DEFINING HEALTH-RELATED QUALITY OF LIFE IN LOCALIZED AND ADVANCED STAGES OF BREAST CANCER – THE FIRST STEP TOWARDS HEREDITARY CANCER GENETIC COUNSELING

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SUMMARY – The important goal in breast cancer treatment is to improve patient quality of life. Due to the huge economic burden, it is necessary to estimate the health state utility values for different breast cancer stages accurately. A group of 114 women filled out the EuroQol-5D-3L questionnaire at two time points. The participants were divided into three groups, as follows: group 1 including healthy high-risk individuals; group 2 including patients with localized stage breast cancer; and group 3 including patients with advanced stage breast cancer. Results were expressed either as summary health state utility score or summary visual-analog score. The EuroQol utility index score and EuroQol visual–analog score were statistically significantly higher in the group of healthy high-risk individuals. The EuroQol visual–analog score was mostly correlated with the anxiety/depression and pain/discomfort quality of life dimensions. Health state utility values for different breast cancer stages are a necessary tool to perform economic analyses in breast cancer management decision making, due to its huge economic burden. Special attention should be paid to assessment of the psychosocial aspects of the disease, as well as pain management.

Key words: Breast cancer; Genetic counseling; Quality of life; Cost–benefit analysis

Introduction

Breast cancer is among the most common cancers in women and the second leading cause of cancer-related death in women¹. It is estimated that one in eight (12.3%) women will develop breast cancer during their lifetime. In 2012, 1,670,000 new cases of breast cancer were recorded worldwide. In Europe, nearly 460,000 women are affected every year²³. Despite available hormonal and targeted therapies, chemotherapy, improved surgical therapy and radio-

therapy of breast cancer, 30%–40% of patients still develop metastatic disease. Locally advanced breast cancer, metastatic breast cancer, inflammatory breast cancer or breast cancer where curative surgical treatment or radiotherapy is not possible are considered advanced breast cancer stages⁴.

Patients diagnosed with breast cancer at an advanced stage are faced with a double burden, i.e. coping with significant adverse physical symptoms and with awareness that advanced stage breast cancer is a treatable but at long-term incurable disease. The success of the modern era of chemotherapy, targeted and hormonal breast cancer therapy has increased the number of patients with metastatic disease who receive several treatment modalities at the same time⁵. Having in mind that none of the advanced breast can-
Cancer treatment modalities leads to permanent cure, the two main treatment goals are to prolong survival and to improve patient quality of life. Assessment of these categories is becoming more important than the traditional treatment outcome measures, such as progression-free survival and overall survival.

Quality of life has two main components, objective and subjective ones. Objective parameters such as personal income, health, education level and employment status are deficient indicators because they do not take into account the views and beliefs of the individual. Therefore, definition of the quality of life should take into account subjective parameters describing subjective reactions to different experiences.

Cummins has described 7 domains of the subjective quality of life component, as follows: material well-being, health, productivity, intimacy, safety, place in society, and emotional well-being. He also explored the connection between the quality of life subjective and objective components and concludes that the correlation is low and has a non-linear character.

There are several definitions in the literature that attempt to define this subjective concept. The World Health Organization defines quality of life as the individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Gotay et al. define quality of life as a state of well being, which consists of a person’s ability to perform daily activities reflecting his/her physical, mental and social well-being and satisfaction with daily functioning and disease control. Calman gives an interesting definition of the quality of life as a clash between the patient’s expectations and achievements. The smaller the clash, the better is quality of life.

Health-related quality of life (HRQoL) is a subjective assessment of health and welfare. It has been designated as a special term to emphasize the fact that this dimension is clearly distinguishable from other phenomena that contribute to better quality of life, such as income, freedom, or the environment.

Due to inconsistency of the quality of life definition, there are many available instruments that measure quality of life with two basic approaches, i.e. generic instruments are multidimensional ones, developed to assess the general quality of life and specific instruments that measure quality of life in certain diseases. Generic instruments are widely used, particularly to determine demographic and cross-cultural differences in the quality of life.

