University of Iceland
Faculty of Nursing

Symptoms and Quality of Life: A Cross-Sectional, Descriptive, Correlation Study, Evaluating the Relationship between Symptoms and Quality of Life in Patients on Opioids with Advanced Cancer

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Thesis submitted for a Master of Science degree in Nursing (60 credits/ECTS)

Advisor: Sigríður Gunnarsdóttir, PhD

October 2008

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The research was supported by a research grant from the Icelandic Research Fund for Graduate Students

Publisher: University of Iceland, Faculty of Nursing

Printed in Iceland by Háskólafjölritun, Reykjavík, 2008

Útdráttur

Bakgrunnur: Sjúklingar með krabbamein finna fyrir mörgum einkennum sem hafa áhrif á lífsgæði þeirra. Krabbameinstengd einkenni orsakast ýmist af sjúkdómnum sjálfum eða meðferð hans, en þættir eins og aldur, kyn og aðrir sjúkdómar geta einnig haft áhrif á einkennamyndina. Einkenna-lífsgæðamódelið sýnir tengslin milli einkenna og lífsgæða hjá sjúklingum með krabbamein.

Tilgangur verkefnis: Að skoða hugtakið lífsgæði og einkennamynd krabbameinssjúklinga, að setja fram módel til að lýsa tengslunum milli einkenna og lífsgæða og að prófa ákveðna þætti módelsins.

Þátttakendur: 150 krabbameinssjúklingar á ópíoíðum. Karlar voru 62 talsins (41%) en konur 88 (59%). Allir þátttakendur voru hvítir. Aldur þátttakenda var á bilinu 20-92 ár en meðalaldur (SF) var 64,7 (12,7) ár.

Rannsóknarnið: Lýsandi, þversniðs, fylgnirannsóknarsnið.

Niðurstöður: Meðalfjöldi (SF) einkenna síðasta sólarhringinn var 6,2 (2,5) en 9,0 (3,3) síðastliðna viku. Algengustu einkenni voru þreyta, verkir og slappleiki. Meðalstyrkur (SF) einkenna var 0,7 (0,4) síðasta sólarhringinn en 0,9 (0,5) síðastliðna viku á skalanum 0-3. Fjöldi einkenna, styrkur þeirra og heilsu/lífsgæðaskor var ekki tengt kyni eða tilvist annarra sjúkdóma. Fjöldi einkenna og styrkur einkenna minnkaði hins vegar með hækkandi aldri þótt heilsu/lífsgæðaskor væri óháð aldri. Fjöldi einkenna skýrði 25,8% af dreifingunni í heilsu/lífsgæðum þegar leiðrétt hafði verið fyrir aldri og kyni. Annað aðhvarfsgreiningarmódel, einnig leiðrétt fyrir aldri og kyni, sýndi að verkir, þreyta, svefnleysi og depurð skýrðu 33,6% af drefingunni í heilsu/lífsgæðum.

Ályktanir: Einkennamynd íslenskra krabbameinssjúklinga á ópíoíðum svipar til krabbameinssjúklinga í öðrum löndum. Fjöldi einkenna sem og verkir, og einkum þreyta, eru tengd skertum lífsgæðum. Á óvart kom að svefnleysi og depurð höfðu ekki marktæk áhrif í aðhvarfsgreiningarmódeli. Niðurstöðurnar benda til þess að hægt sé að stuðla að bættum lífsgæðum krabbameinssjúklinga með því að meta og meðhöndla krabbameinstengd einkenni.
Lykilorð: einkenni, lífsgæði, krabbamein.

Abstract

Background: Cancer patients experience multiple symptoms that affect their quality of life (QOL). Cancer related symptoms may be caused by the disease itself or its treatment, but factors like age, gender, and concurrent diseases may also influence the symptomatology. The symptoms-quality of life model shows the relationship between symptoms and QOL in cancer patients.

Goal of project: To review the literature on quality of life and symptomatology among cancer patients, to pull together a model that explains the relationship between symptoms and quality of life and to test selected aspects of the model.

Participants: 150 cancer patients on opioids, 62 (41%) men and 88 (59%) women, all Caucasians. The patients ranged in age from 20-92 years with a mean (SD) age of 64,7 (12,7) years.

Research design: Descriptive, cross-sectional, and correlational.

Results: The mean (SD) number of symptoms in the past 24 hours was 6,2 (2,5), and 9,0 (3,3) in the past week. The most common symptoms were fatigue, pain, and weakness. Mean (SD) symptom severity was 0,7 (0,4) in

the past 24 hours and 0,9 (0,5) in the past week on a scale from 0-3. Gender and concurrent diseases were not related to number of symptoms, symptom severity or QOL, but increased age was associated with fewer symptoms and less symptom severity although age difference was not found for global health/QOL score. Adjusted for age and gender, number of symptoms explained 25,8% of the variance in global health/QOL. Also adjusting for age and gender, pain, fatigue, insomnia, and depression explained 33,6% of the variance in global health/QOL.

Conclusions: The symptomatology of Icelandic cancer patients is similar to cancer patients in other countries. Number of symptoms and the individual symptoms of pain and notably fatigue are associated with diminished QOL. Surprisingly insomnia and depression did not add significantly to the regression model. These results indicate that QOL of cancer patients may be improved by assessing and treating cancer related symptoms.

Key words: symptoms, quality of life, cancer.

Thanks

I owe my gratitude to many people who have helped me during the time I was working on this thesis. First and foremost I would like to express my deepest appreciation to my advisor, Sigríður Gunnarsdóttir, for her supporting guidance, endless patience, and encouragement during the past year. I would also like to express my thanks to the other members of my master's committee, Valgerður Sigurðardóttir and Nanna Friðriksdóttir, for their constructive supervision and support during this time. I also owe my sincere gratitude to Guðbjörg Guðlaugsdóttir for her impressive work during the data collection and prompt answers to my queries. Thor Aspelund receives my thanks for the statistical advice. To my friend, Katrín Brynjarsdóttir, I owe my thanks for her help with going over the tables, numbers and references in the thesis, what patience! My sister, Guðný Zoëga, receives a big kiss for reviewing the text. My sister Bryndís Zoëga also deserves a kiss for solving the "caption problems". I thank Margrét Gunnarsdóttir, librarian, for useful advice regarding how to cite various "atypical" references. To my boss, Hrafnhildur Baldursdóttir, I owe my thanks for being so flexible concerning my working hours, and I thank Lilja Stefánsdóttir for her encouragement. My heartfelt thanks to my family, friends, and coworkers, who have been most patient and supporting during the past year, even at times when I was a total nuisance! Finally, I would like to express my thanks to my boyfriend, Sigurður Eyþórsson, for his everlasting support and assistance in every way. And to all whom I forgot to mention here: Big thanks!

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Introduction

Each year approximately 1200 individuals are diagnosed with cancer in Iceland and the incidence rate is growing (Krabbameinsskrá Krabbameinsfélags Íslands, 2008b). The annual number of cancer cases from 1993-1997 to 2018-2022 is predicted to increase by 400 (82%) in men and by 286 (62%) in women, mostly due to change in population age structure and size, but to a lesser extent because of the change in risk. Today the Icelandic population is the youngest among the Nordic countries but forecast of population growth suggests that between the years 2002 and 2018-2022 the population will have increased by 18%, mostly because of greater number of elderly citizens (Moller et al., 2002). The prognosis of cancer patients, however, has been improving in the past decades with five year relative survival increasing and mortality rates declining (Jónasson & Tryggvadóttir, 2004; Krabbameinsskrá Krabbameinsfélags Íslands, 2008a; Verdecchia et al., 2007).

The concept of quality of life is widely used in health care practice, especially in the context of cancer and cancer treatment. Quality of life is a multidimensional, subjective, dynamic and yet a quantifiable construct (Niv & Kreitler, 2001) but despite being a central concept, no universal definition of quality of life exists (Jocham, Dassen, Widdershoven, & Halfens, 2006; Kaasa & Loge, 2003; King & Hinds, 1998). Understanding the concept, however, is of importance since one of the three main goals of cancer treatment and cancer nursing is to improve quality of life (King et al., 1997; Penson, Wenzel, Vergote, & Cella, 2006).

A symptom is a subjective phenomenon that patients perceive as an indicator of a change in health status (Rhodes & Watson, 1987). Research has shown that cancer patients experience a number of unpleasant symptoms related to the disease itself or its treatment (Cleeland et al., 2003; Mercadante, Casuccio, & Fulfaro, 2000). According to studies the median number of symptoms per patient is often between eight and eleven (Chang, Hwang, Feuerman, & Kasimis, 2000; Homsi et al., 2006; Peters & Sellick, 2006; Portenoy et al., 1994; Sigurdardottir, Hjaltadottir, Gudmannsdottir, & Jonsson, 2006; Tsai, Wu, Chiu, Hu, & Chen, 2006; Walsh, Donnelly, & Rybicki, 2000) with the most common symptoms being pain, fatigue, lack of energy, weakness and appetite loss (Teunissen et al., 2007). Symptom severity in patients with advanced cancer tends in most cases to be mild or moderate, although comparison between studies is difficult because of different scales and measurement tools (Hoekstra, de Vos, van Duijn, Schade, & Bindels, 2006; Peters & Sellick, 2006; Tsai et al., 2006). A considerable proportion (12-40%) of patients, nevertheless, experience rather severe or very severe symptoms in particular for the symptoms of pain and fatigue (Chang et al., 2000; Modonesi et al., 2005).

Symptoms infrequently appear in isolation (Chang et al., 2000) and a correlation seems to exist between many of the symptoms experienced by cancer patients (Chen & Tseng, 2006). This is not least true for the symptoms of pain, depression and fatigue (Chen & Chang, 2004; Cleeland et al., 2000; Portenoy et al., 1994). This correlation of symptoms has given rise to the concept of symptom clusters but the existence of such clusters may suggest that symptoms in cancer are caused by a shared underlying pathophysiology (Cleeland et al., 2003).

Research has shown that the quality of life of cancer patients is usually worse than that of the general public (Coates, Porzsolt, & Osoba, 1997; Klepstad, Borchgrevink, & Kaasa, 2000; Michelson, Bolund, & Brandberg, 2000) and the suffering of people with advanced cancer is largely determined by the presence of unpleasant symptoms related to their disease (Teunissen et al., 2007). Factors affecting quality of life in this group of patients are recurrent cancer (Bjordal et al., 2000), advanced disease (Hwang, Chang, Fairclough, Cogswell, & Kasimis, 2003) and side effects from cancer treatment (Brans et al., 2002) all factors known to cause symptoms (Cleeland et al., 2003; Lee et al., 2004; Mercadante et al., 2000). Among the specific symptoms shown to negatively affect quality of life are pain, depression, fatigue and insomnia (Ferrell, 1995; Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007; Lis, Gupta, & Grutsch, 2008; Peters & Sellick, 2006; Rustøen, Moum, Padilla, Paul, & Miaskowski, 2005), but research has also shown that the number of symptoms patients experience are important with increasing number of symptoms having greater effect on a patients' quality of life (Chang et al., 2000; Portenoy et al., 1994).

In light of this it is important to look at symptoms experienced by cancer patients in order to alleviate their suffering and hence improve their quality of life (Walsh et al., 2000). The purpose of this master thesis is threefold:

1. To review the literature on quality of life and symptomatology among cancer patients.
2. To pull together a model that explains the relationship between symptoms and quality of life.

3. To test selected aspects of the model with a secondary analysis of data derived from a study of 150 cancer patients on opioids.

The value of the study lies mainly in the fact that it is the first of its kind conducted in Iceland. The results will illustrate the symptomatology of patients with advanced cancer and their quality of life. Furthermore, the information on the relationship between symptoms and quality of life has important clinical value since it can be used to improve patient care.

In the first part of the thesis the theoretical background underlying the study is reviewed. The second part consists of the methodology, the third part holds the results, and the fourth discussion, conclusion, and future studies.

Theoretical background

In this chapter the concepts of quality of life and symptoms will be reviewed. First, the concept of quality of life will be introduced and explored in relation to its definitions, characteristics, boundaries, preconditions and outcomes, followed by a section on the maturity of the concept and how it is used in research. Secondly, the concept of symptoms is reviewed. The number of symptoms and prevalence will be discussed as well as symptom severity, co-occurring symptoms and symptom clusters. Thirdly, there is a section regarding the relationship between quality of life and symptoms where contributing factors to symptomatology, factors affecting quality of life and the quality of life scores of cancer patients are reviewed. Fourth, there is a summary of the theoretical background and the Symptoms-quality of life model, based on the literature, is presented. Finally, the purpose of the current study is introduced and the research questions and hypotheses outlined.

The concept of quality of life in health care

The concept of quality of life is widely used in health care practice, especially in the context of cancer and cancer treatment. This is not surprising, since, the three main goals of cancer treatment are: improvements in cure rate, lengthening survival time, and last but not least, improving the patients' quality of life (Penson et al., 2006). Better quality of life is also one of the main goals of cancer nursing (King et al., 1997) and indeed, improving quality of life is the primary goal of any health care intervention, not only cancer treatment (Revicki et al., 2000). Quality of life is also a widely used concept in social sciences, politics and advertisements,

as well as in health care. The first measurements of the concept became evident around 1960 when there was a growing interest within sociology in what factors affected the daily life of the American public. In health care, the concept became "popular" as a result of the patients' rights movement (Haas, 1999b; Pais-Ribeiro, 2004). In nursing the concept evolved as an important outcome measure to evaluate the impact of nursing care on patients' daily life. The interest of the nursing profession in quality of life lies not least in the multidimensionality of the concept, discussed later, which fits the holistic viewpoint of nursing. In health care in general, interest in the concept as an outcome measure has increased and today quality of life measurements are used widely for example in the development of new cancer drugs (Grant & Dean, 2003).

When reviewing the health care literature it becomes clear that quality of life has been widely studied in the last decade. Entering the concept into the PubMed database results in 69.975 items, mostly articles, published in the last 10 years. But despite being a central concept, no universal definition of quality of life exists (Jocham et al., 2006; Kaasa & Loge, 2003; King & Hinds, 1998) and many authors fail to define the concept in their work (Haas, 1999b; Taillefer, Dupuis, Roberge, & LeMay, 2003). What the concept encompasses is, therefore, not easy to apprehend and in order to get a clearer understanding of the concept it will be discussed in this thesis in accordance with the criteria for concept evaluation developed by Morse and colleagues (Morse, Mitcham, Hupcey, & Tason, 1996). It has to be noted here, though, that a full concept evaluation was by no means attempted. According to Morse (1995, p. 33) concepts are "abstract "cognitive representations" of perceptible reality formed by direct or indirect experiences" and each concept is built of five

main factors: definition, characteristics, boundaries, preconditions and outcomes (Morse et al., 1996).

Definitions of quality of life.

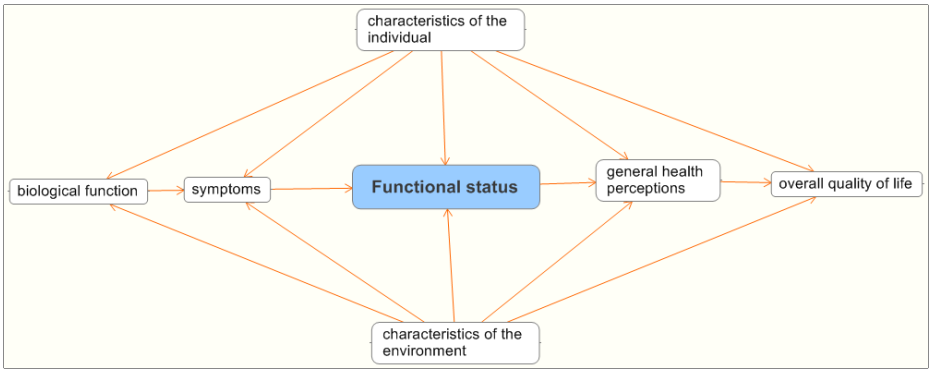
A definition is the label attached to a concept. It is the prerequisite for the concept to be identifiable, to be recognizable, to be referred to, and last but not least, to be communicated (Morse et al., 1996). Although, no universal definition of quality of life exists (Jocham et al., 2006; Kaasa & Loge, 2003; King & Hinds, 1998) multiple definitions of the concept are nevertheless available. It would be a handful to list every existing definition of quality of life and, therefore, only few definitions will be presented here. Before looking at the definitions it has to be observed that there are two quality of life concepts that repeatedly emerge in the health literature: general quality of life and health related quality of life. The term, health related quality of life, was introduced in the health literature to distinguish between the aspects of quality of life that are not related to health, such as political or societal features, in order to focus more clearly on the impact of disease and treatment on quality of life (Ferrans, Zerwic, Wilbur, & Larson, 2005). Health related quality of life is more specific than general quality of life encompassing evaluation of symptoms, function and psychological wellness as to some extent, existential and spiritual issues (Kaasa & Loge, 2003). Therefore, the main use of the concept is for those who are being treated for some disease (Choe, Padilla, Chae, & Kim, 2001) since it is mainly used for those aspects of life affected by healthcare interventions (Velikova, Stark, & Selby, 1999). General quality of life, on the other hand, is a broader concept that not only considers the impact of disease and its treatment on the individual, but rather reflects on the person as a whole (Calman, 1984). The two concepts are therefore not one and the same (Pais-

Ribeiro, 2004) but health related quality of life may be viewed as one aspect of general quality of life (Kaasa & Loge, 2003).

One of the most widely used definition of quality of life in the health literature is that of Cella and Cherin (1988, p. 70) who define it as the "patients' appraisal of, and satisfaction with, their current level of functioning as compared to what they perceive to be possible or ideal." This definition was specifically developed as a working definition of quality of life to use in the cancer population. It is subjective in nature but also considers the evaluative aspect of quality of life as well as the impact of the disease on the patient's functioning (Cella & Cherin, 1988). This definition may seem to be more in line with health related quality of life definitions, reviewed later, than general quality of life with the emphasis on the patient's function. Of note here is that the definition dates back to 1988 when, it seems, that the term health related quality of life had not yet become well-known in the literature. Indeed the definition was modified in 1995 and became: "health related quality of life (QOL) refers to the extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment" (Cella, 1996, p. 234).

The World Health Organization (WHO-QOL Group, 1993, p. 153) defines quality of life as "an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns." This definition is in line with the multidimensional, multicultural quality of life questionnaire, WHOQOL, developed by the organization. The questionnaire is based upon statements from patients with various diseases, well people, and health professionals on what factors constitute important aspects of quality of life, and how quality of life should be inquired about

(WHO-QOL Group, 1997). Another definition, presented here, was developed by Haas (1999, p.738) who after exploring the concept of quality of life in the context of both health and social sciences defined it as "a multidimensional evaluation of an individual's current life circumstances in the context of the culture in which they live and the values they hold. Quality of life is primarily a subjective sense of well-being encompassing physical, psychological, social, and spiritual dimensions. In some circumstances, objective indicators may supplement or, in the case of individuals unable to subjectively perceive, serve as a proxy assessment of quality of life". In similar terms, but more focused on the material well-being, is the definition provided by Felce and Perry (1995, p. 60 & 62) where quality of life is "an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social, and emotional well-being together with the extent of personal development and purposeful activity, all weighted by a personal set of values". Like Haas (1999) Felce and Perry ground their work in social and health sciences, mainly in the field of developmental disabilities. Another approach to define quality of life is the so-called gap-theory (Calman, 1984). According to Calman quality of life is the gap between how an individual perceives a given situation compared to his expectations regarding that situation. A smaller gap, hence, indicates better quality of life. Rooted in oncology, the definition was initially proposed as a hypothesis to be tested. The underlying presumptions of the definition are that quality of life can only be measured in individual terms and the concept is based on past experiences, dreams, hopes, ambitions and lifestyle of the individual.



Picture 1. The revised Wilson and Cleary model of health related quality of life
Source: Ferrans, C.E., Zerwic, J.J., Wilbur, J.E. and Larson, J.L. (2005). Conceptual Model of Health-Related Quality of Life. *Journal of Nursing Scholarship, 37*(4), 336-342. Used with permission from Wiley-Blackwell Publishing Ltd.

Embedded in the health sciences, health related quality of life has been defined as the subjective assessment of the impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and well-being (Ware, 1984; Schipper et al., 1996, in Revicki et al., 2000). Another definition defines it as a multidimensional construct encompassing perceptions of both positive and negative aspects of physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment (Osoba, 1994). Wilson and Cleary (1995) created a conceptual model of health related quality of life that was later revised by Ferrans and colleagues (Ferrans et al., 2005). The model, based on the literature regarding health related quality of life, aims to explain the relationship between health and quality of life: biological function leads to symptoms that affect functional status, which affects health perceptions that finally affect overall quality of life. These factors are then all

influenced by individual characteristics as well as characteristics of the environment. Picture 1 shows the model.

According to van der Steen (1993) a definition must be clear, it should not include accompanying features, it should refer to present features rather than absent ones, it should not be circular and neither too broad or too narrow (Morse et al., 1996). Although not being circular or including absent or accompanying features none of the definitions above clearly define what quality of life actually is. All include subjective wording like "appraisal", "satisfaction", "perception", "concern" and "ideal" with only two definitions considering an objective aspect of the concept (Felce & Perry, 1995; Haas, 1999b). It follows that the quality of life definitions are not specific enough and, hence, lack clarity, which should not be surprising given the subjectivity of the concept and the complexity of the human life in general.

Characteristics of quality of life.

Characteristics are those attributes that define a concept. They must be present in all instances where the concept is used but they may appear in different strength or even form. These characteristics must be abstract enough to define the concept in different situations, but yet, they must still be unique enough to distinguish between the concept and other related concepts. A well-established concept is both easily understood and frequently used in everyday language and a concept can be well-established although its characteristics may not be fully articulated (Morse et al., 1996).

According to Niv & Kreitler (2001), quality of life is a multidimensional, subjective, dynamic, evaluative, phenomenological, but yet a quantifiable construct. Similarly, Haas (1999), in her concept

analysis, has identified five main defining characteristics of quality of life as evident in definitions and uses of the concept. According to Haas (p. 733) quality of life: "a) is an evaluation of an individual's current life circumstances, b) is multidimensional in nature, c) is value based and dynamic, d) comprises subjective and/or objective indicators, and e) is most reliably measured by subjective indicators by persons capable of self-evaluation".

Research varies greatly as to what extend the concept is multidimensional and there is a need for deeper exploring of this area (King & Hinds, 1998). In his attempt to order chaos, Cummins identified 173 domain names in the quality of life literature, both found in the health literature and in other sciences. He was able to classify 83% of these names into seven domains consisting of material well-being (economical situation, food, housing), health (general health, function), productivity (work, school, success), intimacy (children, family, friends), safety (security, privacy, autonomy), community (neighborhood, social life, education) and emotional well-being (existential factors, self-esteem, recreational factors) (Cummins, 1996).

In the health related literature, specifically four dimensions are most apparent: physical, psychological, social/role functioning, and symptoms (King et al., 1997), but other dimensions commonly identified are spiritual, disease- and treatment related, functional well-being, and development and activity, see table 1. Physical well-being encompasses the person's evaluation of his/her physical condition, including symptoms; psychological/emotional well-being is the person's emotional response, such as anxiety and depression; social well-being is how the person senses support from others, and spiritual well-being encompasses the ability of

the person to find meaning and purpose in life (Ferrell, Grant, Padilla, Vemuri, & Rhiner, 1991; Tang, Aaronson, & Forbes, 2004). Disease- and treatment related well-being refers to how the person is affected by the disease or its treatment (King & Hinds, 1998) and functional well-being encompasses the person's ability to perform the activities of daily living, such as bathing, walking and dressing, but also how the person is able to respond to personal needs, social role and ambitions (Cella, 1994). Finally, development and activity refers to the person's independence, his/her ability to choose and control functional activities (e.g. work, leisure, education) and the person's productivity and contribution (Felce & Perry, 1995).

Quality of life is largely determined by a person's experience and how he/she values and attaches meaning to this experience (Stewart, Teno, Patrick, & Lynn, 1999). The concept is, therefore, mainly subjective in nature as evident by the use of words such as "appraisal", "satisfaction", "perception", "concern" and "ideal" in definitions of the concept, as mentioned earlier. Indeed, subjectivity can be classified as a fundamental feature of quality of life, alongside multidimensionality (Cella, 1994). Subjectivity means that quality of life is a result of a mental processing by the individual. The concept can, hence, only be understood in relation to the individual's perception (Cella, 1994). Two persons, living in similar conditions, may consider their quality of life different, and individuals living in what would seem like intolerable situation may, nevertheless, report satisfaction with their quality of life (Felce & Perry, 1995). However, the concept also has its objective features. Persons with a disability or a disease rendering them unable to express their feelings and concern, e.g. unconscious persons in the last days of life, have their

quality of life despite their lack of ability to subjectively evaluate it (Felce & Perry, 1995; Haas, 1999b). Some dimensions of quality of life can also be objectively measured like quality of schools, family income, and so on. Therefore, to measure quality of life a combination of both subjective and objective evaluations is sometimes necessary (Felce & Perry, 1995). Indeed, research in health care quite often relies on measures of objective aspects of quality of life, like function, as well as subjective aspects of the concept (Haas, 1999b).

Quality of life is a dynamic concept. Therefore, it is amenable to changes in the individuals' conditions such as physical or emotional ones. That means, when assessing quality of life, the time period, the state of the individual, (Haas, 1999b; Niv & Kreitler, 2001) and, even different situations have to be considered (Cella, 1994). For instance, a patient experiencing excruciating pain is unlikely to rate his quality of life as good at that moment. Another issue to consider are the changes related to life stages. For example, patients with advanced disease, facing death, find spirituality and existential issues usually more important than before (Kaasa & Loge, 2003; Stewart et al., 1999). Similarly, patients may value personal dignity and the ability to recognize their family and friends more than physical functioning when confronting death. The dimensions of quality of life remain the same as before, but, their importance change in accordance with the course of life (Stewart et al., 1999). Of note here is that although a person’s evaluation of quality of life may easily change, due to some significant event, it remains a relatively stable concept over time (Felce & Perry, 1995).

Table 1. Dimensions of quality of life in the social and health literature

Author(s)	Aaronson (1991)	Ferrell et al. (1991)	Cella (1994)	Cummins (1996)	Felce and Perry (1996)	Ferrans (2005)
Origin:	Studies of cancer patients	Studies of patients with cancer in pain	Studies of cancer patients	Social and health care	Social and health care (developmental disability)	Studies of patients in dialysis
Dimensions:	Disease and treatment related	Physical and symptoms	Physical	Health	Physical	Health and functioning
			Functional			
		Psychological	Emotional	Emotional	Emotional	
				Intimacy		Psychological/ spiritual
		Spiritual				
		Social	Social	Community	Social	
						Social and economic
				Material	Material	Family
				Safety		
				Productivity	Development and activity	

The evaluative aspect of quality of life refers to the individual's values, attitudes and the meaning he attaches to his experience (Haas, 1999b; Stewart et al., 1999). Older patients with cancer, for instance, tend to rate their quality of life better than younger patients while the opposite is true for the general population. This may stem from the fact that older people have different roles than younger people, who are occupied with work, rearing children etc., and, hence, the disease may not be as disruptive in their lives as it is for the younger (Lundh Hagelin, Seiger, & Furst, 2006). Cancer related fatigue, for instance, may be quite disruptive in the life of a young person who is usually more active compared to an old person with arthritis who is largely immobile (Cella & Cherin, 1988). Nevertheless, being evaluative, quality of life does not reveal any specific facts like what the health status of the individual is or in what kind of circumstances he/she lives in. Furthermore, being multidimensional means that when measuring quality of life it has to be considered that it is not just a single global measure but rather a number of measures that together comprise the concept (Niv & Kreitler, 2001).

