The effect of supportive and educational nursing care on quality of life and HE4 gene expression in patients with ovarian cancer

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ABSTRACT

Ovarian cancer is one of the most common malignancies in women and is also the fifth leading cause of cancer death in women worldwide. In recent years, the survival rate of patients with this disease has been long, and at the same time, more emphasis is on their quality of life. Therefore, the present study was conducted to investigate the effect of supportive and educational care of nurses on the life quality of patients with ovarian cancer. The expression of the HE4 gene was also evaluated as a diagnostic marker of ovarian cancer to assess the role of supportive and educational care of nurses in improving the physical health of these patients. In this study, which was a quasi-experimental study, 45 patients with ovarian cancer participated. The instrument was demographic information and quality of life questionnaires related to Beckman Institute, which were completed in two stages before and after patients' training and support sessions. HE4 gene expression was also assessed by Real-time PCR technique. Finally, the obtained data were analyzed using SPSS software and statistical tests. Based on the results, the mean score of quality of life before the intervention was 51.73 ± 13.91, and after the intervention was 60.46 ± 13.80 (P <0.001). Also, in all four dimensions of quality of life, the mean score of individuals after the intervention increased compared to before the intervention, but this difference was recognized as significant in only two dimensions of physical and mental health (P <0.001). The results of HE4 gene expression also showed that supportive and educational care of nurses had a significant effect on the expression of this gene. Therefore, this study confirmed the positive effect of educational and supportive programs in improving the quality of life of patients with ovarian cancer. In general, the design and implementation of such programs are proposed more widely and based on patients' educational and supportive needs.

Introduction

Ovarian cancer is the most controversial of all female cancers. This cancer does not show significant symptoms in its early stages and can be diagnosed in the advanced stages of the tumor and therefore has a high mortality rate (1). Although it accounts for only about 4% of all cancers in the female population, ovarian cancer is the fifth leading cause of death due to malignancy in women (2). In the United States, approximately 31,280 new cases and 29,500 deaths from ovarian cancer are predicted in 2025 (3). One of the fatal causes of ovarian cancer is that more than 70% of women are diagnosed with advanced disease. There is a close relationship between disease onset and survival, so early detection of ovarian cancer is the best way to reduce mortality and long-term disease control (4, 5).

The risk of a woman developing ovarian cancer in her lifetime is 1-1.5%, and the resulting death rate is about 50%. An inverse association of ovarian cancer with the frequency of pregnancy and childbirth has been reported. Ovarian cancer is directly related to infertility (6). Premature puberty and late menopause also increase the risk of ovarian cancer. Suppression of ovulation may be an essential factor in preventing ovarian cancer. Because the superficial epithelium of the ovary experiences frequent destruction and repair, it can lead to an increase in spontaneous mutations that reveal germinal mutations or lead to the oncogenic phenotype (7). Lack of proper diagnosis of the early stages of the disease, lack of appropriate screening tests, and unclear early symptoms lead to late diagnosis of the disease (4).

Different methods are used to treat ovarian cancer, which varies depending on the degree and severity of the disease. Ovarian cancer treatments include surgery, chemotherapy, radiotherapy, and hormone therapy, which can significantly impact patients'

quality of life following ovarian cancer (7). Quality of life is a concept that has always been a challenging topic for centuries. But in recent years, it has attracted particular attention for cancer patients and their survival rate and longevity. One of the reasons for the growing interest in this concept in the new age is that survival is not the only issue today (8). People want a quality life, and quality of life is considered one of the critical outcomes and indicators determining the effectiveness of treating diseases (9).

Today, quality of life is sometimes used instead of health in various studies. But the quality of life has more dimensions than health status and is affected by more factors (10). Its main areas include physical, mental, social, and spiritual health. Although these areas can be separated and each can be examined separately, there is an interaction between them. The disorder in each dimension directly and significantly impacts the others (11).

Mortality from ovarian cancer has been reduced to 30% with the help of screening and early diagnosis of cancer and the proper treatments (12). Radiotherapy, for example, has decreased tumor recurrence significantly, which is associated with increased disability and mortality, from 26% to 7%. In such a situation, the treatment team has to take measures related to tertiary prevention. Because in the third level, prevention and reduction of the patient's complications that have been clinically manifested are attempted (13).

