focus back to your breathing. Do not judge, analyse or follow the thoughts.

- 11. Likewise, you may have physical sensations such as pain, noise, or emotional experiences like sadness. Again, you need only acknowledge the presence of these feelings and bring your focus back to your breathing. You should not judge the physical sensation or your emotion.
- 12. Do not worry that your attention may drift because of physical or emotional feelings. You need only be aware about their presence and bring your focus back to your breathing.

Practise focusing on your breathing for the next five minutes.

#### 8.2.2 Phase 2: Pilot Study

After its initial development, the effect of 5-minute mindful breathing in distress reduction was investigated in a pilot study (Tan et al., 2015). The effect of 5-minute mindful breathing was compared to that of 'listening' (being listened to) in palliative care subjects. The 5-minute mindful breathing was presented as the treatment group while 'listening' as the control group. A total of 20 participants made up of 9 in-patients and 11 family caregivers were recruited from UMMC, Kuala Lumpur for this pilot study. The subjects were at least 18 years of age and receiving care from palliative care team at the UMMC. The participants also demonstrated moderate to severe distress, as indicated by a score of 4 or above measured by the Distress Thermometer.

The subjects were randomly assigned to either 5-minute mindful breathing group or 'listening' group. Participants in the treatment group were led by a facilitator to perform together the 5-minute mindful breathing exercise, using the guidelines developed from phase I. Participants in the control group obtained an equivalent 5-minute but 'listening' session with the same facilitator. Semi structured interview was conducted where the patients in this group were asked questions and expected to verbally express their experiences of illness in this 5-minute listening session. After that they were guided to keep talking so that they were further listened to by the physician for another 15 minutes. The rationale was that only 5 minutes of listening might not be sufficient to help them reduce distress and hence a longer 15 minutes was added.

#### 8.2.3 Phase 3: Randomized Controlled Trial

With the positive findings from the previous pilot study, a similar research was replicated in a non-blinded, randomized controlled trial (RCT) with a larger sample and introduction of some physiological measures (Ng et al., 2016). This RCT was aimed to study the effect of 5-minute mindful breathing on rapid distress reduction among patients in palliative setting. While the subjective report of distress was retained from the pilot study, physiological measurements of the patients were also introduced and studied in this RCT to further prove the efficacy of mindful-breathing. These physiological measures included breathing rate, pulse rate, blood pressure, galvanic skin response, and skin surface temperature of the patients, which have correlation with distress reactions (Cannon, 1929; Jansen et al., 1995; Mcewen & Lasley, 2002; McCance et al., 2006, Hansen & Sawatzky, 2008).

When under stress, humans' sympathetic nervous system will be activated. Catecholamines (e.g., epinephrine, norepinephrine) also known as the stress hormones will then be released by the adrenal glands. Epinephrine escalates the cardiac output and blood flow to take in more oxygen. Norepinephrine on the other hand constricts blood vessels of the viscera and skin and jolts blood to the vessels dilated by epinephrine. These physiological changes in response to stress is known as fight-or-flight mode (Cannon, 1929; Jansen et al., 1995; Mcewen & Lasley, 2002; McCance et al., 2006, Hansen & Sawatzky, 2008). As a result, the person experiencing stress will exhibit physiological reactions such as increased galvanic skin response, blood pressure, heart rate, breathing rate and decreased skin surface temperature (Cannon, 1929; Jansen et al., 1995; Mcewen & Lasley, 2002; McCance et al., 2006, Hansen & Sawatzky, 2008). Although those measurable physiological reactions are not direct indicators and predictors of stress level as they can be influenced by other factors (e.g., side effect of pharmaceutical, medical conditions etc), there is a strong relationship between such physiological changes and stress levels (Cannon, 1929; Jansen et al., 1995; Mcewen & Lasley, 2002; McCance et al., 2006, Hansen & Sawatzky, 2008).

Sixty palliative cancer patients that were at least 18 years old and under palliative care were recruited from UMMC, Kuala Lumpur, Malaysia. They also demonstrated a Distress Thermometer score of 4 or above to be part of this study. Similar to the pilot study, participants were randomly assigned to either 5-minute mindful breathing (treatment) group or 5-minute 'listening' (control) group. The perceived level of distress and physiological were assessed at the beginning of the sessions (T1), then assessed again upon the completion of session (T2) and once again (T3) after a 10-minute short break.

#### 8.3 Results

#### 8.3.1 Phase 2

The results were measured at minute 0 (baseline) and at minute 5 for both treatment and control groups, and at minute 20 only for the 'listening' group (15 minutes after the original 5 minutes). The primary analysis was done for the change in distress score of Distress Thermometer at minute 5 for each group. The secondary analysis on the other hand had two parts. The first part involved comparing the change in distress score during the 5-minute session between the two groups, based on participant's recollection. In the second part, change in distress score was compared between the mindful breathing group at minute 5 and the 'listening' group at minute 20.

Distress score decreased significantly larger in the mindful breathing group after 5 minutes compared to 'listening' group (Tan et al., 2015). Similar finding was also found during the mindful breathing session, where participants recalled significantly greater distress reduction in the treatment group than in the control group (Tan et al., 2015). Interestingly, contrasting the distress reduction between the treatment and 20-minute control groups did not give any significant difference (Tan et al., 2015).

#### 8.3.2 Phase 3

The primary analysis was to investigate the changes in the level of distress and physiological responses (T2 versus T1 and T3 versus T1) for both groups. A secondary analysis was done to compare differences of distress reduction between mindful breathing group and 'listening' group. For Distress Thermometer score and other physiological variables namely breathing rate, systolic and diastolic blood pressure, pulse rate and galvanic skin response; there was a significant reduction at both T2 and T3 for the treatment group but no significant difference for the control group (Ng et al., 2016). As for skin surface temperature, there was a significant increment at T2 and T3 for the treatment group but only at T2 for the control group (Ng et al., 2016). All those physiological changes as a sign of distress reduction were significantly greater in the mindful-breathing group than 'listening' group (Ng et al., 2016).

# 8.4 Discussion

#### 8.4.1 Phase 1

The practice of mindful breathing enables palliative care patients to bring their focus to the present moment (Kabat-Zinn, 1994). Distress experienced by palliative care patients is mainly attributed to their rumination about their past suffering and anticipation of negative outcomes in the future (Kabat-Zinn, 1994). These automatic negative thoughts tend to result in fear, anxiety, depression and distress (Yook et al., 2008; Ando et al., 2009; Bohlmeijer et al., 2010; Foley et al., 2010; Shennan et al., 2011; Cramer et al., 2012; Whitebird et al., 2013, Zainal et al., 2013). Mindful breathing diverts a patient's attention away from painful experiences or thoughts. Awareness about own negative thoughts and emotions is increased so that they can respond mindfully and shift their focus back to the present moment (Kabat-Zinn, 1994). The practice of mindful breathing can lead patients to respond consciously and non-judgmentally in the observation of their unpleasant moment or thoughts. It would give a realization that these are not the reality but "mere thoughts". As a result, their feelings or emotions will not be so affected by these thoughts (Davis & Hayes, 2011; Cramer et al., 2012; Tan et al., 2015).

The principle of mindful exercise is that at any single moment, the mind should only hold one thought. If the subject is able to concentrate on their breathing during a stream of moments, holding any negative thoughts at that same moment will be prohibited. This acts to put a mental block between the negative automatic thoughts and the directly linked negative emotions and distress. The early development of the 5-minute mindful breathing seems to be supported by some theoretical framework and its hypothesized effect in distress reduction should be studied.

#### 8.4.2 Phase 2

It was concluded that the 5-minute mindful breathing rapidly reduced the distress level among the palliative care patients and their care takers (Tan et al., 2015). The distress reduction during the mindful breathing session was larger than after the session. The result showed that performing mindful breathing could rapidly reduce attention on distress (Tan et al., 2015). However, it was noted that the patients would shift their focus back to distressing thoughts after completing the 5-minute mindful breathing where their distress score elevated again (Tan et al., 2015). It is thus advisable for the patients to practice 5-minute mindful breathing frequently to master the skill so that they can constantly keep their distress at a much lower level for a more sustained effect.

As mention earlier, people interrupt attention to the automatic negative thoughts that cause distress when breathing mindfully, practicing this exercise in long run may break them from the old habits of ruminating and worrying, which can in return more strongly and stably reduce distress. Patients with higher levels of distress may need more repetitive practises to enjoy the benefit of mindful breathing. For patients who are inattentive, not motivated, or with high urge to redirect attention back to stressors, learning mindful breathing can be challenging.

The effect of 5-minute mindful breathing was confirmed in this pilot study (Tan et al., 2015). It also achieved the goals to be easy and quick to administer and to learn, with rapid efficacy and no cost incurred. It also addressed conditions such as poor physical fitness, limited life expectancy, inadequate attention or mental alertness and fluctuation of consciousness that are associated with palliative care that impair the effectiveness of conventional psychotherapy. As patients in palliative care usually have a short life span, clinical treatment with immediate therapeutic effect to ease pain and suffering will be greatly appreciated. The mindful breathing exercise is exactly able to provide such advantage. It can also be learned quickly without specific training and hence is suitable for patients with lower cognitive functioning.

However, this pilot study posed some limitations. It was conducted as the stepping stone to preliminarily evaluate feasibility, duration and effect size so that a more appropriate design and sample size can be derived for future studies (Tan et al., 2015). The current relatively small sample makes the finding difficult to be generalized to all palliative care patients (Tan et al., 2015). Also the heterogeneity of the current sample (including both

palliative care patients and caregivers) may contribute to the generalization difficulty too (Tan et al., 2015).Though patients and their caregivers may both experience distress regarding the illness, the nature of their distress may differ from each other patients usually experience higher level of bodily pain/suffering as compared to their caregiver counterparts. It may be interesting to study the specific efficacy of mindful breathing on these two similar yet different populations.

While the results from this pilot study provided preliminary proof that 5-minute mindful breathing is helpful in rapid reduction of distress, further research with much larger sample size is needed to support this finding. Gaining more biological/physiological support for the stress reduction effect of mindful breathing to explain its scientific mechanism is also something worth exploring.

#### 8.4.3 Phase 3

The effect of 5-minute mindful breathing in rapidly reducing distress among palliative care patients was confirmed in this RCT (Ng et al., 2016), consistent with the previous pilot study (Tan et al., 2015). Other than just subjective report of distress level, the finding was also further supported by the significant physiological changes associated with distress reduction such as decreased breathing rate, blood pressure, pulse rate, galvanic skin and increased skin surface temperature (Ng et al., 2016). The rapid outcome of mindful breathing can be due to the purposeful redirection of attention from distressing thoughts or experiences to mindful breathing (Tan et al., 2015).