Being quantifiable means that quality of life is measurable and can be both assessed and compared between individuals, diseases, and countries. Since the concept is mainly subjective, the individual himself/herself is the person best capable of evaluating his/her quality of life and, therefore, quality of life should be measured by self-report questionnaires when possible (Niv & Kreitler, 2001). In those cases where proxy ratings are needed it has to be considered that they might not truly reflect the individual's quality of life (Jocham et al., 2006). Studies indicate that doctors emphasize physiological factors while nurses, social workers and significant others rather stress psychosocial factors (Schipper

et al., 1990, in King & Hinds, 1998). In a study comparing symptom ratings between doctors, nurses and patients in palliative care, doctors tended to significantly underestimate the symptoms of drowsiness and shortness of breath compared to the patients' and nurses' ratings. This difference was also clinically significant with difference in ratings exceeding 12 mm on the 100 mm Visual Analogue Scale. The doctors also rated pain significantly lower than the patients. Nurses' ratings, however, did not differ significantly from those of the patients (Nekolaichuk et al., 1999). In general both health care workers and significant others tend to rate quality of life and physical functioning of patients lower than the patients themselves, but overestimate psychological factors like depression and anxiety, as well as other symptoms (Sneeuw, Sprangers, & Aaronson, 2002; Sprangers & Aaronson, 1992). Indeed it seems that proxy raters have more difficulty evaluating factors that have psychological components than physical factors (Nekolaichuk, Maguire, Suarez-Almazor, Rogers, & Bruera, 1999) or factors that are more tangible and observable (Sprangers & Aaronson, 1992). In summary, there seems to be difference between ratings of patients and proxies regarding symptoms and quality of life, but the discrepancy is, however, usually low (Jocham et al., 2006; Nekolaichuk, Maguire et al., 1999; Sneeuw et al., 2002). Substantial difference between raters seems to be rare but it has to be considered that studies in this field are often based on small samples making comparisons between raters difficult to evaluate (Sneeuw et al., 2002).

Quality of life can be assessed by both qualitative and quantitative methods (Haberman & Bush, 1998) and there are a number of instruments available that have proven to be both reliable and valid in quantitative

research. These instruments vary, however, as to how many items, as well as what dimensions of quality of life they measure (Niv & Kreitler, 2001) and, indeed, there is no single instrument available that completely covers all aspects of the concept (Revicki et al., 2000). There are three main types of instruments: generic instruments that can be used with any population regardless of disease; disease-specific instruments that are used with specific groups of patients, such as cancer patients; the third type are domain-specific instruments, and these are used to measure any specific domain of health related quality of life, such as symptoms (Kaasa & Loge, 2003).

The phenomenological aspect of quality of life mainly refers to its antecedents and hence, is discussed in the section *preconditions and outcomes of quality of life* on page 20.

It seems that quality of life is a very broad concept with many dimensions. This multidimensionality is one of the main reasons for the complexity of the concept, making it difficult to apprehend and evaluate. There seem to be, however, certain core domains: physical, social, psychological, material, and spiritual. As well as being multidimensional the concept is also dynamic and evaluative with both subjective and objective features. All of these factors complicate measures of the concept so it is not surprising that no single instrument, designed to measure quality of life, completely covers all those aspects. Hence, measures of the concept may not reflect all aspects of quality of life.

Boundaries of quality of life.

Boundaries are the borders of a concept, refining both what is and what is not a part of it. A well developed concept has clear boundaries that delineate it from others, while a poorly developed one may overlap with

similar concepts (Morse et al., 1996). There are four concepts that are often mistaken as being synonyms of quality of life: functional status, well-being, health, and satisfaction with life. None of these concepts fully capture what quality of life encompasses, but nevertheless, each of those concepts can be considered a part of quality of life.

Functional status refers to the individual's ability to perform activities of daily living, like bathing, walking, cleaning and, getting around (Revicki et al., 2000). Like quality of life, the concept is multidimensional since function is not only related to physical factors but psychological, social and spiritual as well. The main difference between quality of life and functional status lies in that the latter is mainly measured objectively (Haas, 1999a). Indeed, the difference between the two concepts is highlighted in some definitions where functional status is viewed as one aspect of quality of life rather than being synonymous with it (Niv & Kreitler, 2001).

Health status is also a multidimensional concept that can be evaluated with both objective and subjective methods like quality of life (Revicki et al., 2000). Health is often thought of as the most important aspect of quality of life, but although being closely related the concepts are not synonymous. It is not easy to differentiate between the two concepts since they are tightly interwoven and it is not obvious whether quality of life is a component of an individual's health, or, health an integral part of quality of life. Health is often viewed as being free from diseases, despite, the notion that many people with diseases, like e.g. diabetes, do not define themselves as unhealthy (Haas, 1999a). Health can, nevertheless, be distinguished from quality of life since there are other dimensions that comprise the concepts. Quality of life encompasses

more than simply health (Revicki et al., 2000). A person may consider his health excellent, but yet experience diminished quality of life because of undesirable working conditions or family conflicts. Similarly, individuals with terminal illness, a state most people would consider unhealthy, may experience good quality of life. For instance, a study on 60 American patients in hospice care, the majority with cancer, showed that the patients rated their quality of life high and, indeed, they had an above average quality of life (Tang et al., 2004).

Another concept that lies closely to the core of quality of life is satisfaction with life (Felce & Perry, 1995). The concept, however, differs mainly from quality of life in that it is purely subjective in nature (Haas, 1999a).

Similar to satisfaction well-being is also a subjective concept and, hence, not synonymous with quality of life. The concept is, however, used extensively in the quality of life literature, not least, in definitions of the concept (Haas, 1999a).

Preconditions and outcomes of quality of life.

Every concept must have similar preconditions that are the prerequisite for the factors that define the characteristics of the concept (Morse et al., 1996). Haas (1999) has stated that the antecedent to quality of life is mainly life itself, alongside a person capable of evaluating his quality of life, since quality of life is present from birth to death. Niv and Kreitler (2001), on the other hand, have stated, that because of the phenomenological nature of the concept it is like a photograph where one can see what is in the picture but not what preceded or caused the moment captured. However, there are many factors that influence quality of life that may be considered antecedents. To name but a few, violence, poverty,

housing and health are all factors known to influence quality of life (Haas, 1999b). In cancer patients, however, symptoms caused by the disease itself or its treatment are important factors affecting quality of life as discussed later in the section *factors affecting quality of life* on page 43.

Outcomes refer to what the consequences of the concept are (Morse et al., 1996) and since quality of life is always present the consequences are the results of an evaluation of the concept (Haas, 1999b). The evaluation can result in unchanged, diminished or improved quality of life. For cancer patients the disease usually affects quality of life negatively as discussed in the following section *quality of life scores of cancer patients* on page 52.

The maturity of the concept of quality of life.

For a concept to be mature, according to Morse and colleagues (1996), it must be clearly defined, its characteristics described, its boundaries delineated and the preconditions and outcomes fully described and demonstrated.

Although no single, universal definition of quality of life exists all of the definitions discussed earlier point to the multidimensionality of the concept where the focus is on the well-being of the individual as evaluated by himself/herself, factors that according to Cella (1994) are prerequisite to a useful definition of the concept. The problem with defining quality of life is the fact that it is mainly subjective, but, also dynamic and, hence, amenable to changes, making it difficult to define as a constant entity (King et al., 1997). The concept of health related quality of life is narrower than general quality of life, and hence, does not capture the global meaning of quality of life. Indeed, it can be argued that health

related quality of life merely constitutes one aspect of the greater construct of quality of life (Kaasa & Loge, 2003).

The characteristics of quality of life seem to be fairly well described, although, the objective feature of the concept is often overlooked in the literature. Due to the complexity of quality of life it may happen, that not all the characteristics of the concept are apparent at the same time indicating a lack of a conceptual structure (Morse et al., 1996). This may, however, stem from the dynamic nature of the concept resulting in some characteristics being more pronounced in a given situation like spirituality in the dying person (Stewart et al., 1999) rather than a lack of conceptual structure.

Similarly, it may seem that the boundaries of quality of life are not always clearly delineated with the concept often mistaken to be synonymous with functional status, well-being, health, and life satisfaction. However, these four concepts are distinguishable from quality of life by their characteristics or inherent meaning. Indeed, these concepts constitute important aspects of quality of life, although, they may also be amenable to independent measurement. Thus the boundaries of quality of life may be outlined, although, some authors may fail to distinguish between the different concepts.

The preconditions and outcomes of quality of life are not easy to describe and indeed they may not be good indicators of the maturity of the concept. Quality of life is a phenomenon that exists throughout life and there are no clear indicators of what quality of life should be like. However, there are factors that influence quality of life, but since the concept is both dynamic and evaluative different factors may be influential across individuals and situations. Similarly, the outcomes of

quality of life are related to the individual's evaluation and, hence, may be different across individuals and situations as well. In light of this, it is clear that describing the preconditions and outcomes of quality of life is an impossible task. Quality of life simply exists and its outcomes are mainly subjective, resulting in improved, diminished or unchanged quality of life as perceived by the individual.

It is evident that the concept of quality of life is a complex one and more work is still to be done to understand it better. Unfortunately, this lack of conceptualization has its disadvantages. Being so vague, quality of life can encompass almost anything as is evident from different definitions and dimensions presented in the literature. It also means that some factors may be considered a part of quality of life in one study but not in another study, thereby, blurring the concept (Taillefer et al., 2003). Despite this lack of maturity, the concept is, nevertheless, quite well-established (Morse et al., 1996) as evident from its common use in the literature as well as in marketing, politics and advertising (Haas, 1999a; Pais-Ribeiro, 2004). This gives rise to the notion that a concept may be generally understood despite being conceptually unclear. Indeed, it has been argued that the meaning of a concept cannot be clarified beforehand (Paley, 1996). According to Paley the meaning of a concept is specified in theory, i.e. the theory defines the concept not vice versa. However, being derived from one theory does not mean that the concept has been defined finitely. Indeed, the concept may have a different meaning when derived from another theory. Therefore, concepts are amenable to changes, according to the context they are situated in, and, furthermore, two concepts may share the same characteristics, but they need not be synonymous with each other.

The quality of life concept in research.

Whether unambiguous or not, concepts are theoretically important, and the role of a concept in research is dependent on how the researcher chooses to use it (Morse, 1995). To counteract the blurring of the concept of quality of life it is important for researchers exploring the concept to clearly define their perspective of it (Taillefer et al., 2003). According to Cella (1996) there is no gold standard in measuring quality of life so the operationalization of the concept should be determined by the theoretical framework underlying the study (Paley, 1996). When choosing an instrument it is of uttermost importance to clearly define the purpose of the study and the research questions, since the choice of an instrument should rely on these factors rather than vice versa. The instrument must also be appropriate to the population under study (Cella, 1996). Another thing to consider is that the authors must state how they define quality of life and ensure that there is correspondence between the definition, instrument chosen, and the dimensions of quality of life the researcher wants to study (Jocham et al., 2006; Kaasa & Loge, 2003; King et al., 1997; Pais-Ribeiro, 2004). Also, in order to try to fully capture a person's quality of life it can be useful to include a single rating of overall quality of life when measuring the concept. The benefit of such a single rating is that it gives the individual opportunity to define quality of life in his/her own terms rather than relying on specifically defined aspects of the concept (Stewart et al., 1999).

The concept of symptoms

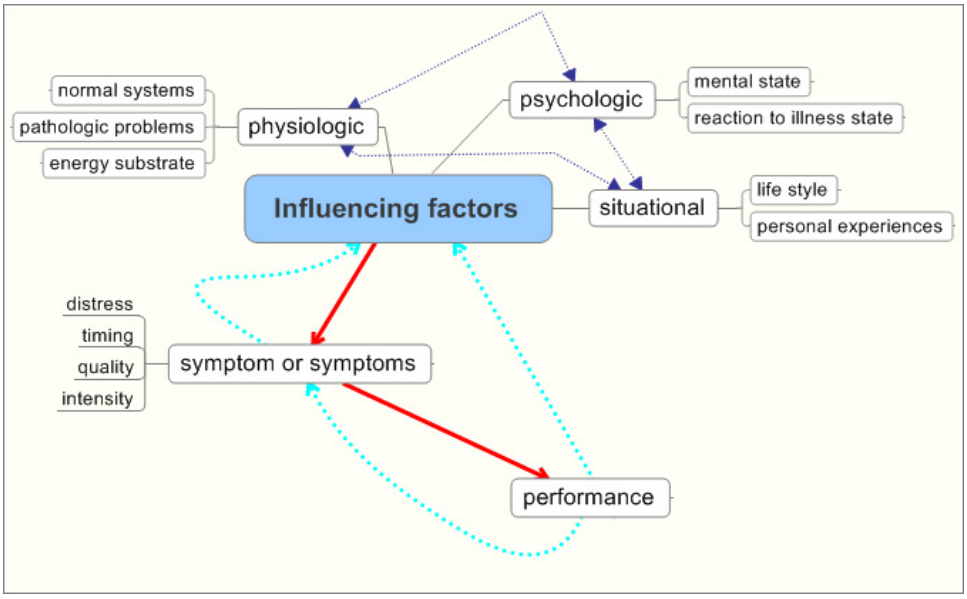
A symptom is a subjective phenomenon regarded by individuals as an indication of a condition departing from normal function, sensation, or

appearance (Rhodes & Watson, 1987). The concept of symptom is multidimensional in nature and can be measured separately or in combination with other symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). A symptom differs from the concept of sign, which is an objective phenomenon that is observable and indicates a change in health status (Liehr, 2005).

When reviewing the literature only few theories or models regarding symptoms have been described. One example is the middle range Theory of Unpleasant Symptoms (Lenz, Suppe, Gift, Pugh, & Milligan, 1995; Lenz et al., 1997) which will be discussed here to shed some light on the concept of symptoms. The theory is the outcome of collaboration between three investigators, two who studied fatigue in childbearing women, and a third who studied dyspnea in COPD and asthma patients. They generated a theory that could be used for multiple symptoms as well as in diverse clinical populations (Lenz et al., 1995). The theory is based on the assumption that diverse symptoms have enough in common so that it is possible to generate a theory not limited to only one symptom. Three components are the cornerstones of the theory: influencing factors that either cause symptoms or affect the symptom experience, the symptom or symptoms the individual is experiencing, and the consequences of experiencing symptoms. The concept of symptoms is believed to encompass several dimensions such as severity (intensity), duration and frequency, symptom distress, and quality of the symptom. According to the theory, symptoms are known to co-occur and they interact with one another. The model, illustrating the theory, see picture 2, is interactive in nature. The influencing factors cause or affect symptoms and the existence of these symptoms leads to worse performance. Worse

performance can then affect both the influencing factors as well as the symptoms. Symptoms can similarly affect the contributing factors (Lenz et al., 1997).

It has to be noted that the development of the theory was not based on symptoms studied in the cancer population. It has, however, been used to guide the formation of research questions and selection of variables (Gift, Stommel, Jablonski, & Given, 2003) and as framework to understand the symptom experience of cancer patients (Redeker, Lev, & Ruggiero, 2000).



Picture 2. **The Theory of Unpleasant Symptoms.** The arrows show the relationship between the components. Red arrows indicate influence, turquoise arrows indicate feedback and the blue arrows indicate interaction.
Source: Lenz, E.R. Pugh, L.C., Milligan, R.A., Gift, A., and Suppe, F. (1997). The Middle-Range Theory of Unpleasant Symptoms: An Update. *Advances in Nursing Science, 19*(3), 14-27. Used with permission from Lippincott Williams & Wilkins.

The number of symptoms and symptom prevalence.

The number of symptoms, patients with cancer experience varies greatly but research indicate that the median number of symptoms per patient is often between eight and eleven (Chang et al., 2000; Homsi et al., 2006; Lidstone et al., 2003; Peters & Sellick, 2006; Portenoy et al., 1994; Tsai et al., 2006; Walsh et al., 2000), but some patients may experience up to 30 symptoms at a given time (Chang et al., 2000). Having no symptoms at all, however, seems to be rare. In a study of 480 patients with cancer attending an outpatient clinic in the UK, only 2% of the participants were symptom free (Lidstone et al., 2003). In an Icelandic study of patients entering palliative service for the first time, the mean number of symptoms ranged from 4,95 in palliative home care service to 7,17 in medical/surgical wards (Friðriksdóttir & Sigurðardóttir, 2004, April). Another Icelandic study on patients in the last 72 hours of life, in palliative care, showed that around 11% of the patients had four or fewer symptoms, 30% had 5-7 symptoms, 42% had 8-10 symptoms, and 17% had more than 10 symptoms (Sigurdardottir et al., 2006). It is important to note that questionnaires and other methods of assessing symptoms vary greatly. Some studies use questionnaires that include ten or fewer symptoms (Chen & Chang, 2004; Hoekstra et al., 2006; Modonesi et al., 2005) while a great quantity of symptoms is assessed in other studies (Homsi et al., 2006; Walsh et al., 2000). In some cases, the researchers do not use validated questionnaires, but design their own, interview the patients or use methods commonly used in clinical practice (Homsi et al., 2006; Tsai et al., 2006; Walsh et al., 2000).

Cancer patients experience more symptoms than the general public, as can be expected (Fu, McDaniel, & Rhodes, 2007; Rhodes,

McDaniel, Homan, Johnson, & Madsen, 2000; Schuit et al., 1998). This is not at least true for the symptoms of fatigue, depression and pain which not only are more prevalent in cancer patients than the general public, but also than in other patient populations (Reyes-Gibby et al., 2006). In a study evaluating an instrument to measure symptom experience (the Adapted Symptom Distress Scale), the symptom occurrence was significantly higher in cancer patients compared with healthy individuals and medical-surgical patients, although symptom distress did not differ between the cancer and medical-surgical patients (Rhodes et al., 2000). It is noteworthy, however, that the symptomatology in advanced AIDS, heart disease, COPD and kidney diseases is quite similar to that in advanced cancer with the symptoms of pain, fatigue and breathlessness occurring in more than 50% of patients across the five diseases (Solano, Gomes, & Higginson, 2006).

Teunissen et al. (2007) performed a systematic review, based on 44 studies, on the symptom prevalence in 25.074 patients with advanced cancer. The results showed the five most common symptoms were fatigue, pain, lack of energy, weakness, and appetite loss, and that over half of the participants experienced these symptoms. Similar results have been obtained in other studies. Peters and Sellick (2006) assessed the symptomatology in 58 patients in palliative care in Australia. In their study the most prevalent symptoms were weakness, fatigue, dry mouth, and pain, with about 2/3 of participants experiencing those symptoms. In an Icelandic study of cancer patients receiving chemo- and/or radiotherapy the symptoms of fatigue, sleep disturbances, dry mouth, drowsiness, and pain occurred in over 47% of the participants (Skúladóttir, Birgisdóttir, & Friðriksdóttir, 2005). When reviewing the

literature there seems to be a core of symptoms that the majority of patients with advanced cancer experience. Of note are the symptoms of pain and fatigue that seem to be almost universal in this group of patients with pain prevalence ranging from 59,0-88,3% and fatigue prevalence from 72,5 – 97,4% (Hoekstra et al., 2006; Homsi et al., 2006; Modonesi et al., 2005; Peters & Sellick, 2006; Tsai et al., 2006; Walsh et al., 2000). In the systematic review, cited above, the pooled prevalence of pain and fatigue were 71% and 74% respectively (Teunissen et al., 2007). In a recent German study of 4.538 ambulatory cancer patients, however, the prevalence of pain was only 30%, while the most frequent symptoms were fatigue (60%), hair loss (54%), nausea (51%), sleep disturbance (42%), and weight loss (36%) (Feyer, Kleeberg, Steingraber, Gunther, & Behrens, 2008). Table 2 shows the number of symptoms and symptom prevalence in a number of studies of cancer patients.

Symptom severity.

Symptom severity, also called symptom intensity, defined as the strength or amount of the symptom experienced (Lenz et al., 1997), is also an important concept when discussing symptoms. However, it is not easy to compare symptom severity between studies since various questionnaires are used to measure symptoms and different scales are used for severity. Some studies measure severity with words such as mild, moderate or severe (Chang et al., 2000; Homsi et al., 2006) while others use various types of numeric or Likert scales (Modonesi et al., 2005; Peters & Sellick, 2006; Tsai et al., 2006). In some cases there are even different scales within one study (Tsai et al., 2006). It seems, though, that the words mild, moderate and severe may be linked to numeric scales. In a study exploring this relationship it was found that when pain was assessed on a scale

ranging from 0-10, ratings of 1-4 indicated mild pain, moderate pain corresponded to ratings of 5-6 and finally, 7-10 indicated severe pain. Participants in the study were patients with metastatic cancer experiencing pain in the USA, France, China and the Philippines (Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995). This classification has also been used with other symptoms than pain (Cleeland et al., 2000), but a recent study (Given et al., 2008) showed that severity cut points differ between individual symptoms in cancer, with the symptoms of pain, remembering, alopecia, fatigue, and depression being moderate in strength when rated as low as 2 on á 0-10 point scale.

It seems that the symptom severity in patients with advanced cancer is, in most cases, mild or moderate in severity. In a study by Peters and Sellick (2006) the mean symptom severity was 1,90, on a scale from 1-4[1], in home-based patients while it was 2,16 in inpatients. Similarly, the mean symptom severity ranged from 3,4-5,6, on a scale from 0-10[1] in a study on 159 patients with advanced cancer in the Netherlands (Hoekstra et al., 2006) and a Taiwanese study showed average symptom severity ranging from 4,6- 5,9 on a scale of 0-10[1]; 0,1-1,7 on a scale of 0-3[1]; and 1,7-2,2 on a scale of 1-5[1] indicating mild to moderate symptom severity (Tsai et al., 2006). In an Icelandic study of cancer patients the mean symptom severity was 3,98 (on a scale from 0-10[1]) with dry mouth being the most severe symptom (4,48) followed by fatigue (4,41) (Skúladóttir et al., 2005). Despite this, there are a number of patients who experience severe or very severe symptoms.

[1] Higher number indicating more severe symptoms

Table 2. Median or mean number of symptoms and symptom prevalence of the five most common symptoms in patients with various types of cancer

Authors	Sample	Questionnaire	Number of symptoms	Five most common symptoms (%)
Walsh et al., (2000)	N = 1000 (USA) patients in palliative care with various types of cancer	Empirically derived clinical assessment tool	median = 11 range 1-27	pain (84), fatigue (69), weakness (66), anorexia (66), lack of energy (61)
Portenoy et al., (1994)	N = 243 (USA) patients with colon, breast, prostate, and ovarian cancer	MSAS	median = 11 range 0-25	lack of energy (73,7), worrying (70,7), feeling sad (65,0), pain (64,0), feeling nervous (61,3)
Chang et al., (2000)	N = 240 (USA) patients (males = 97%) with various types of cancer	MSAS	median = 8 range 0-30	lack of energy (62), pain (59), dry mouth (54), shortness of breath (50), difficulty sleeping (45)
Chen & Tseng (2006)	N = 151 (Taiwan) patients with various types of cancer	MDASI	mean = 8,32 (SD = 3,72) median and range not reported	dry mouth (84,1), fatigue (82,1), lack of appetite (76,2), pain (72,8), sleep disturbance (72,2)
McMillan & Small (2002)	N= 178 (USA) patients with various types of cancer newly admitted to hospice home care	MSAS	Not reported	lack of energy (89), pain (83), dry mouth (78), shortness of breath (70), lack of appetite (57)
Tsai et al., (2006)	N = 77 (Taiwan) patients in palliative care with various types of cancer	Symptom Reporting Form, designed by experienced specialists	median = 11 range 1-18	weakness (98,7), fatigue (97,4), anorexia (96,0), pain, (88,3), depression (81,9)
Friðriksdóttir and Sigurðardóttir (2004)	N = 111 (Iceland) patients in palliative care with various types of cancer in four different wards	ESAS	mean = 4,95 home care 5,18 palliative ward 5,83 oncology ward 7,17 medical/surgical ward	tiredness (84), not feeling well (80), lack of appetite (75), pain (68), dyspnea (66)
Modonesi et al., (2005)	N = 162 (Italy) patients in palliative care with various types of cancer	ESAS	Not reported	fatigue (88), drowsiness (79), anxiety (74), depression (71), anorexia (70)
Homsi et al., (2006)	N = 200 (USA) patients in palliative care with various types of cancer	a) investigator developed checklist	median = 10 range 0-25	a) dry mouth (65,5), weight loss (50,5), fatigue (47,0), early satiety (46,5), anorexia(45,5)
		b) symptoms volunteered by patients	median = 1 range = 0-6	b) pain (50,5), fatigue (25,5), anorexia (13,5), dizziness (3,0), vomiting (2,5)

Over 40% of the patients admitted to palliative care, in a study by Modonesi et al. (2005), experienced rather intense pain, fatigue, depression, anxiety, drowsiness and anorexia, ranging from 7,13-7,46 on a scale from 0-10[11]. Similarly severe pain was mentioned at least once by 20,3% of a large sample of hospice patients (73,9% of the sample had cancer) in the USA (Strassels, Blough, Hazlet, Veenstra, & Sullivan, 2006). The symptoms of pain, lack of energy, difficulty sleeping, shortness of breath, and lack of appetite were also experienced as severe or greater in intensity by 12-22% of the patients receiving treatment at a Veterans affairs medical center in the USA (Chang et al., 2000). Similarly, more than 20% of a large sample (N= 670) of cancer patients in the USA, rated the symptoms of dry mouth, lack of appetite, drowsiness, disturbed sleep, distress, worrying, weak, not being able to get things done, and fatigue as severe or ≥7 on a scale from 0-10 (Cleeland et al., 2000). However, it is not only different scales and questionnaires that are of importance when symptom severity is assessed. In a prospective study by Homsi et al. (2006) symptom severity differed as to what method was used to assess symptoms. When symptoms were assessed systematically (patients directly asked about 48 symptoms) 48% were mild, 35% moderate and 17% severe. When patients volunteered their symptoms, however, 17% were considered mild, 32% moderate and 51% severe indicating that patients report their severe symptoms rather than their mild ones. Another factor to consider is the effect of symptom severity. In their study, on advanced cancer patients with pain, Serlin and colleagues (1995) found that the relationship between pain severity and interference of function was non-linear. When pain was assessed with a numeratic rating

[1] Higher number indicating more severe symptoms

scale, ranging from 0-10, the steps between 4 and 5 and between 6 and 7 were significantly more important in relation to interference of function than other steps.

But the severity of symptoms does not quite depict the whole picture since the symptom distress, defined as the degree or amount of physical or mental upset, anguish, or suffering experienced from a specific symptom (Rhodes & Watson, 1987), can be great although the severity of symptoms is not. In a study by Homsi et al. (2006) a large percentage of symptoms was rated as mild, but yet patients perceived them as distressing. Similar results were obtained by Chang et al. (2000) in a study of 240 patients with various kinds of cancer. Only 16% of the participants rated lack of energy as severe but nevertheless 60% found it distressing. Pain was similarly severe in 22% of cases but 52% found the symptom distressing. In line with this are the results of a study assessing the "most troublesome" (most distressing) symptom among 146 patients in palliative care (Hoekstra, Vernooij-Dassen, de Vos, & Bindels, 2007). Although, there usually was a relationship between the most troublesome symptom and the most severe symptom, the study showed that around 29% of the patients rated other symptoms as the most distressing than the most prevalent or severe ones. Another study, on 175 patients in palliative care, showed comparable results (Stromgren et al., 2006). In that study the symptoms the patients found most troublesome were usually the same as those rated as most severe, like pain, constipation and dyspnea. Fatigue, physical function, role function, and activity, however, were frequently mentioned as distressing, despite not being considered severe by the patients.