A quite often utilized and validated instrument from the group of generic instruments is EuroQol-5D (EQ-5D), which is used to assess health status for the purpose of health-economic analysis. It has been developed by the EuroQol Group in 1987 and used in numerous clinical trials, observational studies and research. EQ-5D is a standardized measure of health status developed as a simple, generic measure of health status for use in clinical and economic analysis. As it can be administered to a large number of diseases and types of treatment, this form is a simple descriptive profile of health status expressed as a ‘utility index score’ at the time of completion of the questionnaire. Cognitively undemanding, it is designed so as not to be time-consuming but easily filled out by the subject alone.

Quality of life estimated by the EQ-5D questionnaire is part of the Quality Adjusted Life Years (QALY) metrics, a term that incorporates life expectancy, as well as quality of life. It is used in health economics to determine priorities in redistribution of resources.

The present study was conducted as part of the cost-effectiveness analysis of the implementation of hereditary cancer genetic counseling and testing program for the first time in Croatia. The aim of the study was to compare the HRQoL measured by EQ-5D questionnaire and expressed as EQ-utility index score (EQ-US) or EQ visual-analog score (EQ-VAS) in localized and advanced stage breast cancer patients with healthy high-risk population. The second goal of the study was to investigate the dimensions of the questionnaire that mostly affect the quality of life expressed as VAS.

Subjects and Methods

The study was approved by the Central Ethics Committee, School of Medicine, University of Zagreb and Ethics Committee, Sestre milosrdnice University Hospital Centre, Zagreb. Participants were informed verbally and in writing about the purpose and methods of the study prior to giving their informed consent for participation and publication of the results.

The study was conducted at the Genetic Counseling Unit, University Hospital for Tumors, Sestre milosrd-
of University Hospital Centre from January 1, 2016 until December 31, 2016. Participation in the study was offered to all women having presented for genetic counseling during the mentioned period irrespective of age. The inclusion criteria were as follows: women diagnosed with breast cancer in any stage, and healthy women that were eligible for BRCA1/2 gene genetic testing according to the recent National Comprehensive Cancer Network (NCCN) guidelines. The questionnaire was offered at first consultation (first time point) and 3 months later (second time point). The exclusion criteria were as follows: men with breast cancer; women diagnosed with cancer other than breast cancer; and participants that failed to fill out the questionnaire completely and at both time points.

Out of 135 participants that were offered to fill out the questionnaire, 114 women were included in the study according to the inclusion criteria. They were divided into three groups: group 1 including healthy high-risk individuals; group 2 including patients with localized stage breast cancer; and group 3 including patients with advanced stage breast cancer. The group of high-risk subjects consisted of healthy women that were eligible for BRCA1/2 gene genetic testing according to the recent NCCN Guidelines.

The participants filled out the questionnaire during their visit to the Genetic Counseling Unit at two time points, i.e. at the time of diagnosis of breast cancer in case of women diagnosed with breast cancer or at the time of first consultation in case of healthy women, and 3 months later.

**Instrument**

The first part of the questionnaire consists of 5 questions (i.e. EQ-5D descriptive system), each of them representing one of the 5 health state dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. A total of 243 possible health states are defined in this way and converted to ED-5D utility index score using the time trade-off (TTO) valuation technique, ranging from -0.594 to 1.000. For translation of EQ-5D-3L scores into health utilities, we used the United Kingdom value set according to the EuroQol Group instructions. The health state described with negative utility index values is considered worse than death itself.

The second part of the questionnaire consists of EQ Visual-analog scale (EQ-VAS). The EQ-VAS records the respondent’s self-rated health on a vertical, visual analog scale where the endpoints are labeled “Best imaginable health state” and “Worst imaginable health state”. This information is used as a quantitative measure (“Best imaginable health state” ranged as 100 and “Worst imaginable health state” ranged as 0) of health outcome as judged by the individual respondents. The participants filled out the questionnaire with the help of an experienced examiner.