While the current study showed that reduction of distress by 5-minute mindful breathing was immediate and lasted for 10 minutes, the earlier pilot study suggested that patients may revert their attention back to distress afterwards (Tan et al., 2015). Though both significant, the lower distress reduction at a longer time lapse (T3 versus T1) than at the moment mindful breathing just completed (T2 versus T1) gave an insight about people's

tendency to revisit distressing thought as time passed, even if it was just 10 minutes later. As such, after patients have been guided during the early introduction, they should practice 5-minute mindful breathing regularly for a more continuous result. Practicing mindful breathing frequently can break the cycle of ruminating and worrying about an automatic negative thought that induces distress, which then makes the effect of mindful breathing more stable and sustainable. Repetitive practices may be required for those who have much higher distress, inattention, and tendency to ruminate about a stressor in order to bring out the beneficial effect of mindful breathing.

Nevertheless, this study posed its own limitations. The sample size was tabulated based on the effect size from the previous pilot study (Tan et al., 2015; Ng et al., 2016). An even much larger sample size may be required to demonstrate the significant effect of 5minute mindful breathing on the physiological changes associated with distress reduction among the palliative care patients. This will also strengthen the generalization of the findings. This RCT however managed to address the heterogeneity problem in the previous pilot study (participants made up of patients and their caregivers) by recruiting only homogenous cancer patients (Tan et al., 2015; Ng et al., 2016).

The present study managed to prove the instant influence of 5-minute mindful breathing on distress reduction (Ng et al., 2016). The sustainability of this positive effect however was not examined in the RCT and should be given attention in the future research (Ng et al., 2016). It may require a longitudinal study (e.g., 6 months) to look into its possible long term impact in reducing stress. As mentioned earlier, people tend to revert their attention back to distressing thoughts after a short period of mindfulness (Tan et al., 2015). The present study also provided preliminary insight into this notion where distress reduction appeared to be lesser as time passed. There are questions as to the "right" frequency and interval to aim for a longer lasting desired outcome, where the beneficial effect of 5-minute mindful breathing would not be diluted in earlier stages of diseases.

Besides, the presence of a palliative physician as a facilitator in the treatment group may also present itself as a nuisance variable which may have interacted with the genuine effect of mindful breathing (Ng et al., 2016). For example, having to close eyes and learn mindful breathing with a perceived authority may be stressful to some patients and this may affect the efficacy of mindful breathing in distress reduction. Different facilitators would have different personalities as well where some may be more reassuring and some may be more intimidating, indirectly inducing different stress levels among the patients. Perhaps, the instruction of 5-minute mindful breathing can be first learned by the participants, before they practice on their own and have their physiological changes measured. This is to make sure that the effects measured will be more sensitively attributed to the breathing exercise itself instead of the facilitator's influence (Ng et al., 2016).

Last but not least, future studies may also opt to use a more advanced and more sensitively devised tools for the measurement of the physiological indicators (Ng et al., 2016). For instance, Biopac MP36R with AcqKnowledge software which is specially designed to measure galvanic skin reactions for clinical research purpose can be considered. Some previous studies have also recommended this particular device (Gillan et al., 2014; Levita et al., 2014). Future research can also attempt to study the effect of mindful breathing out of palliative setting or in other populations.

# 8.4.4 Special Considerations for 5-Minute Mindful Breathing in Palliative Care Patients

There are some considerations when conducting the 5-minute mindful breathing technique with terminally ill patients. It is a challenge to get a physically ill patient to

bring their focus onto their breathing. Their level of concentration is usually low due to their frail physical condition and the associated negative emotions. When practising the breathing exercise, they are often easily distracted by the surrounding noises and ward activities.

Preferably, the first session of the 5-minute mindful breathing technique should be conducted in a quiet room. The ward staffs should be informed during the practice of the exercise to minimize unnecessary interruption. In a quiet and relaxed environment, patients will be able to enter the mindfulness stage more quickly and easily. Most palliative care patients need many practise sessions to get into the mindful state. Most patients feel impatient while trying to bring their focus onto their breathing and subsequently feel discouraged. Some may even conclude that the exercise is not helpful after only the first few trials. There is a need for continuous encouragement and explanation.

Another consideration is that many palliative care patients are dyspnoeic or have a persistent cough (Young et al, 2009). The 5-minute mindful breathing technique involves slow and deep breathing. Some patients may complain that the breathing exercise worsens their dyspnoea or coughing (Young et al, 2009). In addition, the 5-minute mindful breathing exercise may be interrupted by their coughing. There were patients who reported that they actually tried to suppress their coughing during the 5-minute mindful breathing. However, voluntary suppression of coughing will distract their concentration. We do not encourage patients to continue with the 5-minute mindful breathing exercise in the event of chronic coughing or acute severe coughing. Those with hiccups are also not suitable for the 5-minute mindful breathing exercise. A study conducted by Young et al. found that short durations of mindfulness in an outpatient programme fail to decrease cough reflex sensitivity among patients with chronic cough (Young et al, 2009). Thus there is insufficient evidence that mindfulness can benefit

117

such type of patients. Therefore, the practice of the 5-minute mindful breathing should exclude patients that are suffering from severe coughing or dyspnoea.

# 8.5 Conclusion

Mindful breathing is an easy and flexible intervention with no restriction in the number of sessions. It can be learned by anyone including patients or caregivers. It can also be practised at any settings, such as the home, hospital, rehabilitation centre or office; and anytime, such as before or after bedtime, during religious activities or while waiting for a clinic appointment. It can also be incorporated into any other psychotherapy intervention, such as cognitive behavioural therapy. In conclusion, we believe that the practice of 5-minute mindful breathing can be a simple, easy, efficient and effective psychological intervention to reduce distress in palliative care patients.

# CHAPTER 9: THE CORRELATION BETWEEN PERCEIVED LEVEL OF DISTRESS AND PHYSIOLOGICAL PARAMETERS IN PALLIATIVE CANCER PATIENTS

# 9.1 Introduction

Psychological comorbidities, such as anxiety, depression, and adjustment disorders, are common among palliative cancer patients. Since 2003, the National Comprehensive Cancer Network (NCCN) used the word "distress" to describe these psychiatric problems in cancer patients because as there are more accepted and less stigmatizing. Distress is defined as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment" (NCCN, 2003). About 18 to 43% of cancer patients are reported to suffer from a certain level of distress depending on the type, duration and stage of the disease. These distress in palliative patients tends to be under-diagnosed and under-treated (Kelly et al, 2006). Furthermore, palliative patients often experience distress that is not well characterized within the context of the Diagnostic and Statistical Manual of Mental Disorders (DSM) phenomenology (Chochinov, 2003). Therefore, it is important to examine the psychological distress among palliative cancer patients by utilizing methods that is tailored for their condition.

There are many challenges in measuring psychological distress in palliative cancer patients. Somatic symptoms such as poor appetite, weight loss, fatigue, insomnia and inability to concentrate may be related to cancer and treatment, as well as being manifestations of depression (Beck et al., 1997; Ciaramella & Poli, 2001; Zigmond & Snaith, 1983). The use of common tools such as The Beck Depression Inventory (Beck et al., 1997) and the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)

119

is of limited use in palliative settings. Patients answer the self-rated questionnaires based on their perceived feelings and the answer reflect the patient's feeling subjectively. However, the answer may susceptible to satisficing and response biases (Phillips & Clancy, 1970). For example, a patient may respond based on social desirability. In the palliative care setting, patients are often too fatigued, weak and unmotivated to go through the self-rating questionnaires and interview questions, and may answer with response biases. Therefore, a relatively non-burdensome and nonsubjective method would be more ideal in measuring psychological distress among palliative cancer patients. A single item tool called the Distress Thermometer (DT) has shown comparatively favourable with longer measures such as the Hospital Anxiety and Depression Scale and an 18- item Brief Symptom Inventory (Jacobsen et al., 2005) in measuring distress in cancer patients. The main drawback is that none of the instruments commonly used has been specifically developed to match the peculiarities of psychological distress observed in people with cancer. As stress triggers physiological changes in the autonomic nervous and immune systems (Steptoe et al. 2007), these could be used as the proxy-indicators in measuring psychological distress in cancer patients

When humans are stressed, the sympathetic nervous system stimulates the adrenal glands to release catecholamines which consist of epinephrine and norepinephrine. Epinephrine elevates the cardiac output, which increases blood flow to the heart, brain, and the airway. This increases the supply of oxygen to the bloodstream and muscle. Simultaneously, norephinephrine constricts blood vessels of the viscera and skin; and shunts blood to the vessels dilated by epinephrine. In addition, endocrine and cardiovascular systems also respond to stress with elevated cortisol levels and increased heart rate and blood pressure (Schneiderman et al. 2005). If stress is persistent, these changes can result in health problems such as a hypertension and dysregulated immune

120

system (Schneiderman et al. 2005), memory problems (McEwen and Sapolsky 1995), and mental illnesses such as depression (Hammen 2005).

Heart rate variability (HRV) is the commonest used indicator of psychological distress. HRV is the beat-to-beat alterations (R-R intervals) in heart rate and is considered an indicator of a person's capacity to respond adaptively to stress (Appelhans & Luecken, 2006). The autonomic nervous system regulates the body's stress response via the vagus nerve and HRV is recommended as a physiological marker of the vagal tone of resting heart rate. Other direct indicators of increased catecholamine levels include blood pressure, heart rate and respiratory rate and galvanic skin response (Hansen & Sawatzky, 2008).

To date, there is no study looking into the relationship between the physiological responses with perceived level of distress among palliative cancer patients. Therefore, this aims to study the correlation between the changes of physiological response with the changes in perceived level of distress among palliative cancer patients after undergoing therapies. We hope to show that the physiological responses such as systolic blood pressure, diastolic blood pressure, pulse rate, breathing rate, skin surface temperature and Galvanic skin response could be used as the proxy-indicators in measuring psychological distress in cancer patients.

# 9.2 METHODOLOGY

This is part of another large study looking into the efficacy of 5 minutes "mindful breathing exercise" in palliative cancer patients. The study was conducted at the palliative unit, University Malaya Medical Centre. The inclusion criteria were those above the age of 18 years diagnosed with a of any type of cancer of, under palliative care, a distress score of more than 4 based on the distress thermometer and able to understand and follow simple instructions. The exclusion criteria were those who were

delirious or confused, those with breathing difficulties or unable to maintain concentration for at least 20 minutes. Those who consented had their sociodemographic information collected, while relevant clinical data such as type of cancer, comorbid medical conditions and medications were obtained from the medical records.

The following measurements were taken before and after intervention:

- 1. Perceived level of distress using Distress Thermometer
- 2. Skin Surface Temperature
- 3. Galvanic skin response
- 4. Blood Pressure
- 5. Pulse Rate
- 6. Breathing Rate

# 9.2.1 Distress Thermometer

The Distress Thermometer is a validated rapid screening tool for distress and has been endorsed by the NCCN Distress Management Guidelines panel. It serves as an initial single item question screen, which identifies distress from any source. The word ''distress'' was chosen because it sounds ''normal'' and is less embarrassing to patients. It assesses how much distress patients are going through in the past week from a scale of 0 to 10 (National Comprehensive Cancer Network, 2013).