Co-occurring symptoms and symptom clusters.

Patients rarely experience only one symptom at a time (Chang et al., 2000) and research has shown a correlation between many of the symptoms experienced by cancer patients (Chen & Tseng, 2006). It is also widely acknowledged that one symptom can lead to another. Pain may, for instance, lead to insomnia, because it may interrupt sleep or inhibiting the individual from falling asleep. Pain may also lead to depression or anxiety that furthermore can lead to insomnia and vice versa. Finally, pain may induce fatigue that may lead to insomnia, but insomnia, may also lead to fatigue, since people deprived of sleep usually lack energy. Hence, one symptom can lead to another, resulting in a vicious cycle of cause and effect (Theobald, 2004). This relationship between symptoms was evident in a study of the physical symptom profiles of cancer patients with, and without depression. The results showed that depressed patients had significantly more symptoms than non-depressed patients (3,77 vs. 2,52) with the symptoms of insomnia, pain, anorexia and fatigue being significantly more prevalent in the former group than the latter (Chen & Chang, 2004). Similarly, a moderate but significant relationship has also been shown between the symptoms of pain, fatigue and sleep disturbance in a study of 84 patients with various cancer diagnoses experiencing pain (Beck, Dudley, & Barsevick, 2005). In that study, pain explained 20% of the variance in fatigue and it influenced fatigue both directly as well as indirectly through its effect on sleep. Other studies have also shown that fatigue, pain and depression tend to occur together in cancer patients (Cleeland et al., 2000; Portenoy et al., 1994). A significant relationship was also found in a study where the prevalence of fatigue was compared between patients with advanced cancer (n=95) and volunteers without

cancer (n=98). Fatigue severity proved to be significantly related with dyspnea and pain scores in the patients as well as with anxiety and depression in the control group (Stone et al., 1999). In a study by Chang et al. (2000) pain never occurred in isolation and those patients experiencing moderate pain had a median number of 11 symptoms compared to the median number of 8 symptoms in the whole sample. Patients with pain also had an increased relative risk of experiencing nausea, fatigue, dry mouth, lack of appetite, dyspnea, and constipation of moderate severity. Similar results were obtained for fatigue. Patients with moderately severe fatigue experienced 13 other symptoms on average with increased relative risk of having moderate dyspnea, nausea, lack of appetite, pain, difficulty sleeping, and difficulty swallowing. In accordance with these results the symptoms of dry mouth, anorexia, dysphagia, dyspnea, and weight loss also seem to occur in relationship with other symptoms. These five symptoms have been found to be predictive of earlier mortality in hospice patients and when analyzed with other symptoms it showed that as the number of these five symptoms grew the number of other symptoms also grew. Patients experiencing all these five symptoms had a median of 16 other symptoms while those who had none of these five symptoms had a median of 4 symptoms (Walsh, Rybicki, Nelson, & Donnelly, 2002).

Research has also begun on the concept of symptom clusters (Miaskowski, 2006) a concept closely related to that of co-occurring symptoms. The existence of symptom clusters gives rise to the possibility of underlying shared pathophysiology of symptoms (Cleeland et al., 2003) but the concept has been defined as either two or more symptoms (Kim, McGuire, Tulman, & Barsevick, 2005) or three or more concurrent symptoms that are related to each other and may or may not have the same

etiology (Dodd, Miaskowski, & Paul, 2001). According to Kim et al. (2005) symptom clusters are formed by stable groups of symptoms that are independent of other clusters and a stronger relationship should exist within symptoms in a cluster than between symptoms in other clusters. The importance of studying symptom cluster lies in better understanding and knowledge of what causes symptoms, the way symptoms affect other symptoms and the effects of symptoms on patients' lives (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). Research in this area to date has, however, been scarce (Chow, Fan, Hadi, & Filipczak, 2007) and most studies so far are secondary analysis of data with different instruments used to assess symptoms, as well as different methods used to identify the clusters (Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Chen & Tseng, 2006; Gift, Jablonski, Stommel, & Given, 2004; Walsh & Rybicki, 2006). The data on symptom clustering also vary between studies both in number of clusters as well as to what symptoms the clusters consists of. However, there seems to be some concordance between clusters in different studies. Table 3 shows the results of five studies of symptom clusters.

Table 3. Symptom clusters, according to five studies, of patients with lung, breast, or various types of cancer

Study	Gift et al., 2004	Chow et al., 2007	Walsh & Rybicki, 2006	Chen & Tseng, 2006	Bender et al., 2005
Sample	N=220 elderly patients newly diagnosed with lung cancer	N=518 patients with various types of cancer and bone metastases in radiotherapy	N=922 patients with various types of cancer	N=151 patients with various types of cancer	N=154 (n1=40, n2=88, n3=26) women with breast cancer
Research design	secondary analysis of data	longitudinal (1, 2, 4, 8, and 12 weeks)	retrospective analysis of prospective, cross-sectional data	secondary analysis of data, cross-sectional	pooled analysis of data from three studies of women with breast cancer
Comments	patients in various treatments	clusters changed during radiotherapy			Different instruments were used in the three studies
Clusters	1cluster: fatigue, nausea, weakness, appetite loss, weight loss, altered taste, vomiting	3 clusters: 1) fatigue, pain, drowsiness, poor sense of well-being 2) anxiety, depression 3) shortness of breath, nausea, poor appetite	7 clusters: 1) easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, taste changes 2) sleep problems, depression, anxiety 3) dizzy spells, dyspepsia, belching, bloating 4) nausea, vomiting 5) dysphagia, dyspnea, cough, hoarseness 6) edema, confusion 7) pain, constipation	3 clusters: 1) pain, fatigue, sleep disturbance, lack of appetite, drowsiness 2) nausea, vomiting 3) distress, sadness	Here only 1 cluster identified in each sample of women with breast cancer is presented: fatigue, feeling a lack of energy, decreased physical strength/weakness, feeling depressed or blue, feeling anxious or nervous, loss of concentration

Quality of life and symptoms in cancer patients

According to Teunissen and colleagues (2007) the suffering of people with advanced cancer is largely determined by the presence of unpleasant symptoms related to their disease. A relationship exist between symptoms and quality of life (Chang et al., 2000; Portenoy et al., 1994) so it is not surprising to see that the factors most affecting quality of life in advanced cancer patients are indeed factors that are known to cause symptoms (Bjordal et al., 2000; Brans et al., 2002; Cleeland et al., 2003; Hwang et al., 2003; Lee et al., 2004; Mercadante et al., 2000) as well as individual symptoms (Ferrell, 1995; Lis et al., 2008; Peters & Sellick, 2006; Rustøen et al., 2005). Before looking at what factors influence quality of life in cancer patients it is important to look at what factors contribute to the symptomatology in this group of patients.

Factors that cause or influence symptoms.

Symptoms in cancer patients stem from various reasons, but much is yet to be known about the relationship among symptoms and contributing factors. Some of the etiological factors are directly related to the tumor, e.g. type of cancer and existence of metastases, but treatment, such as chemotherapy, radiation and surgery, can also cause symptoms (Cleeland et al., 2003; Lee et al., 2004; Mercadante et al., 2000; Morita, Tsunoda, Inoue, & Chihara, 1999). Psychological and physical debility may also play a role in the symptomatology of patients with advanced cancer, but organ failure and metabolic abnormalities secondary to the disease or its treatment can also cause symptoms (Mercadante et al., 2000). Recently, scientist have become interested in whether the symptoms cancer patients experience may be related to cytokines that act on the nervous system,

both centrally and peripherally. This hypothesis is supported by the fact that patients treated with cytokine therapy often develop symptoms similar to those observed in the cancer population (Cleeland et al., 2003; Lee et al., 2004). Other factors that may affect the symptomatology in cancer patients are age, gender, performance status, and indeed other symptoms and their treatment. In Portenoy and colleagues' (1994) study on 243 patients with prostate, ovarian, colon and breast cancer, no difference in symptom prevalence was noted in relation to gender, age, extent of disease and tumor type, but other studies show different results.

Regarding the type of cancer, various studies show that lung cancer patients tend to experience more dyspnea than other cancer patients (Jordhoy et al., 2001; Lundh Hagelin et al., 2006; Mercadante et al., 2000; Morita et al., 1999) as well as cough/sputum and death rattle (Morita et al., 1999). Lung cancer patients were also the group experiencing both the highest number of symptoms as well as the most severe symptoms, followed by patients with brain tumors, in the study of Lidstone et al. (2003). A study by Morita et al. (1999) on hospice inpatients in Japan showed that brain tumors contributed to paralysis and gastric/pancreas cancer to abdominal swelling.

The existence of metastases can also cause symptoms. In Morita and colleagues' (1999) study the existence of bone metastasis contributed to pain and paralysis, and peritoneal metastasis contributed to general malaise, nausea/vomiting, edema, abdominal swelling and dry mouth. Similar findings were obtained in a study by Jordhoy et al. (2001) where patients with bone metastases had more pain and constipation as well as lower physical functioning than other patients. Furthermore research

indicates that patients in an advanced stage of cancer have more symptoms than those in remission (Lidstone et al., 2003).

Treatment is a known etiological factor producing symptoms (Cleeland et al., 2003; Lee et al., 2004; Mercadante et al., 2000). In a study of patients (N=1.569) in chemotherapy and/or radiotherapy (Henry et al., 2008) 88% of the participants reported at least one symptom (side effect) of their treatment. Among the symptoms reported fatigue was prevalent in 80% of patients and pain, nausea and/or vomiting, anxiety and insomnia in 45-48%. Different treatments, however, may cause different symptoms. An Icelandic study on 177 patients with prostate cancer showed that patients, that had been treated surgically, experienced more incontinence symptoms than those treated with hormonal therapy, radiation, or were under observation (watchful waiting). Patients treated with hormonal therapy or in watchful waiting, on the other hand, experienced more irritative urinary symptoms, like hematuria, than patients treated with surgery or radiation (Sigurðardóttir, 2006).

Psychological and physical debility may further play a role in the symptomatology of patients with cancer (Mercadante et al., 2000). In patients with prostate cancer (N=177) worse health before diagnosis was associated with more irritative urinary symptoms and worse bowel symptoms. Similarly, patients with two or more diseases other than cancer experienced more irritative urinary symptoms than patients with only one or no concomitant disease (Sigurðardóttir, 2006). Correspondingly, two studies exploring the existence of symptom clusters found that concurrent medical conditions increased the risk of both individual symptoms as well as symptom clusters (Gift et al., 2004; Reyes-Gibby, Aday, Anderson, Mendoza, & Cleeland, 2006). In a longitudinal study of symptom clusters

in patients with lung cancer, however, comorbid conditions did not affect symptoms or symptom clusters (Gift et al., 2003).

The relationship between symptoms and gender is not clear cut, but it seems that some symptoms may be more prevalent in women than in men, not least gastro-intestinal symptoms. Women appear to experience more symptom distress (McMillan & Small, 2002) than men, but the number of symptoms may be the same for both genders (Lidstone et al., 2003). Research has shown that women more often have diarrhea (Lundh Hagelin et al., 2006; Mercadante et al., 2000), nausea and vomiting (Jordhoy et al., 2001; Lundh Hagelin et al., 2006; Mercadante et al., 2000; Walsh et al., 2000), early satiety (Walsh et al., 2000), and change in appetite/weight (Lidstone et al., 2003) than men. Correspondingly, results have revealed that women more frequently experience anxiety (Redeker et al., 2000; Walsh et al., 2000), feel more tense/worried/fearful, are more concerned about their appearance (Lidstone et al., 2003), more often have fatigue (Jordhoy et al., 2001; Redeker et al., 2000), pain (Lidstone et al., 2003), confusion (Mercadante et al., 2000), and have worse physical functioning (Jordhoy et al., 2001) than men. On the other hand, men tend to more often have hoarseness, more than 10% weight loss, sleep problems, and dysphagia (Walsh et al., 2000) as well as dyspnea (Mercadante et al., 2000) than women.

As to age, older patients seem to experience fewer symptoms than younger patients. In a study of a large sample of cancer patients (N=480) the mean (SD) number of symptoms was 12 (6,5) for the age groups 30-39 and 40-49, but, decreasing per decade thereafter by an average of 0,82 (Lidstone et al., 2003). Another study showed that patients younger than 65 tended to have more symptoms than older patients (Walsh et al., 2000).

In addition, older patients experience less symptom distress than those who are younger (McMillan & Small, 2002). According to studies younger patients have more intense gastric pyrosis, dyspnea (Mercadante et al., 2000), insomnia, anxiety, fatigue, and depression (Redeker et al., 2000) and more frequently experience pain, dry mouth and abdominal swelling (Morita et al., 1999), than older patients. Confusion, however, was more common in older patients in relation to their performance status (Mercadante et al., 2000). This relationship between gender and age on the one hand versus symptoms on the other hand was also noted in the systematic review by Teunissen et al. (2007). However, the authors concluded that this relationship was limited because of lack of studies in this area and therefore no conclusions could be drawn about it.

Various studies show a relationship between performance status and symptoms. In the study of Walsh et al. (2000) patients with low performance status were more likely to experience blackouts, hallucinations, weakness, confusion, sedation, mucositits, anorexia, memory problems, dry mouth, and constipation than patients with better performance status. Similarly, better performance status was associated with less symptoms and a better function, in a study of severely ill cancer patients, while the worst ratings were found in patients with the poorest status (Jordhoy et al., 2001). Dysphagia, was found to be more intense in head and neck cancer patients at Karnofsky performance levels 50 and 40 compared with patients with other types of cancer in the study of Mercadante and colleagues (2000) and in the same study, patients with liver and pancreas, urogenital, breast, gastrointestinal, and lung cancer had more severe dry mouth at Karnofsky level 40 than patients with other

types of cancer. Another study showed that performance status influenced general malaise, edema, dyspnea and anorexia (Morita et al., 1999).

It also has to be considered that one symptom, as discussed earlier, and symptom management may lead to the rise of yet another symptom. Treatment of pain, such as opioids and some adjuvant medications to reduce side effects from opioids, may lead to insomnia. Similarly, treatment of fatigue such as use of corticosteroids may further exacerbate insomnia (Theobald, 2004). In the Japanese study of hospice patients that opioids contributed to dry mouth, myoclonus, and constipation. Furthermore, anticholinergic and antidopaminergic medications influenced dry mouth and myoclonus respectively (Morita et al., 1999). Symptoms may also lead to changes in the biological function of the body. Insomnia, for instance, can cause changes in both cytokines and stress hormones that may affect the immune function of the body and, presumably, result in more symptoms (Theobald, 2004).

Factors affecting quality of life.

There seem to be many factors that affect the quality of life in cancer patients such as individual symptoms, number of symptoms, impaired functioning, symptom severity, symptom distress, age, disease progression and recurrence, general health, and treatment side effects. The relationship between gender and quality of life is, however, not as clear.

Among the individual symptoms affecting quality of life are pain, fatigue, insomnia and depression. Since pain is one of the most distressing symptoms of cancer (Kaasa & Loge, 2003) its negative effect on patients' quality of life is not surprising (Ferrell, 1995; Niv & Kreitler, 2001). Ferrell and colleagues investigated pain and quality of life in various studies both quantitatively and qualitatively. When analyzing the data, the

authors discovered that pain had an impact on all four dimensions of quality of life in their model: physical, psychological, social and spiritual well-being (Ferrell et al., 1991). In a review of the literature regarding pain and quality of life Niv and Kreitler (2001) concluded that pain affects most domains of quality of life, mainly physical and emotional functioning, and that effect is based on factors like the extent of the pain, acuteness, intensity, duration, affectivity, underlying disease, individual's characteristics and meaning of the pain. However, according to Niv and Kreitler, the studies done to evaluate pain and quality of life are quite diverse and the vast number of variables makes comparison between studies difficult. In a study of 320 individuals, aged 16-65, both well, and representative of the range of diseases in Britain, a profound impact of pain on quality of life was demonstrated (Skevington, 1998). The study, using the WHOQOL questionnaire, showed that the physical domain of the questionnaire explained 57% of the total variance in quality of life and that pain and discomfort were found to play a significant role within that domain. Indeed, pain and discomfort were found to be significantly important in all the other domains of the questionnaire, except the domain on spirituality, religion and personal beliefs. Pain was found to be predictive of poorer quality of life, despite the existence of other health problems, and the study further showed that the duration of pain was associated with diminished quality of life. Pain free participants had the best quality of life, followed by those in acute pain, but the poorest quality of life was found among participants with chronic pain. The link between pain and quality of life has been less clear in other studies. Although pain relief was associated with better quality of life in a study by Rustøen et al. (2005) this relationship was weak (*r=0,17)* and when entered into a

blockwise hierarchical multiple regression analysis the effect of pain relief disappeared. In a study exploring the effects of morphine on the health related quality of life in cancer patients (Klepstad et al., 2000) no major changes in quality of life were observed despite pain being significantly reduced by the treatment. Of note is, however, that the participants in the study experienced more fatigue, pain, nausea/vomiting, appetite loss and constipation than the general public. In addition, their physical, role and social function were also worse than in the general public, as well as their global health. The complex symptomatology may, therefore have obscured the effect of treating pain.

Fatigue, like pain, is also both a common and distressing symptom for cancer patients. Its impact on quality of life is mainly through its effects on physical functioning and self care abilities, although, it also influences psychological well-being and even financial status, since fatigued patients have limited ability to work (Hofman et al., 2007). In a randomized clinical trial, of 98 patients with advanced cancer in the Netherlands (Beijer, Kempen, Pijls-Johannesma, de Graeff, & Dagnelie, 2008), using the EORTC QLQ-C30, fatigue correlated strongly with quality of life (r=-0,63). The fatigue scale was also the scale of the instrument that explained the largest proportion of the variance in quality of life or 39%. In another study, exploring fatigue in cancer patients and using the same instrument, fatigue correlated negatively with physical, role and social functioning, as well as with the global quality of life score. This relationship was, however, not explored further statistically in that study (Stone et al., 1999). Fatigue, on the other hand, was a significant predictor of quality of life in patients with lung cancer, alongside emotional functioning, accounting for 28% of the variance (Östlund,

Wennman-Larsen, Gustavsson, & Wengström, 2007). Fatigue, similarly, had a moderate negative effect (r=-.50) on quality of life of patients in chemotherapy (Redeker et al., 2000).

Insomnia, the most common sleep disorder in cancer patients, is also among those symptoms that have been shown to affect quality of life. In a study with a heterogeneous sample of 954 patients, with various types of cancer, a 10 unit increase in insomnia resulted in a decreased quality of life in the domains of physical, social and economic, psychological and spiritual, family and overall quality of life functioning, measured with Ferrans and Powers Quality of Life Index (Lis et al., 2008). Insomnia was also a contributing factor to poorer quality of life in a study by Redeker et al. (2000).

The prevalence of depression in cancer patients is estimated to lie somewhere between 10-25% (Pirl, 2004) and the symptom has proved to be an important predictor of quality of life. In a study on patients with pain from bone metastases, depression together with physical functioning, explained 42,4% of the variance in quality of life (Rustøen et al., 2005). Similarly, depression, alongside anxiety, explained 43% of the variance in quality of life in patients with various types of cancer in chemotherapy (Redeker et al., 2000). An Icelandic study on patients in chemotherapy also showed that patients experiencing anxiety and/or depression had a significantly worse quality of life than those who did not have these symptoms (Saevarsdottir, Fridriksdottir, & Gunnarsdottir, 2008). In line with these results are those of Peters and Sellick (2006) who studied 58 patients with advanced cancer receiving either home-based or inpatient palliative care. In their study, the variables that contributed significantly to the overall quality of life were global physical condition explaining 73%

of the variance, total personal control (encompassing personal control over medical care, treatment and symptoms) explaining a further 9,3% and finally depression adding 2,1% to the variance in quality of life.

The number of symptoms a patient experiences is also important. In their study on 240 patients with various types of cancer, Chang et al. (2000) found that as the number of symptoms per patient grew the poorer was their quality of life. Similar results were also obtained in a study of 246 patients with colon, prostate, ovary and breast cancer (Portenoy et al., 1994). Symptoms may also affect quality of life indirectly through its effect on the patients functioning (Östlund et al., 2007). In a study analyzing data from 157 patients with various cancer diagnoses, all experiencing pain from bone metastases, better physical and social functioning had a positive effect on quality of life (Rustøen et al., 2005).

Symptom severity (intensity) may as well affect quality of life. In a study of 191 patients in active cancer therapy the symptoms of pain, fatigue, depression, and sleep disturbance were clustered together according to the intensity of the symptoms. The four groups were "all low", "low pain high fatigue", "low fatigue high pain" and "all high". The results showed that those in the "all high" group had significantly lower quality of life scores than the other subgroups and those who were in the "all low" group had better quality of life scores than the other subgroups. However, the scores of those in the "low pain high fatigue" and "low fatigue high pain" were similar to the mean score of the total sample or 5,9 vs. 5,8. It has to be noted, though, that 50% of the sample belonged to these two last groups while only 28 (15%) patients belonged to the "all high" group (Miaskowski et al., 2006). Symptom intensity was also the main variable affecting quality of life, in a small study on cancer patients

who had esophagectomy, with symptom intensity explaining 50% of the variance in quality of life scores (Sweed, Schiech, Barsevick, Babb, & Goldberg, 2002).

Yet another factor associated with poorer quality of life is symptoms distress. In a sample of 178 adults with advanced cancer, receiving palliative homecare, total symptom distress score as well as severity of pain, constipation and dyspnea were all negatively related to quality of life. Regression analysis, however, showed that only symptom distress was significantly related to quality of life, explaining 35% of the variance (McMillan & Small, 2002).

Unlike studies, in the general population, older patients with cancer seem to evaluate their quality of life better than younger patients. In studies with random samples from the general population in Sweden and Norway, global quality of life score was lowest in the those 70 years old or older with the exception of Swedish men where the score remained similar to other age groups (Hjermstad, Fayers, Bjordal, & Kaasa, 1998a; Michelson, Bolund, Nilsson, & Brandberg, 2000). However, patients 60 years or older had better social and role functioning than younger patients in a study on 278 cancer patients in palliative care. The illness also had less financial impact on their lives and they rated their general health and quality of life significantly better than patients younger than 60 years (Lundh Hagelin et al., 2006). Older patients also experienced better quality of life than younger patients in an Icelandic study on 144 patients in chemotherapy (Saevarsdottir et al., 2008) and in a study on 351 outpatients with cancer in Texas (Parker, Baile, de Moor, & Cohen, 2003). Older cancer patients also seem to have fewer symptoms (Mercadante et al., 2000; Morita et al., 1999; Walsh et al., 2000) and/or lower levels of

symptoms than younger patients (Redeker et al., 2000) contributing to a better quality of life. Redeker et al. (2000) have also postulated that the same might be true for gender, with women experiencing poorer quality of life because of higher levels of symptoms, since, the effect of age and gender on quality of life disappeared when included in a regression analysis in their study. The relationship between gender and quality of life is, however, not clear. A study on 344 rural residents with cancer in Maine and Vermont showed that women experienced better quality of life than men (Schultz & Winstead-Fry, 2001) and similar results were obtained in a study on 146 patients with gastro-intestinal cancer in China (Yan & Sellick, 2004). Women, however, reported worse quality of life than men, both in the physical as well as the mental domain in the study of Parker et al. (2003) but no relationship was found between gender and quality of life in the Icelandic study, mentioned earlier (Saevarsdottir et al., 2008). In addition, studies are not in accordance whether other demographic variables may influence quality of life. In the study of Parker et al. (2003) patients with more education and those who were married had better quality of life in the mental domain but in the study of Saevarsdottir et al. (2008) no relationship existed between education or marital status and quality of life.

Quality of life also seems to get worse as the disease progresses. In the before mentioned study by Bjordal et al. (2000) patients with recurrent cancer of the head and neck not only had lower quality of life values than those who were disease free, but also than those who were newly diagnosed. This was true for the general quality of life score, but patients with recurrent disease also scored lower on all the functional scales and experienced more severe symptoms in all cases except for dyspnea and

diarrhea. Longitudinal data similarly suggests that quality of life worsens with disease progression. A study assessing the quality of life in 67 patients with advanced cancer showed that quality of life scores declined gradually in the last six months until death. This decline was more prominent in the last two to three months of life and psychological symptoms increased substantially in this time period (Hwang et al., 2003). In accordance with these results are those of Parker et al. (2003). In their study on 351 patients with breast, urologic, gynecologic, and gastro-intestinal cancers those without recurrent disease experienced better quality of life in the physical domain and those with less advanced disease had better quality of life in the mental domain (Parker et al., 2003). Similarly, patients with metastases from prostate cancer experienced diminished quality of life in the hormonal/vitality domain of quality of life assessed with the The Expanded Prostate Cancer Index Composite (EPIC-26) compared to patients without metastases (Sigurðardóttir, 2006).

General health may as well impinge on quality of life. In patients with prostate cancer worse health before diagnosis and the existence of two or more other concomitant diseases had a negative effect on quality of life in the hormonal/vitality quality of life domain (Sigurðardóttir, 2006). Multiple chronic health problems were likewise indicative of worse health related quality of life in a large sample of the general public in Sweden (Michelson, Bolund, & Brandberg, 2000).

Finally, cancer treatment and its side effects can affect quality of life. Brans et al. (2002) did a feasibility study on 20 patients treated with radionuclide therapy for inoperable hepatocellular carcinoma. Quality of life was evaluated before (0) treatment and one (1) and three (3) months after treatment. The results showed that quality of life was affected by

clinical side-effects of the treatment and worsened significantly from between both 0-1 month as well as 1-3 months. Physical functioning of these patients got worse both between 0-1 and 1-3 months and pain increased as well on these time points. Fatigue increased between 0-3 months but nausea/vomiting got worse between 0-1 months and then declined. It has to be noted that these result must be interpreted cautiously because of the small sample size. In line with this is the before mentioned study of Parker et al. (2003). In that study patients who were not in treatment at the study time had a significantly better quality of life in the physical domain than those who were in treatment. Treatment also affected quality of life in a study by Bjordal et al. (2000). For the patients treated with radiotherapy, surgery or chemotherapy, the physical, role and social functioning was impaired, the symptoms of fatigue, nausea and vomiting, pain, insomnia, appetite loss, and constipation got worse and the global quality of life score was lowered to 54 from that of 62 before treatment. Similarly, treatment had a negative impact on patients' life in a study of adult cancer patients in the USA (Cleeland et al., 2000). For those patients who either had blood/bone marrow transplantation (n=30) or chemotherapy (n=240) the mean symptom interference was significantly greater than in patients not receiving any treatment (n=69), despite that the mean symptom severity was similar between the three groups. Chemotherapy, correspondingly, had an effect on quality of life in an Icelandic study (Saevarsdottir et al., 2008). The study compared the quality of life score of patients before (T1) the initiation of chemotherapy and again three months later (T2). The results showed that quality of life was significantly worse at T2 than T1 with the worst scores in the physical and sexual domains. Different from these results are those of a

Turkish study on patients with advanced cancer receiving palliative radiotherapy (Hicsonmez, Kose, Andrieu, Guney, & Kurtman, 2007). In this study the global quality of life scores improved from 55,8 for those with better performance status before treatment up to 75,2 at the end of the treatment. Similarly the scores for those with worse performance status went from 45,8, before treatment, to 61,1 after treatment. It has to be noted here that only 20 and 16 patients had low performance status in the pre and post treatment groups respectively. Diverse treatments may also affect quality of life differently. In a study of patients with prostate cancer, the best quality of life in the hormonal/vitality domain was experienced by patients in watchful waiting followed by patients treated with surgery, then radiation, and finally hormonal therapy. In the sexual domain, however, quality of life of patients was mostly affected by hormonal therapy, followed by surgery, radiation and watchful waiting respectively (Sigurðardóttir, 2006).