One of the most important measures at this level is supportive, educational care and thus increasing people's quality of life with cancer. But unfortunately, not enough attention is paid to this issue (10). For example, the study results by Eghtedar *et al*. (14) showed that the majority (6.63%) of patients with ovarian cancer received moderate supportive care from nurses. Moursy and Ead (15) also concluded in their study of self-care in patients with ovarian cancer that the self-care practices performed by the subjects were inadequate. They believe that nurses, due to their longer and more direct contact with the patient, have an essential role in improving the quality of life of cancer patients by encouraging and promoting proper care. Thus, patients can return to their everyday lives and return to the community. Orem's theory (16) can be helpful in this regard and in achieving these goals.

According to Orem's theory (16, 17), self-care is a learned behavior that a person takes to maintain or improve life, health, well-being, prevention, and treatment of disease. According to this model, the patient himself needs to cooperate in self-care, and it is clear that the person needs the knowledge to accept such a responsibility. Nurses are the most central member of the health group in meeting this need, which is necessary, along with training by improving patients' behavioral skills and creating a sense of responsibility and self-sufficiency in self-care, to help patients make more efforts to control the disease and improve quality (17). Therefore, this study aimed to investigate the effect of supportive and educational care of nurses on the quality of life of patients with ovarian cancer. We also evaluated the expression of the HE4 gene in ovarian cancer tissue samples and its relationship with disease progression and the role of supportive and educational nursing care on its expression.

Materials and methods
Studied patients and inclusion and exclusion criteria

This study was a before and after quasi-experimental study in which 45 patients with ovarian cancer participated. Sampling was done by available, and according to recent studies on quality of life (on 35 hemodialysis patients (18) and 44 liver cirrhosis patients (19)), 45 patients who met the inclusion criteria were selected. Inclusion criteria included being 18-65 years old, pathology and medical diagnosis, at least three weeks between the end of chemotherapy and starting radiotherapy, literacy, physical and mental strength, and willingness to participate in the study. Exclusion criteria were considered as unwillingness to continue participating in the research and lack of access to participants during the study for any reason (including death). Sampling lasted for six months, and the status of three demographic information questionnaires was assessed Orem's health and quality of life. The demographic information questionnaire was adjusted by the researcher and included the variables of patient's age, age at diagnosis, duration of disease, age of first pregnancy, history of other diseases, history of existing ovarian cancer among the relatives, and education of the patient.

Quality of life assessment

The quality of life of the participants in this study was performed using standard tools to assess the quality of life of patients with ovarian cancer (related to the National Medical Center and Beckman Research Institute). This tool examines the quality of life of women with ovarian cancer in four dimensions of physical, mental, social, and spiritual health and includes 44 items, each of which is scored on a scale of 0 to 10. Thus, a score of zero is assigned to the worst case, and a score of 10 is assigned to the best case. Scoring several cases in this tool (41, 33-37, 31, 17-29, 10, 9, 1-7) is the opposite of the rest. Also, items 1 to 8 of this questionnaire get 80 points. In the physical dimension, items 9 to 30 earn 220 points. Items 31 to 37 get 70 points. Finally, items 38 to 44 get 70 points. The highest sample that the research unit can obtain after completing this tool is 440 and the lowest score is zero.

In this study, due to the different number of questions in each area, the obtained scores in each dimension were first multiplied by 100 and then divided by the maximum score of that dimension to compare the average scores of different dimensions of quality of life. As a result, all obtained scores ranged from 0 to 100. Also, two indicators were used: Content Validity Ratio (CVR) and Content Validity Index (CVI). All CVR values were more than 0.51 (minimum set value for 14 specialists), and CVI was more than 0.79.

The internal consistency method was used for the reliability of the tool. In this way, the participants calculated Cronbach's alpha coefficient after completing the questionnaires, and the validity coefficient was 0.8. Similarly, Joly *et al*. (20) used the same questionnaire in their research, and a validity coefficient of 0.8 was obtained, which confirms the acceptable validity and reliability of this tool.

To carry out the intervention, the researcher first explained all the steps for each patient in simple language, allowed them to decide to participate in the study, and then obtained informed written consent and completed demographic information questionnaires. Orem's health and quality of life preceded the intervention, and patients were invited to attend eight 45-minute sessions held on Wednesdays each week in the hospital's radiotherapy room. In this study, the quality of life questionnaire scores, which patients completed before the intervention, were recorded as a pre-test. Patients' self-care needs were identified based on the Orem health status questionnaire. Training sessions were held in groups and based on the identified needs of patients according to the Orem self-care model, regarding "Familiarity with ovarian cancer and how to cope with this disease, treatment methods and Complications of radiotherapy, type of nutrition, spiritual health, mental health, physiotherapy of organs, etc."