# 9.2.2 Skin surface temperature measurement

Dr. Lowenstein's Stress Thermometer SC911 is widely used in clinical research to measure the skin surface temperature and identify stress and relaxation levels as well as see how cognition and emotion impact the human body (Shah et al., 2015; Stephenson,

Swanson, Jesse & Brown, 2013; Burnett, Solterbeck & Strapp 2004; Forest, Heuvel, Lushington & Koninck, 2012; Prato & Yucha, 2013). The degree of decrease of skin surface temperature indicates tension when a person is nervous, worried or stressed; where else an increase indicates relaxation where a person is in a peaceful emotional state. The Stress Thermometer (ST) is able to measure hand skin surface temperature from the -58 F to 158 F range. Skin temperature below 79 F indicates an extremely stressed state, where else a reading of above 95 F indicates a highly relaxed state.

#### 9.2.3 Galvanic skin response measurement

Galvanic skin response, or skin conductance or electrodermal response, is a measurement of the bio-electrical properties of the skin (Wang, 1957). The galvanic skin response in this study will be measured by using the Mindfield's eSense biofeedback system that has been widely used in clinical research (Gillan, 2014; Levita, Howsley, Jordan & Johnston, 2014). This device applies a very small voltage and safe electrical current to the skin to measure conductance in microsiemens ( $\mu$ S). When individuals are stressed, activity of the perspiratory glands increases and this leads to an increase in skin conductance response. Conversely, when individuals are calm, activity of the perspiratory glands decreases and this leads to decrease in skin conductance response.

# 9.2.4 Blood pressure and heart beat measurement

A standardized calibrated blood pressure monitor capable of measuring blood pressure from from 0 - 299 mmHg, and the pulse rate from 40 - 180 beats/min was used. Blood pressure and heart rat e are expected to increase when a person is stressed.

#### 9.2.5 Procedure

The subjects were assigned to either 5 minutes "mindful breathing" or normal listening
groups. The perceived level of distress and physiological responses were measured at the beginning of the sessions, and again after the completion of either intervention.

# 9.2.5.1 Normal Listening

In the normal listening group, the subjects were interviewed using a list of standard semi-structured questions as followed for five minutes:

- 1. Could you tell me about your illness?
- 2. Could you tell me about yourself?
- 3. What about your life?
- 4. What about your family and friends?
- 5. What are the things that are important to you?
- 6. Is there anything else that you would like to share with me?

# 9.2.5.2 Five Minutes of Mindful Breathing

In Mindfulness Based Therapy, the subjects are taught to increase their awareness through paying attention in a particular way, on purpose, in the present moment, and non-judgmentally, following the steps below:

1. Step 1 – Adopt a Physical Posture

A good physical posture helps to maintain a healthy mental posture. Eg: Sitting upright/ on a chair.

2. Step 2 – Establish a Mindfulness Anchor.

Tie the mind to the present moment. Eg: Pay awareness to the breathing.

3. Step 3 – Maintenance of Mindfulness

Maintain the focus to the present moment and regulate ruminations. Eg: Count the breathing. Do not force breathing.

The participants are instructed to relax their body, close their eyes and focus their attention on their breathing. If they notice any distractions, such as sounds, body sensations, thoughts or feelings, they are told to gently redirect their attention back to their breathing. They are told to focus their attention on their breathing for 5 minutes, and the palliative care physician will sit and practice the mindfulness breathing together with the participants during the sessions.

# 9.2.6 Statistical Analysis

The differences between post and pre therapy in the levels of perceived distress, and the levels of physiological responses were calculated. The correlation between the changes of physiological responses with perceived level of distress was determined using Spearman's correlation analysis. All the tests are two tailed with significant levels of 0.05.

### 9.3 Results

Table 9.1: Socio-demographic characteristics and types of cancer of the study subjects

(]	N	=	6	0	)	

Characteristics					
Age (years), mean (Terwijn et al.)	47.03 (16.46)				
Gender, n (%)					
Male	29 (48.30)				
Female	31 (51.70)				

Characteristics	
Ethnicity, n (%)	
Malay	14 (23.3)
Chinese	36 (60.0)
Indian	9 (15.0)
Others	1 (1.7)
Religion, n (%)	
Muslim	14 (23.3)
Buddhist	24 (40.0)
Christian	12 (20.0)
Hindu	8 (13.3)
Others	2 (3.3)
Marital status, n (%)	<i>A</i> ,
Single	19 (31.7)
Married	41 (68.3)
Types of cancer, n (%)	
Breast	10 (16.7)
Bone	11 (18.3)
Lungs	6 (10.0)
Hepato-pancreatic	4 (6.6)
Esophageal	2 (3.3)
Nasopharyngeal	6 (10.0)
Prostate	3 (5.0)
Testicular	3 (5.0)
Brain	2 (3.3)
Cervical	1 (1.7)
Others	12 (20.0)

 Table 9.1, continued.

# 9.3.1 Participants

Sixty palliative cancer patients were recruited. The mean age of the study patients was 47 years old. Majority of them were Chinese (60%) followed by Malay (23%) and Indian (15%). The commonest religion of the study subjects was Buddhism (40%)

followed by Muslim (23%) and Christianity (20%). There were more female (51%) than male in the study group. Most of the patients were married (68%). The commonest types of cancer were bone (18%) and breast (16%). Other cancer types included lungs, nasopharyngeal, liver, pancreas, prostate, testicular, oesophageal and cervical (Table 9.1).

There were significant positive correlations between the changes of systolic blood pressure (r = 0.445), pulse rate (r = 0.344) and breathing rate (r = 0.473) with perceived level of distress. In other words, the reduction of systolic blood pressure, pulse rate and breathing rate are positively correlated with the reduction of perceived level of distress after therapy. There was also a positive correlation between the changes of diastolic blood pressure with the changes of perceived level of distress but it was not statistically significant. There was significant negative correlation between the changes of skin surface temperature with perceived level of distress (r = -0.286), indicating skin temperature increases as level of distress reduces. The correlation between the changes of Galvanic skin response with perceived level of distress was minimal (r = 0.042) and statistically insignificant (Table 9.2).

Table 9.2: Correlation between the changes in perceived level of distress with blood pressure, breathing rate, pulse rate, Galvanic skin

Changes after 5 minutes mindful therapy	Perceived distress	Breathing rate	Systolic blood pressure	Diastolic Blood pressure	Pulse Rate	Skin surface Temperature	Galvanic skin response	
Perceived distress	1.000	.473**	.445**	.243	.344***	286*	.042	
Breathing rate	.473**	1.000	.339**	.069	.090	121	134	
Systolic blood	.445**	.339**	1.000	.451**	.420**	336**	.352**	
pressure Diastolic blood	.243	.069	.451**	1.000	.421**	205	.154	
pressure Pulse rate	.344**	.090	.420***	.421**	1.000	391**	.150	
Skin surface	286*	121	336**	205	391**	1.000	102	
temperature Galvanic skin	.042	134	.352**	.154	.150	102	1.000	
response								

response and skin surface temperature

Distress = psychological distress based on distress thermometer, breathing rate = breathing per minute, systolic and diastolic blood pressure in mmHg, pulse rate = pulse per minute, skin surface temperature in  $\mathcal{F}$  measured using Dr. Lowenstein's Stress Thermometer SC911, Galvanic skin response in microsiemens ( $\mu$ S) measured using Mindfield's eSense skin response biofeedback system, statistical analysis (*p* value) for Spearman's correlation, \**p* < 0.05, \*\**p* < 0.01

In this study, we aimed to establish the correlation between the reductions of perceived level of distress with changes in physiological responses after 5 minutes of mindful therapy in palliative cancer patients. The findings showed that the reduction of perceived distress was significant correlated with reduction in systolic blood pressure, breathing rate and pulse rate; and correlated with increases of skin surface temperature. There was no significant association between the changes in Galvanic skin response and diastolic blood pressure with the changes in perceived level of distress in the palliative cancer patients.

# 9.4.1 Blood pressure

We managed to demonstrate the correlation of acute reduction of perceived level of distress with reduction of systolic blood pressure in palliative cancer patients. It has been hypothesized that heightened cardiovascular reactivity could be the pathophysiological processes involved in the etiology of hypertension, mediated by the autonomic nervous system (alpha and beta adrenergic responses) (Manuck et al, 1994; Rozansk et al., 2006; Sparrenberger et al., 2008; Treiber et al., 2003). Psychological distress leads to an increase in cardiovascular responses, typically blood pressure as emotional distress produces more stress hormone, nervous stimulation and endocrine secretion (Friedman, 2011; Fink, 2010). Chida and Hamer (2008) showed that increased heart rate and blood pressure was also related to aggression, hostility or Type-A behavior; fatigue, burnout, or exhaustion.

In this study, we failed to demonstrate any association between reductions in diastolic blood pressure with reduction of perceived stress. This is in contrast to a previous study that showed that acute mental stress was associated with both increase systolic and diastolic blood pressure (Carroll et al. 2011). However, diastolic blood pressure reactivity to stress, is much less commonly studied as compared to systolic blood pressure (Carroll et al. 2003; Carroll et al. 2011).

In this study, we used 5 minutes of mindful therapy to reduce levels of perceived level of distress that demonstrated a reduction in systole blood pressure. This is in keeping with a study on the impact of 8 weeks mindful stress reduction therapy (MBST) that demonstrated a reduction in systolic blood pressure in women with cancer (Campbell et al., 2012).

#### 9.4.2 Pulse rate

We demonstrated the association between reductions of pulse rate with reduction of perceived distress after therapy in palliative cancer patients. There were not many studies looking into the association of stress with pulse rate. One of the earliest studies was conducted in 1954 by Baker and Taylor, showed that an increase in pulse rate with emotion provoking stimulation. Acute stress produces transient elevations in pulse rate and blood pressure via increased sympathetic and decreased vagal activity (Lucini et al., 2005; Vale, 2005). In a study that involved fifty four adolescents, heart rate and blood pressure were both raised either during exercise or during a psychological stressful day. The assumption was that metabolic demands which lead to increase cardiovascular reactivity were both equally significant during exercise or stress (Lambiase et al., 2012).

# 9.4.3 Breathing rate

In this study, the findings showed that as the perceived stress reduced, there was a decrease in breathing rate. We only measured the breathing rate but not the tidal volume in the study. This is consistent with a previous study where a positive correlation was found between stress induced by mirror drawing test with breathing rate (Homma, 2005). It is believed that breathing rate is another indicator of sympathetic tone which

changes following the change in perceived level of distress. However, in a study on the sympathetic-parasympathetic hypothesis on stress and depression, no correlation was found between stress and respiratory rate. The authors concluded that respiratory rate was the physiological parameter with lowest rank order in the sensitivity toward stress or depression (Lin et al., 2011).