Quality of life scores of cancer patients.

Quality of life seems to be worse in cancer patients than in the general public (Coates et al., 1997; Klepstad et al., 2000; Michelson, Bolund, & Brandberg, 2000). Comparing results of studies of quality on life, however, is not an easy task. Many quality of life instruments are in use, the levels of measurement within each instrument are not always the same, and it is unknown which difference in instruments' scores has clinical value (Kaasa & Loge, 2003). A common quality of life instrument is the EORTC QLQ-C30, further discussed in the methodology section. In this instrument a 10% difference in scores is considered a significant clinical change. A mean change of 5-10 in raw scores is considered little change, a difference between 10-20 moderate; and a difference of 20 or

more a great change (Osoba, Rodrigues, Myles, Zee, & Pater, 1998). It should be noted that only a fraction of the literature regarding quality of life scores of cancer patients will be presented here. The reason for choosing primarily studies using the EORTC QLQ-C30 and Icelandic studies is to ease the comparison with results from the current study. Since the literature on quality of life of cancer patients is very extensive it would have been impossible to review in its entirety.

In a study of 622 patients with head and neck cancer, quality of life score, assessed with the EORTC QLQ-C30, was significantly lower for patients newly diagnosed or with a recurrent disease compared to disease-free patients. In patients with a recurrent disease, indicating a more advanced state, the quality of life score was 55[2] while it was 63 for newly diagnosed patients and 73 for those who were disease-free. Patients with a recurrent disease also experienced worse pain, fatigue and appetite loss than those free of disease and similarly their role, emotional and social functioning was worse (Bjordal et al., 2000). A striking difference in quality of life was observed in a study comparing patients with advanced cancer in palliative care to healthy subjects. Measured with the EORTC QLQ-C30 the global quality of life score in cancer patients was 33[2], but 83 in healthy individuals. On the five functioning scales (role, emotional, physical, cognitive and social) of the instrument the scores of the healthy individuals ranged from 83-100[2] while the range was 17-67 for the cancer patients. The cancer patients also experienced much more severe symptoms than the healthy group (Stone et al., 1999). Similar results were also obtained in a cluster randomized trial in Norway (N=395) (Jordhoy et al., 2001), and a Dutch randomized clinical trial

[2] scale 0-100 with higher number indicating better quality of life

(N=98) (Beijer et al., 2008), of patients with advanced cancer, where global quality of life score, measured with the EORTC QLQ-C30, was 39[2] and of 48,5 respectively. Another Norwegian study, using the same instrument, of patients (N=40) being treated with opioids, further showed that the global health/quality of life score was 40[2] for patients treated with weak opioids, 49 when the patients were treated with immediate-release morphine, and 44 when they were treated with slow release morphine (Klepstad et al., 2000).

A difference between the general population and cancer patients is also evident when studies that use the EORTC QLQ-C30 are compared. In a large random sample of the Swedish population (n=3.069) the mean score for global quality of life for women was 74,7[3]and 78,1 for men (Michelson, Bolund, Nilsson et al., 2000). In a random sample of 3.000 Norwegians, however, the quality of life score was 75,3[3]for the total sample, 59,9 for cancer patients, 58,0 for patients with cardiac problems, and 86,6 for people reporting no health problems (Hjermstad, Fayers, Bjordal, & Kaasa, 1998a). In patients, with advanced chest malignancies (n=112) in palliative care in Sweden, the global quality of life score was only 50,1[3] (Nicklasson & Bergman, 2007). In patients receiving palliative radiotherapy for advanced cancer in Turkey the same score was 55,8[3] in patients with higher performance status but 45,8 in those with lower performance status (Hicsonmez et al., 2007).

An Icelandic study of 177 patients with prostate cancer (Sigurðardóttir, 2006), assessed quality of life with the SF-36 health survey. That study showed that quality of life was generally good with scores ranging from 62,07-84,72[3]. The lowest score was in the role-

[3] scale 0-100 with higher number indicating better quality of life

physical domain but the highest in mental health. The quality of life in this patients' group was comparable to the general USA norm used for comparison with the SF-36. The same study further assessed quality of life with the EPIC-26. The results indicated good quality of life with scores ranging from 86,77-92,61[3] in all scales except the sexual domain were the score was only 24,10 indicating diminished quality of life (Sigurðardóttir, 2006). Another Icelandic study, of 144 patients with various types of cancer, assessed the impact of chemotherapy on patients' quality of life. Quality of life was measured with the CARES-SF instrument and the scores were 0,76[4] before chemotherapy, but 0,95 after three months in treatment, indicating a relatively good quality of life. Of individual subscales the worst quality of life was found in the sexual and physical domains but the highest in the medical interaction domain (Saevarsdottir et al., 2008).

Summary of the theoretical background

Quality of life is a complex concept and despite its widespread use no collective definition of it exists. The concept is multidimensional in nature with the most prominent dimensions in the health literature being: physical, psychological, social/role functioning, emotional, and symptoms. Quality of life is both dynamic and evaluative, referring to that it may change in accordance with the state of the individual and the meaning he/she attaches to his/her situation. It is also quantifiable with measures of the concept being most reliable when subjectively assessed by a person competent of self-evaluation. Although the concept is mainly subjective it also has objective features which for some reasons are often

[4] scale 0-4 with lower scores indicating better quality of life

overlooked in research. The boundaries of quality of life are not clear cut, but, the concepts most often mistaken as being synonymous with quality of life are health, functional status, satisfaction and well-being. The characteristics of these concepts, however, differentiate them from quality of life, but nevertheless, they constitute important aspects of it. Like general quality of life, health related quality of life is also loosely defined, but the main difference between the concepts lies in the use of health related quality of life as an outcome measure to evaluate the impact of treatment or diseases on patients. Quality of life is affected by various factors, although it can be said that the concept has no preconditions since it simply exists throughout life. There are no criteria for what quality of life should be like so evaluation of the concept can only result in either improved or diminished quality of life.

Cancer patients experience around eight to eleven symptoms simultaneously that affect their daily life. Factors that cause symptoms are the disease itself and its treatment but psychological and/or physical factors may also play a role. Research is, however, inconclusive regarding the effects of age and gender. The Theory of Unpleasant Symptoms aims at explaining the relationship between influencing factors, symptoms and function. The most common symptoms experienced by cancer patients are fatigue, pain, lack of energy, weakness and appetite loss. The majority of symptoms are considered to be mild by cancer patients but nevertheless a number of patients experience severe symptoms. Many symptoms seem to co-occur and some symptoms seem to be the product of other symptoms. This relationship between symptoms has raised questions about the existence of symptom clusters. Research in that area is in its early state.

The quality of life of cancer patients is related to their symptomatology. Fatigue, insomnia, pain and depression are among the symptoms known to affect quality of life but the number of symptoms is also important since patients with more symptoms seem to have worse quality of life. Symptoms may both act directly to reduce quality of life but also through their effects on the functional status of the patient. Other factors that have impact on quality of life of cancer patients are the progression of the disease as well as side effects from treatment. Research has shown that cancer patients generally experience worse quality of life than the general public. Of interest is that older patients with cancer seem to have better quality of life than younger patients which is opposite to what is found in the general public.

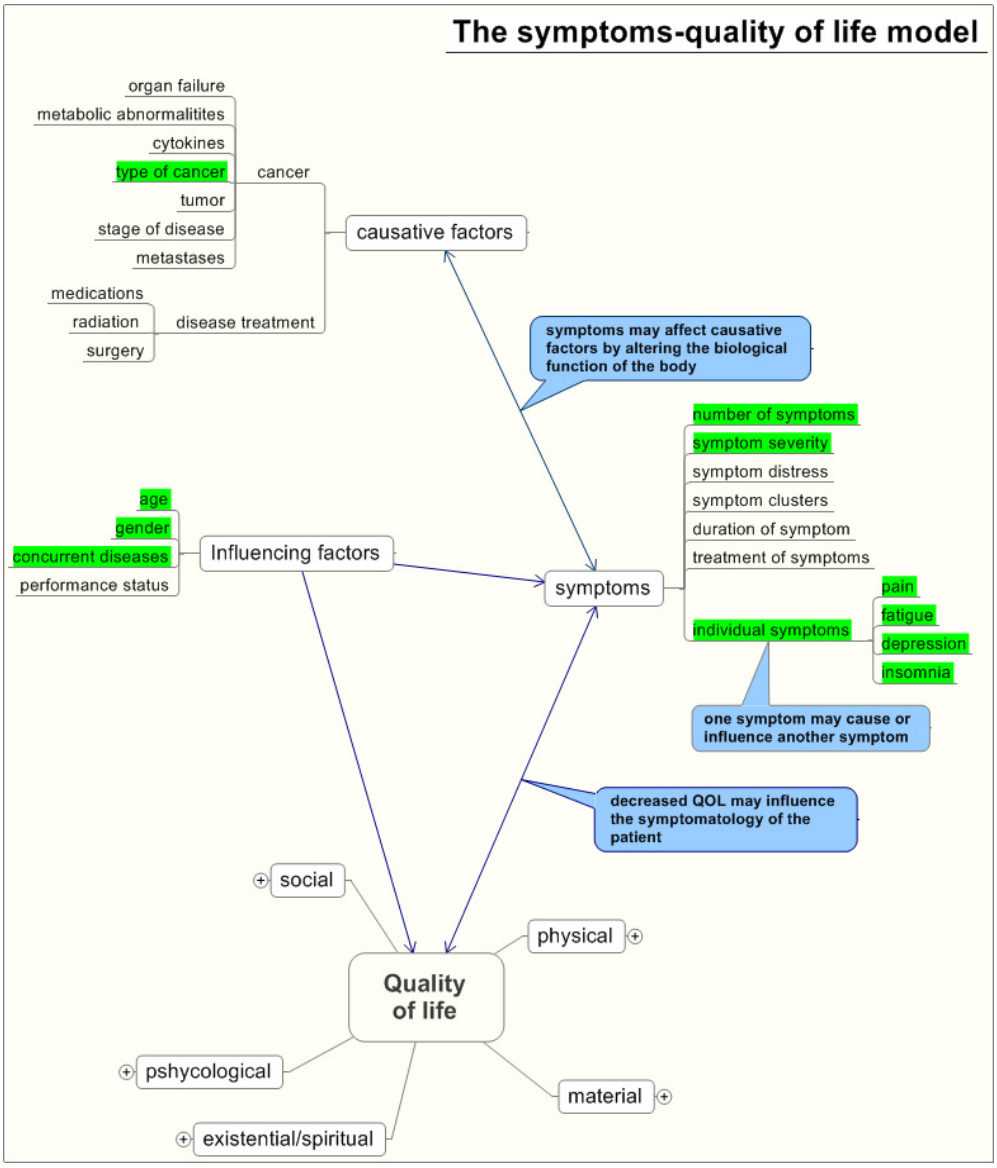
Although quality of life does not quite fulfill the prerequisites for a mature concept according to Morse and colleagues (1996) it is, nonetheless, a well-established one. It is widely used in research and it seems to be generally understood in the literature. As mentioned earlier the role of a concept in research depends on in what way the researcher chooses to use. Therefore, it is important for a researcher to define his perspective of the concept and the operationalization of it must be determined by the underlying theoretical framework of the study. When measuring quality of life, the instrument used must be appropriate for the population under study, but there also has to be correspondence between the instrument, the definition of the concept, and the dimensions of quality of life that will be measured.

The making of a model

After reviewing the literature the author has pulled together a model that attempts to explain the relationship between symptoms and quality of life, hereafter called the Symptoms-quality of life model. The first part of the Symptoms-quality of life model, see picture 3, shows the factors that may cause symptoms in cancer patients like the type of disease, metastases, cytokines etc. The second part displays the symptoms and factors associated with them that play a role in how the individual perceives his symptoms, like distress, severity, duration and number of symptoms. The third part, influencing factors, points out factors like age and gender, which may affect the symptomatology of the individual and how he/she evaluates his/her quality of life. The fourth part depicts quality of life and the dimensions of the concept. The model shows that causative factors set off symptoms and those symptoms can affect the well-being of the individual and, hence, affect all the dimensions of his/her quality of life. Influencing factors further modify how symptoms and quality of life are perceived. It has to be noted that one symptom may cause another symptom and that the model is reciprocal in such a way that symptoms may affect the causative factors and changes in quality of life may also influence how the individual experiences his symptoms.

The Symptoms-quality of life model bears some resemblance to the Theory of Unpleasant Symptoms (Lenz et al., 1997). In both instances there are influencing factors that affect symptoms and there are factors, like distress, that affect how the individual perceives the symptoms. The discrepancy, however, is that the former is based on the cancer literature and specifically shows the factors that affect symptoms in this patient

cohort. Furthermore the model illustrates how symptoms may modify patients' quality of life.



Picture 3. The Symptoms-quality of life model. **The arrows show the relationship between the factors of the model. The parts of the model that will be tested in this study are colored green.**

A resemblance is also found between the Symptoms-quality of life model and the revised health related quality of life model (Ferrans et al., 2005). The similarity is that both models show how biological function induces symptoms that ultimately affect the quality of life of the individual. The dissimilarity between the models, however, is that in the health related quality of life model symptoms influence the functional status which in turn affects the general health perceptions of the individual that finally affects the overall quality of life. In the symptom-quality of life model, however, symptoms need not affect health perceptions or function in order to influence quality of life. Another discrepancy between the models is that in the health related quality of life model the components of the model are affected by individual and environmental characteristics like body mass index, developmental status, culture, and neighborhood. In the symptom-quality of life model, however, no attempt has been made to review such relationships.

Purpose and value of study, definition and measurements of quality of life, research questions and hypotheses

The purpose of this study is to assess symptoms and quality of life among Icelandic patients diagnosed with advanced cancer. The prevalence of symptoms will be assessed as well as symptom severity. The relationship between symptoms and quality of life will be examined as well as the association of both the number of symptoms and individual symptoms with quality of life. The aims of the study are to add knowledge to the growing body of evidence regarding symptoms and quality of life in cancer patients and to test some parts of the Symptoms-quality of life model. However, since this study is a secondary analysis of data it was not designed to test the Symptoms-quality of life model. Therefore, many

factors that are included in the model are not amenable for testing in this study. The parts of the model, however, that will be tested in this study are the relationship between different types of cancers and the symptoms patients experience; the association of number of symptoms and symptom severity with quality of life; how the existence and severity of the individual symptoms of pain, fatigue, insomnia, and depression are associated with quality of life; and the difference in both symptoms and quality of life in relationship with age, gender and number of concurrent diseases.

The value of the study lies mainly in the fact that the study is the first of its kind conducted in Iceland. The results will illustrate the symptomatology of patients with advanced cancer and their quality of life. Furthermore, the information on the relationship between symptoms and quality of life has important clinical value since it can be used to improve patient care.

In this study quality of life is used as an outcome measure to evaluate the impact of cancer on patients. Therefore, the definition of the concept used here is the one by Cella (1996) where health related quality of life (QOL) is defined as to what extent one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment. This definition emphasizes how a disease, such as cancer, affects the quality of life of patients which is in line with the purpose of the study. Furthermore, the dimensions covered in the definition are in accordance with the dimensions of quality of life, assessed with the EORTC QLQ-C30 questionnaire, used in the study. The EORTC QLQ-C30 instrument is a questionnaire that has been widely used

in the cancer population, discussed in detail later, and hence, is appropriate for the participants in this study.

The research questions are:

1. How many symptoms do patients with advanced cancer experience?
2. What symptoms are most prevalent in patients with advanced cancer?
3. What is the symptom severity in patients with advanced cancer?
4. What is the quality of life score of patients with advanced cancer?
5. Do patients with different cancer diagnoses experience dissimilar symptoms?
6. Is there a relationship between gender and number of symptoms, symptom prevalence, symptom severity, and quality of life score in patients with advanced cancer?
7. Is there a relationship between age and number of symptoms, symptom prevalence, symptom severity, and quality of life score in patients with advanced cancer?
8. Is there a relationship between number of concurrent diseases and number of symptoms, symptom severity, and quality of life score in patients with advanced cancer?

The research hypotheses are:

1. Number of symptoms is associated with worse quality of life in patients with advanced cancer.
2. The symptoms of pain, depression, fatigue, and poor sleep are associated with worse quality of life in patients with advanced cancer.

Methodology

In this chapter the methodology of the study is introduced. The topics discussed in this chapter are the research design, the European Pharmacogenetic Opioid Study, participants and sample, instruments used in the study, demographic and clinical data, study procedure, ethical aspects and data analysis.

Research design

The research design is cross sectional, descriptive and correlational. It is a secondary analysis of data from the European Pharmacogenetic Opioid Study (described later). Correlational design is applicable when there is supported evidence that a relationship exists between variables (Brink & Wood, 1998). Descriptive, cross sectional design, however, is used to describe, observe and document phenomenona as they naturally occur at one time point. Descriptive correlational design can, hence, be used to describe the relationship between variables, in this study the relationship between symptoms and quality of life. However, this method is not suitable for inferring about cause and effect (Polit & Beck, 2004).

European Pharmacogenetic Opioid Study (EPOS)

This study is a part of a large international study, European Pharmacogenetic Opioid Study (EPOS), conducted in 10 European countries. The study sample consists of 3.000 participants, of which 150 come from Iceland (Klepstad et al., n.d.). The main purpose of EPOS is to examine:

- The pharmacogenetics of opioids, especially mutations that may have effect on the pharmacokinetics and receptors of opioid pain medications
- The serum concentration of opioide medication and their efficacy
- What types of opioides are used in clinical practice and in what doses
- The patients' evaluation of their pain and quality of life as well as the relationship between these factors
- Patients' barriers to pain treatment.

Participants and sample

The sample in this study is the convenience sample of 150 Icelandic patients recruited for the EPOS study. A convenience sample consists of the people most available to the researcher and although this sampling method is the weakest one (Beck et al., 2005) it is often the only possible way in the context of very sick populations. The size of the sample was chosen by the steering committee of the EPOS study with 150 being the minimum number of participants from each center (Klepstad et al., n.d.). The participants in this study were patients, 18 years or older who had a confirmed diagnosis of malignant disease and had been taking opioid pain medication for three days or more. Excluded were those who did not understand Icelandic or were otherwise unable to fill out the questionnaires because of confusion or illness.

Instruments

Instruments used in this study were the Icelandic version of the EORTC QLQ-C30 and a questionnaire assessing 17 symptoms and their severity, hereafter called the Symptom Checklist.

The EORTC QLQ-C30.

The EORTC QLQ-C30, version 3.0, is a 30 item quality of life instrument developed by the European Organization for Research and Treatment of Cancer (EORTC) and based on several preceding versions, the first in 1987 (Fayers & Bottomley, 2002). The purpose of the questionnaire is to measure general aspects of health related quality of life (Hjermstad, Fossa, Bjordal, & Kaasa, 1995; Lundh Hagelin et al., 2006; Michelson, Bolund, Nilsson et al., 2000) and it was designed to be cancer specific, appropriate for self administration, multidimensional and applicable in various cultural settings (Fayers & Bottomley, 2002). The EORTC QLQ-C30 is a core questionnaire designed to be used with additional modules. Today various types of disease specific modules are available such as breast, lung and ovarian, as well as modules specific to treatment modality or a quality of life dimension (EORTC, n.d.a). The dimensions covered in the questionnaire are physical, psychological and social but the main focus is on physical functioning and symptoms (Bruley, 1999).

The EORTC QLQ-C30 consists of both multi-item and single scales. There are five functional scales: physical (5 items), emotional (4 items), social (2 items), role (2 items) and cognitive (2 items); three symptom scales: fatigue (3 items), nausea and vomiting (2 items) and pain (2 items); two global scales for health status and quality of life; and finally six single item scales for the symptoms of dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties, resulting in total of 30 questions/items (EORTC, n.d.b). The global scales for health and quality of life are rated on a visual analogue scale ranging from 1 ("very poor") to 7 ("excellent"). All other scales, however, are four point Likert scales answered by the participants with "not" (1), "a little" (2), "quite a

bit" (3), and "very much" (4). The time frame is the past week (Brans et al., 2002; Michelson, Bolund, Nilsson et al., 2000). Examples of questions from the EORTC QLQ-C30:

	Not at all	A little	Quite a bit	Very much
Do you have any trouble taking a short walk outside of the house?	1	2	3	4
During the past week:				
Have you had pain?	1	2	3	4
Did you feel irritable?	1	2	3	4

The EORTC QLQ-C30 has been translated and validated in 81 languages, including Icelandic (Valgerður Sigurðardóttir, unpublished data) and has been used in around 3.000 studies worldwide (EORTC, n.d.a). The questionnaire has consistently been well accepted by patients with low percentage of missing items (Bjordal et al., 2000; Brans et al., 2002; Rodary et al., 2004). In studies of the general population, in Norway and Sweden, the percentage of missing items has ranged from 1,1 - 4,0% (Hjermstad, Fayers, Bjordal, & Kaasa, 1998a; Michelson, Bolund, Nilsson et al., 2000) and in studies on cancer patients the range of missing items has been about 3-5% (Bjordal et al., 2000; Rodary et al., 2004). Older people seem to leave more items behind than young people, ranging from 4,3% up to 12,5%, and women tend to leave more questions unanswered than men at least in the general population (Hjermstad et al., 1998a). It takes approximately 10-13 minutes to complete the list and most patients do not need assistance with completion (Aaronson et al., 1993; Bjordal et al., 2000). Patients also seem to understand the questions in a similar way as the researchers interpreting the results. In a study, where an observers

rating of the answers of patients during an interview was compared to the patients self assessment on the EORTC QLQ-C30, the general agreement was good with mean *kappa=0.85* (range 0,49-1,0) (Groenvold, Klee, Sprangers, & Aaronson, 1997). Furthermore, the questions are non-threatening and hence do not impose psychological distress on the participants (Brans et al., 2002; Rodary et al., 2004).

The reliability of the EORTC QLQ-C30 has proved to be adequate. The test/retest reliability of the EORTC QLQ-C30, measured with the *Pearson's correlation coefficient,* ranged from .82-.91 on the functional scales, .63-.86 on the symptom scales and single item scales ranged from .72-.84 in a study on 190 patients with various kinds of cancer. *Pearson's* r for global health related quality of life was .85 (Hjermstad et al., 1995). Internal consistency of the EORTC QLQ-C30 has also been good with *Cronbach's alpha* usually over .70 in various studies (Bruley, 1999) indicating an acceptable reliability (Fredheim, Borchgrevink, Saltnes, & Kaasa, 2007). In a study of lung cancer patients, performed in 12 countries, *Cronbach's alpha* ranged from .54-.86 before the start of treatment but .52-.89 during treatment (Aaronson et al., 1993).

The validity of the EORTC QLQ-C30 has also been tested. In a multicenter study the questionnaire had acceptable discriminant validity and furthermore the questionnaire turned out to be both reliable and valid for assessing the quality of life in cancer patients in various cultural settings (Aaronson et al., 1993). The EORTC QLQ-C30 has also been shown to have an adequate construct validity with scales of the questionnaire converging and diverging where appropriate (Niezgoda & Pater, 1993). In addition, the questionnaire can be used to assess the clinical difference between groups (Bjordal et al., 2000). The EORTC

QLQ-C30 has, however, been criticized for not measuring spiritual and/or existential issues indicating a lack of construct validity (Bruley, 1999). This lack of existential issues also raises questions as to whether the instrument can be used in palliative care. Recently, however, the questionnaire was tested in the palliative care setting and turned out be both reliable and valid for this patient group except for cognitive functioning (Nicklasson & Bergman, 2007). A shorter version of the C-30 has also been developed: the EORTC QLQ-C15-PAL, a core questionnaire that is appropriate for patients with advanced disease in palliative care (Groenvold et al., 2006).

The Symptom Checklist.

The Symptom Checklist consists of 17 symptoms common in cancer patients, such as, fatigue, anxiety, depression, dyspnea, constipation and nausea. The questionnaire was to be completed by the research nurse, according to the study plan, who asked the patients if they had the symptoms and if they did they were asked how severe their symptoms were. The scoring range is 0-3 with 0 being not experiencing the symptom, 1 is mild severity, 2 moderate, and 3 indicates that the symptom is severe. The time frame is the past 24 hours.

A drawback of the questionnaire is that it does not have an established reliability or validity. However, the choice of items in the questionnaire was based upon the European Association for Palliative Care (EAPC) research network 2002 survey (P. Klepstad, personal communication, June 24th 2008) and have been used to assess symptoms and symptom severity before (Klepstad et al., 2005). In addition, studies using lists with similar content have yielded results that are in line with results of other studies using validated symptom questionnaires (Homsi et

al., 2006; Tsai et al., 2006; Walsh et al., 2000). Homsi et al. (2006) have even criticized the instruments available for the lack of number of symptoms assessed and hence ignoring many common symptoms in patients with generalized cancer.

Demographic and clinical data

Demographic data regarding gender and age, and clinical data regarding diagnosis, existence of metastases, and concurrent diseases were also gathered, both from the patients themselves as well as from their medical charts.

Study procedure

A research nurse was responsible for recruitment of 150 participants according to the study plan. The nurse worked in close collaboration with the oncology ward (11E), hematology ward (11G), outpatients ward (11B), gynoncology ward (21A), and the hospital palliative care team in Landspítali University Hospital, palliative inpatient-wards in Kopavogur and in Landakot, and the palliative home care units of Landspítali Universtiy Hospital and the privately funded Karitas. If an eligible patient was in care in these units the nurse and/or doctor responsible for the patient's care introduced the study to the patient. If the patient was interested in participating the research nurse sent out or gave the patient a letter of introduction to the study. In the palliative units, responsible nurse gave an introduction letter to the patients explaining the study and if the patient wanted to participate the nurse notified the research nurse. In all cases where the patient was willing to participate the research nurse met with the patient and explained the study to him/her. After signing an

informed consent the research nurse administered the questionnaires and gathered information from the patient at a time suitable for him/her. This took about 1-1 1/2 hours where about 40 minutes were spent on answering the questionnaires (a total of 6 questionnaires were used in the EPOS study). The research nurse also collected information from medical charts and took blood samples for the EPOS study. Patients only needed to answer questionnaires and donate a blood sample once. The research nurse, however, usually met every participant at least twice, once to do the interview and administer the questionnaires and a second time to collect the blood sample. Participants met with the research nurse either at the hospital wards or in their own home. Recruitment began in October 2005 and ended in March 2008.

Ethical aspects

To minimize the pressure to participate in the study the research nurse did not approach the patient until a member of staff had spoken to the patient and checked if he/she was interested in participating. Consent from the patient's responsible doctor was also obtained and all participants signed an informed consent before participating in the study. Both the informed consent, and the data gathering procedure, were in accordance with regulation set by the Data Protection Authority regarding informed consent in health science research (Reglur um upplýst samþykki í vísindarannsókn á heillbrigðissviði Nr. 170/2001). The patients did not get paid for their participation nor were they compensated in any other way.