In each session, the necessary explanations were given about one of the cases, and the patients' questions and problems were answered. We also performed items such as individual referrals to psychologists, paramedics, palliative medicine, nutritionists, and meetings with survivors to support patients. Finally, pamphlets and educational CDs were provided to patients to understand the subject better and remind them of essential points. In the last session, according to the previous appointment, a general test of the learned material was taken, and the items in need of retraining were identified, and in a 6-hour session, one-day training, all the required material was reviewed intensively. Finally, the quality of life of 45 patients was assessed using a quality of life questionnaire, and all data were collected.

Evaluation of HE4 gene expression

Ovarian tissue samples were obtained from patients by biopsy before and after the intervention. The total RNA was extracted by RNeasy PowerLyzer Tissue & Cells Kit (Qiagen, USA) according to its protocol. After extraction, the quality of RNAs was evaluated by spectrophotometric study of light absorption at 260/280nm.

First, 10μl of RNA template was mixed with 1μl of 10Mm dNTP and 1μl of Random Hexamer followed by 1μl of Oligo dt to synthesize cDNA from RNA. The tube was then placed at 65°C for 5 minutes. Then two microliters of MMuLV 10X buffer and 0.5 microliters of M-MuLV enzyme were added to the mixture. Finally, double distilled water was added, and the final volume reached 20μl. The tube was incubated for 1 hour at 42°C. The GAPDH gene sequence (as an internal control) and the HE4 gene sequence were obtained from the NCBI gene bank, and the Express Primer software designed their

specific primers. The obtained sequences were blasted at NCBI and Gene Runner to confirm the specificity and accuracy of the designed primers. The primer sequences are listed in Table 1.

Table1. The sequences and the production size of HE4 and GADPH primers

Gene	Primer Sequence (5'-3')	Production Size
HE4 (forward)	GTGTCCTGTGTCACTCCCAA	62 bp
HE4 (reverse)	CTCTCCTCACTGCTCAGCCT	
GAPDH (forward)	ATGGAGAAGGCTGGGGCT	124 bp
GAPDH (reverse)	ATCTTGAGGCTGTTGTCATACTTCTC	

Then, the essential factors of the Real-time PCR technique were optimized for GAPDH and HE4 genes. For this purpose, separate reactions were prepared for the desired gene and internal control gene in a final volume of 20μl. The reactions were placed in parallel on the ABI7500. In each reaction, MM SYBRTM (2X), Premix10 (10μM Reverse and Forward Primer), and template cDNA at a concentration of 2μg were used. The temperature reaction included 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. Separation curve analysis confirmed the amplified fragment and ensured the absence of nonspecific product, primer dimer, and contamination. After test optimization, RNA was extracted from all samples, and after confirming the quality of the obtained RNAs, cDNA was synthesized on the samples.

After the amplification reaction, the CT samples were calculated by the device and converted to Relative Quantification (RQ), and then the expression of the gene was measured by ΔΔCT method. The gene expression diagram was drawn using Graph pad software. In this study, the Real-time PCR method was used to analyze gene expression, which was performed in less time and at a higher speed than the previous conventional methods. In addition, the sensitivity of this method is very high, which allows diagnosis before and after treatment.

Statistical analysis

Data analysis was performed using SPSS statistical software (Ver. 16) and using descriptive indicators (frequency, percentage, mean, and standard deviation) and analytical (paired t-test) at a significant level of $P < 0.05$.

Results

The mean age of patients was 44.68±8.43, and 68.9% were between 40 to 59 years old. Their mean age at diagnosis was 43.77±8.34. About the education, 62.2% of patients did not finish the high school, and the duration of infection in 80% of the samples was less than one year. 91.1% of patients, no history of this disease was observed in their relatives. The mean age of the first pregnancy and lactation were 19.14±2.69 and 19.87±2.70, respectively. The paired t-test shows individuals' scores in four dimensions of quality of life before and after the intervention and the difference between the two, shown in Table 2. In all four dimensions of quality of life, the average score of individuals after the intervention increased compared to before the intervention. But this difference is known to be significant only in two dimensions of physical and mental health ($P < 0.001$). Also, regarding the general dimension of quality of life before and after the intervention, it was observed that before the intervention, the average score of the sample was 73.51 and after the intervention, this score increased to 46.60. In the post-test compared to the pre-test, an average of 77.13 units increased. The effect of supportive and educational care of nurses on the quality of life of patients with ovarian cancer is known to be significant.