## 9.4.4 Skin surface temperature

Our results showed that as the perceived level of distress reduced, there was increase in the skin surface temperature. Skin temperature change is a vasomotor phenomenon, where vasodilatation of arterioles increases cutaneous blood flow leading to an increase in skin temperature Decrease in skin temperature with emotion-provoking stimulation has been demonstrated in both humans (Baker and Taylor, 1954) and animals (Herborn et al., 2015).

## 9.4.5 Galvanic skin response

It has been evidenced that distress such as frustration and anxiety causes higher physiological reactivity such as changes in skin conductance level (Nock & Mendes, 2008). However in our study, we failed to demonstrate any significant correlation between the changes in perceived distress in palliative cancer patients with changes in the Galvanic skin response. Our findings are more in keeping with a previous study that also used Galvanic skin response as one of the indicator for psychological stress evaluation but failed to show any correlation (Horvath, 1978). Currently, there were other proposed methods such as Galvanic Skin Response (GSR) device to measure the skin conduction or sweat glands activities during stress (Villarejo et al., 2012).

# 9.5 CONSLUSION

There is not much research done reviewing the relationship between psychological distress and physiological responses. Previously the relationship between psychological distress and physiological disturbance was said to be insufficient and inconsistent (Dawe et al, 2014, Turner, Beidel & Larkin, 1986). However, we demonstrated that psychological distress does have an interrelated effect on certain physiological parameters such as cardiovascular reactivity and skin surface temperature.

An important implication of our study is that it shows that measuring physiological parameters may be an important method in monitoring psychological distress. We feel that measuring physiological parameters may be a more reliable than self-rated questionnaires as it measures more objectively and would provide less bias. Somatic symptoms caused by cancer and its treatment would be falsely captured by self-rated questionnaires. Measuring physiological parameters also offers greater convenience to the palliative care patients as they do not need to put in much effort compared to self-rated questionnaires that can be time consuming. The time consuming nature of self-rated questionnaires coupled with the fatigue and weakness seen in palliative care patients would invariably lead to bias. Other than that, this study also provides insight for future interventional strategies to focus on the physiological responses of the palliative care patient.

Nevertheless, there is also a few shortcoming discovered in this study. For instance, the patient might have the tendency of developing observer effects that will influence the readings of the physiological parameter as they are being closely observed. Lastly, physiological responses can be influenced by medication, physical pain or other biological factors. Although physiological responses are indirect indicators and can't predict the stress level per se, but the relationship between its changes and stress levels

can be an important method to monitor psychological intervention methods in palliative care patients.

133

# CHAPTER 10: THE EFFECT OF FIVE MINUTES MINDFUL BREATHING TO THE PERCEPTION OF DISTRESS AND PHYSIOLOGICAL RESPONSES IN PALLIATIVE CARE CANCER PATIENTS: A RANDOMIZED CONTROLLED STUDY

# 10.1 Introduction

Psychological distress, such as anxiety, depression, and adjustment disorders, are common among palliative cancer patients. Most cancer patients report having high levels of distress ((Holland, J C., 2003) and up to one in four cancer patients suffer from clinical depression (Sellick, S. M & Crooks, D. L., 1999). The use of conventional pharmacotherapy in this group of patients is hampered by the issue of adverse effects, tolerability and delay in the onset of action (Ng, C. G et al., 2014). As a result, various psychosocial methods were introduced for reduction of distress in palliative cancer patients. Of all the psychosocial interventions, mindfulness based intervention has shown some efficacy in promoting relaxation and reducing psychological stress (Baer., 2003; Cramer, H et al., 2012; Kabat, Z., 2003; Ledesma, D & Kumano, H., 2009; Tan, S. B et al., 2015). Although mindfulness-based interventions are useful in reducing various forms of psychological stress, its application in the palliative care settings is not without its challenges. Patients may have fluctuating levels of consciousness, psychological distress or physical disabilities. Palliative care cancer patients are physically weak and lethargic to go through a series of lengthy psychotherapy sessions. In order to address these challenges, a five-minute mindful breathing technique was proposed (Tan, S. B et al., 2015).

The five-minute mindful breathing is based on a series of mindful practices. From a range of mindfulness practices, mindful breathing was selected for the study because humans breathe every second of every day. Breathing is both an involuntary and

voluntary physiological process, it is controlled voluntarily by the motor cortex but also controlled automatically by the brainstem. Practicing mindful breathing allows the patients to practise it anytime and anywhere they want. Mindful breathing represents a main practice that serves as an anchor for the other mindful practices, such as mindfulness walking and mindfulness meditation (Tan, S. B et al., 2012).

Current literature suggests that psychological distress in palliative patients tends to be under-diagnosed and under-treated (Kelly, S., McClement, S., Chochinov, H. M., 2016). This is because palliative patients often experience distress that is not well characterized within the context of Diagnostic and Statistical Manual of Mental Disorders (DSM) phenomenology (Chochinov, H. M., 2003). Therefore, it is important to screen for psychological distress among palliative cancer patients by using a measurement that is suitable for them. Common tools used in measuring psychological distress are selfrating questionnaires such as Hospital Anxiety and Depression Scale (Zigmoid, Snaith, 1983) and Beck Depression Inventory (Beck, A. T et al., 1961). The patients answer the self-rated questionnaires subjectively, based on their feelings. However, their answers may be susceptible to response biases (Phillips, D. L & Clancy, K. J., 1970). For example, patients may respond based on social desirability. In the palliative care setting, patients are often too fatigued and weak to go through the self-rating questionnaires and interview questions. Individuals are assumed to answer the question with response biases when they are more fatigued, more burdened and less motivated. Therefore, a non-burdensome and non-subjective method should be considered in measuring the psychological distress among palliative cancer patients. The present study suggests that physiological responses could be one of the indicators in measuring psychological distress.

When humans are stressed, the sympathetic nervous system is activated and it stimulates the adrenal glands to release catecholamines (eg. Epinephrine, norepinephrine,). Epinephrine elevates the cardiac output, which increases blood flow to the heart, brain, and airways to increase available oxygen to the bloodstream and muscles. Norepinephrine constricts blood vessels of the viscera and skin, and shunts blood to the vessels dilated by epinephrine. In response to these hormones, the human body experiences physiological changes and enters the "fight or flight" mode (Cannon, W. B., 1929; Jansen et al., 1995; McCance, Forshee & Shelby., 2006; McEwen & Lasley, 2002). Measurable indicators of increased catecholamine levels include blood pressure, heart rate and respiratory rate and galvanic skin response (Hansen & Sawatzky., 2008). However, the physiological responses only are indirect indicators and are not conclusively diagnostic because they can be influenced by side effects of certain pharmaceuticals, pain or medical conditions. Although physiological responses are indirect indicators and it cannot predict stress levels per se, but it is suggested that there will be a relationship between physiological changes and stress levels (Cannon, W. B., 1929; Jansen et al., 1995; Hansen& Sawatzky., 2008; McCance, Dorshee & Shelby., 2006; McEwen & Lasley., 2002).

To date, there is no study on the effect of mindful breathing on the perceived level of distress together with the changes in the physiological responses among palliative cancer patients. Therefore, the present study aims to study the efficacy of 5-minutes of mindful breathing on the reduction of perceived level of distress among palliative cancer patients. At the same time, this study aims to study the changes of the physiological responses in palliative care cancer patients with 5-minutes of mindful breathing therapy.

## 10.2 Methodology

This randomised controlled study was conducted in the palliative care unit, University Malaya Medical Centre. The inclusion criteria are: (1) 18 years and above, (2) with the diagnosis of cancer of any types, (3) under palliative care, (4) the score of distress is more than 4 based on the measurement on the distress thermometer (5) able to understand and follow simple instruction and (6) consented. The exclusion criteria are: (1) those who are delirious or confused, (2) those with breathing difficulties/ respiratory distress and (3) unable to maintain concentration for at least 20 minutes (based on the subjective assessment of the researcher during the process of interview and explanation of the study). Patients from the palliative care unit were approached and screened for eligibility. Those who fulfilled the criteria were recruited into the study, and explanation about this study was offered to their family members and care-takers. Their socio-demographic background information was collected. The relevant clinical data (type of cancer, other comorbid medical condition and medications were obtained from the medical records)

Based on the previous literatures, we measured the physiological parameters that were correlated with psychological distress (Cannon, W. B., 1929; Jansen et al., 1995; Hansen& Sawatzky., 2008; McCance, Dorshee & Shelby., 2006; McEwen & Lasley., 2002). The following measurements were taken:

- 7. Perceived level of distress using Distress Thermometer
- 8. Skin Surface Temperature
- 9. Galvanic skin response
- 10. Blood Pressure
- 11. Pulse Rate

## 12. Breathing Rate

## **10.2.1 Distress Thermometer**

The Distress Thermometer is a validated rapid screening tool for psychological distress and has been endorsed by the NCCN Distress Management Guidelines panel. It serves as an initial single item question screen, which identifies distress from any sources. The word "distress" was chosen because it sounds "normal" and is less embarrassing to patients. It assesses how much distress patients are going through in the past week. The subjects were instructed to circle from a scale of 0 to 10 to indicate their distress level. "0" means no ditress and "10" means extremely distress<sup>22</sup> In the previous literature review, most studies showed that the score of 4 has the maximum sensitivity and specificity relative to established criterion (National Comprehensive Cancer Network, 2003).

# 10.2.2 Skin surface temperature measurement

Dr. Lowenstein's Stress Thermometer SC911 was used to measure the skin surface temperature. The stress thermometer SC911 is widely used in clinical research to identify stress levels and relaxation as well as to see how cognition and emotion impact the human body (Burnett, Solterbeck & Strapp., 2004; Forest et al., 2012; Prato & Yucha, 2013; Shah, L. B. I et al., 2015; Stephenson, Swanson, Jesse & Brown., 2013). A decrease in skin surface temperature indicates tension, during which individuals experience nervousness, worry or stress; while an increase in skin surface temperature indicates relaxation, during which individuals are in a peaceful emotional state. The Stress Thermometer (ST) displays the hand skin surface temperature ranging from - 58 F to 158 F. When individuals are extremely stressed, their skin temperature will drop to less than 79 F; while when individuals are very relaxed, their skin temperature will increase to more than 95 F.

## 10.2.3 Galvanic skin response measurement

Skin response, also known as galvanic skin response, skin conductance or electrodermal response, is a measurement method based on bio-electrical properties of the skin (Wong, G. H., 2013). The galvanic skin response was recorded by using Mindfield's eSense skin response biofeedback system. It has been used in previous clinical research (Gillan et al., 2014; Levita, L et al., 2014). The Mindfield's eSense skin response biofeedback system applies a very safe and small electrical voltage and sets up an electrical current in the skin. Activity of the sweat glands in the skin is measured by changes of the electrical current. When individuals are stressed, the activity of the perspiratory glands will increase and this is indicated by an increase in the skin conductance response. When individuals are calm, the skin conductance response will decrease, indicating low activity of perspiratory glands. The skin conductance was measured in microsiemens ( $\mu$ S).