It can be both physically and psychologically difficult to participate in a study, not least for patients with a generalized disease. Filling out questionnaires and answering questions can cause or increase

fatigue and some questions may be worrisome for individual patients. In this study the research nurse, who gathered all the data, was both an experienced nurse and a deacon. Therefore, she was well suited to both assess the patients' physical and mental state, as well as to deal with the patients' worries and questions. To minimize the burden of participation the research nurse collected data in close collaboration with the patients. Although the patients only needed to answer questionnaires and donate a blood sample once, data gathering was time consuming and the patients easily tired. Therefore, the research nurse met each participant more than once, according to his/hers wishes, so that he/she would not get too tired. To reduce the amount of discomfort from needle stabs blood samples for the study were preferably collected by during routine blood tests.

The study was approved by the National Bioethics Committee, The Data Protection Authority, and the Chief Medical Executive of Landspítali University Hospital.

Data analysis

Statistics.

Descriptive statistics were used to describe the number of symptoms, symptom prevalence, symptom severity, quality of life and demographic data. Categorical variables were summarized as frequencies and percentages, but the mean, standard deviation (SD), median, and range were reported for continuous variables. Of inferential statistics the *T-test for independent samples* was used to compare means between dichotomous and continuous variables, but *One way ANOVA* was used to compare means of categorical (three or more) and continuous variables. When the dependent variable was not normally distributed *Mann-Whitney*

and *Kruskal-Wallis tests* were also used, in addition to *T-test* and *One way ANOVA* respectively, to compare means between groups. *Chi-square test* was used to test the difference between nominal and ordinal variables. *Pearson's r* and *Spearman's ρ* were used to assess correlations between continuous and ordinal variables respectively. *Multiple linear regression* was used to model the association between a) number of symptoms and quality of life, and b) the individual symptoms of pain, fatigue, poor sleep, and depression, and quality of life. In the latter case hierarchical method was used, with variables entered into the model based on their importance. For the inferential statistics the significance level was set at $p = 0{,}05$. The SPSS software 16.0 was used for analysis.

Variables.

Age was either used as a continuous variable or categorized into four groups, 20-55, 56-65, 66-75, and 76 years and older. The reasons for this categorization were several. In the first place, very few patients were younger than 50 years making statistical testing less accurate. Secondly, this grouping reflects different aspects of the life stages. Patients 55 years and younger are generally working full time and many still have children living at home. People 56-65 are still working full time but entering the role of grandparents. The age group 66-75 represents retirement and adjustment to old age. Finally the 76+ group corresponds to the elderly. Similar categorization has been reported elsewhere (Jordhoy et al., 2001).

Cancer diagnoses were categorized into eight groups: Prostate, breast, female reproductive, lung, gastro/intestinal, multiple, other, and unknown cancers. Multiple cancers include those with more than one cancer diagnoses. Other cancers, however, contains hematological cancers, urological cancers other than prostate, and other cancers not

specified. Because of the sample size further categorization was not possible.

Concurrent diseases were tested as: a) no disease versus one or more diseases, b) no-two diseases versus three-six diseases, c) no disease, one-two diseases, and three-six diseases, and d) as a continuous variable. Further categorization was not optional because of few patients having more than three concurrent diseases.

In the regression models the global health/quality of life scale of the EORTC QLQ-C30 was used as the outcome (dependent) variable. The predictor (independent/covariates) variables, however, were number of symptoms in the model in research hypothesis one, but pain, fatigue, poor sleep, and depression in the model in research hypothesis two. In both models age and gender were adjusted for as recommended by Hjermstad and colleagues (1998).

Use of questionnaires.

Number of symptoms, prevalence, and severity was reported for both the Symptom Checklist and the EORTC QLQ-C30. The reason for using both questionnaires to evaluate the symptomatology of the participants is that the Symptom Checklist assessed symptoms the last 24 hours but the time frame in the EORTC QLQ-C30 is the past week.

The Symptom Checklist was used to assess symptoms in the past 24 hours. The research nurse asked the patients if they had a symptom assessed with the list and if so the patient rated the severity of the symptom as mild, moderate, or severe. If patients were unable to answer these questions, because of illness or for other reasons, data was gathered from the ward nurse, who was taking care of the patient, according to study protocol. This was only done on less than five occasions.

The EORTC QLQ-C30 was used to evaluate the symptoms and quality of life in the past week. Patients filled out the questionnaire themselves, but many patients needed assistance with filling it out because they felt too weak to do so themselves. This should, however, not lessen data quality since according to Aaronson et al. (1993) patients' responses are not influenced by being interviewed instead of filling out the questionnaire themselves. Raw scores of the questionnaire were converted into 0-100 scales according to the EORTC QLQ-C30 scoring manual (Fayers et al., 2001). For the five functional scales and the global health status/quality of life scales a higher score indicates better function and quality of life. For the symptom scales and single items a higher score, however, indicates more symptom severity or symptom burden (Fredheim et al., 2007). When interpreting the scores of the EORTC QLQ-C30, as previously mentioned, a mean change of 5-10 is considered a little change; a difference of 10-20 is deemed to be moderate; and finally, a difference of 20 or more is considered a great change in scores. However, 10% difference represents a significant clinical change in scores (Osoba et al., 1998).

To explore the relationship between symptoms and quality of life the symptoms assessed with the EORTC QLQ-C30 were used in the regression models. The reason for not using the symptom checklist was the different time frame of the questionnaires, rendering it illogical to evaluate the quality of life in the past week based on symptoms in the last 24 hours. The EORTC QLQ-C30 evaluates 16 symptoms, see table 4 and although the questionnaire was not designed as a symptom assessment tool it, nonetheless, covers many of the most common symptoms in cancer (Stromgren, Groenvold, Pedersen, Olsen, & Sjogren, 2002). Four

symptoms are included in the EORTC QLQ-C30 that are not in the Symptom Checklist and five of the seventeen symptoms of the checklist are not found in the EORTC QLQ-C30. Table 4 shows the symptoms assessed with both questionnaires and the correlation between the symptoms. In line with Stromgren and colleagues' (2002) categorization of the symptoms in the EORTC QLQ-C30 tiredness was chosen as a synonym of fatigue and weakness as synonymous with generalized weakness.

The reason for using individual symptoms instead of the symptom scales in the EORTC QLQ-C30 is that the scales evaluate both the symptom as well as the impact of the symptom on the individual or other symptoms. Depression is for instance included in the emotional function scale, alongside worry, feeling tense, and feeling irritable. The pain scale includes pain and the interference of pain on the patient's daily activities. Finally, the fatigue scale incorporates feeling tired, weakness and the need to rest. Since it was the researcher's intension to evaluate the relationship between the individual symptoms and quality of life this method was chosen. The scores for the individual symptoms were used on their original scale, 1-4 (not converted into 0-100).

Unlike the symptom checklist in the EORTC QLQ-C30 the patient is asked to rate if he/she experiences a symptom as "a little", "quite a bit" and "very much", but not as mild, moderate or severe. In both questionnaires, however, the questions are scaled on a four point Likert scale and to aid in comparison these scales were converted to 0-3 (instead of 1-4) where 0 means no symptom, 1 = a little/mild, 2 = quite a bit/moderate, 3 = very much/severe. As to whether "a little" connotes to

mild etc. is not certain, but since the scaling is the same it is reasonable to use them in comparison of symptom severity.

Table 4. Correlation between symptoms in the Symptom Checklist (the past 24 hours) and the EORTC QLQ-C30 (the past week)

Symptom Checklist	Spearman's ρ	EORTC QLQ C-30
Symptoms that do match in the questionnaires		
pain	ρ (144) = .568, *p*=0,000	pain
fatigue	ρ (143) = .492, *p*=0,000	tiredness
generalized weakness	ρ (143) = .501, *p*=0,000	weakness
anxiety	ρ (144) = .529, *p*=0,000	worry
anorexia	ρ (145) = .780, *p*=0,000	lack of appetite
depression	ρ (145) = .541, *p*=0,000	depression
constipation	ρ (145) = .634, *p*=0,000	constipation
poor sleep	ρ (143) = .416, *p*=0,000	insomnia
dyspnea	ρ (145) = .584, *p*=0,000	short of breath
nausea	ρ (145) = .674, *p*=0,000	nausea
vomiting	ρ (145) = .416, *p*=0,000	vomiting
diarrhea	ρ (144) = .370, *p*=0,000	diarrhea
Symptoms that do not match in the questionnaires		
itching		difficulty remembering
hallucination		difficulty concentrating
hiccups		feeling tense
local weakness		irritation
confusion		

Results

Demographics

One hundred and fifty patients were included in the study. Of those, 62 (41%) were men and 88 (59%) women, all Caucasians. The patients' age ranged from 20-92 years with the mean (SD) age of 64,7 (12,7) years. Most participants were out-patients (67%), attending day- and ambulatory care and/or homecare, and the main cancer diagnoses, covering two-thirds of the participants, were gastro/ intestinal (n=33), lung (n=24), breast (n=22), and prostate (n=21) cancer. The vast majority had metastases (91,3%) and a large number of patients (81,3%) had a concurrent disease, other than cancer, mainly heart (41%) and vascular diseases (43%). Demographic data and clinical characteristics are in table 5.

Data quality

The Symptom Checklist.

The Symptom Checklist was used to assess symptoms in the past 24 hours. Data was missing from one patient and in addition two patients did not answer the question if they had poor sleep or not.

The internal consistency of the symptom checklist in this study, measured with *Cronbach's α,* was .74, indicating an acceptable reliability.

Table 5. Main demographic and clinical characteristics of patients with advanced cancer (N=150)

		n (%)♠
Age	20-55 years	31 (20,7)
	56-65 years	42 (28,0)
	66-75 years	46 (30,7)
	76 years and older	31 (20,7)
Gender	Male	62 (41,3)
	Female	88 (58,7)
Ward	Palliative care unit/hospice	31 (20,7)
	General oncology ward	15 (10,0)
	Surgical ward	4 (2,7)
	Out-patients clinic/homecare	100 (66,7)
Cancer diagnoses	Female reproductive	17 (11,3)
	Lung	24 (16,0)
	Breast	22 (14,7)
	Prostate	21 (14,0)
	Gastro/intestinal	33 (22,0)
	Other	16 (10,7)
	More than one type of cancer	10 (6,7)
	Unknown	7 (4,7)
Number of concurrent diseases		
	none	28 (18,7)
	1-2	73 (48,7)
	3-6	49 (32,7)
Metastases	yes	137 (91,3)
	no	13 (8,7)

♠ due to rounding percentage may exceed 100%

The EORTC QLQ-C30.

The EORTC QLQ-C30 was used to evaluate the symptoms and quality of life in the past week. Five patients were unable to complete the questionnaire, three women and two men, all because they felt they were too sick to answer. The lowest response rate was found for the questions "were you tired" and "have you felt weak", or 95,3%.

Table 6. Internal consistency coefficients/ *Cronbach's α* for the EORTC QLQ-C30 subscales

Scale	*Cronbach's α*
Functional scales	
Physical functioning	.85
Role functioning	.74
Emotional functioning	.82
Cognitive functioning*	.49
Social functioning*	.69
Symptom scales	
Fatigue	.79
Nausea and vomiting	.76
Pain	.73
Global scale	
Global health status/QOL	.78

* *Chronbach's α* lower than .70

The *Cronbach's α* for the total EORTC QLQ-C30 was .82. Of individual scales cognitive functioning and social functioning had *Cronbach's α* lower than .70. The internal consistency of the scales in the questionnaire is presented in table 6.

Question 1. How many symptoms do patients with advanced cancer experience?

Number of symptoms in the past 24 hours.

The Symptom Checklist, which includes a total of 17 symptoms, was used to assess symptoms in the past 24 hours. The number of symptoms per patient ranged from 0-12. Only one patient (0,7%) had no symptoms at all, but 15 (10,2%) patients had experienced 10 or more symptoms in the past 24 hours. The mean (SD) number of symptoms for the total sample was 6,2 (2,5). Women had a mean (SD) of 6,5 (2,7) symptoms, but men 5,9 (2,2). Descriptive statistics for the number of symptoms is presented in tables 7 and 8.

Table 7. Number of advanced cancer patients (N=148) with symptoms in the past 24 hours assessed with the Symptom Checklist

number of symptoms	n (%)
0-3 symptoms	20 (13,5)
4-6 symptoms	60 (40,5)
7-9 symptoms	53 (35,8)
10-12 symptoms	15 (10,2)
13 or more	0 (0,0)

Table 8. Mean (SD), median, and range of number of symptoms of advanced cancer patients according to age and gender in the past 24 hours, assessed with the Symptom Checklist

		N	mean (SD)	median	range
All patients		148	6,2 (2,5)	6,0	0-12
Gender	men	62	5,9 (2,2)	6,0	1-12
	women	86	6,5 (2,7)	6,5	0-12
Age	20-55 years old	30	6,4 (2,9)	7,0	1-12
	56-65 years old	42	6,6 (2,3)	7,0	2-12
	66-75 years old	45	6,6 (2,5)	6,0	2-12
	76 years and older	31	4,9 (2,3)	5,0	0-11

Number of symptoms in the past week.

Table 9. Number of advanced cancer patients (N=148) with symptoms in the past week assessed with the EORTC QLQ-C30

number of symptoms	n (%)
0-3 symptoms	8 (5,8)
4-6 symptoms	26 (18,4)
7-9 symptoms	47 (33,3)
10-12 symptoms	36 (25,5)
13 and more	24 (17,0)

Number of symptoms in the past week was evaluated with the EORTC QLQ-C30. The questionnaire contains a total of 16 symptoms. The number of symptoms per patient ranged from 1-16. The mean (SD) number of symptoms for the total sample was 9,0 (3,3) and 60 (42,5%)

patients had 10 or more symptoms in the past week. The mean (SD) number of symptoms for men was 8,8 (2,8) but 9,1 (3,7) for women. Descriptive statistics for the number of symptoms is presented in table 9 and 10.

Table 10. Mean (SD), median, and range of number of symptoms of advanced cancer patients according to age and gender in the past week, assessed with the EORTC QLQ-C30

		N	mean (SD)	median	range
All patients		141	9,0 (3,3)	9	1-16
Gender	men	58	8,8 (2,8)	9	3-15
	women	83	9,1 (3,7)	9	1-16
Age	20-55 years old	27	9,7 (3,8)	10	1-16
	56-65 years old	41	9,7 (3,1)	10	3-16
	66-75 years old	42	8,9 (3,2)	9	3-15
	76 years and older	31	7,6 (3,0)	8	3-15

Question 2. What symptoms are most prevalent in patients with advanced cancer?

Prevalence of symptoms in the past 24 hours.

The five most common symptoms for the whole sample were fatigue (85,2%), pain (82,6%), generalized weakness (81,9%), dyspnea (54,4%), and anorexia (51,7%), measured with the Symptom Checklist. For women pain (90,8%) was the most common symptom followed by fatigue (83,9%), but for men, fatigue (87,1%) was the most prevalent symptom

followed by generalized weakness (83,9%). The least prevalent symptoms were hallucinations, vomiting, and hiccups, with less than 10% of the patients experiencing these symptoms. Table 11 shows the symptom prevalence in the past 24 hours.

Table 11. Symptom prevalence in patients with advanced cancer in the past 24 hours, assessed with the Symptom Checklist, for total sample and men and women respectively

Symptom	Total sample N(%)	Men n(%)	Women n(%)
Fatigue	127 (85,2)	54 (87,1)①	73 (83,9) ②
Pain	123 (82,6)	44 (71,0) ③	79 (90,8) ①
Generalized weakness	122 (81,9)	52 (83,9) ②	70 (80,5) ③
Dyspnea	81 (54,4)	33 (53,2) ④	48 (55,2) ⑤
Anorexia	77 (51,7)	28 (45,2) ⑤	49 (56,3) ④
Local weakness	63 (42,3)	26 (41,9)	37 (42,5)
Constipation	53 (35,6)	22 (35,5)	31 (35,6)
Nausea	52 (34,9)	16 (25,8)	36 (41,4)
Anxiety	49 (32,9)	20 (32,3)	29 (33,3)
Depression	43 (28,9)	16 (25,8)	27 (31,0)
Poor sleep	32 (21,6)	12 (19,4)	20 (23,3)
Itching	29 (19,5)	11 (17,7)	18 (20,7)
Diarrhea	26 (17,4)	9 (14,5)	17 (19,5)
Confusion	20 (13,4)	10 (16,1)	10 (11,5)
Hiccups	10 (6,7)	4 (6,5)	6 (6,9)
Vomiting	9 (6,0)	3 (4,8)	6 (6,9)
Hallucination	8 (5,4)	3 (4,8)	5 (5,7)

Numbers in circles indicate the rank within gender

Prevalence of symptoms in the past week.

The five most common symptoms for the whole sample were fatigue (90,9%), pain (90,3%), weakness (89,5%), memory loss (68,3%), and loss of appetite (62,8), measured with the EORTC QLQ-C30. For women, pain (92,9%) was the most common symptom followed by fatigue (90,5%) ,

but for men, fatigue and weakness were the most prevalent symptoms (91,5%) followed by pain (86,4%). Of the sixteen symptoms assessed, only vomiting and irritation were experienced by less than 30% of the participants the past week. Table 12 shows the symptom prevalence the past week and comparison of symptom prevalence in the past 24 hours versus in the past week is presented in table 13.

Table 12. Symptom prevalence in patients with advanced cancer in the past week, assessed with the EORTC QLQ-C30, for total sample and men and women respectively

Symptom	Total sample N(%)	Men n(%)	Women n(%)
Fatigue	**130 (90,9)**	**54 (91,5) ①②**	**76 (90,5) ②**
Pain	**130 (90,3)**	**51 (86,4) ③**	**79 (92,9) ①**
Weakness	**128 (89,5)**	**54 (91,5) ①②**	**74 (88,1) ③**
Memory loss	**99 (68,3)**	**39 (65,0) ④⑤**	**60 (70,6) ④**
Loss of appetite	**91 (62,8)**	**39 (65,0) ④⑤**	**52 (61,2) ⑤**
Constipation	85 (58,6)	38 (63,3)	47 (55,3)
Worry (anxiety)	84 (58,3)	35 (58,3)	49 (58,3)
Dyspnea	82 (56,6)	35 (58,3)	47 (55,3)
Lack of concentration	80 (55,2)	33 (55,0)	47 (55,3)
Feeling tense	71 (49,0)	27 (45,0)	44 (51,8)
Depression	70 (48,3)	28 (46,7)	42 (49,4)
Nausea	66 (45,5)	26 (43,3)	40 (47,1)
Diarrhea	61 (42,4)	31 (51,7)	30 (35,7)
Insomnia	57 (39,6)	22 (37,3)	35 (41,2)
Irritation	42 (29,0)	13 (21,7)	29 (34,1)
Vomiting	27 (18,6)	7 (11,7)	20 (23,5)

Numbers in circles indicate the rank within gender

Table 13. Comparison of symptoms in patients with advanced cancer in the past 24 hours versus the past week, assessed with two different questionnaires

Symptoms in the past 24 hours♠		**Symptoms in the past week♦**	
Symptom	n (%)	Symptom	n (%)
Fatigue	**127 (85,2)**	**Fatigue**	**130 (90,9)**
Pain	**123 (82,6)**	**Pain**	**130 (90,3)**
Generalized weakness	**122 (81,9)**	**Weakness**	**128 (89,5)**
Dyspnea	81 (54,4)	Memory loss	99 (68,3)
Anorexia	**77 (51,7)**	**Loss of appetite**	**91 (62,8)**
Local weakness	63 (42,3)	Constipation	85 (58,6)
Constipation	53 (35,6)	Worry (anxiety)	84 (58,3)
Nausea	52 (34,9)	Dyspnea	82 (56,6)
Anxiety	49 (32,9)	Lack of concentration	80 (55,2)
Depression	43 (28,9)	Feeling tense	71 (49,0)
Poor sleep	32 (21,6)	Depression	70 (48,3)
Itching	29 (19,5)	Nausea	66 (45,5)
Diarrhea	**26 (17,4)**	**Diarrhea**	**61 (42,4)**
Confusion	20 (13,4)	Insomnia	57 (39,6)
Hiccups	10 (6,7)	Irritation	42 (29,0)
Vomiting	**9 (6,0)**	**Vomiting**	**27 (18,6)**
Hallucination	8 (5,4)		

♠ assessed with the Symptom Checklist
♦assessed with the EORTC QLQ-C30

Question 3. What is the symptom severity in patients with advanced cancer?

Symptom severity in the past 24 hours.

The mean (SD) symptom severity was 0,7 (0,4) on a scale from 0-3[5] for the total sample. The symptoms that had the highest mean severity were: generalized weakness, fatigue, pain, dyspnea, and anorexia. The mean (SD) symptom severity for women was 0,7 (0,4) versus 0,6 (0,3) for men. The mean symptom severity is presented in table 14.

Table 14. Mean (SD) symptom severity in advanced cancer patients in the past 24 hours of the five most severe symptoms and all symptoms combined for the total sample, gender, and age

Symptom	Total sample:	Gender:		Age:			
		men	women	20-55	56-65	66-75	76+
Generalized	1,91	1,95	1,87	1,87	2,00	1,96	1,74
weakness	(1,1)	(1,1)	(1,2)	(1,1)	(1,1)	(1,2)	(1,2)
Fatigue	1,83	1,82	1,84	2,07	1,98	1,87	1,35
	(1,1)	(1,0)	(1,1)	(1,0)	(0,9)	(1,1)	(1,1)
Pain	1,39	1,03	1,64	1,47	1,55	1,35	1,16
	(1,0)	(0,9)	(0,9)	(0,9)	(1,0)	(0,9)	(0,9)
Dyspnea	1,07	1,10	1,05	1,20	1,40	1,04	0,52
	(1,2)	(1,2)	(1,1)	(1,1)	(1,2)	(1,2)	(1,0)
Anorexia	1,03	0,85	1,15	0,87	0,93	1,24	1,00
	(1,2)	(1,1)	(1,2)	(1,3)	(1,0)	(1,2)	(1,2)
All symptoms	0,7	0,6	0,7	0,7	0,8	0,7	0,5
	(0,4)	(0,3)	(0,4)	(0,5)	(0,4)	(0,4)	(0,3)

[5] 0 means no symptom,1 mild, 2 moderate, and 3 a severe symptom

Table 15. Proportion of advanced cancer patients with none, mild, moderate, and severe symptoms in the past 24 hours, measured with the Symptom Checklist

Symptom	N	Symptom severity % (n)			
		None	Mild	Moderate	Severe
Generalized weakness	149	18,1 (27)	14,8 (22)	25,5 (38)	41,6 (62)
Fatigue	149	14,8 (22)	20,8 (31)	30,9 (46)	33,6 (50)
Anorexia	149	48,3 (72)	19,5 (29)	13,4 (20)	18,8 (28)
Dyspnea	149	45,6 (68)	20,1 (30)	16,1 (24)	18,1 (27)
Constipation	149	64,4 (96)	9,4 (14)	8,7 (13)	17,4 (26)
Pain	149	17,4 (26)	41,6 (62)	25,5 (38)	15,4 (23)
Local weakness	149	57,7 (86)	19,5 (29)	14,1 (21)	8,7 (13)
Nausea	149	65,1 (97)	19,5 (29)	6,7 (10)	8,7 (13)
Depression	149	71,1 (106)	16,8 (25)	6,7 (10)	5,4 (8)
Anxiety	149	67,1 (100)	13,4 (20)	14,1 (21)	5,4 (8)
Poor sleep	148	78,4 (116)	9,5 (14)	6,8 (10)	5,4 (8)
Itching	149	80,5 (120)	10,7 (16)	3,4 (5)	5,4 (8)
Vomiting	149	94,0 (140)	2,0 (3)	0,7 (1)	3,4 (5)
Confusion	149	86,6 (129)	8,7 (13)	2,0 (3)	2,7 (4)
Diarrhea	149	82,6 (123)	11,4 (17)	4,0 (6)	2,0 (3)
Hallucination	149	94,6 (141)	4,7 (7)	0,0 (0)	0,7 (1)
Hiccups	149	93,3 (139)	4,7 (7)	1,3 (2)	0,7 (1)

The total number of symptoms, in the past 24 hours, reported by the whole sample was 924. Of these, 368 (39,8%) were rated as mild, 268 (29,0%) as moderate, and 288 (31,2%) as severe. The highest prevalence of severe symptoms were generalized weakness (41,6%), fatigue (33,6%), anorexia (18,8%), dyspnea (18,1), and constipation (17,4%). Vomiting,

hallucinations, hiccups, diarrhea, and confusion were, however, considered severe by less than five percent of the patients. Table 15 shows the portion of patients with none, mild, moderate, and severe symptoms.

Symptom severity in the past week.

The mean (SD) symptom severity was 0,9 (0,5) on a scale from 0-3[6] for the total sample. The symptoms that had the highest mean severity were: weakness, fatigue, pain, loss of appetite, and constipation respectively. The mean (SD) symptom severity for women was 1,0 (0,5) versus 0,9 (0,5) for men. The mean symptom severity is presented in table 16.

Table 16. Mean (SD) symptom severity in advanced cancer patients in the past week of the five most severe symptoms and all symptoms combined for the total sample, gender, and age

Symptom	Total sample:	Gender:		Age:			
		men	women	20-55	56-65	66-75	76+
Weakness	1,87	1,83	1,90	1,89	2,10	1,86	1,58
	(1,0)	(1,0)	(1,0)	(0,9)	(0,9)	(1,0)	(1,1)
Fatigue	1,73	1,69	1,76	1,89	1,95	1,67	1,39
	(1,0)	(1,0)	(1,0)	(0,8)	(0,9)	(0,9)	(1,1)
Pain	1,56	1,47	1,61	1,46	1,78	1,41	1,55
	(0,9)	(0,9)	(0,8)	(0,9)	(1,0)	(0,6)	(0,9)
Loss of appetite	1,10	1,02	1,16	0,93	1,00	1,29	1,13
	(1,1)	(1,0)	(1,2)	(1,0)	(1,2)	(1,1)	(1,1)
Constipation	1,04	1,13	0,98	1,07	1,00	0,89	1,29
	(1,1)	(1,1)	(1,1)	(1,1)	(1,1)	(1,0)	(1,2)
All symptoms	0,9	0,9	1,0	1,0	1,1	0,9	0,8
	(0,5)	(0,5)	(0,5)	(0,5)	(0,4)	(0,5)	(0,5)

[6] 0 means no symptom, 1 a little, 2 quite a bit, and 3 very much symptoms

The total number of symptoms, for the whole sample, in the past week was 1303. Of these, 692 (53,1%) symptoms were experienced by patients as “a little”, 349 (26,8%) as “quite a bit” and 262 (20,1) as “very much”. The highest prevalence of symptoms perceived as “very much” were weakness (35,0%), fatigue (26,6%), loss of appetite (16,6), constipation (16,6) and pain (15,3). Depression, memory loss, vomiting, and irritation were, however, only considered severe by less than five percent of the patients. Table 17 shows the portion of patients with none, a little, quite a bit, and very much symptoms.