Table 2. Comparison of different dimensions of participant's life quality before and after the intervention

Dimension of Life Quality	Mean ± SD			P-value
	Before intervention	After intervention	Score Difference	
Physical Health	53.83 ± 15.22	68.75 ± 15.55	14.91 ± 17.12	0.001*
Mental Health	45.62 ± 19.07	55.46 ± 18.36	9.83 ± 18.11	0.001*
Social Health	45.26 ± 20.85	49.65 ± 18.50	4.38 ± 16.68	0.085
Spiritual Health	74.98 ± 10.36	77.55 ± 11.12	2.57 ± 10.54	0.109
Average Overall Score	51.73 ± 13.91	60.46 ± 13.80	8.73 ± 13.77	0.001*

*: P<0.05

The optical absorption results of the extracted RNAs for use in the cDNA synthesis step were

confirmed by spectrophotometry. The melting curve diagram (Figure 1) for HE4 and GAPDH genes separately was drawn by Real-time PCR (7500 ABI) to investigate the specificity of primers and fluorescence dyes (Syber green), ensure the duplication of specific components, and investigate the absence of non-specific components in the PCR product. It confirms the correct binding of the primers to the HE4 gene and the product of Real-time PCR obtained exactly for the desired gene.
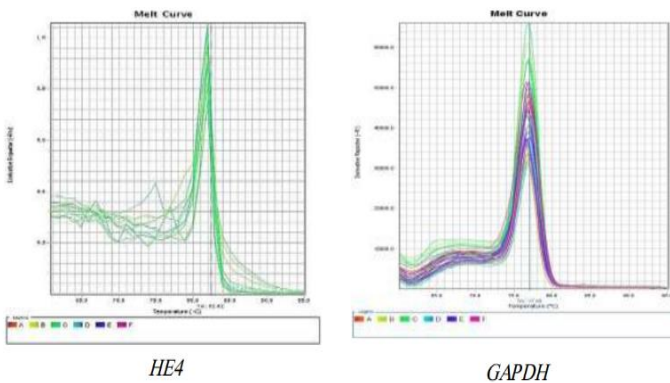

Figure 1. Melting curve analysis of HE4 and GAPDH genes

The results of HE4 gene expression showed that before intervention, there was not statistically different between control and intervention group (P = 0.23). But there was statistically different between groups after intervention (P = 0.04) (Figure 2).
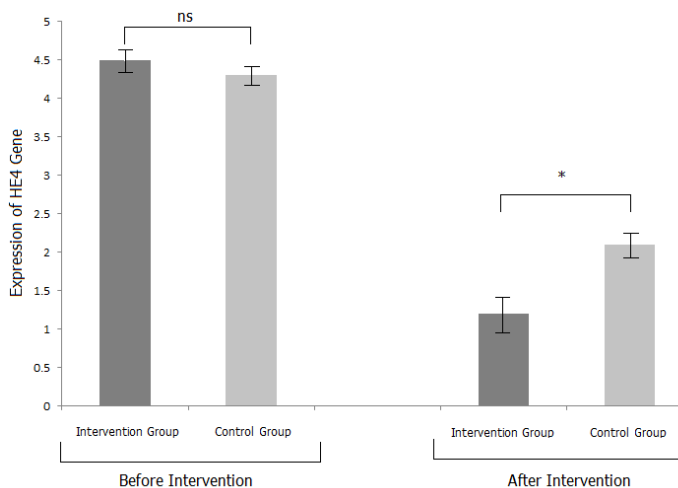

Figure 2. The expression of HE4 gene in intervention and control groups before and after intervention; <ns> and <*> means non-significant and significant at 0.05 level of probability, respectively.

Discussion

The present study results showed that the quality of life of patients after supportive and educational care from nurses has improved, which is consistent with the study of Deng *et al*. (21). In their study, the quality of life after applying the self-care model in the experimental group was significantly improved compared to the control group. According to them, in a self-care program, a person learns activities that, as a result, take responsibility for their health. It also improves the ability to communicate with the environment, perform adaptive actions and behaviors, and thus the quality of life. Similarly, the results of the Zhang *et al*. (22) study on self-care education program in improving the quality of life of patients with esophageal cancer are consistent with the present study's findings. Regarding different dimensions of quality of life in this study, it was observed that the physical health dimension of patients has the highest increase, and this increase is significant. Also, the current results were consistent with Wang et al. (23). Their research aimed to investigate the effect of education on the quality of life of patients with ovarian cancer. They concluded that after counseling and training in the treatment and care of ovarian cancer, patients' quality of life in all dimensions has increased. The most significant increase was related to the physical dimension. Eyl *et al*. (24) and Ho *et al*. (25) concluded that the mean scores of individuals in terms of physical health after training were significantly higher. Because one of the most critical aspects of quality of life is the physical dimension, and cancer disturbs it. Getting help from a specialist and familiarity with problems solutions such as extreme fatigue, pain, oral and dental problems, changes in the nervous system (neuropathy), intestinal and bladder control problems, and many other things have a significant impact on the performance of daily activities and, consequently, the quality of life of cancer patients.