**Statistical analysis**

Final EQ US and EQ VAS were calculated as mean of the values obtained in the first and second time point. Mean value, standard deviation, median with minimum and maximum values were calculated for the EQ US and EQ VAS for each group of patients.

Comparison of the groups was made using non-parametric Mann-Whitney test. To evaluate which of the five health state dimensions was mostly correlated to HRQoL expressed as EQ VAS, we used linear regression model employing the stepwise backwards regression method. A p-value of 5% was set as statistically significant. Statistical analysis was performed with the statistical tool R (http://www.r-project.org/).

**Results**

The total number of participants that met the inclusion criteria was 114. The group of healthy high-risk individuals (group 1) consisted of 33 women, the group of patients with localized stage breast cancer (group 2) of 49 women, and the group of patients with advanced stage breast cancer (group 3) of 32 women.

Table 1 shows the EQ US and EQ VAS measured in the first and second time point and overall EQ US and EQ VAS expressed as mean, standard deviation, and median with minimum and maximum for each group of patients. The overall EQ US and EQ VAS were highest in the group of healthy high-risk individuals (0.85) and lowest in the advanced stage breast cancer group (0.68). The EQ US was statistically significantly different between group 1 and group 2 (p=0.013) and between group 1 and group 3 (p=0.004). The EQ US was not statistically different between group 2 and group 3 (p=0.469).
Difference in eq v AS between group 1 and group 2 was at the border of statistical significance (p=0.055). The eq v AS was statistically significantly different between group 1 and group 3 (p=0.006). The eq v AS was not statistically different between group 2 and group 3 (p=0.212).

A linear regression model using the stepwise backwards regression method was performed to evaluate which of the five health state dimensions mostly affected eq v AS. The results were calculated separately for eq v AS in each time point. The results of multivariate analysis are shown in Table 2. The odds ratio (OR) for eq v AS in the first time point was lowest for the anxiety/depression level 3 (OR 0.64, 95% CI 0.56-0.74). The eq v AS in the second time point was mostly correlated with the pain/discomfort level 3 (OR 0.79, 95% CI 0.69-0.89). The Oral level was not statistically different between group 1 and group 3 (p=0.05). The Oral level was statistically significantly different between group 1 and group 3 (p=0.006). The Oral level was not statistically different between group 2 and group 3 (p=0.212).

### Discussion

Results of our study provided the health state utility values for localized and advanced breast cancer stages and compared them with the utility values of stages and group 1 individuals (n=33).

### Table 1. EQ utility index score and EQ visual-analog score measured in the first and second time point and overall EQ utility index score and EQ visual-analog score expressed as mean, standard deviation, median with minimum and maximum for each group of patients

|                 | Age (yrs) | US 1st time point | US 2nd time point | Overall US | VAS 1st time point | VAS 2nd time point | Overall VAS |
|-----------------|-----------|--------------------|--------------------|------------|--------------------|--------------------|------------|
| **All (n=114)**|           |                    |                    |            |                    |                    |            |
| Mean            | 52.28 (13.95) | 0.77 (0.24)       | 0.77 (0.26)        | 0.77 (0.23) | 0.72 (0.20)        | 0.73 (0.18)        | 0.73 (0.17) |
| Median          | 51 (24-91) | 0.80 (-0.43-1.00) | 0.80 (-0.59-1.00) | 0.82 (-0.51-1.00) | 0.75 (0.05-1.00) | 0.75 (0.30-1.00) | 0.75 (0.30-1.00) |
| **Group 1: healthy high-risk individuals (n=33)** |           |                    |                    |            |                    |                    |            |
| Mean            | 44.70 (11.96) | 0.88 (0.15)       | 0.82 (0.24)        | 0.85 (0.17) | 0.78 (0.21)        | 0.78 (0.20)        | 0.78 (0.20) |
| Median          | 45 (24-76) | 1.00 (0.41-1.00) | 0.85 (0.082-1.00) | 0.90 (0.38-1.00) | 0.85 (0.10-1.00) | 0.85 (0.30-1.00) | 0.87 (0.30-1.00) |
| **Group 2: localized stage breast cancer patients (n=49)** |           |                    |                    |            |                    |                    |            |
| Mean            | 56.24 (12.96) | 0.78 (0.16)       | 0.78 (0.20)        | 0.78 (0.16) | 0.73 (0.18)        | 0.72 (0.17)        | 0.72 (0.15) |
| Median          | 57 (30-82) | 0.80 (0.25-1.00) | 0.80 (0.16-1.00) | 0.80 (0.20-1.00) | 0.70 (0.30-1.00) | 0.70 (0.30-1.00) | 0.75 (0.40-1.00) |
| **Group 3: advanced stage breast cancer patients (n=32)** |           |                    |                    |            |                    |                    |            |
| Mean            | 54.03 (14.60) | 0.62 (0.34)       | 0.71 (0.37)        | 0.68 (0.31) | 0.66 (0.20)        | 0.69 (0.16)        | 0.68 (0.13) |
| Median          | 52 (33-91) | 0.72 (-0.43-1.00) | 0.80 (-0.59-1.00) | 0.79 (-0.51-0.94) | 0.70 (0.05-0.90) | 0.70 (0.30-0.90) | 0.70 (0.40-0.90) |