Table 17. Proportion of advanced cancer patients with none, a little, quite a bit, and very much symptoms the past week, measured with the EORTC QLQ-C30

Symptom	N	Symptom severity % (n)			
		None	A little	Quite a bit	Very much
Weakness	143	10,5 (15)	26,6 (38)	28,0 (40)	35,0 (50)
Fatigue	143	9,1 (13)	35,0 (50)	29,4 (42)	26,6 (38)
Loss of appetite	145	37,2 (54)	31,7 (46)	14,5 (21)	16,6 (24)
Constipation	145	41,4 (60)	29,7 (43)	12,4 (18)	16,6 (24)
Pain	144	9,7 (14)	40,3 (58)	34,7 (50)	15,3 (22)
Lack of concentration	145	44,8 (65)	24,8 (36)	17,2 (25)	13,1 (19)
Dyspnea	145	43,4 (63)	26,9 (39)	19,3 (28)	10,3 (15)
Insomnia	144	60,4 (87)	19,4 (28)	10,4 (15)	9,7 (14)
Feeling tense	145	51,0 (74)	29,7 (43)	11,7 (17)	7,6 (11)
Diarrhea	144	57,6 (83)	26,4 (38)	9,0 (13)	6,9 (10)
Worry (anxiety)	144	41,7 (60)	36,1 (52)	16,7 (24)	5,6 (8)
Nausea	145	54,5 (79)	27,6 (40)	12,4 (18)	5,5 (8)
Depression	145	51,7 (75)	35,9 (52)	7,6 (11)	4,8 (7)
Memory loss	145	31,7 (46)	51,7 (75)	12,4 (18)	4,1 (6)
Vomiting	145	81,4 (118)	11,7 (17)	3,4 (5)	3,4 (5)
Irritation	145	71,0 (103)	25,5 (37)	2,8 (4)	0,7 (1)

Question 4. What is the quality of life score of patients with advanced cancer?

Quality of life was assessed with the EORTC QLQ-C30. The mean (SD) global health/quality of life score for the total sample was 41,6 (23,8). The mean (SD) score for men was 39,0 (24,6) but 43,5 (23,3) for women. Table 18 shows the global health/quality of life scores for patients based on age and gender, but table 19 shows the mean scores for the total EORTC QLQ-C30 scales.

Table 18. Mean (SD) global health/quality of life score of advanced cancer patients based on gender and age

Gender	Age	n	Mean (SD)	Min	Max
Men	20-55 years	9	39,8 (21,6)	8,3	66,7
	56-65 years	13	27,6 (21,9)	0	66,7
	66-75 years	22	38,3 (26,2)	0	100
	76 years and older	16	49,0 (23,7)	0	75,0
	Total	60	39,0 (24,6)	0	100
Women	20-55 years	19	43,9 (23,2)	16,7	100
	56-65 years	28	38,1 (21,9)	0	75,0
	66-75 years	22	51,1 (20,9)	0	83,3
	76 years and older	15	41,7 (27,8)	0	83,3
	Total	84	43,5 (23,3)	0	100

Table 19. Quality of life scores of advanced cancer patients, measured with the EORTC QLQ-C30, for the total sample, gender, and age

	Total		Men		Women		20-55		56-65		66-75		76+	
	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
Global health/QOL•	41,6 (23,8)	144	39,0 (24,6)	60	43,5 (23,3)	84	42,6 (22,4)	28	34,8 (22,2)	41	44,7 (24,3)	44	45,4 (25,6)	31
Physical functioning•	42,0 (26,3)	145	44,8 (27,6)	60	40,0 (25,4)	85	55,2 (21,3)	28	37,1 (28,0)	41	42,4 (23,4)	45	35,9 (28,9)	31
Role functioning•	35,4 (35,9)	145	38,3 (37,9)	60	33,3 (34,6)	85	32,1 (33,0)	28	29,3 (33,9)	41	37,8 (38,7)	45	43,0 (37,0)	31
Emotional functioning•	78,2 (22,0)	145	80,1 (20,3)	60	76,9 (23,2)	85	70,2 (26,2)	28	75,2(21,2)	41	79,8 (22,5)	45	87,1 (14,6)	31
Cognitive functioning•	68,7 (25,4)	145	70,3 (24,6)	60	67,6 (26,0)	85	73,8 (24,2)	28	62,2 (27,6)	41	67,8 (25,2)	45	74,2 (22,3)	31
Social functioning•	53,6 (34,1)	145	52,8 (34,1)	60	54,1 (34,4)	85	42,3 (30,6)	28	48,0 (34,6)	41	58,1 (35,1)	45	64,5 (32,1)	31
Fatigue*	59,6 (26,9)	144	58,8 (27,7)	59	60,1 (26,5)	85	63,3 (24,3)	28	65,6 (23,8)	41	58,0 (27,4)	44	50,5 (30,6)	31
Nausea/ vomiting*	16,3 (23,9)	145	14,4 (22,4)	60	17,6 (25,0)	85	15,5 (22,2)	28	19,5 (24,4)	41	16,3 (26,0)	45	12,9 (22,2)	31
Pain*	48,3 (30,3)	145	45,3 (31,3)	60	50,4 (29,7)	85	46,4 (28,5)	28	55,7 (33,9)	41	43,3 (27,6)	45	47,3 (30,5)	31
Dyspnea*	32,2 (34,1)	145	36,7 (38,2)	60	29,0 (30,8)	85	40,5 (34,4)	28	39,0 (34,9)	41	31,9 (34,8)	45	16,1 (27,0)	31
Insomnia*	23,1 (33,5)	144	22,6 (34,2)	59	23,5 (33,3)	85	32,1 (36,8)	28	24,4 (35,0)	41	24,2 (34,7)	44	11,8 (23,6)	31
Appetite loss*	36,8 (36,2)	145	33,9 (32,2)	60	38,8 (38,8)	85	31,0 (32,6)	28	33,3 (39,4)	41	43,0 (36,0)	45	37,6 (35,2)	31
Constipation*	34,7 (36,6)	145	37,8 (36,5)	60	32,5 (36,7)	85	35,7 (35,1)	28	33,3 (38,0)	41	29,6 (32,7)	45	43,0 (41,4)	31
Diarrhea*	21,8 (30,4)	144	25,0 (29,2)	60	19,4 (31,1)	84	13,1 (27,7)	28	26,0 (32,9)	41	22,7 (29,4)	44	22,6 (30,3)	31
Financial problems*	21,1 (32,8)	145	25,6 (35,5)	60	18,0 (30,7)	85	28,6 (33,6)	28	30,9 (36,8)	41	19,3 (32,2)	45	4,3 (18,7)	31

• A higher score for global health/quality of life and the functional scales indicates better health/qol and functioning.
*A higher score for the symptom scales indicates worse symptomatology

Question 5. Do patients with different cancer diagnoses experience dissimilar symptoms?

Symptoms in the past 24 hours based on cancer diagnosis.

The difference between symptoms based on cancer diagnoses was explored, but because there were too few patients in the groups statistical testing was not an option. Table 20 shows the proportion of patients with symptoms in the past 24 hours based on cancer diagnosis.

Symptoms in the past week based on cancer diagnosis.

The difference between symptoms based on cancer diagnoses was explored, but because there were too few patients in the groups statistical testing was not an option. Table 21 shows the proportion of patients with symptoms in the past week based on cancer diagnosis.

Question 6. Is there a relationship between gender and number of symptoms, symptom prevalence, symptom severity, and quality of life score in patients with advanced cancer?

Gender difference was not found for number of symptoms or symptom severity in either the past 24 hours or in the past week. Similarly no statistical significance was found between genders in global health/quality of life score or scores in any other scale of the EORTC QLQ-C30, tested both with *t-test* and *Mann Whitney U.*

Table 20. Proportion (%) of advanced cancer patients with symptoms in the past 24 hours based on cancer diagnoses

Symptom	Cancer diagnoses							
	Prostate (n=21)	Breast (n=22)	Female reproductive (n=17)	Lung (n=24)	Gastro/ intestinal (n=33)	Multiple cancers (n=10)	Other cancers (n=16)	Unknown (n=7)
	%	%	%	%	%	%	%	%
Pain	66,7	95,5	87,5	83,3	87,9	80,0	81,2	57,1
Fatigue	76,2	81,8	100,0	91,7	78,8	100,0	81,2	85,7
Generalized weakness	76,2	72,7	100,0	83,3	81,8	70,0	87,5	85,7
Anxiety	14,3	40,9	43,8	29,2	30,3	50,0	31,2	42,9
Anorexia	38,1	54,5	81,2	45,8	54,5	40,0	50,0	42,9
Depression	19,0	27,3	31,2	33,3	33,3	20,0	25,0	42,9
Constipation	28,6	31,8	50,0	29,2	45,5	30,0	31,2	28,6
Poor sleep	4,8	27,3	31,2	16,7	21,9	30,0	25,0	28,6
Dyspnea	47,6	50,0	56,2	79,2	36,4	70,0	62,5	42,9
Local weakness	47,6	40,9	56,2	37,5	39,4	30,0	50,0	28,6
Nausea	19,0	45,5	50,0	33,3	36,4	30,0	25,0	42,9
Confusion	19,0	0,0	12,5	25,0	15,2	10,0	12,5	0,0
Vomiting	0,0	4,5	6,2	0,0	12,1	10,0	6,2	14,3
Diarrhea	9,5	4,5	25,0	8,3	24,2	40,0	12,5	42,9
Itching	14,3	18,2	25,0	12,5	18,2	30,0	31,2	14,3
Hallucinations	9,5	4,5	6,2	8,3	0,0	10,0	0,0	14,3
Hiccups	0,0	4,5	12,5	4,2	12,1	0,0	6,2	14,3

Table 21. Proportion (%) of advanced cancer patients with symptoms in the past week based on cancer diagnoses

Symptom	Cancer diagnoses							
	Prostate (n=21)	Breast (n=22)	Female reproductive (n=17)	Lung (n=24)	Gastro/ intestinal (n=33)	Multiple cancers (n=10)	Other cancers (n=16)	Unknown (n=7)
	%	%	%	%	%	%	%	%
Weakness	95,0	85,7	100	87,5	84,8	100	87,5	83,3
Fatigue	95,0	95,2	100	87,5	84,8	100	93,8	66,7
Loss of appetite	60,0	59,1	71,4	58,3	75,8	50,0	56,2	50,0
Constipation	75,0	59,1	64,3	58,3	51,5	50,0	68,8	16,7
Pain	85,0	100	85,7	87,5	96,9	80,0	87,5	83,3
Lack of concentration	60,0	59,1	57,1	50,0	57,6	40,0	62,5	33,3
Dyspnea	60,0	72,7	50,0	62,5	45,5	40,0	56,2	66,7
Insomnia	20,0	54,5	42,9	33,3	48,5	33,3	43,8	16,7
Feeling tense	40,0	59,1	35,7	45,8	45,5	80,0	62,5	16,7
Diarrhea	50,0	33,3	42,9	29,2	48,5	80,0	25,0	50,0
Worry (anxiety)	50,0	57,1	50,0	54,2	54,5	100	68,8	50,0
Nausea	35,0	45,5	57,1	58,3	39,4	40,0	50,0	33,3
Depression	35,0	50,0	35,7	41,7	57,6	60,0	62,5	33,3
Memory loss	55,0	72,7	57,1	70,8	69,7	90,0	68,8	66,7
Vomiting	5,0	40,9	35,7	12,5	15,2	20,0	6,2	16,7
Irritation	20,0	40,9	28,6	25,0	30,3	30,0	31,2	16,7

Regarding symptom prevalence gender difference was found for two symptoms in the past 24 hours assessed by the Symptom Checklist: pain, ($\chi^2(1, N=149)=9,89$, $p=0,002$), and nausea, ($\chi^2(1, N=149)=3,86$,

p=0,049). In both instances more women than men experienced the symptoms. Symptom prevalence, however, did not differ between genders in the past week.

Question 7. Is there a relationship between age and number of symptoms, symptom prevalence, symptom severity, and quality of life score in patients with advanced cancer?

A weak, but significant, negative correlation was found between age and number of symptoms, ($r(148) = -.23$, p=0,004), in the past 24 hours, as well as in the past week, ($r(141) = -.28$, p=0,001).

As for symptom prevalence, age difference in the past 24 hours was noted for the symptoms of anxiety, ($\chi^2(3, N=149)=7,93$, p=0,047), depression, ($\chi^2(3, N=149)=8,20$, p=0,042), and dyspnea, ($\chi^2(3, N=149)=11,55$, p=0,009). In all cases the symptoms were less prevalent in the patients aged 76 years and older than other age groups. In the past week, however, age difference was noted for the symptoms of dyspnea, ($\chi^2(3, N=145)=9,55$, p=0,023), and feeling tense, ($\chi^2(3, N=145)=13,73$, p=0,003). In both instances the symptoms were less prevalent in the patients aged 76 years and older than other age groups.

Symptom severity was negatively associated with age in the past 24 hours, that is, severity lessened with increasing age although the correlation was weak, ($r(148)= -.24$, p=0,004). Similarly, symptom severity was negatively associated with age in the past week, ($r(141)= -.25$, p=0,003).

Global health/quality of life scores did not change with age. Physical function, however, declined with increasing age, ($r(145)= -.18$, p=0,034), but emotional, ($r(145)= .29$, p=0,000), and social functioning,

(r(145)= .29, p=0,001), were better among older than younger patients. Of the symptom scales fatigue, (r(144)= -.21, p=0,010), dyspnea, (r(145)= -.25, p=0,002), insomnia, (r(144)= -.21, p=0,012), and financial problems, (r(145)= -.27, p=0,001), were negatively associated with age, that is older patients scored lower on the symptom scales than younger patients, indicating less symptomatology.

Question 8. Is there a relationship between number of concurrent diseases and number of symptoms, symptom severity, and quality of life score in patients with advanced cancer?

No relationship was found between number of concurrent diseases and number of symptoms and symptom severity in neither the past 24 hours nor in the past week. Similarly, no difference was found for quality of life score regardless of whether concurrent diseases were grouped into no diseases versus one or more disease; no-two diseases versus three-six diseases; or as no disease, one-two diseases, and three or more diseases.

Hypothesis 1. Number of symptoms is associated with worse quality of life in patients with advanced cancer

The relationship between number of symptoms in the past week and global health/quality of life (QL2), measured by the EORTC QLQ-C30, was linear with a moderate, negative correlation, (r(140)= -.50, p=0,000). When entered into a multiple linear regression model the number of symptoms added significantly to the model, (p= 0,000), and explained 25,8% of the variance in global health/quality of life, adjusted for gender

and age. The model shows that with each symptom the predicted value of global health/quality of life is lowered by 3,60 for a 65 year old male. The hypothesis of an association between number of symptoms and diminished quality of life was, therefore, supported. Table 22 shows the regression model.

Table 22. Regression model showing the association between number of symptoms and quality of life in advanced cancer patients (N=140)

Variable	B	SE	β•	t	p
Constant (QL2)	70,80	5,7		12,4	0,000
Number of symptoms	-3,60	0,6	-.50	-6,5	0,000
Age (c65)♠	-0,02	0,1	-.01	-0,1	0,887
Gender*	5,46	3,6	.11	1,5	0,134

F (3,139) = 15,76, p = 0,000.
R^2 = 25,8, adjusted R^2 = 24,2
•Standardized β.
♠age centered at 65 years
** gender was coded 0 for male, 1 for female*

Hypothesis 2. The symptoms of pain, depression, fatigue, and poor sleep are associated with worse quality of life in patients with advanced cancer

The second regression model shows the association of fatigue, pain, poor sleep, and depression with global health/quality of life (QL2), measured with the EORTC QLQ-C30. All four symptoms were linearly and negatively related with global health/quality of life indicating lower quality of life scores with the presence and increased severity of the

symptoms. For pain, insomnia, and depression the relationship was weak, but for fatigue the association was moderate. A significant correlation also existed between the four symptoms. In all instances the relationship was weak and positive, suggesting that the presence and strength of one symptom was associated with the presence and strength of the other symptom. The correlation between the variables is shown in table 23.

Table 23. Correlation between variables in a regression model showing the association between fatigue, pain, insomnia and depression with quality of life in patients with advanced cancer (N=141)

	QL2	fatigue	pain	insomnia	depression	gender	age (c65)
QL2	1,00	-0,49*	0,38*	-0,32*	-0,27*	0,10	0,11
fatigue	0,4*	1,00	0,34*	0,33*	0,25*	0,04	0,21°
pain	0,38*	0,34*	1,00	0,22°	0,19°	0,08	-0,07
insomnia	0,32*	0,33*	0,22°	1,00	0,35*	0,03	0,21°
depression	0,27*	0,25*	0,19°	0,35*	1,00	0,01	0,20°
gender	0,10	0,04	0,08	0,03	-0,01	1,00	0,17°
age (c65) ♠	0,11	-0,21°	-0,07	-0,21°	-0,20°	0,17°	1,00

°p < 0,05
**** p ≤ 0,001***
♠age centered at 65 years

The model was built in five steps using hierarchical method. In the first step only fatigue was added to the model. As seen in table 24 fatigue explained 24,2% of the variance in global health/quality of life. In the second step age and gender were entered, but these variables did not have a significant influence on the model. In the third step pain was added to

the model and together the two symptoms explained 31,0% of the variance in global health/quality of life, adjusted for age and gender. Pain was confounding for fatigue. In the fourth step insomnia was included in the model and, as seen in table 25, all three symptoms significantly contributed to the model with R^2 increasing by further 2.0%. Insomnia was confounding for age in step four. Depression was added in the fifth step, contributing to a further 0,7% in the variance in global health/quality of life which was not significant. Depression was confounding for both insomnia and age. Until the final step age had a positive value and as depression was included in the model the contribution of insomnia was no longer significant. The hypothesis that the four symptoms were associated with worse quality of life was, therefore, only partially supported. The final model shows that the four symptoms, adjusted for age and gender, explained 33,6% of the variance in global health/quality of life. The model (step five), adjusted for gender and age, shows that the presence of "a little" pain, fatigue, insomnia, and depression in a 65 year old male lowered the predicted value of global health/quality of life by 20,6. Table 25 shows the predicted values of global health/quality of life, adjusted for age and gender, based on the existence and severity of pain and fatigue (step three). As seen in the table global health quality of life scores are lowered as the severity of the symptoms increase.

Table 24. Regression model showing the association between fatigue, pain, insomnia, and depression with quality of life in patients with advanced cancer (N=141)

Step	Variable	B	SE	β•	t	p	R^2	F (df)
Step 1	Constant (QL2)	75,00	5,3		14,2	0,000	0,242°	44,3 (1)*
	Fatigue	-12,19	1,8	-.49	-6,7	0,000		
Step 2	Constant (QL2)	71,52	5,8		12,3	0,000	0,256	15,7 (3)*
	Fatigue	-12,16	1,9	-.49	-6,5	0,000		
	Gender♦	5,79	3,6	.12	1,6	0,111		
	Age (c65) ♠	0,05	0,1	.03	0,3	0,743		
Step 3	Constant (QL2)	82,55	6,5		12,6	0,000	0,310°	15,2 (4)*
	Fatigue	-10,08	1,9	-.41	-5,3	0,000		
	Pain	-6,75	2,1	-.25	-3,3	0,001		
	Gender♦	6,68	3,5	.14	1,9	0,059		
	Age (c65) ♠	0,05	0,1	.03	0,4	0,702		
Step 4	Constant (QL2)	84,73	6,6		12,9	0,000	0,330°	13,3 (5)*
	Fatigue	-9,09	2,0	-.37	-4,6	0,000		
	Pain	-6,23	2,1	-.23	-3,0	0,003		
	Insomnia	-3,63	1,8	-.15	-2,0	0,046		
	Gender♦	6,54	3,5	.14	1,9	0,061		
	Age (c65) ♠	0,01	0,1	.01	0,1	0,942		
Step 5	Constant (QL2)	87,00	6,8		12,7	0,000	0,336	11,3 (6)*
	Fatigue	-8,86	2,0	-.36	-4,5	0,000		
	Pain	-6,01	2,1	-.22	-2,9	0,004		
	Insomnia	-3,06	1,9	-.13	-1,6	0,104		
	Depression	-2,65	2,3	-.09	-1,2	0,247		
	Gender♦	6,35	3,5	.13	1,8	0,069		
	Age (c65) ♠	-0,01	0,1	-.01	-0,1	0,946		

° significant F change at step
**** p = 0,000***
adjusted R^2 for step 5 = 0,307
• Standardized β
♠ age centered at 65 years
♦ gender was coded 0 for male, 1 for female
df = degrees of freedom

Table 25. Predicted value of global health/quality of life score of advanced cancer patients, according to the existence and severity of pain and fatigue, adjusted for age and gender (N=141)

Men						Agegroup	Women					
		Pain						Pain				
		1	2	3	4			1	2	3	4	
Fatigue	1	84	77	70	63	76+	1	90	83	77	70	1
	2	73	67	60	53		2	80	73	67	60	2
	3	63	57	50	43		3	70	63	57	50	3
	4	53	47	40	33		4	60	53	46	40	4
Fatigue	1	83	76	69	63	66-75	1	90	83	76	69	1
	2	73	66	59	52		2	79	73	66	59	2
	3	63	56	49	42		3	69	63	56	49	3
	4	53	46	39	32		4	59	53	46	39	4
Fatigue	1	82	76	69	62	56-65	1	89	82	76	69	1
	2	72	65	59	52		2	79	72	65	59	2
	3	62	55	49	42		3	69	62	55	49	3
	4	52	44	39	32		4	59	52	45	39	4
Fatigue	1	81	74	68	61	20-55	1	88	81	74	68	1
	2	71	64	58	51		2	78	71	64	58	2
	3	61	54	48	41		3	68	61	54	47	3
	4	51	44	37	31		4	58	51	44	37	4

Scale 0-100, higher score indicates better quality of life
1 = no pain/fatigue
2 = little pain/fatigue
3 = quite a bit pain/fatigue
4 = very much pain/fatigue

Discussion

In this chapter the results of the present study will be discussed and compared to other studies in this field. The strength and limitations of the study will be addressed and finally there are conclusions and suggestions for future studies.

Symptomatology and quality of life scores

Being symptom free was rare in this study which is in line with Lidstone's et al. (2003) study of a similar group of patients. Only one patient (0,7%) had experienced no symptoms at all in the past 24 hours and all the patients had at least one symptom in the past week. The median number of symptoms in the past week was higher than in the past 24 hours which was not an unexpected finding. As can be anticipated, symptoms may fluctuate with patients experiencing e.g. insomnia for one night, but not the other, and the same is true for most other symptoms except, perhaps, fatigue and weakness that tend to be more constant over time. The median number of nine (mean 9,0) symptoms in the past week was similar to findings of several other studies (Chang et al., 2000; Homsi et al., 2006; Lidstone et al., 2003; Peters & Sellick, 2006; Portenoy et al., 1994; Tsai et al., 2006; Walsh et al., 2000), despite different time frames (at the moment or in the past 24 hours versus the past week). The median number of six (mean 6,2) symptoms in the past 24 hours in this study, however, was somewhat lower than found in other studies, but nonetheless in line with another Icelandic study of patients entering palliative service where the mean number of symptoms ranged from 4,95-7,17 (Friðriksdóttir & Sigurðardóttir, 2004, April). In the present study the proportion of patients

with 10 or more symptoms the past week (42,5%) was noticeably higher than in the past 24 hours (10,2%). This is also higher than the proportion of patients in the last 72 hours of life (17%) in another Icelandic study (Sigurdardottir et al., 2006). The proportion of patients in the past 24 hours (10,2%), on the other hand, is rather lower. The difference between the two studies may stem from different assessment methods, self reported versus nurse assessed. In the last hours of life people are often unconscious and, therefore, evaluation of symptoms is more troublesome since symptoms are primarily a subjective phenomenon (Rhodes & Watson, 1987). The different time frames may also explain the difference, since the proportion of patients with 10 or more symptoms in the past 24 hours was lower than in patients in the last 72 hours of life.

The most prevalent symptoms in the past 24 hours in this study were fatigue, pain, generalized weakness, dyspnea, and anorexia. For the past week, however, memory loss took the place of dyspnea. These results are in line with a systematic review by Teunissen et al. (2007) where pain, fatigue, weakness, and anorexia were among the five most common symptoms. Dyspnea has also been among the five most prevalent symptoms in other studies (Chang et al., 2000; McMillan & Small, 2002; Friðriksdóttir & Sigurðardóttir, 2004, April). However, no studies were found where memory loss was among the most common symptoms, possibly because it is a symptom that often is not assessed. It can also be speculated that memory loss may be a salient symptom that is difficult for patients to acknowledge, since cognitive impairment is generally associated with considerable stigma in the society.

Resembling other studies, the prevalence of fatigue, pain, and weakness was quite high (Chen & Tseng, 2006; McMillan & Small, 2002;

Tsai et al., 2006) with over 80% of the patients experiencing these symptoms in the past 24 hours and around 90% in the past week. These numbers are somewhat higher than the pooled prevalence of pain (71%) and fatigue (74%) in Teunissen's et al. (2007) systematic review, but nonetheless, they conform to the notion of these two symptoms being nearly universal in patients with advanced cancer (Hoekstra et al., 2006; Homsi et al., 2006; Modonesi et al., 2005; Peters & Sellick, 2006; Tsai et al., 2006; Walsh et al., 2000). It should be noted here, however, that to participate in the present study patients had to be on opioid pain medications. The results might, therefore, me skewed in the direction of higher pain prevalence than found in other studies.

Symptom severity in this study was usually mild or moderate, and the mean severity was in line with other studies (Skúladóttir et al., 2005; Hoekstra et al., 2006; Peters & Sellick, 2006; Tsai et al., 2006). Nonetheless, one third of the patients had severe symptoms in the past 24 hours, and one fifth had "very much" symptoms in the past week. Comparing the results with other studies is, however, difficult because of different scaling in different studies.

The symptoms with the highest mean severity in the past 24 hours were the same as the five most common symptoms: generalized weakness, fatigue, pain, dyspnea, and anorexia. For the past week, the same symptoms had the highest mean severity, but with constipation taking the place of dyspnea. These symptoms were also among those most frequently rated as severe, with severe fatigue and weakness prevalent in about one third of the participants, but the other symptoms in little less than one fifth. These results are in line with other studies that show these symptoms as being frequently rated as severe by cancer patients (Chang et

al., 2000; Cleeland et al., 2000; Modonesi et al., 2005; Strassels et al., 2006).

The results of this study illustrate a diminished quality of life in Icelandic patients with advanced cancer. The mean global health/quality of life score was considerably lower than data from the general population (Hjermstad, Fayers, Bjordal, & Kaasa, 1998a; Michelson, Bolund, Nilsson et al., 2000), but similar to results of studies of patients with advanced cancer (Jordhoy et al., 2001), and cancer patients treated with opioids (Klepstad et al., 2000). The quality of life score in the current study was also similar to scores found in patients with advanced cancer in palliative care, although slightly higher (41,6 vs. 33) (Stone et al., 1999). These findings, however, differ from two Icelandic studies, evaluating the quality of life in men with prostate cancer (Sigurðardóttir, 2006) and patients with various types of cancer in chemotherapy (Saevarsdottir et al., 2008) where the scores indicated a generally good quality of life. These results might stem from different samples in the three studies and of note is also that different instruments were used in the studies making comparison between them more complicated.

The association between symptoms and quality of life, testing of the Symptoms-quality of life model

One of the goals of the present study was to test the relationship between symptoms, selected demographic and clinical variables, and quality of life.

Testing for difference in symptomatology based on cancer diagnose was not possible because of the sample size. Comparison with other studies is difficult for the same reason. Looking at the proportion of patients with symptoms, based on diagnosis, it shows that fatigue is

present in the vast majority. It can also be speculated that diarrhea may be more common in patients with multiple cancers, and that anorexia/loss of appetite is common in women with female reproductive cancers.