The results of HE4 gene expression also showed that supportive and educational care of nurses had a significant effect on the expression of this gene. Studies have shown that the HE4 gene can be used as a marker in the diagnosis and progression of ovarian cancer (26). HE4 was first detected in the outer membrane of the distal epididymis and was initially

predicted as a suppressive protease involved in sperm maturation (27, 28). It has also been reported that HE4 is more commonly expressed in ovarian neoplastic tissue and rises in the serum of patients with ovarian cancer. The high sensitivity of HE4 compared to CA125, especially in the early stages of the disease, and the monoclonal antibodies produced against it, including D83 and H52, are known as different epitopes (27). These monoclonal antibodies have been used to develop ELISA-based methods for measuring HE4 in postmenopausal women. Therefore, a higher level of expression indicates the progression of the disease and the deterioration of the patient (29). In this study, a significant decrease in HE4 gene expression after the intervention indicates the role of supportive and educational care of nurses in improving patients' physical health.

Patients' mental health is another dimension of quality of life that, in this study, with the implementation of supportive and educational care of nurses, has increased significantly compared to before the intervention. Cancer treatment is associated with several psychological pressures, some of which reduce the quality of life and lead to anxiety or depression. In a study conducted by Fafouti *et al*. (30) to study depression and anxiety in women with breast cancer, it was shown that the rate of depression and anxiety in the patient group was significantly higher than in the healthy group. In Pedram *et al*.'s study (31), patients rated the psychological side effects of treatment such as anger, anxiety, or worry more severely than physical side effects such as hair loss and nausea. Some rated chemotherapy for problems and crises caused by illness and treatment. But self-care programs and promoting information and awareness about the disease can reduce anxiety, strengthen a person's perception of life goals, reduce mood disorders, and improve patients' adaptation and adaptive behaviors, which can improve the quality of life. It is similar to the research of Coleman *et al*. (32) that examined the effect of a self-care program on the quality of life of 70 patients with acute leukemia undergoing chemotherapy and found that the implementation of this program has significantly improved the quality of life and especially the psychological dimension in the experimental group compared to the control group. However, Walker *et al*. (33) conducted a study of 200 people with lung

cancer, and nurses telephoned patients to provide effective antidepressant care for 6 to 8 sessions per month. But the positive effects of the results were determined after 32 months. In this regard, Kravitz *et al*. (34) concluded that shorter results are obtained through routine nursing care.

Regarding the two dimensions of social health and spiritual health in this study, it was found that the average score of people after the intervention has increased compared to before the intervention. But this difference was not significant. Regarding the social health dimension, it can be said that cancer restricts people's social activities and affects their relationships and access to interpersonal resources. As a result, it increases the likelihood of reducing relationships with others and isolating them in society. In many studies, we see that at the end of treatment, the social health of cancer patients was lower than at the beginning of treatment (34). Accordingly, very little or no change in the quality of life score and especially the social health of patients is a success for researchers (29). Regarding the dimension of spiritual health, the obtained results are in line with the study of Golchin *et al*. (35). They showed that in most cases, the quality of life of clients has improved. But the difference in the spiritual dimension before and after the intervention was not significant. However, the research results of Symonds *et al*. (36) showed that spiritual health has a strong effect on end-of-life despair in cancer patients and for cancer patients who are in the final stages of their disease, spiritual and religious peace may even be more important than physical and mental health.

Finally, it is interesting to note that the non-probability sampling method in this study has made it difficult to generalize the findings. Also, according to the results of this study, in future research, it is suggested that a more specific study of the role of supportive and educational care on the dimensions of the social and spiritual health of patients with ovarian cancer is needed. On the other hand, it seems that the continuation of supportive and educational care of nurses in different stages of diagnosis and treatment of this disease and consequently the existence of permanent centers for this is a necessity that requires serious attention of officials in this field.

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