# 10.2.4 Blood pressure and heart beat measurement

An OMRON Blood Pressure monitor was used to measure the blood pressure and heart rate. The monitor measures blood pressures between 0 - 299 mmHg, and a pulse rate between 40 - 180 beats/min. When individuals are stressed, the blood pressure and heart rate will increase in response to the activation of the sympathetic nervous system.

# **10.2.5 Procedure**

The perceived level of distress and physiological responses were measured at the beginning of the sessions (T1). The subjects were then randomly assigned to the intervention arm (5 minutes mindful breathing, MB) or the control arm (normal listening) for five minutes. The perceived level of distress and physiological responses

were reassessed after the completion of the first session (T2). After a short break (5 to 10min), the measurements were taken again (T3).

# 10.2.5.1 Normal Listening

In the normal listening group, the subjects were interviewed using a list of standard semi-structured questions as followed for five minutes:

- 1. Could you tell me about your illness?
- 2. Could you tell me about yourself?
- 3. What about your life?
- 4. What about your family and friends?
- 5. What are the things that are important to you?
- 6. Is there anything else that you would like to share with me?

# 10.2.5.2 Five Minutes of Mindful Breathing

In Mindfulness Based Therapy, the subjects are taught to increase their awareness through paying attention in a particular way, on purpose, in the present moment, and non-judgmentally, following the steps below:

4. Step 1 – Adopt a Physical Posture

A good physical posture helps to maintain a healthy mental posture. Eg: Sitting upright/ on a chair.

5. Step 2 – Establish a Mindfulness Anchor.

Tie the mind to the present moment. Eg: Pay awareness to the breathing.

6. Step 3 – Maintenance of Mindfulness

Maintain the focus to the present moment and regulate ruminations. Eg: Count the breathing. Do not force breathing.

The participants are instructed to relax their body, close their eyes and focus their attention on their breathing. If they notice any distractions, such as sounds, body sensations, thoughts or feelings, they are told to gently redirect their attention back to their breathing. They are told to focus their attention on their breathing for 5 minutes, and the palliative care physician will sit and practice the mindfulness breathing together with the participants during the sessions.

## **10.2.6 Statistical Analysis**

The within-subjects changes in level of distress and physiological responses (systolic blood pressure, diastolic blood pressure, pulse rate, breathing rate, skin surface temperature and Galvanic skin response) pre- and post- session were analysed using Wilcoxon Signed Ranks test. The between groups (MBT vs normal listening) differences in the changes of level of distress (T2 vs T1 and T3 vs T1) were compared using Mann Whitney test. All the tests were two tailed with significant level of 0.05. All the analyses were performed using SPSS version 12.

## 10.3 Results

# **10.3.1** Participants

60 patients were recruited for the study. All patients completed their participation in this study. Figure 1 provides an overview of the numbers of subjects screened, excluded, randomized and completed the study.

**Figure 10.1:** Disposition of patients in the randomized controlled trial between 5 minutes mindful breathing and normal listening for cancer patients under palliative care.



**10.3.2** Socio-demographic characteristics and cancer types

The average age of the patients is 47 years old. The majority of them were Chinese (60%) followed by Malay (23%) and Indian (15%). The commonest religion was Buddhist (40%) followed by Muslim (23%) and Christian (20%). There were slightly more female (51%) than male participants. Most of the patients were married (68%). The two commonest types of cancer were bone (18%) and breast (16%). The others

cancer types included lung, nasopharyngeal, liver, pancreatic, prostate, testicular, oesophageal and cervical cancer (Table 10.1).

 Table 10.1: Socio-demographic characteristics and types of cancer of the study subjects

(N	=60)
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Characteristics	
Age (years), mean (Terwijn et al.)	47.03 (16.46)
Gender, n (%)	
Male	29 (48.30)
Female	31 (51.70)
Ethnicity, n (%)	XU
Malay	14 (23.3)
Chinese	36 (60.0)
Indian	9 (15.0)
Others	1 (1.7)
Religion, n (%)	
Muslim	14 (23.3)
Buddhist	24 (40.0)
Christian	12 (20.0)
Hindu	8 (13.3)
Others	2 (3.3)
Marital status, n (%)	
Single	19 (31.7)
Married	41 (68.3)
Type of cancer, n (%)	
Breast	10 (16.7)
Bone	11 (18.3)
Lungs	6 (10.0)
Hepato-pancreatic	4 (6.6)
Esophageal	2 (3.3)
Nasopharyngeal	6 (10.0)
Prostate	3 (5.0)
Testicular	3 (5.0)
Brain	2 (3.3)
Cervical	1 (1.7)
Others	12 (20.0)

Table 10.2: Comparing the changes of the perceived distress and physiological responses between palliative cancer patients with five

	Intervention arm: Five minutes mindful breathing						Control arm: Normal listening			Five minutes mindful breathing vs normal listening		
	T1	T2	T3	T1-T2	T1-T3	T1'	T2'	Т3'	T1'-T2'	T1'-T3'	(T1-T2) vs	(T1-T3) vs
	(Terwijn et al.)	mean (Terwijn et (T al.)	(Terwijn et al.)	(p value)	(p value)	mean (Terwijn et al.)	(Terwijn et al.)	(Terwijn et (p value) al.)	(p value)	(p value)	(11 -12 ) ( <i>p</i> value)	(11 -13 ) ( <i>p</i> value)
Distress	6.29 (1.66)	4.71 (1.57)	4.71 (1.40)	< 0.01	< 0.01	6.00 (1.77)	5.79 (2.01)	5.76 (2.04)	0.06	0.05	< 0.01	< 0.01
Breathing Rate	19.90 (5.42)	18.90 (5.00)	19.39 (5.44)	< 0.01	< 0.01	20.34 (4.29)	20.31 (4.13)	20.45 (3.67)	0.92	0.34	< 0.01	< 0.01
Systolic pressure	126.71 (16.44)	120.10 (15.52)	124.48 (21.24)	< 0.01	0.06	127.66 (19.31)	128.07 (18.90)	130.38 (21.42)	0.96	0.27	< 0.01	< 0.01
Diastolic pressure	77.84 (11.91)	75.00 (9.32)	74.81 (10.74)	0.02	0.02	77.97 (16.03)	78.66 (14.23)	78.31 (15.01)	0.58	0.94	0.03	0.03
Pulse rate	91.00 (14.51)	86.97 (15.62)	87.87 (15.40)	< 0.01	0.06	89.76 (11.83)	91.72 (11.83)	89.66 (10.78)	0.07	0.72	< 0.01	0.09
Skin temperature	86.76 (6.00)	89.22 (5.18)	88.56 (4.91)	<0.01	<0.01	87.34 (5.31)	88.78 (6.00)	87.81 (5.57)	0.02	0.50	0.05	0.03
Skin response	0.96 (1.05)	0.75 (0.65)	0.73 (0.65)	< 0.01	< 0.01	0.93 (0.78)	0.95 (0.97)	0.97 (1.01)	0.33	0.81	0.13	<0.01

minutes mindful breathing (n=30) and normal listening (n=30)

Distress = psychological distress based on distress thermometer, breathing rate = breathing per minute, systolic and diastolic blood pressure in mmHg, pulse rate = pulse per minute, skin surface temperature in  $\mathcal{F}$  measured using Dr. Lowenstein's Stress Thermometer SC911, Galvanic skin response in microsiemens ( $\mu$ S) measured using Mindfield's eSense skin response biofeedback system, the within group changes (T1 vs T2 and T1 vs T3) were analyzed with Wilcoxon Signed Ranks test, the between group (five minutes mindful breathing vs normal listening) differences in changes were analyzed using Mann-Whitney Test. T1 = Time point before intervention, T2 = time point immediately after intervention, T3 = 10 minutes after intervention.

## 10.3.3.1 Perceived level of distress

There was significant reduction of perceived levels of distress post intervention at T2 and T3 for patients in the intervention group (p < 0.01). There were no changes in the levels of perceived distress before and after intervention for patients in the control group. As such, the reduction of perceived distress in the intervention group was significantly more than the control group (p < 0.01) (Table 10.2).

# **10.3.3.2** Breathing rate

The mean breathing rate of patients in the intervention group reduced from 20 breaths per minute at the baseline to 19 breaths per minute at T2 and T3. These changes were statistically significant (p<0.01). For the patients in the control group, there were no changes in the breathing rate. There was a significant difference in the comparison of the reduction of breathing rate between the two groups at T2 and T3 (p < 0.01) (Table 10.2).

# 10.3.3.3 Systolic blood pressure

The mean systolic blood pressure of patients in the control group reduced from 127mmHg at baseline to 120mmHg at T2 and 124mmHg at T3. The reduction of systolic blood pressure was statistically significant within the interventional group (p<0.01). There were no significant changes in the control group. The reduction in the mean systolic blood pressure in the mindful breathing group was significantly higher than the control group (p < 0.01). (Table 10.2).

## 10.3.3.4 Diastolic blood pressure

Similar to data from patients' mean systolic blood pressure, there was a reduction of

mean diastolic blood pressure of patients from the intervention group from 78mmHg at baseline to about 75mmHg at T2 and T3, which is statistically significant (p=0.02). There was no change in the control group. Overall, there was a significant difference between the intervention and control groups in the reduction of mean diastolic blood pressure (p<0.05) (Table 10.2).

## 10.3.3.5 Pulse rate

There was also significant reduction of pulse rate from an average of 91 beats per minute to 87 beats per minute at T2 (p<0.01) and 88 beats per minute at T3 (p=0.06) in the intervention group. The average pulse rates were about 88 to 89 in the control group. In the comparison between the two groups, the intervention group showed significant reduction of pulse rate (p<0.01) (Table 10.2).

# 10.3.3.6 Skin surface temperature

The skin temperature in the intervention group increased significantly from from 87 °F to 89 °F at T2 and T3 (p<0.01). Although, there was also significant increment in the skin temperature in the control group from T1 to T2 (p=0.02), but the changes diminished at T3 (p=0.05). The changes in the intervention group were significantly higher than the normal listening group at T2 (p=0.05) and T3 (p=0.03) (Table 10.2).

# 10.3.3.7 Galvanic skin response

The Galvanic skin response in the intervention group reduced from the average of  $0.9\mu$ S to  $0.75\mu$ S at T2 and  $0.73\mu$ S at T3. The changes were statistically significant (*p*<0.01). The Galvanic skin response was measured using the Mindfield's eSense skin response biofeedback system. There was no reduction in the Galvanic skin response in the control group. The reduction of Galvanic skin response in the treatment group was significantly different from the control group at T3 (*p*<0.01) (Table 10.2).