Symptom severity did not differ between genders and corresponding to Lidstone's et al. (2003) study neither did number of symptoms. Similarly, the prevalence of symptoms in the past week did not differ between genders, but of symptoms in the past 24 hours, pain and nausea were more common in women than men. Pain was also more prevalent among women than men in Lidstone's et al. (2003) study, and similarly nausea has been found to be more frequent in women than men in various studies (Jordhoy et al., 2001; Lundh Hagelin et al., 2006; Mercadante et al., 2000; Walsh et al., 2000). It must be noted here that in these studies vomiting was often assessed alongside nausea. In this study, though, gender difference was not found for vomiting, possibly because of few patients (9 in 24 hours, 27 in a week) with the symptom. Why pain and nausea were more prevalent among women than men in this study is not clear. Nausea may be related to female reproductive cancers, since surgical and radiation treatments of those cancers are usually aimed at the pelvis and hence may disrupt bowel function resulting in nausea. The same, however, is true for prostate cancer. Unfortunately, testing of the prevalence of nausea between cancer diagnoses was not possible because of small sample size as previously mentioned. Nausea is also a frequent side effect of chemotherapy which might explain some of the difference between genders. One third of the men in the current study had prostate cancer which is infrequently treated with chemotherapy. As for pain in the past 24 hours, there is no obvious reason for it being more prevalent in women than men. Perhaps this difference is simply coincidental since

gender difference was not apparent for any symptoms in the past week. The same might also be true for nausea.

Studies have shown that women may either experience better (Schultz & Winstead-Fry, 2001; Yan & Sellick, 2004) or worse (Parker et al., 2003) quality of life than men. In this study, however, gender difference was not apparent for either global health/quality of life score or any other EORTC QLQ-C30 scale. The results are, however, in line with another Icelandic study where quality of life did not differ between genders (Saevarsdottir et al., 2008).

As previous studies have shown (Lidstone et al., 2003; Walsh et al., 2000) number of symptoms decreased with increasing age in the current study and so did symptom severity. It may seem strange that older people have fewer symptoms than younger, since older people usually have poorer health and hence it would appear normal that they had more symptoms. A possible explanation to this finding is that older people may adapt better to symptoms than younger people. Because of their age and already diminishing health older people might have become accustomed to several symptoms and therefore they might not acknowledge, experience, or report them.

In line with other studies anxiety/feeling tense, depression (only in the past 24 hours, not in the past week) (Redeker et al., 2000), and dyspnea (Mercadante et al., 2000), were less prevalent in the oldest age group (76 years and older) in the current study. This might stem from the previously mentioned adaption to symptoms of older people. Having cancer may inspire more depression and anxiety in younger people, since the disease may be more disrupting in their lives. The oldest age group is already settling in to old age, expecting diseases to occur. Younger

people, however, have the responsibility of working, are perhaps still rearing children and so forth, and are therefore less prepared to deal with a difficult disease like cancer (Cella & Cherin, 1988).

Surprisingly, global health/quality of life did not differ depending on age, a finding that is in contrast with several other studies (Lundh Hagelin et al., 2006; Parker et al., 2003; Saevarsdottir et al., 2008). On the other hand, older patients had better emotional and social functioning, as well as lower scores on the fatigue, dyspnea, insomnia, and financial problems symptom scales than younger patients, similar to what was found in the study of Lundh Hagelin et al. (2006). As could be expected, however, older patients had worse physical functioning than younger patients, which is in line with data from both the general population (Hjermstad, Fayers, Bjordal, & Kaasa, 1998b) as well as patients with cancer (Jordhoy et al., 2001).

Concurrent diseases were not related to number of symptoms or symptom severity. These were surprising findings since it seems logical that the number and severity of symptoms should increase in line with number of concurrent diseases. Perhaps this can be explained by the fact that symptomatology is already high in this patients cohort. Because of the advanced cancer, the symptoms related to concurrent diseases might be obscured by the cancer related symptoms. The results were, nonetheless, in accordance with a longitudinal study of patients with lung cancer (Gift et al., 2003) were number of symptoms was not related to number of concurrent diseases. The findings differed, however, from several other studies that have shown the reverse (Gift et al., 2004; Sigurðardóttir, 2006; Reyes-Gibby et al., 2006). Similarly, the number of concurrent diseases was not associated with any of the EORTC QLQ-C30 scales.

This was also an unexpected finding and in contrast with other studies that have shown the opposite, both in patients with cancer (Chang et al., 2000; Portenoy et al., 1994) and in the general population (Michelson, Bolund, & Brandberg, 2000).

When entered into a regression model, adjusted for age and gender, the number of symptoms explained 25,8% of the variance in global health/quality of life. The study, therefore, supported the hypothesis of an association between number of symptoms and worse quality of life. Comparable to the studies of Portenoy and colleagues (1994) and Chang and colleagues (2000), there was a highly significant correlation between number of symptoms and quality of life, indicating worse quality of life with increasing number of symptoms.

The second regression model shows the relationship between the existence and severity of four individual symptoms, adjusted for age and gender, with quality of life. All of the symptoms were significantly correlated with quality of life and with each other. Fatigue was the symptom that explained the largest proportion of the variance in quality of life, followed by pain. Insomnia also added significantly to the model until depression was entered. Gender and age were, however, not significant in the model. The complete model explained 33,6% of the variance in global health/quality of life. The results, therefore, only partially supported the hypothesis of an association between the four symptoms and worse quality of life.

The importance of fatigue in relation to quality of life was not an unexpected finding, since several studies have shown fatigue to be either moderately or strongly correlated with quality of life (Redeker et al., 2000; Stone et al., 1999) or explaining a substantial proportion of the

variance in it (Beijer et al., 2008; Östlund et al., 2007). Similarly, pain has been shown to be negatively related to quality of life (Ferrell et al., 1991; Skevington, 1998). This is also in line with studies that show the importance of symptom distress in relation with quality of life (McMillan & Small, 2002; Portenoy et al., 1994). Fatigue and pain are both symptoms that have been found to be very distressing (Chang et al., 2000; Hoekstra et al., 2007) and, hence, it comes of no surprise that they explain a large amount of the variance in quality of life in this study.

Insomnia (Lis et al., 2008; Redeker et al., 2000) and depression (Peters & Sellick, 2006; Redeker et al., 2000; Rustøen et al., 2005; Saevarsdottir et al., 2008) are symptoms that have also been linked to reduced quality of life so the lack of significant contribution to the regression model in this study was surprising. A possible explanation for this might be the low prevalence of patients who experienced "quite a bit" (N=11) or "very much" (n=7) depression in the past week, compared to 75 without depression and 52 who experienced it as "little". Therefore, it might be that there were too few patients with more severe depression to detect a difference. The same might be true for insomnia, since only about one third of the sample (n=57) had the symptom, and thereof, only 15 experienced it as "quite a bit" and 14 as "very much". Another explanation is that perhaps the patients who experienced depression were not clinically depressed and, hence, depression was not significant in the model. It must be noted that the EORTC QLQ-C30 was not designed to diagnose clinically significant depression and, hence the results should not be interpreted as such. Studies that have shown a relationship between depression and quality of life, however, have used instrument designed for measuring depression, either the Profile of Mood States (POMS) (Redeker

et al., 2000; Rustøen et al., 2005) or the Hospital Anxiety and Depression Scale (HADS) (Peters & Sellick, 2006; Saevarsdottir et al., 2008). Nonetheless, the proportion of patients who said they felt either quite a bit (7,6 %) or very much (4,8%) depression in the last week in this study was similar to another Icelandic study of cancer patients (Saevarsdottir et al., 2008), were rate of depressive symptoms was 4% at the initiation of chemotherapy and 6% three months later. A third explanation of this finding might be that the contribution of insomnia and depression to the variance in quality of life might have become diluted because of correlation between the two symptoms. Of note, however, is that the correlation between depression and insomnia was only slightly higher than the correlation with the other symptoms, but the correlation of depression with global health/quality of life was the lowest of the four symptoms.

Although depression did not enter as significant in the regression model, the results of the study are similar to another study, of 102 patients with advanced cancer, where depressive symptomatology was not related to quality of life (Mystakidou et al., 2007). On the other hand they differ from two other studies, one of patients with various cancers in chemotherapy (Redeker et al., 2000), the other of patients with high grade glioma (Fox, Lyon, & Farace, 2007), where depression explained the largest proportion of the variance in quality of life while the contribution of fatigue was only moderate or minimal.

Testing of the relationship between symptoms, selected demographic and clinical variables, and quality of life showed that the number of symptoms and symptom severity lessened with increasing age. Furthermore, the number of symptoms and the individual symptoms of

pain and fatigue were associated with diminished quality of life. The Symptoms-quality of life model was, therefore, only partially supported.

Strength and limitations of the study

The strengths of the study lie in a very consistent and rigorous data collection with low amount of missing data. Furthermore, there was a correspondence between the purpose of the study, research questions and hypotheses, definition of quality of life and instruments used in the study as recommended by several authors (Jocham et al., 2006; Kaasa & Loge, 2003; King et al., 1997; Pais-Ribeiro, 2004). The instruments used were also appropriate to the population under study (Cella, 1996). The main advantage of the study is that it is the first study specifically exploring the relationship between symptoms and quality of life in Icelandic patients with advanced cancer. It therefore adds knowledge to a previously little explored area, and hopefully the results can be used in clinical practice to improve quality of life of Icelandic cancer patients.

The study has its limitations as well. Firstly, it is a secondary analysis of data. Data analyzing and testing of the Symptoms-quality of life model was therefore restricted to the data available. Secondly the study design was descriptive and correlational, based on a convenience sample consisting solely of Caucasians. Consequently, it was not possible to explore the prognostic value of symptoms on quality of life. It must be observed here, however, that convenience sample is often the only available sample in patients with advanced cancer, not least in small communities like Iceland. Thirdly, the sample size did not allow for the testing of some relationships like between cancer diagnosis and symptoms. Finally, the Symptom Checklist did not have an established

reliability or validity. The internal consistency of the symptom checklist in this study (α=.74), however, indicates an acceptable reliability. Furthermore, the consistency between the Symptom Checklist and the EORTC QLQ-C30 strengthens the results of the study.

Conclusions

This study shows that the symptomatology of Icelandic patients with advanced cancer is similar to cancer patients in other countries. The patients experience multiple symptoms, and although symptoms severity is usually mild, both fatigue and weakness were considered severe in about one third of the participants. The study further showed that there is an association between symptoms and quality of life, with pain and fatigue explaining nearly one third of the variance in quality of life. Surprisingly, however, insomnia and depression did not add significantly to the regression model. The number of symptoms patients experience is also related to quality of life, with quality of life scores diminishing with each additional symptom. These results indicate that quality of life of patients with advanced cancer may be improved by assessing, and treating, cancer related symptoms.

Testing of the Symptoms-quality of life model supported the association between number of symptoms and quality of life. Furthermore, the relationship of the existence and severity of fatigue and pain with quality of life was sustained, but the study failed to show a significant contribution of depression and insomnia to quality of life. Testing of difference between cancer diagnoses was not possible because of few participants in each category. No association between gender or concurrent diseases with symptoms or quality of life was found, although,

pain and nausea were more prevalent in women than in men. Similarly, age was not related to quality of life, but some difference was, however, found between age and symptomatology with older patients having fewer symptoms and less symptom severity. Due to the limited number of patients at each end of the age line the results must be interpreted with caution. In light of this, further studies are warranted to test the Symptoms-quality of life model.

Recognizing and treating symptoms is an important nursing and medical intervention and understanding the symptomatology of cancer patients helps medical professionals to assess patients' needs and aids in clinical decision making and evaluation of treatment (Higginson & Addington-Hall, 2005). Assessing quality of life is also imperative since one of the main goal of cancer nursing is to improve quality of life, as mentioned before (King et al., 1997). Of note, however, is that evaluating quality of life per se is inadequate in order to improve quality of life of cancer patients, but the concept should rather be used as an outcome measure to assess the effect of treatment aimed at improving quality of life (Rosenbloom, Victorson, Hahn, Peterman, & Cella, 2007).

The role of nursing is to enhance health, relieve suffering, and improve well-being of patients (Félag íslenskra hjúkrunarfræðinga, 2007). Since quality of life is associated with the symptomatology of cancer patients, nurses need to evaluate, and treat, the symptoms of cancer patients in order to improve their quality of life and hence their well-being. This is not least true for the symptoms of pain and especially fatigue which are both common in this patients' cohort and explain a great amount of the variance in quality of life. Of note are also dyspnea, weakness, constipation, and anorexia that were both common and rated as

severe in this study. Memory loss is also a symptom worth noticing. Although it was only severe in small proportion of patients it was surprisingly common and it may be a symptom difficult for patients to acknowledge. Nurses should also be alert to the number of symptoms patients endure, since increased number of symptoms is associated with reduced quality of life. Nursing interventions should, therefore, aim at reducing individual symptoms as well as the number of symptoms and symptom severity. Vigilant treatment of pain is important and specific interventions should be targeted at reducing fatigue.

Future studies

Further studies are needed to both evaluate the relationship between symptoms and quality of life as well as studies to gain a deeper understanding of what the concept of quality of life encompasses for cancer patients. In this study the relationship between individual symptoms and quality of life was only tested with four symptoms, but other symptoms may affect quality of life as well. Future studies should also be aimed at exploring further the relationship between age, gender and concurrent diseases with both symptoms and quality of life. Similarly, studies are needed to evaluate symptom clusters, their etiology, which symptoms cluster together, and the effect of symptom clusters on cancer patients. There is also a need to look at the importance of individual domains of quality of life to explore how important they are for cancer patients. This is not least true for the spiritual/existential domain which seems to become more vital as patients are nearing end of life. There is also need to assess the importance of various symptom factors, such as severity, distress, number of symptoms, symptom clusters, and/or

individual symptoms, in relation to quality of life. Last, but not least, studies are needed on interventions to improve symptom evaluation and management.

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Appendix

Definitions of concepts

Definitions of concepts

This appendix contains defintions of concepts that commonly appear in the thesis.

Advanced cancer: Cancer that has spread to other places in the body and usually cannot be cured or controlled with treatment (National Cancer Institute, n.d.).

Health related quality of life: A multidimensional construct encompassing perceptions of both positive and negative aspects of physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment (Osoba, 1994).

Health related quality of life (QOL): refers to the extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment (Cella, 1996).

Quality of life: Patients' appraisal of, and satisfaction with, their current level of functioning as compared to what they perceive to be possible of ideal (Cella & Cherin, 1988).

Symptom: Subjective phenomenon regarded by individuals as an indication of a condition departing from normal function, sensation, or appearance (Rhodes & Watson, 1987).

Sign: An objective phenomenon that is observable and indicates a change in health status (Liehr, 2005)

Symptom severity: The strength or amount of the symptom being experienced (Lenz, Pugh, Milligan, Gift, & Suppe, 1997)

Symptom distress: The degree or amount of physical or mental upset, anguish, or suffering experienced from a specific symptom (Rhodes & Watson, 1987).

Symptom occurrence: The frequency and severity with which the symptom occurs and the duration or persistence of the symptom (McDaniel & Rhodes, 1995).

Symptom experience: An individual's perception of a symptom, evaluation of the meaning of a symptom and response to a symptom (M. Dodd et al., 2001).

Symptom cluster:

a) Three or more concurrent symptoms that are related to each other, which may or may not have the same etiology (M. J. Dodd, Miaskowski, & Paul, 2001).
b) Two or more symptoms that are related to each other and that occur together. Symptoms clusters are composed of stable groups of symptoms are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms. Relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters. Symptoms in a cluster may or may not share the same etiology (Kim, McGuire, Tulman, & Barsevick, 2005).

Attachment A

Approvals for study

The National Bioethics Committee
The Data Protection Authority
Chief Medical Executive of Landspítali University Hospital

Landspítali-Háskólasjúkrahús, Krabbameinssvið
Sigríður Gunnarsdóttir, hjúkrunarfræðingur
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Reykjavík 13. september 2005
Tilvísun: VSNb2005030002/03-15 Umsóknir frá Landspítala-háskólasjúkrahúsi/BH/--

Varðar: 05-041-S2 Evrópsk rannsókn á lyfjaerfðafræði ópíða (European Pharmacogenetic Opioid Study EPOS).

Vísindasiðanefnd þakkar svarbréf þitt, dags. 08.09.2005, vegna áðursendra athugasemda við ofangreinda rannsóknaráætlun, sbr. bréf nefndarinnar dags. 25.08.2005.

Með bréfinu fylgdu ný og endurbætt kynningarbréf og samþykkisyfirlýsingar fyrir þátttakendur rannsóknarinnar, auk staðfestingar frá Lífsýnabanka Krabbameinsfélags Íslands um varðveislu lífsýna, sem undirrituð er af Helgu K. Ögmundsdóttur.

Fjallað hefur verið um svarbréf þitt og önnur innsend gögn og eru þau talin fullnægjandi.

Rannsóknaráætlunin er endanlega samþykkt af Vísindasiðanefnd.

Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina. Jafnframt fer Vísindasiðanefnd fram á að fá send afrit af birtum greinum um rannsóknina. Rannsakendur eru minntir á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju,
f.h. Vísindasiðanefndar,

Ólöf Yr Atladóttir, framkvæmdastjóri

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Leyfi til aðgangs að sjúkraskrám, samkvæmt 3. mgr. 15. gr. laga nr. 74/1997 um réttindi sjúklinga og til vinnslu persónuupplýsinga, samkvæmt 2. tl. 1. mgr. 7. gr. reglna nr. 698/2004, sbr. 33. gr. laga nr. 77/2000.

I.
Umsókn

Persónuvernd hefur borist umsókn Valgerðar Sigurðardóttur yfirlæknis á Líknardeild LSH og Sigríðar Gunnarsdóttur hjúkrunarfræðings og verkefnisstjóra klínískra rannsókna á Lyf 2 LSH, dags. 16. mars sl., um leyfi til aðgangs að sjúkraskrám og vinnslu persónuupplýsinga vegna rannsóknar sem ber yfirskriftina „Evrópsk rannsókn á lyfjaerfðafræði ópíóíða (European Pharmacogenetic Opiod Study)".

Í umsókninni er tilgangi rannsóknarinnar lýst á eftirfarandi hátt:

> Rannsóknin er hluti af stóru alþjóðlegu verkefni sem miðar að því að safna viðtækum upplýsingum um verki og verkjameðferð krabbameinssjúklinga. Meginmarkmiðið er að skoða lyfjaerfðafræði ópíóíða, tegund og skammtastærðir verkjalyfja, mat sjúklinga á verkjum og lífsgæðum og innbyrðis tengsl þessara þátta. Einnig verða skoðaðar hugmyndir meðal sjúklinga sem hafa áhrif á verkjameðferð. Áætlað er að safna gögnum frá 150 krabbameinssjúklingum á Íslandi en alls verður safnað gögnum frá 3000 sjúklingum frá 15 stöðum í 11 löndum.

Í umsókninni er gerð rannsóknaráætlunar lýst á eftirfarandi hátt:

> Markmiðið er að skoða (1) lyfjaerfðafræðilegar breytur s.s. stökkbreytingar sem tengjast niðurbroti á ópíóíðum, ópíóíð móttækjum og áhrifum polymorphism í MDR1 geni á virkni ópíóíða, (2) Lyfjafræðilega þætti s.s. styrkleika ópíóíða í blóði og skoða í tengsl við lýðfræðilegar breytur og sjúkdóms/meðferðarbreytur sem og við útkomu (verki og aukaverkanir), (3) Klíníska þætti s.s. tíðni og styrkleika aukaverkana tengda mismunandi

tegundum ópíoíða, áhrif verkja og aukaverkana á almenna virkni og möguleika Brief Pain Inventory (stutt verkjaskrá) til að aðgreina áhrif verkja frá öðrum orsökum á almenna virkni (4) bera saman á milli landa lýðfræðilegar breytur, ástæður innlagna, og tíðni og styrkleika einkenna við innlögn. Skoða hindrandi viðhorf meðal sjúklinga (patient related barriers) og bera saman á milli landa og skoða samband slíkra viðhorfa og verkja, aukaverkana og notkunar á verkjalyfjum. Gera úttekt og samanburð á milli landa á notkun á ópíoíðum og öðrum verkjalyfjum. Gera úttekt og samanburð á milli landa á meðferðum sem notaðar eru við aukaverkunum.

Í séríslenska hlutanum er einnig markmið að skoða; (1) Fræðslu til sjúklinga um verki og verkjameðferð sem og fræðsluþarfir þeirra, (2) Aðstoð annarra við verkjalyfjagjöf, (3) Ánægju sjúklinga með verkjameðferð, (4) Skráningu og mat á verkjum, (5) Hverjir eru ábyrgir fyrir verkjameðferð (uppáskriftir), (6) Tegund uppáskrifta.

Safnað verður upplýsingum um; (1) Lýðfræðilegar breytur og sjúkdómsbreytur, (2) Lyfjanotkun, (3) Notkun viðbótarmeðferða við verkjum, (4) Verkir og áhrif verkja á daglegt líf, (5) Heilsutengd lífsgæði, (6) Vitræna starfsemi (cognitive function), (7) Virkni ópíoíð meðferðar, (8) Önnur einkenni en verkir, (9) Hindrandi viðhorf sjúklinga, (10) Fræðslu og fræðsluþarfir, (11) Aðstoð við verkjalyfjagjöf, (12) Ánægju sjúklinga, (13) Skráningu og mat verkja, (14) Uppáskriftir verkjalyfja og (15) Tegund uppáskrifta.

Eftirfarandi blóðsýnum verður safnað; (1) Serum til að meta lifrar og nýrnastarfsemi, (2) Serum til úrvinnslu á styrkleika ópíoíða og niðurbrotsefna þeirra, (3) Serum í geymslu til að geta síðar staðfest fyrri rannsóknir og/eða fyrir frekari úrvinnslur, (4) Heilblóð fyrir lyferfðafræðilega rannsókn, (5) Heilblóð í geymslu til að geta síðar staðfest fyrri rannsóknir og/eða fyrir frekari úrvinnslur.

[...]

Öllum blóðsýnum verður safnað í eitt og sama skiptið og reynt verður að gera það á sama tíma og blóðsýni eru tekin í tengslum við meðferð sjúklings ef þess er nokkur kostur.

Engar erfðafræðilegar úrvinnslur verða gerðar fyrir utan þær sem tengjast verkjum og verkjameðferð.

[...]

Hver staður (center) ber ábyrgð á að þýða spurningalista og rannsóknargögn á viðeigandi tungumál, fá sjúklinga til þátttöku, safna gögnum, og safna og geyma blóðsýni. Haldið er utan um gögn í rannsóknarstöðinni í Þrándheimi. Blóðsýni verða fryst og geymd á hverjum rannsóknarstað fyrir sig þar til þau verða send til Þrándheims. Unnið verður úr blóðsýnum í Þrándheimi - skoðað verður styrkleiki ópíoíða í serum og framkvæmd verður lyfjaerfðafræðileg úrvinnsla. Í Þrándheimi verða einnig geymd blóðsýni sem geymd eru til síðari rannsókna (til staðfestingar eða nýgreininga). Í Þrándheimi verður boðið upp á vinnuaðstöðu fyrir vísindamenn frá öðrum rannsóknarstöðvum sem fara af stað með rannsóknir á geymdum blóðsýnum. Öll notkun á gögnum, notkun á niðurstöðum úr blóðrannsóknum, og notkun á geymdum blóðsýnum verður að fá samþykki frá stýrinefnd rannsóknarinnar.

Við munum fá öll íslensk gögn til úrvinnslu hjá okkur auk þess sem við höfum til úrvinnslu hér á landi þau gögn sem eingöngu er safnað hér.

Héðan frá Íslandi verður stýrt alþjóðlegri vinnu við listann sem metur hindrandi viðhorf sjúklinga (patient related barriers).

Samkvæmt umsókninni verður úrtakið valið með eftirfarandi hætti:

Ætlað er að safna gögnum frá 150 krabbameinssjúklingum á Íslandi. Starfsmaður rannsóknarinnar (hjúkrunarfræðingur með reynslu af vinnu við krabbameinssjúklinga) leitar að sjúklingum á lyfklækningasviði 2 Landspítala háskólasjúkrahúsi (LSH) (lyfjameðferð go geislameðferð krabbameina, blóðsjúkdómadeild, líknardeild), líknardeild Öldrunarsviðs á Landakoti, skurð- og lyflæknisdeildum (gegnum líknarteymi LSH) og í Heimahlynningu Krabbameinsfélagsins og hjúkrunarþjónustunni Karitas. Sjúklingur þarf að vera 18 ára eða eldri, skilja íslensku og hafa getu til að fylla út spurningalista. Hann verður að hafa staðfest krabbamein og hafa verið á ópíóíða verkjameðferð í a.m.k. 3 sólarhringa.

Samkvæmt umsókninni er ætlað að afla upplýsinga úr sjúkraskrám hjá Landspítala háskólasjúkrahúsi, Heimahlynningu Krabbameinsfélagsins og hjúkrunarþjónustunni Karitas. Eftirfarandi upplýsingum verður safnað í þágu rannsóknarinnar:

Fæðingardagur, kyn, hæð og þyngd, kynflokkur, ofnotkun lyfja/áfengis, fæmismat, meðferðarstaður, ástæða komu/innlagnar, sjúkdómsgreining og útbreiðsla sjúkdómsins, dagsetning sjúkdómsgreiningar, tegund verkja, óhefðbundin meðferð, ópíóíðgjöf síðasta sólarhringinn, eftir þörfum lyfjagjafir ópíóíða, hvernig gefið, dagsetning fyrstu ópíóíðagjafar, dagsetning þegar ópíóíðagjöf var síðast breytt, árangur núverandi verkjameðferðar, fyrri ópíóíðameðferð, aðrir sjúkdómar, önnur lyf síðasta sólarhringinn. Skráning og mat verkja í hjúkrunar- og læknaskýrslum.

Varðandi skráningu persónuauðkenna og varðveislu rannsóknargagna í tengslum við rannsóknina segir eftirfarandi:

Hver þátttakandi fær rannsóknarnúmer, upphafsstafir, rannsóknarstaður og hlaupandi rannsóknarnúmer, sem fer á öll gögn (t.d. VS-IS-001) og þau send þannig merkt til Þrándheims. Greiningarlykill verður varðveittur á Krabbameinsmiðstöðinni og verður eytt af yfirmanni hennar þegar íslensku gögnin berast aftur til Íslands.

Nauðsynlegt að hafa greiningarlykil þar til gagnasöfnun lýkur og innslætti gagna er lokið til þess að geta leiðrétt villur og sjá til þess að rétt blóðsýni fari ef merking hefur farið úrskeiðis. Einnig nauðsynlegt fyrir starfsmann að geta athugað hvort sjúklingur hafi tekið þátt í rannsókninni áður en hún mun standa yfir í 2 ár.

1. Blóðsýni, sem tekin verða í sérstök sýnaglös sem koma frá Noregi, verða varðveitt með rannsóknarnúmeri í sérstökum frystiboxum (koma frá Noregi) á Rannsóknarstofu LSH þar til þau verða send til Noregs.
2. Spurningalistar sem sjúklingur fyllir út eru allir skráðir á viðkomandi rannsóknarnúmer og varðveittir í læstri hirslu á Krabbameinsmiðstöðinni þar til þeir verða sendir til Noregs. Aðeins starfsmaður og ábyrgðarmennirnir tveir hafa aðgang að þeirri hirslu.
3. Upplýsingar úr sjúkraskrám eru skráðar á sérstök eyðublöð merkt rannsóknarnúmeri og varðveittar ásamt spurningalistunum í læstri hirslu á Krabbameinsmiðstöðinni þar til þær verða sendar til Noregs.