US = utility index score; VAS = visual-analog score

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**Table 2. Results of the linear regression model expressed in the final model with OR and 95% CI for different levels of health state dimensions that were significant and incorporated in the final model**

| VAS 1st time point | Anxiety/depression level 3 | Mobility level 2 | Pain/discomfort level 2 | Mobility level 3 | Anxiety/depression level 2 |
|--------------------|-----------------------------|------------------|------------------------|------------------|-----------------------------|
| OR                 | 0.64 (0.56-0.74)            | 0.69 (0.63-0.74) | 0.88 (0.81-0.94)       | 0.79 (0.71-0.85) | 0.69 (0.63-0.74)            |
| 95% CI             | 0.56-0.74                   | 0.70-0.89        | 0.83-0.93              | 0.69-0.83        | 0.93-0.93                   |

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healthy high-risk individuals. The health state utility values were expressed as the mean value at three months of diagnosis. The health state utility values were highest in the group of healthy individuals and decreased in breast cancer patients according to the breast cancer stage. The VAS as a subjective indicator of the individual’s health state was mostly influenced by the pain/discomfort and anxiety/depression score. It is impossible to reach the ideal health state utility value that accurately describes the health state in each breast cancer stage. Our approach was based on the fact that in the period of three months of the diagnosis patients usually experienced different psychological states (from disbelief to depression) and different treatment modalities (surgery, radiotherapy, chemotherapy) that could influence their quality of life. The summary health state utility value was obtained as a cross-section value during this period. The cross-section time approach allows measurements in a moderate number of study participants and gives a more accurate health state utility value than single measurement.

Comparing our results with the results from the study by Folse et al., we can conclude that the overall quality of life differed significantly in the healthy high-risk group (utility value 0.85) compared to healthy population (utility value 1.00). There is a possibility that this family burden puts an additional psychological burden that ultimately results in poorer quality of life. We assume that this additional psychological pressure could be facilitated by the genetic counseling process prior to genetic testing and afterwards, according to the study by Eijzenga et al.

In our study, the health state utility values of localized and advanced breast cancer stage were similar to other reported studies.

Our study additionally highlighted the importance of early psychological support and pain management during breast cancer treatment. Taking into account great progress in the development of various breast cancer therapeutic options in recent years, the society as a whole is facing new challenges. During and after the initial treatment, patients with breast cancer are faced with serious psychosocial issues such as personal and professional social disruption, depression, distress/anxiety problems, fertility and sexuality doubts. We are witnessing a period in which there is an increased number of breast cancer survivors and these psychosocial problems are even more pronounced in this group of patients. Breast cancer survivors are a vulnerable group with sometimes limited life expectancy. Younger breast cancer patients are prone to depressive disorders, and depression by itself could be an underdiagnosed state in older cancer patients. This raises a question of routine psychological assessment of breast cancer patients during treatment and afterwards. The idea of death and dying should be appropriately processed rather than avoided during the process of psychological counseling and patients should be empowered to reorder their life priorities. One of the top clinical research needs in breast cancer is to increase efforts in survivorship research including supportive care and quality of life. The results of quality of life assessments in breast cancer patients are rarely used to guide clinical practice decisions.