#### 10.4 Discussion

This is the first study to examine the efficacy of five minutes of mindful breathing on the rapid reduction of perceived distress among palliative cancer patients. The effect of five minutes of mindful breathing on physiological responses was also studied. Five minutes of mindful breathing showed favorable results where there was a significant reduction of distress among the study subjects. For the physiological parameters, there was a reduction in the mean breathing rate, blood pressure, pulse rate and Galvanic skin response in the patients who were randomized to the intervention arm with increases in the skin surface temperature.

The effectiveness of 5 minutes of mindful breathing in the reduction of perceived distress among palliative cancer patients is consistent with our previous pilot study. In our pilot study, 20 subjects who were either patients or care givers demonstrated a significant rapid reduction in distress levels with 5 minutes of mindful breathing therapy (Tan, S. B et al., 2015). There are a number of meta-analyses on the efficacy of mindfulness-based therapy or mindfulness-based stress reduction (MBSR) therapy in cancer patients. In the meta-analysis by Ledesma and Kumano, which included 10 randomized controlled trials and observational studies, showed that MBSR was helpful for the mental health of the cancer patients with a Cohen's effect size of 0.48 (Ledesma, D & Kumano, H., 2009). This finding was confirmed in another meta-analysis by Cramer et al (Cramer, H et al., 2012). A more recent meta-analysis by Zainal et al suggests that the efficacy of MBSR in cancer patients lasts for a year (Zainal, Buoth & Suppert., 2013). MBSR is a structured 8-week group program, with each session lasting about 2.5-hours (Kabat, Z. J., 1982). MBSR is different and much more intensive than 5 minutes mindful breathing. The application of MBSR in the palliative setting is challenging. As mentioned in our previous pilot, its application is limited by the

intention and determination of terminally ill patients to break the long-standing habitual reactions to distressing experiences. Secondly, palliative cancer patients have a limited attention span. Lastly, palliative patients are often too lethargic to participate in regular stress reduction sessions (Tan, S. B et al., 2015).

As a result, this five minute mindful breathing therapy was introduced to address the aforementioned challenges. This five minute mindful breathing therapy is an easy to administer therapeutic practice with rapid efficacy for terminally ill patients. From a variety of mini-mindfulness practices, mindful breathing was chosen for the study because it represents a core practice that serves to anchor the other mindful practices (Tan, S. B et al., 2012). The efficacy in rapid reduction of distress using five minutes mindful breathing in our previous pilot study (Tan, S. B et al., 2015) is replicated in this larger scale controlled trial. The rapid onset of effects of 5 minutes of mindful breathing could be explained by the fact that focused attention on breathing reduced the attention given to distressing experiences or thoughts (Tan, S. B et al., 2015). In the current study the result show that the reduction of distress lasted for 10 minutes after the therapy. In our pilot study, we have demonstrated that a subject's attention may return to focus on distress after the therapy has stopped. Therefore, after the initial guided practices, the patients are encouraged to have multiple sel-practiced sessions of five minute mindful breathing to produce a more sustained effect. The effects of this 5-minute mindful therapy were measured using both a subjective self-rated assessment scale and physiological parameters.

From a physiological aspect, the sympathetic nervous system is activated when a human is under stress. Levels of circulating catecholamines (eg. epinephrine, norepinephrine,) are then increased. Blood flow to the heart, brain and muscles is elevated but blood vessels in the viscera and skin are constricted. The physiological parameters as

indicators of increased catecholamine levels include blood pressure, heart rate and respiratory rate and galvanic skin response (Hansen & Swatzky, 2008). Our current results demonstrated that blood pressure, breathing rate, pulse rate and galvanic skin response reduced after five minutes of mindful breathing. It is consistent with studies that indicate a reduction of psychological distress leads to physiological changes, which include decrease cardiac output, blood pressure and pulse rate. In addition to these common physiological parameters, we also measured the skin surface temperature and skin response in this study. Changes in hand or foot temperature are a reflection of peripheral blood flow – a measure of the stress response. A decrease in skin surface temperature indicates tension, in which individuals are experiencing nervousness, worry or stress. Conversely, an increase in skin surface temperature indicates relaxation, in which individuals are in a peaceful emotional state. When individuals are stressed, their skin temperature will drop below 79 °F; while when individuals are relaxed, their skin temperature will increase to more than 95°F. Dr. Lowenstein's Stress Thermometer SC911 was used to measure skin surface temperatures in this study. The stress thermometer SC911 is widely used in clinical research (Burnett, Solterbeck & Strapp., 2004; Forest et al., 2012; Prato & Yucha, 2013; Stephenson, Swanson, Jesse & Brown., 2013) to identify stress levels and relaxation as well as see how cognition and emotion impact the human body. Skin response, also known as the galvanic skin response, is a measurement method based on bio-electrical properties of the skin. The present study used Mindfield's eSense skin response biofeedback system to record the galvanic skin response based on the activity of the perspiratory glands on the skin (Wong, G. H., 2013). When individuals are stressed, the activity of the perspiratory glands will increase and vice versa.

Physiological measurements are indirect and non-subjective indicators of psychological distress but can be influenced by many external factors such as the room temperature,

effects of drugs and medical conditions of the patients. In this study, the skin temperature increased after five minutes of mindful breathing, which was reflecting the constricting blood supply to the skin with lower perceived distress. However, skin temperature is the most sensitive physiological indicator toward the external factors. It is easily influenced by the environment and is easily changed according to the surrounding temperature. Overall, the current study demonstrated that there was rapid reduction of perceived distress after the five minute mindful breathing exercise in the palliative setting. The efficacy is indicated by the self-rating responses by the study subjects. The clinical efficacy is also demonstrated by the concurrent physiological changes.

There are several limitations in this study. The sample size of the current study was calculated based on the effect size of the reduction of distress in the previous pilot study. In a future study, a larger sample size is needed to illustrate the significant effect of five minutes of mindful breathing to the changes of physiological responses among the palliative cancer patients. Second, the current study aimed to examine the rapid and immediate effect of five minute mindful breathing. The sustainability of the effect was not examined. It requires a longer study period in the future. Furthermore, the presence of a staff member during the interventional sessions in the current study may have introduced "attention" as an intervening variable, which by itself has been shown to have significant effects on the psychological distress of the patients. This is especially dependent on the personality attributes of the staff member. In the future studies, the instruction of five minutes mindful breathing could be delivered in a practice session, before the actual testing sessions so that the effects would be more purely a measure of the technique itself rather than the staffs' impact. With limited funds, the current study was not able to afford to use the expensive instruments for the measurement of the physiological parameters. Future research could consider a better instrument to measure

the Galvanic skin responses such as Biopac MP36R with AcqKnowledge software. This instrument is specially designed for the use of psychological experiments and research. It has been used in previous clinical research (Gillan et al., 2014; Levita, L et al., 2014). Lastly, it is a single-centred study conducted in a university hospital setting. The application of the five minutes mindful breathing in palliative care should be study in other settings in the future.

# 10.5 Conclusion

At the end stage of life, palliative care cancer patients experience high level of distress. There is a need for a non-pharmacological or alternative therapy with rapid efficacy for the reduction of distress in this group of patients. Five minute mindful breathing therapy is a simple, quick and easy to practice therapeutic option. It produces a rapid reduction of perceived distress in terminally ill cancer patients. It also reduces the stress-related physiological responses in the patients. In view of the risk of recurrence of distress, it is advisable to have regular practice of five minute mindful breathing to achieve a sustainable reduction of perceived distress among the palliative cancer patients.

# **CHAPTER 11: SUMMARY**

### **11.1 Summary Overview**

This project started by looking into psychological distress associated with cancer, raising question as to whether depression or anxiety was more associated with distress as a predominant psychological state in cancer patients. Various psychotherapies available for cancer patients and their relevant efficacy to reduce such distress were examined. Other coping factors that could increase the quality of life of cancer patients, such as perceived social support, religious coping, and mindfulness practice were discussed as well. Finally, the 5-minute mindful breathing was proposed to address the limitations of common interventions and coping strategies among cancer patients.

To prove that psychological distress was more commonly present in patients with cancer than patients with other medical conditions, a study was done to compare the prescription rates of three common psychotropic drugs: anxiolytic/ hypnotic, antidepressant and antipsychotic between oncology and cardiology inpatients (**Chapter 3**). The results showed that prescription rates were indeed significantly higher in cancer patients than in cardiology patients, indicating their higher prevalence of distress.

Once cancer patients were found to have more psychological distress, this project was interested to investigate if depression or anxiety contributed more to the psychological distress in cancer patients. It was then the next step to compare the levels of depression and anxiety with level of psychological distress among cancer patients (**Chapter 4**). Interestingly, anxiety but not depression was found to be significantly associated with the psychological distress. Only anxiety reduction was positively related with distress reduction in cancer patients. It appeared that anxiety – a sense of stress arising from

uncertainty and confusion seemed to play a more significant role in the psychological state of distress among cancer patients.

Psychotherapy is generally conducted to relieve psychological distress, be it anxiety or depression. This thesis was curious about the potential types of psychotherapies that were useful in helping cancer patients cope with their psychological distress. Thus, all the published trials on psychotherapy available for cancer patients were critically and systematically reviewed using online database for this purpose (**Chapter 5**). Results indicated that most of these psychological interventions were able to improve quality of life and coping to certain extent. However, the number and quality of clinical trials for each type of psychotherapy were rather poor. The meta-analysis of four trials involved APT showed no significant changes in depression but only significant short-term improvement in anxiety.

With the advancement in clinical cancer treatment, there should also be an increased attention in improving the quality of life among cancer patients. Besides the conventional psychotherapies, other coping methods that can increase their quality of life were also examined and discussed. This project was particularly interested in perceived social support, where its association with quality of life, anxiety and depression levels was examined (**Chapter 6**). It was concluded that perceived social support played a crucial role in better quality of life with lower distress level. This finding also shed light on the need to maintain the social well-being of cancer patients as a way to improve their overall quality of life.

Religious coping was another self-initiated coping strategy that was looked into where the association between religiosity and religious coping with anxiety and depression among cancer patients was examined (**Chapter 7**). As predicted, higher religiosity and more positive religious coping were able to reduce distress. Such coping was encouraged when dealing with cancer as an additional support. This result provided an opportunity for cancer patients in Malaysia to turn to many available religions in the country which are rich in diversities when fighting against cancer.

Next, the attention of this thesis project shifted to other alternatives that may help cancer patients cope with their illness condition by keeping distress at a low level. Many forms of mindfulness-based interventions were mentioned. From there, the theory of mindfulness-based interventions was simplified into a 5-minute mindful breathing technique that can be learnt and practiced by palliative care patients (**Chapter 8**). The preliminary evidences from the pilot study showed that the technique was effective to rapidly reduce distress when being performed by cancer patients. This exercise was highly recommended as a useful psychological intervention for reducing acute distress in cancer patients.