Öll rannsóknargögn sem send verða til Noregs eru einungis merkt rannsóknarnúmeri. Það sama gildir um gögnin sem unnin verða á Íslandi. Öllum gögnum verður eytt 2 árum eftir að rannsókn lýkur ásamt greiningalykli sem varðveittur er á Íslandi. Niðurstöður verða kynntar þannig að ekki verði hægt að persónugreina einstaklinga.

Engar erfðafræðilegar úrvinnslur verða gerðar fyrir utan þær sem tengjast verkjum og verkjameðferð.

Öll notkun á gögnum, notkun á niðurstöðum úr blóðrannsóknum, og notkun á gleymdum

blóðsýnum verður að fá samþykki frá stýrinefnd rannsóknarinnar.

Um flutning gagna til erlendra samstarfsaðila segir:

> Nákvæm fyrirmæli eru um undirbúning og flutning í rannsóknaraðstöðu stóru rannsóknarinnar. Sýnin verða send í tveimur hlutum með hraðpósti (sérstakt fyrirtæki ákveðið) til: Dept. of Circulation and Medical Imaging, Medical Faculty, NTNU, MTFS 3.et. vest, Olav Kyrresgt. 3, N-7489, Trondheim, Norway. Att: Turid Nilsen.
>
> Gögn verða ekki flutt úr landi fyrr en gagnasöfnun er lokið og Norðmenn tilbúnir að taka á móti þeim.

Að auki kemur fram að aflað verði upplýsts samþykkis hjá öllum þátttakendum og þeir einungis beðnir að svara spurningalistum í eitt skipti.

Persónuvernd barst tilkynning um ofangreinda rannsókn þann 24. febrúar sl. Í framhaldinu sendi starfsmaður Persónuverndar Valgerði Sigurðardóttur bréf, dags. 7. mars sl., þar sem bent var á að sækja þyrfti um leyfi til Persónuverndar vegna rannsóknarinnar, í ljósi þess að 3. mgr. 15. gr. laga nr. 74/1997 um réttindi sjúklinga gerði slíkt að skilyrði þegar aflað væri upplýsinga úr sjúkraskrám vegna vísindarannsókna. Í framhaldinu barst ofangreind umsókn frá Valgerði Sigurðardóttur.

II.
Leyfisskyld vinnsla persónuupplýsinga

Af framangreindu er ljóst að í rannsókninni felst öflun upplýsinga um þátttakendur úr sjúkraskrám þeirra. Samkvæmt 3. mgr. 15. gr. laga nr. 74/1997, um réttindi sjúklinga, þarf leyfi Persónuverndar til aðgangs að sjúkraskrám í þágu vísindarannsókna. Getur stofnunin bundið slíkt leyfi þeim skilyrðum sem hún telur nauðsynleg hverju sinni. Að auki þarf leyfi stofnunarinnar til að vinna megi með persónuupplýsingar í vísindarannsókn þar sem gerðar eru erfðaefnisrannsóknir, sbr. 2. tölul. 1. mgr. 7. gr. reglna nr. 698/2004 um tilkynningarskylda og leyfisskylda vinnslu persónuupplýsinga, sbr. 33. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga.

III.
Leyfi og leyfisskilmálar

Persónuvernd hefur nú ákveðið, m.a. að virtum ákvæðum 29., 33. og 34. gr. í formálsorðum persónuverndartilskipunarinnar nr. 95/46/EB, ákvæði 9. tölul. 1. mgr. 9. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga, 3. mgr. 15. gr. laga nr. 74/1997, sem og 3. mgr. 9. gr. laga nr. 110/2000 um lífsýnasöfn og 2. tl. 1. mgr. 7. gr. reglna nr. 698/2004, að veita yður umbeðið leyfi til aðgangs að sjúkraskrám , lífsýnum og vinnslu persónuupplýsinga vegna rannsóknarinnar: „Evrópsk rannsókn á lyfjaerfðafræði ópíóíða (European Pharmacogenetic Opiod Study)".

Leyfi þetta gildir til 31. desember 2009 og er bundið eftirfarandi skilyrðum:

1. Ábyrgðaraðilar að vinnslu persónuupplýsinga
Valgerður Sigurðardóttir yfirlæknir á Líknardeild LSH og Sigríður Gunnarsdóttur hjúkrunarfræðingur og verkefnisstjóra klínískra rannsókna á Lyf 2 LSH (sem hér eftir kallast leyfishafar), teljast vera ábyrgðaraðilar vinnslunnar í skilningi 4. tölul. 2. gr. laga nr. 77/2000. Fer Valgerður Sigurðardóttir með allt fyrirsvar gagnvart Persónuvernd um alla þætti er varða

þetta leyfi, þ.á m. álitaefni, er upp kunna að rísa, um það hvort vinnsla persónuupplýsinga hafi verið í samræmi við lög, reglur og ákvæði þessa leyfis.

2. *Lögbundnir leyfisskilmálar*

a. Þegar leyfishafar fara þess á leit við ábyrgðarmenn sjúkraskráa, sbr. reglugerð nr. 227/1991 um sjúkraskrár og skýrslugerð varðandi heilbrigðismál, að fá aðgang að viðkomandi sjúkraskrám, ber þeim að framvísa leyfi þessu.

b. Leyfi þetta er bundið því skilyrði að ábyrgðarmenn umræddra sjúkraskráa hafi lýst því yfir að þeir séu því samþykkir fyrir sitt leyti að leyfishafar fái aðgang að þeim. Ef óskað er aðgangs að persónuupplýsingum úr öðrum skrám en sjúkraskrám verður með sama hætti að fá samþykki ábyrgðarmanna þeirra skráa.

c. Leyfi þetta er bundið því skilyrði að ábyrgðarmenn umræddra sjúkraskráa veiti ekki aðgang að þeim nema fyrir liggi að siðanefnd, eða eftir atvikum vísindasiðanefnd, hafi lagt mat á rannsóknina og látið í té skriflegt álit sitt þess efnis að hvorki vísindaleg né siðfræðileg sjónarmið mæli gegn framkvæmd hennar, sbr. 3. mgr. 15. gr. laga nr. 74/1997, sbr. 4. mgr. 2. gr. sömu laga.

d. Þegar leyfishafar skoða sjúkraskrá á grundvelli leyfis þessa ber þeim að skrá það í sjúkraskrána, sbr. 4. mgr. 15. gr. laga nr. 74/1997.

3. Upplýst samþykki

Öll notkun persónuupplýsinga um lifandi og sjálfráða einstaklinga er óheimil án skriflegs, upplýsts samþykkis hlutaðeigandi, enda séu þeir nægilega heilir heilsu til þess að gera sér grein fyrir þýðingu og afleiðingum slíks samþykkis. Sé um að ræða sjálfræðissviptan mann skulu lögráðamenn hans ákveða hvort samþykki verði veitt til að vinna með persónuupplýsingar um hann. Fylgt skal reglum Persónuverndar nr. 170/2001 um það hvernig afla skal upplýsts samþykkis fyrir vinnslu persónuupplýsinga í vísindarannsókn á heilbrigðissviði. Eru fyrirmæli reglnanna hluti skilmála þessa leyfis.

4. Lögmæt vinnsla persónuupplýsinga og þagnarskylda

a. Leyfishafar bera ábyrgð á því að vinnsla persónuupplýsinga vegna rannsóknarinnar fullnægi ávallt kröfum 1. mgr. 7. gr. laga nr. 77/2000.

b. Farið skal með upplýsingar úr sjúkraskrám, sem skráðar eru vegna rannsóknarinnar, í samræmi við lög nr. 77/2000, lög nr. 74/1997, læknalög nr. 53/1988 og reglugerð nr. 227/1991. Hvílir þagnarskylda á leyfishöfum og öðrum þeim sem koma að rannsókninni um heilsufarsupplýsingar sem unnið er með, sbr. 15. gr. laga nr. 53/1988. Þagnarskylda helst þótt látið sé af störfum við rannsóknina.

c. Taki háskólanemar eða aðrir, sem ekki teljast til löggiltra heilbrigðisstétta, þátt í framkvæmd rannsóknarinnar skulu þeir undirrita sérstaka þagnarskylduyfirlýsingu, þar sem þeir m.a. ábyrgjast að tilkynna leyfishöfum ef í rannsóknargögnum eru viðkvæmar persónuupplýsingar um þá sem eru eða hafa verið maki viðkomandi, skyldir eða mægðir honum í beinan legg eða að öðrum lið til hliðar eða tengdir honum með sama hætti vegna ættleiðingar. Er viðkomandi þá óheimilt að kynna sér gögn um þá einstaklinga. Valgerði Sigurðardóttur eða fulltrúa hennar ber að votta rétta undirskrift hlutaðeigandi og dagsetningu slíkrar yfirlýsingar og koma henni til Persónuverndar innan tveggja vikna frá útgáfu leyfis þessa, enda hafi það ekki þegar verið gert. Þagnarskyldan er byggð á 3. mgr. 35. gr. laga nr. 77/2000. Á heimasíðu Persónuverndar er að finna staðlað eyðublað fyrir þagnarskylduyfirlýsingu. Ef þagnarskylduyfirlýsingum er ekki skilað innan tilskilins frests getur Persónuvernd afturkallað leyfi þetta.

d. Leyfi þetta heimilar einvörðungu að unnið verði úr lífsýnum og safnað verði úr sjúkraskrám þeim heilsufarsupplýsingum sem gildi hafa fyrir rannsókn leyfishafa og samrýmast markmiðum hennar.

5. Auðkenning rannsóknargagna

a. Í rannsóknargögn má skrá upplýsingar um fæðingarmánuð, fæðingarár og kyn hvers sjúklings.
b. Óheimilt er að skrá í rannsóknargögn upplýsingar um nöfn sjúklinga, naftnúmer, heimilisfang, símanúmer, fax-númer, tölvupóstfang eða aðrar sambærilegar upplýsingar um sjúklinga.
c. Heimilt er við framkvæmd rannsóknar þessarar að skrá og varðveita *tímabundið* í sérstakri skrá upplýsingar um kennitölur einstaklinga á meðan verið er að undirbúa rannsóknargögn. Slík skrá skal ávallt varðveitt aðskilin frá öðrum rannsóknargögnum.

6. Öryggi við vinnslu persónuupplýsinga

Leyfishöfum ber að gera viðeigandi tæknilegar og skipulagslegar öryggisráðstafanir til að vernda persónuupplýsingar gegn óleyfilegum aðgangi í samræmi við 11. og 12. gr. laga nr. 77/2000. Þar er meðal annars áskilið að:

a. beita skuli ráðstöfunum sem tryggja nægilegt öryggi miðað við áhættu af vinnslunni og eðli þeirra gagna sem verja á, með hliðsjón af nýjustu tækni og kostnaði við framkvæmd þeirra, og
b. tryggja skuli að áhættumat og öryggisráðstafanir við vinnslu persónuupplýsinga séu í samræmi við lög, reglur og fyrirmæli Persónuverndar um hvernig tryggja skal öryggi upplýsinga, þ.m.t. þá staðla sem hún ákveður að skuli fylgt.

Leyfishafar bera ábyrgð á því að hver sá er starfar í umboði þeirra og hefur aðgang að persónuupplýsingum vinni aðeins með þær í samræmi við skýr fyrirmæli sem þeir gefa og að því marki að falli innan skilyrða leyfis þessa, nema lög mæli fyrir á annan veg, sbr. 3. mgr. 13. gr. laga nr. 77/2000.

7. Varðveisla og eyðing gagna

Ávallt skal tryggt að rannsóknargögn séu varðveitt á tryggum stað og aðeins þar sem lögum samkvæmt er heimilt að varðveita þau.

Að lokinni þeirri rannsókn sem leyfi þetta tekur til, þó eigi síðar en við lok gildistíma leyfisins þann 31. desember 2009, ber að eyða öllum rannsóknargögnum eða gera þau ella ópersónugreinanleg, þ.e. með því að eyða greiningarlykli. Þó er heimilt að varðveita lífsýni í samræmi við ákvæði laga nr. 110/2000 um lífsýnasöfn.

8. Almennir skilmálar

a. Leyfishafar bera ábyrgð á að farið sé með öll persónuauðkennd gögn sem sjúkragögn í samræmi við lög, reglur og ákvæði þessa leyfis.
b. Leyfishafar skulu ábyrgjast að engir aðrir en þeir fái í hendur persónugreinanleg gögn sem sérstaklega verður aflað í þágu þessarar rannsóknar.
c. Óski leyfishafar þess að hætta rannsókn ber þeim að leggja þetta leyfi inn til Persónuverndar á skriflegan og sannanlegan hátt. Skal þá tilgreina hvort þeim persónuupplýsingum, sem unnar voru á grundvelli þessa leyfis, hafi verið eytt. Að öðrum kosti úrskurðar Persónuvernd um hvort persónuupplýsingunum skuli eytt eða þær varðveittar með ákveðnum skilyrðum.
d. Leyfishöfum ber að veita Persónuvernd, starfsmönnum og tilsjónarmönnum hennar allar umbeðnar upplýsingar um vinnslu persónuupplýsinga sé eftir því leitað í þágu eftirlits. Brot á ákvæði þessu getur varðað afturköllun á leyfinu.
e. Persónuvernd getur látið gera úttekt á því hvort leyfishafar fullnægi skilyrðum laga nr. 77/2000 og reglna sem settar eru samkvæmt þeim eða einstökum fyrirmælum. Getur Persónuvernd ákveðið að þeir skuli greiða þann kostnað sem af því hlýst. Persónuvernd getur einnig ákveðið að leyfishafar greiði kostnað við úttekt á starfsemi, við undirbúning

útgáfu vinnsluleyfis og annarrar afgreiðslu. Persónuvernd skal þá gæta þess að sá sérfræðingur, sem framkvæmir umrædda úttekt, undirriti yfirlýsingu um að hann lofi að gæta þagmælsku um það sem hann fær vitneskju um í starfsemi sinni og leynt ber að fara eftir lögum eða eðli máls. Brot á slíkri þagnarskyldu varðar refsingu samkvæmt 136. gr. almennra hegningarlaga. Þagnarskyldan helst þótt látið sé af starfi.

f. Leyfi þetta er háð því skilyrði að einungis verði safnað þeim upplýsingum sem *nauðsynlegar* eru vegna rannsóknarinnar.

Virðingarfyllst

Sigrún Jóhannesdóttir

LANDSPÍTALI
HÁSKÓLASJÚKRAHÚS

Sigríður Gunnarsdóttir
hjúkrunarfræðingur
lyflækningasviði II
Landspítala Hringbraut

04.03.2005
Tilv. 16
ÞH/ei

Efni: Evrópsk rannsókn á lyfjaerfðafræði ópíoíða

Ágætu Valgerður og Sigríður.

Vísað er til bréfs ykkar til lækningaforstjóra, dags. 22.02.2005 þar sem óskað er heimildar til að framkvæma ofangreinda rannsókn á Landspítala – háskólasjúkrahúsi. Fram kemur að Sigríður er ábyrgðarmaður rannsóknarinnar en aðrir umsækjendur eru auk ykkar, Paul Klepstad, Stein Kaasa, Ole Dale og Frank Skorpen sem eru allir starfsmenn Tæknihaskólans í Þrándheimi auk fjórtán vísindamanna, evrópskra og bandarískra.

Hér með er veitt heimild til að framkvæma ofangreinda rannsókn á Landspítala – háskólasjúkrahúsi undir stjórn Sigríðar Gunnarsdóttur og Valgerðar Sigurðardóttur. Jafnframt er veittur aðgangur að sjúkraskrám sem kunna að tengjast rannsókninni. Leyfi þetta er háð því að fyrir liggi samþykki Vísindasiðanefndar og Persónuverndar en fram kemur að sótt hefur verið um slík leyfi.

Með kveðju og ósk um gott rannsóknargengi,

Þórður Harðarson
prófessor, yfirlæknir

Vilhelmína Haraldsdóttir
framkvæmdastjóri lækninga

Samrit:
Valgerður Sigurðardóttir, dr.med, yfirlæknir

Afrit:
Björn Guðbjörnsson, formaður
Sigrún Jóhannesdóttir, forstjóri

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Attachment B

Letter of introduction and informed consent

LANDSPÍTALI
HÁSKÓLASJÚKRAHÚS

Upplýst samþykki sjúklings

vegna rannsóknarinnar „ Evrópsk rannsókn á lyfjaerfðafræði ópíoíða".

Ábyrgðarmaður rannsóknarinnar er Sigríður Gunnarsdóttir hjúkrunarfræðingur á Lyflækningasviði II (krabbameins- og blóðlækninga) á Landspítala-háskólasjúkrahúsi og meðrannsakandi Valgerður Sigurðardóttir, yfirlæknir á líknardeild Landspítala-háskólasjúkrahúss, Kópavogi.

Ég undirrituð/ritaður hef kynnt mér skriflegar upplýsingar um ofangreinda rannsókn og eðli þátttöku minnar í henni:

Ég hef verið upplýst/ur um að rannsóknin er fjölþjóðleg og miðar að því að afla upplýsinga um lyfjaerfðafræði verkjalyfja (ópíoíða).

Ég skil að þátttaka mín felur í sér (1) að svara spurningum hjúkrunarfræðings um bakgrunn minn, verkjameðferð og hugræna virkni, (2) að svara spurningalistum um verki og önnur einkenni, lífsgæði, þá verkjameðferð sem ég hef fengið ásamt hugmyndum mínum um krabbameinsverki og meðferð þeirra og (3) að teknar verða 5 blóðprufur (samtals 20-30 ml) í eitt skipti til þess að meta lifrar- og nýrnastarfsemi, til að skoða blóðþéttni verkjalyfja (ópíoíða) og lyfjaerfðafræði verkjalyfja. Áætlað er að þátttaka mín taki um eina klukkustund.

Ég skil að áhætta við blóðtöku er lítil og aukaverkanir sjaldgæfar. Helstu aukaverkanir eru óþægindi við stungu og mar.

Ég skil að upplýsingar um mig sem teknar hafa verið úr sjúkraskrám, ásamt spurningalistum og blóðprufum verða sendar til Noregs þar sem úrvinnsla gagna fer fram.
Ég skil að blóðprufurnar verða sendar til Íslands að úrvinnslu lokinni og geymdar í viðurkenndu lífsýnasafni.
Ég skil að í framtíðinni verður hægt að sækja um leyfi til Vísindasiðanefndar til að nota blóðsýnin til frekari rannsókna á lyfjaerfðafræði verkjalyfja.

Ég hef verið upplýst/ur um að mér sé frjálst að hafna þátttöku í rannsókninni og að það muni ekki hafa nein áhrif á umönnun mína né meðferð. Einnig að ég geti hvenær sem er óskað eftir því að hætta í rannsókninni. Ef ég hætti þátttöku verður öllum gögnum um mig eytt og sú ákvörðun mun á engan hátt hafa áhrif á umönnun mína né meðferð.

Ég lýsi mig samþykka/n þátttöku og gef leyfi til að starfsmenn rannsóknarhópsins safni blóðprufum og skrái upplýsingar um mig einu sinni á þar til gerð eyðublöð.

Dagsetning:_____ Nafn þess er aflar upplýsts samþykkis:

_____

Nafn þátttakanda:

_____

LANDSPÍTALI
HÁSKÓLASJÚKRAHÚS

Kynningarbréf

vegna rannsóknarinnar „Evrópsk rannsókn á lyfjaerfðafræði ópíóíða"

Ágæti viðtakandi.

Ég undirrituð, Sigríður Gunnarsdóttir hjúkrunarfræðingur á Lyflæknissviði II (krabbameins- og blóðlækninga) á Landspítala-háskólasjúkrahúsi, sími **543-6021**, netfang **sigridgu@landspitali.is**, er ábyrgðarmaður rannsóknarinnar **„Evrópsk rannsókn á lyfjaerfðafræði ópíóíða".** Meðrannsakandi minn er Valgerður Sigurðardóttir, yfirlæknir á líknardeild Landspítala-háskólasjúkrahúss, Kópavogi, **sími 543-6602**.

Þar sem þú hefur verið greind/ur með krabbamein og færð verkjameðferð með sterkum verkjalyfjum (ópíóíðum) förum við þess á leit við þig að þú takir þátt í rannsókn á verkjameðferð. Stefnt er að því að 150 Íslendingar taka þátt í rannsókninni en samtals 3000 einstaklingar víðsvegar um heim.. Rannsóknin er því fjölþjóðleg og unnin í samvinnu við rannsakendur víða í Evrópu og í Bandaríkjunum.

Við biðjum þig að lesa þetta kynningarbréf vandlega og gera upp hug þinn um hvort þú vilt taka þátt í rannsókninni eða ekki. Hjúkrunarfræðingur sem er starfsmaður rannsóknarinnar mun síðan hafa samband við þig, annað hvort símleiðis eða þegar þú kemur til eftirlits eða meðferðar á Landspítalanum.

Rannsókninni er ætlað að afla upplýsinga um lyfjaerfðafræði sterkra verkjalyfja (ópíóíða), m.a. til að skoða hvað geti skýrt mismunandi verkun þessara lyfja á milli einstaklinga. Rannsókninni er ennfremur ætlað að varpa ljósi á stöðu verkjameðferðar á Íslandi og víðar og á þætti sem hafa áhrif á meðferð krabbameinsverkja. Þessi þekking er liður í því að bæta meðferð krabbameinsverkja.

Í þátttöku þinni felst: **(1)** Að svara í einu stuttu viðtali við hjúkrunarfræðing spurningum um bakgrunn þinn, verkjameðferð og hugræna virkni. **(2)** Að svara einu sinni spurningalistum um verki og önnur einkenni, lífsgæði, þá verkjameðferð sem þú hefur fengið ásamt hugmyndum þínum um krabbameinsverki og meðferð þeirra. **(3)** Að gefa blóðsýni — teknar verða í eitt skipti 5 blóðprufur (samtals 20-30 ml) sem notaðar verða til að meta lifrar- og nýrnastarfsemi, til að skoða blóðþéttni verkjalyfja (ópíóíða) og lyfjaerfðafræði verkjalyfja. Tvær af þessum prufum verða geymdar til að staðfesta síðar fyrri rannsóknir eða til frekari rannsókna á þáttum sem tengjast lyfjaerfðafræði verkjalyfja. **(4)** Einnig förum við fram á að þú veitir okkur leyfi til að nálgast upplýsingar um heilsufar þitt og meðferð úr sjúkraskrám og nota í rannsóknina.

Rannsóknin fer þannig fram að hjúkrunarfræðingur tekur við þig eitt viðtal og lætur þig hafa spurningalista til að svara í eitt skipti. Síðan mun hjúkrunarfræðingur eða meinatæknir taka blóðprufur. Þær verða teknar einu sinni og reynt verður að gera það á sama tíma og aðrar blóðprufur eru teknar vegna meðferðar þinnar. Áætlað er að þátttaka þín í rannsókninni taki um 1 klst, en einnig er hægt að hittast oftar í styttri tíma allt eftir getu þinni og óskum.

Áhætta við blóðtöku er lítil. Helstu aukaverkanir eru smá sársauki við stungu , mar gæti myndast en litlar líkur eru á bólgumyndun (sýkingu).

Fyllsta trúnaðar verður gætt. Allar upplýsingar verða geymdar í læstri hirslu. Spurningalistar ásamt blóðprufunum verða sendar til Noregs til úrvinnslu en áður en það er gert verður öllum persónugreinanlegum upplýsingum um þig eytt svo ekki verði hægt að tengja blóðsýnin við þig persónulega. Ópersónugreinanlegar upplýsingar verða geymdar í Noregi til frambúðar en lífsýni send aftur til Íslands og geymd í lífsýnabanka (Lífsýnabanka Krabbameinsfélags Íslands) sem er viðurkenndur af heilbrigðisráðuneytinu. Í framtíðinni verður hægt að sækja um leyfi til Vísindasiðanefndar til að gera frekari rannsóknir á blóðsýnunum og þá er hugsanlegt að þau verði send aftur til útlanda tímabundið. Þetta er gert svo hægt sé að halda áfram að vinna að rannsóknum á krabbameinsverkjum og lyfjaerfðafræði ópíóíða en slíkar rannsóknir eru nýjar af nálinni og fyrstu niðurstöður geta leitt okkur áfram næstu skref. Sýnin verða eingöngu notuð við rannsóknir sem tengjast lyfjaerfðafræði verkjalyfja. Niðurstöður verða birtar í viðurkenndum vísindatímaritum og á vísindaráðstefnum. Í framsetningu á niðurstöðum verður þess gætt að aldrei sé hægt að rekja þær til einstakra þátttakenda heldur kynntar fyrir hópinn í heild sinni.

Þér er frjálst að hafna þátttöku í rannsókninni og mun það ekki hafa nein áhrif á umönnun þína né meðferð. Þú getur hvenær sem er óskað eftir því að hætta í rannsókninni. Þá mun öllum gögnum um þig verða eytt og sú ákvörðun mun á engan hátt hafa áhrif á umönnun þína né meðferð.

Ef þú hefur einhverjar spurningar varðandi rétt þinn sem þátttakandi í rannsókninni eða vilt hætta þátttöku í henni getur þú snúið þér til Vísindasiðanefndar, Vegmúla 3, 108 Reykjavík,sími 551-7100, fax: 551-1444. Jafnframt veita ábyrgðarmenn rannsóknarinnar allar upplýsingar.

Með vinsemd,

Valgerður Sigurðardóttir, yfirlæknir

Sigríður Gunnarsdóttir, hjúkrunarfræðingur

Attachment C

Permission for citing unpublished theses

Mat á einkennum hjá sjúklingum með krabbamein: Forprófun á M.D. Anderson Symptom Inventory (MDASI).

Validation of the Icelandic translation of the Expanded Prostate Cancer Index Composite-26-item v.

Reykjavík 28. mars 2008

Ég, undirrituð, gef Sigríði Zoëga leyfi til að vitna í lokaritgerð mína til MS. prófs, Validation of the Icelandic translation of the expanded prostate cancer index composite-26-item version : a disease-specific questionnaire to evaluate the quality of life of men diagnosed with prostate cancer, sem gerð var við Hjúkrunarfræðideild Háskóla Íslands vorið 2006.

Guðrún Sigurðardóttir

Reykjavík 28. mars 2008

Við undirritaðar gefum Sigríði Zoëga leyfi til að vitna í lokaritgerð okkar til BS. prófs, Mat á einkennum hjá sjúklingum með krabbamein: forprófun á M.D. Anderson symptom inventory (MDASI), sem gerð var við Hjúkrunarfræðideild Háskóla Íslands vorið 2005.

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Attachment D

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Ferrans, C.E., Zerwic, J.J., Wilbur, J.E. and Larson, J.L. (2005). Conceptual Model of Health-Related Quality of Life. *Journal of Nursing Scholarship, 37*(4), 336-342.

Source: Lenz, E.R. Pugh, L.C., Milligan, R.A., Gift, A., and Suppe, F. (1997). The Middle-Range Theory of Unpleasant Symptoms: An Update. *Advances in Nursing Science, 19*(3), 14-27.

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With kind regards
Sigridur Zoëga, RN, master student

Sigríður Zoëga
RN, master student
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