Assessing HRQoL is an important part of QALY metrics that has been widely used in economic analyses. QALY is a measure that is defined by the duration and quality of life that can be generated by health interventions. It represents the product of life expectancy and the health state utility value. QALY puts weight on the time spent in a particular health state. It is far away from the ideal outcome measure, with a number of shortcomings of technical and methodological nature. However, the use of QALY as an outcome measure that will guide the decision on redistribution of resources means that the choice between the two groups of patients that are competing for the same medical intervention is explicit, and that the groups are compared to the universal principle. In this way, the benefit that the health care system generates from new investments is transparent.

The breast cancer economic burden is evident from the fact that treatment expenses will reach $157 billion annually by 2020, with an overall 27% increase in medical costs in the United States. The costs are highest for patients in the advanced stage. Having in mind this huge economic burden of breast cancer treatment and the need for economic analyses in the field, it is clear that it is necessary to estimate the health state utility values for different breast cancer stages as accurately as possible. Additional studies are needed to explore the HRQoL in different breast cancer stages with special attention to psychological and pain issues.
Conclusion

In conclusion, we can say that the health state utility values for different breast cancer stages are a necessary tool for performing economic analyses in breast cancer management decision making, due to its huge economic burden. Our paper for the first time brings the health state utility values expressed as time cross-section values for localized and advanced breast cancer stages, as well as for healthy high-risk population.

The results of our study showed the importance of anxiety/depression and pain/discomfort dimensions in the overall quality of life of breast cancer patients. Quality of life is an important treatment outcome and special attention has to be paid to the psychological burden of the disease, as well as to pain management.

Our study emphasized the importance of early psychological counseling in breast cancer patients and its implementation at the national level. The study was conducted as part of a cost-effectiveness analysis of the implementation of genetic counseling and testing program for hereditary breast cancer in Croatia. The results from this study will be used in further economic analysis.

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Sažetak

DEFINIRANJE KVALITETE ŽIVOTA
KOD BOLESNICA S LOKALIZIRANIM I UZAPREDOVALIM STADIJEM RAKA DOJKE
– PRVI KORAK PREMA ONKOLOŠKOM GENETSKOM SAVJETOVANJU

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Važan cilj u liječenju raka dojke je poboljšanje kvalitete života bolesnika. Zbog velikog financijskog opterećenja važno je točno procijeniti parametre kvalitete života (engl. health state utility values) za različite stadije raka dojke. Skupina od 114 žena ispunila je upitnik EuroQol-5D-3L u dvije vremenske točke. Sudionice su podijeljene u 3 skupine: 1. skupina – zdrave visokorizične osobe; 2. skupina – bolesnice s lokaliziranim stadijem raka dojke i 3. skupina – bolesnice u uznnapredovalom stadiju raka dojke. Rezultati su predočeni ili kao sveukupni indeks kvalitete života bolesnika (engl. summary health state utility score) ili kao rezultat na vizualno-analognoj ljestvici (engl. summary visual-analog score). EuroQol index score i EuroQol visual-analog score bili su statistički značajno viši u skupini zdravih visokorizičnih osoba. Utvrđeno je da EuroQol visual-analog score korelira sa sljedećim dimenzijama kvalitete života: anksioznost/depresija i bol/nelagoda. Parametri kvalitete života (engl. health state utility values) za različite stadije raka dojke važan su alat za provođenje ekonomske analize pri donošenju odluka o liječenju raka dojke, prvenstveno zbog velikog financijskog opterećenja. Osobitu pozornost trebalo bi usmjeriti na procjenu psihosocijalnih aspekata bolesti, kao i liječenju boli.

Ključne riječi: Rak dojke; Genetsko savjetovanje; Kvaliteta života; Analiza troškova i koristi