With the success from the pilot study in chapter 7, the efficacy of the 5-minute mindful breathing in distress reduction then required more robust support, particularly with physiological evidences. Prior to that, it was important to establish the relationship between certain physiological changes with distress as proposed by the "fight-or-flight" mechanism, justifying the research objective of **Chapter 9**. Many physiological parameters such as systolic blood pressure, pulse rate and breathing rate were indeed related to distress and could be used as proxy indicators to monitor distress level of cancer patients in the future studies.

In the final study of this project series, the efficacy of the 5-minute mindful breathing for rapid distress reduction in cancer patients was studied again in a randomized controlled trial, with the introduction of physiological changes as the dependent variables other than the usual subjective report of distress score (**Chapter 10**). A significant reduction of perceived distress and physiological changes associated with distress reduction were found. So the 5-minute mindful breathing was concluded to be effective in rapidly reducing distress among cancer patients, though there was a need for future study to establish the long-term efficacy of this therapy.

# 11.2 Primary Conclusion

Mindfulness-based intervention was successfully simplified by this study into a simple, free, quick and easy-to-administer 5-minute mindful breathing exercise that can rapidly reduce distress in palliative care patients. The efficacy of this 5-minute mindful breathing in distress reduction was also confirmed.

## **11.3 Secondary Conclusions**

**Chapter 1:** While mindfulness-based interventions were found to be effective and beneficial, their delivery and application in palliative care setting posed some limitations. Thus, there was a need to devise such interventions into a more practical and effective method, for example a 5-minute mindful breathing technique that can rapidly reduce distress among cancer patients.

Chapter 2: Literature review related to the current study and recent publications.

**Chapter 3:** The prescription rates of three common psychotropic drugs: anxiolytic/ hypnotic, antidepressant and antipsychotic were found to be more common in cancer patients than in cardiology patients. Thus, psychological distress was more common in cancer patients.

**Chapter 4:** Distress reduction was positively correlated with anxiety reduction but not depression. Anxiety was hence a more significant psychological state that contributed to perception of distress in breast cancer patients as compared to depression.

**Chapter 5:** There was a reduction in distress, anxiety and depression after a psychological intervention. However, the number and quality of clinical trials for each type of psychotherapy were poor. The evidence on the efficacy of psychotherapy in cancer patients was unsatisfactory. There was a need for more rigorous and well-designed clinical trials to gain better support the efficacy of psychotherapy in cancer patients.

**Chapter 6:** Malaysian breast cancer women had relatively better quality of life with level of anxiety and depression lower than previous studies. Perceived social support was an important factor for better quality of life and lower level of psychological distress. Activities that enhanced and maintained the social support system for breast cancer patients were important.

**Chapter 7:** Subjects with higher anxiety or depression used more negative religious coping and had lower non-organization religiosity. Higher religiosity and more positive religious coping were thus linked to lower anxiety and depression among cancer patients.

**Chapter 8:** The 5-minute mindful breathing was successfully developed from mindfulness-based interventions and its efficacy in distress reduction was found to be positive. It was a useful psychological intervention for reducing psychological distress in palliative care patients.

**Chapter 9:** Apart from diastolic blood pressure and galvanic skin response, other physiological indicators were found to share relationship with changes of distress level. These physiological parameters could be used as proxy indicators in the monitoring of distress in palliative cancer patients.

**Chapter 10:** A significant reduction of perceived distress and physiological changes associated with distress reduction were found in subjects that practiced 5-minute mindful breathing. The efficacy of the newly developed 5-minute mindful breathing technique on distress reduction was confirmed in this randomized controlled study.

## 11.4 Strengths

Many researches included in this project were the first studies to ever examine the relationships between variables of interest using Malaysian sample of cancer patients. For example, most studies on the psychotropic prescriptions in cancer patient were done in the Western countries, the Asian counterparts especially Malaysia has been lacking such literatures on the topic (Ng et al., 2014). This study took the initiative to examine this aspect and confirmed the notion that cancer patients were indeed more prone to psychological distress. It also raised awareness about the need to address the psychological comorbidity of cancer such as anxiety and depression (Ng et al., 2014).

While both depression and anxiety have remarkably negative impact on cancer patients' quality of life (Hutter et al., 2013), there was a lack of conclusive findings as to whether anxiety or depression was more significantly related to distress level as a psychological symptom. Chapter 3 of this thesis was the first study in Malaysia to ever look into this question using female breast cancer sample. Furthermore, there was also no prospective literature examining the changes in quality of life and its relationship with depression, anxiety and perceived social support among these cancer patients in Malaysia prior to this thesis research. Same goes to chapter 6 of the present study which found the beneficial effects of religiosity and religious coping in Malaysian cancer patients (Nurasikin et al., 2012).

There were also limited literature looking into the relationship between physiological responses and perceived level of distress among palliative cancer patients (Dawe et al.,

2014) until this study, which established a correlation in accordance with the "fight-orflight" theory. Consequently, many physiological parameters can be used as proxy indicators in the monitoring of distress in palliative cancer patients. All put together, this series of thesis studies have taken the first imitative of attempting to achieve their respective research goals using local Malaysian sample. All the findings are valuable for providing more insight about the Asian counterparts which are usually overlooked. The significant results can also set as a stepping stone and encourage even more similar research to develop in order to strengthen the proposed theory among Asian subjects.

On top of that, there was also a lack of meta-analyses on different types of psychotherapies for cancer patients including their efficacy. Given the previous literature review was a decade ago (Newell et al., 2002) and no quantitative analysis on this topic, this study managed to fill in those gaps by critically and systematically reviewing all published trials on psychotherapy in cancer patients. This study highlighted the crucial need for future work to determine any specific type of psychotherapy with positive result for cancer patients. Besides, the study also assessed the quality of the previous studies using Quality Assessment Tool for Quantitative Studies Scale, which was developed by Effective Public Health Practice Project to assess the quality of quantitative studies for interpretation of meta-analysis results (Thomas et al., 2004). The review protocol and extraction forms were also in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The proper uses of this system make the findings more valid and convincing.

The appropriate nature of study employed across different research in this thesis work is also a strength. The longitudinal study across 12-month period was able to show the changing patterns of anxiety and depression over time in the course of coping with cancer. The same longitudinal nature was also able to identify how depression, anxiety, together with perceived social support and quality of life changed since the diagnosis of cancer. These changes provided valuable information on the psychological development of a cancer patient so that interventions can be devised to address the related needs. These longitudinal studies can also help establish the causal relationship between the variables measured. On the other hand, due to the nature of randomized controlled trial, the causal effect of the 5-minute breathing in stress reduction was established – performing the technique did instantly make the cancer patients feel less distressed. Randomly assigning cancer patients to the treatment and control groups without their knowledge also minimized the allocation bias and confounding of unknown variables.

On looking for other non-pharmacological or psychological interventions that can help cancer patients cope with distress, this thesis posed a strength that it managed to identify the beneficial effects of perceived social support, religiosity and religious coping. These factors associated with distress reduction are readily available, totally free, and applicable to anyone regardless of gender, race, religion, financial or socio-economical status, educational background and so on. For example, Malaysia is a country filled with racial, cultural and religious diversities. The many religions available may be used as a natural source to cope with distress related to cancer. This study stands out in terms of its practicability for pinpointing those convenient, efficient and effective distress coping methods among cancer patients.

One of the greatest strengths of this thesis research is that it managed to develop the 5minute mindful breathing which can be an effective psychological intervention to rapidly reduce distress in cancer patients. It achieved the goals to be easy and quick to administer and to learn, with rapid efficacy and no cost incurred. It also addressed conditions such as poor physi
cal fitness, limited life expectancy, inadequate attention or mental alertness and fluctuation of consciousness that were commonly associated with caner that also impaired the effectiveness of conventional psychotherapy.

Apart from the typical measurement of psychological distress through self-report questionnaires, this project successfully introduced some physiological parameters to objectively quantify distress other than the subjective verbal report using Distress Thermometer. Such objective measurement of psychological distress can decrease the susceptibility to response biases like socially desirable answers. On the other hand, somatic symptoms caused by cancer and its treatment would be falsely captured if selfrated questionnaires such as Beck Depression Inventory were to be used. The findings set a stepping stone for future research to support the efficacy of 5-minute mindful breathing by the objective physiological changes, rather than just the conventional selfreport method. With the support of from both objective and subjective measurement of psychological distress, the efficacy of the 5-minute mindful breathing technique can be confirmed with better validity.

## 11.5 Limitations

This thesis has some areas of improvement as well. While studying the relationships between variables of interest with psychological distress, other coping factors that could help reduce psychological distress, together with clinical variables such as type or stage of cancer and presence of physical comorbidity which were likely to affect patients' distress level were not taken into consideration. All these nuisance variables may confound the results and reduce the validity of the genuine relationships found between variables studied. The psychological distress scale used in this study may also be too parsimonious, generic and less valid with only a single self-report item. Many cancerspecific distresses may be overlooked and a lot of valuable information may have been missed. Future studies may attempt to examine and improve these gaps for a better reliability and validity.

The second potential limitation in this thesis research is the generalizability issue. Recruiting only from a single hospital setting, the subjects were homogenous and prone to sampling bias, reducing the generalizability of the findings as the study subjects may not be representative of the whole cancer population in the country. This particular limitation was further exacerbated by the fact that only one type of cancer (breast cancer) was studied in most of studies except the research in chapter 6 which examined three common types of cancer, namely breast, gastrointestinal and haematological cancer.

Another possible shortcoming that may render the findings less generalizable is the disproportionate gender, racial and religious ratios across many studies in this thesis. Since there are gender differences in depression where women are twice more prone to depression than men (Piccinelli & Wilkinson, 2000), the total absence of male patients in most of the studies (i.e., female breast cancer patients only) could not discount the effect of gender and make the findings less generalizable to cancer patients of both sexes. The ratio of the ethnicities and religions were also not proportionate in research of chapter 6 for example where more than half of the sample was of Malay ethnicity and Muslim faith, creating a potential bias in sampling. Future research may improve this generalization issue by recruiting patients from different sittings or regions of the country and of various cancer types with more proportionate gender and racial ratios.

Timeline wise, although 12 months of longitudinal study was decent to conclude the findings, the relationship between distress with various factors such as anxiety and depression could be studied for an even longer period to examine the possible changes of psychological distress as potential relapse. The observational period of a year may still be insufficient to demonstrate the changes of psychological distress in cancer

patients. Thus the long term impact of cancer on psychological well-being can be taken into consideration by extending the study period, to see the effect of different cancer stages on psychological well-being for example. The retrospect research in chapter 2 restricted to only five years of the study period would also mean that patients out of this study period were neglected, underestimating the sample data obtained.

The present study managed to prove the instant effect of 5-minute mindful breathing on distress reduction. However, its sustainability was not examined and should be given attention in the future research. This was particularly true when the same study provided preliminary insight where distress reduction appeared to be lesser as time passed. It may require a longitudinal study to look into its possible long term impact in reducing stress. Besides, the presence of a palliative physician as a facilitator in the treatment group may also present itself as a nuisance variable which may have interacted with the genuine effect of mindful breathing.

It was suggested that future studies may also opt to use a more advanced and more sensitively devised tools for the measurement of the physiological indicators like Biopac MP36R with AcqKnowledge software which is specially designed to measure galvanic skin reactions for clinical research purpose. However, despite the advantage of objective physiological measurement of psychological distress, the patients might be susceptible to observer effects that will influence the readings of the physiological parameter as they were being closely monitored. In addition, physiological responses measured can be influenced by medication, physical pain or other biological factors which were all not taken into account by this study. In the future studies, all these confounding variables must be ruled out before the administration of the physiological measurement for a more valid quantification of psychological distress.

## 11.6 Implications

This study showed that psychological distress is a common comorbid of cancer that should not be overlooked as it can have detrimental impact on the life and treatment outcome of cancer patients (American Cancer Society, 2016). This study particularly showed that the cancer patients studied had significant anxiety level. Due to the traditional biomedical approach in the medical field, specific clinical treatments targeting cancer such as chemotherapy and pharmacology have always been the primary focus, while the psychological distress associated with cancer like anxiety and depression are treated as a less important issue. However this study managed to indicate that in order to have the best treatment outcomes of cancer, any related psychological comorbid should be addressed as well, hence pushing for a paradigm shift from biomedical to biopsychosocial view in cancer treatment.

The biological aspect of this biopsychosocial model would be the traditional pharmacological treatment of cancer as mentioned. It aims to eliminate or reduce the spreading of cancer cells to promote a better physical health. Psychologically, cancer patients' potential anxiety and depression stemming from cancer diagnosis should be given attention. Psychiatrists, clinical psychologists or counsellors can be assigned to look into the mental health of cancer patients to improve their overall functioning. For example, these professionals can help alleviate their anxiety and depression levels, monitor or improve their treatment compliance, devise a holistic plan that includes exercise routine and activities to release stress. The objective is to foresee and eradicate or at least minimize any potential non-pharmacological risk factors that can interfere with treatment outcome of cancer.

Social wise, there is a need to enhance the coping strategies of cancer patients as a way to improve their quality of life and reduce psychological distress. This study managed to identify a few aspects related to this domain of the biopsychosocial model, namely perceived social support, religiosity or religious coping. Cancer patients are encouraged to maintain a stable supportive social network which they can derive support from and confide in whenever they are in distress. The social network can consist of family members, friends, cancer support group or those from religious institution. It is also important to improve the caregiver system for cancer patients. Caregiver support group, educational program, and other activities that enhance the social support system are likely to benefit the caregivers and indirectly increase the quality of life among cancer patients.

Another aspect of social well-being is related to religiosity and religious coping. Turning to religion for help by attending religious meetings or activities can be a form of healthy social support to gain more strength and determination in facing cancer. With high level of intrinsic faith and more practices of religious activities, depression and anxiety levels among the cancer patients can be minimized. While Malaysia is a multicultural country with many established religions available, cancer patients are encouraged to derive extra strength from these natural sources around them.

Given the holistic view of the biopsychosocial model, a multidisciplinary approach is greatly needed in the treatment of cancer. Any risk factors that can impede the various aspects of functioning in cancer patients should be pinpointed and addressed quickly by different professional teams. Mental health professionals like psychiatrist and clinical psychologists can work hand-in-hand with oncologists or physicians to address the psychological condition of cancer. Oncologists and nurses should be alert to any distress symptoms among cancer patients and notify the mental health team as soon as possible should the need arise. The psychosocial care should also be part of the routine cancer care. Perhaps there can be a team of social workers who help cancer patients to increase their social support system in and out of palliative care setting. They may also have ready information pertaining to different religious institutions that cancer patients may be interested to be involved in. Furthermore, they may also organize regular cancer support group meetings for the patients to mutually encourage and support each other.

More importantly, the present study managed to develop and prove the efficacy of the 5-minite mindful breathing as a brief, quick and easy to administer psychological intervention that rapidly reduces distress in palliative care patients. The 5-minute mindful breathing can instantly reduce attention on distress when being performed (Ng et al., 2016). Its rapid onset of therapeutic action is of major benefit in clinical practice, particularly in terminally ill patients with fluctuating health conditions. However, patients are likely to shift their attention back to distressing experiences after completing the breathing exercise. They are thus advised to practice the 5-minute mindful breathing frequently so that they can constantly keep their distress at a much lower level for a more sustained effect. Repetitive practices may be required for those who have much higher distress, inattention, and tendency to ruminate about a stressor in order to bring out the beneficial effect.

## 11.7 Future Research

The 5-minute mindful breathing is an easy and flexible intervention with no restriction in the number of sessions. It can be learned by anyone, anywhere and anytime. It can also be incorporated into other mainstream psychotherapy interventions, such as cognitive behavioral therapy. In conclusion, the practice of 5-minute mindful breathing is a simple, easy to administer and effective psychological intervention for distress reduction in palliative care patients. However, there are some relevant gaps and questions that future research may attempt to answer in order to further improve the effectiveness of this newly developed technique. While the results from this study provided preliminary evidence that 5-minute mindful breathing can reduce distress rapidly in cancer patients, an even larger scale research in the future may be needed to further substantiate the robustness of this notion. Also, the sustainability of the distress reducing effect was not examined and still remains unclear. A future study may employ a longitudinal study (e.g., 6 months) to look into its possible long term impact in distress reduction. Patients tend to revert their attention back to distressing thoughts after a short period of mindfulness, reducing the positive effect of this 5-minute mindful breathing as time passes by. There are questions as to the frequency and interval needed to achieve a sustained positive effect. Perhaps, aside from the instant effect in reducing distress when it is being performed, practicing this exercise for a long period may also gradually dissociate cancer patients from the habitual pattern of distress. Long term practice of this 5-minute breathing may break them from the old habits of ruminating and worrying, which can in return more strongly and stably reduce distress.

Furthermore, future research can also recruit cancer patients and derive data from multiple medical centers instead of just one as done in this project which potentially limits the generalizability of the findings. All the research data in the present study was obtained from University Malaya Medical Centre (UMMC) in Kuala Lumpur, the capital of Malaysia and probably the most developed region in the whole country. The cancer patients studied may hence represent a specific type of population with better socio-demographic or socio-economic status. It is interesting to also investigate the effect of 5-minute mindful breathing among patients from other states like Kedah, Kelantan and East Malaysia, as their general functioning may be more impaired given the various constraints in real life compared to their counterparts in urban areas.

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- 2. Ng Chong Guan, Salina Mohamed, See Mee Hoong, Faizah Harun, Ahmad Hatim Sulaiman, Nor Zuraida Zainal, Nur Aishah Taib, on behalf of the MyBCC Study group. Anxiety, depression, perceived social support and quality of life in Malaysian breast cancer patients: a 1-year prospective study. *Health and Quality* of Life Outcomes (2015) 13:2015.
- Ng Chong Guan, Salina Mohamed, Nor Zuraida Zainal, Ahmad Hatim Sulaiman. Anxiety and Depression in Cancer Patients: The Association with Religiosity and Religious Coping. *Journal of Religion and Health*, 2016. Online First
- 4. Ng Chong Guan, Lai Kiah Tian, Tan Seng Beng, Ahmad Hatim Sulaiman, Nor Zuraida Zainal. Perception of Distress and Physiological Responses in Palliative Care Cancer Patients: A Randomized Controlled Study. *Journal of Palliative Medicine*, 2016. Online First.
- 5 Ng Chong Guan, Salina Mohamed, Lai Kiah Tian, Teoh Kar Mun, Ahmad Hatim Sulaiman, Nor Zuraida Zainal. Psychotherapy for cancer patients: A systematic review and meta-analysis. *International Journal of Psychiatry in Medicine*, 2016 51(5), 414-430.
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group. Perceived distress and its association with depression and anxiety in breast cancer patients. *PLoS One* (Accepted).

## **MANUSCRIPTS UNDER REVIEW:**

- Ng Chong Guan, Tan Seng Beng, Lai Kian Tiah, Nor Zuraida Zainal, Ahmad Hatim Sulaiman, Chong Joo Chien. Report On the Development of a Brief Psychological Intervention for Reduction of Distress in Palliative Care: 5-Minute Mindful Breathing. Submitted to *Psychological Reports*.
- Ng Chong Guan, Lai Kiah Tian, Lim Ping Ping, Tan Seng Beng, Ahmad Hatim Sulaiman, Jesjeet Singh Gill, Nor Zuraida Zainal. The Correlation between Perceived Level of Distress and Physiological Parameters in Palliative Cancer Patients. Submitted to *BMJ Supportive and Palliative Care*.

## **CONFERENCE PRESENTATIONS**

 Poster presenter, 24<sup>th</sup> European Congress of Psychiatry, Madrid, Spain, 12-15 March, 2016.

Title: Anxiety, depression, perceived social support and quality of life in Malaysian breast cancer patients: a 1-year prospective study

 Poster presenter, 29<sup>th</sup> European College of Neuropsychopharmacology, Vienna, Austria, 17 – 20 September, 2016.

Title: The Correlation between Perceived Level of Distress and Physiological Parameters in Palliative Cancer Patients

 Poster Presentation, 25<sup>th</sup> European Congress of Psychiatry, Florence, Italy, 1 – 4 April, 2017.

Title: The Development of a Brief 5-Minute Mindful Breathing Therapy for The Reduction of Distress in Palliative Cancer Patients

- 4. Invited Speaker, Psycho-Oncology Course, 28 29 September 2015, Hotel Concord Inn, Organized by Hospital Putrajaya and Hospital Selayang.
  Title: Psychiatric Presentation in Cancer Patient: Depression
- Invited Speaker, CNS Summit Malaysia, 18 October 2015, Kuala Lumpur, Malaysia.

Title: Depression in Cancer Patients: Recognition and Treatment

 Invited Speaker, Annual Scientific Meeting, 10 – 12 April 2015, Kuala Lumpur, Malaysia. Organized by the College of Physician, Academy of Medicine of

## Malaysia.

Title: Dealing with Psychological Symptoms

- Invited Speaker, 1<sup>st</sup> University Malaya Medical Centre Breast Cancer Public Forum, 18 October, 2014, Kuala Lumpur, Malaysia. Title: Coping with Cancer
- Invited Speaker, 18<sup>th</sup> Malaysian Conference in Psychological Medicine, 22 24 May 2014, Kuala Lumpur, Malaysia.

Title: Depression in Cancer Patients