Relationship between Death Anxiety and Spiritual Well-Being in Patients with Gynecologic Cancer

Yasmin Kamyab Mansori 1, Mahrokh Dolatian 2, Jamal Shams 3, Maliheh Nasiri 4

1 1 MSc, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2 Assistant Professor, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3 Associate Professor, Department of Psychiatry, Behavioral Research Center. Shahid Beheshti University of Medical Sciences, Tehran, Iran
4 Assistant Professor, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran

* Corresponding author: Mahrokh Dolatian, Assistant Professor, Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: m_dolatian@sbmu.ac.ir

Abstract

Introduction: Concerns about death may negatively affect the health-related quality of life. The relationship between death anxiety and spiritual well-being in life-threatening diseases is still a matter that needs to be addressed, especially in patients with gynecologic cancer. This study was conducted to investigate the relationship between death anxiety and spiritual well-being in patients with the gynecologic cancer.

Methods: This descriptive-correlational study was conducted on 230 women with gynecologic cancer selected through convenience sampling from Shohada-e Tajrish Hospital, affiliated to Shahid Beheshti University of Medical Sciences, in Tehran, Iran, from April to May 2016. The data collection instruments included a demographic questionnaire, the 15-item Templer Death Anxiety Scale and the Spiritual Well-Being Scale. The data were analyzed using descriptive (mean, standard deviation, frequency and percentage) and inferential (Pearson’s correlation coefficient and the linear regression model) statistics by the SPSS 22 software.

Results: The mean scores of death anxiety and spiritual well-being were 48.57 ± 12.55 and 95.27 ± 14.40. There was a significant relationship between death anxiety and spiritual well-being (r = -0.35, P = 0.001). The results of the regression analysis showed that age (b = -0.23, P = 0.001) and stage of cancer (b = -5.176, P = 0.001) are the only significant predictors of death anxiety. This model explained 40.3% of the variance in death anxiety.

Conclusions: This study shows a significant relationship between death anxiety and spiritual well-being in patients with gynecologic cancer. It is therefore necessary for healthcare providers to address certain demographic variables such as age, marital status and disease progression for regulating death anxiety and improving the patients’ spiritual well-being.

INTRODUCTION

Cancer is a disease diagnosed by uncontrollable cell growth and the invasion of local tissues [1]. After cardiovascular diseases, cancer is the second cause of mortality in developed countries and the third cause of death in developing countries [2, 3]. The diagnosis of cancer is an undesirable and unimaginable experience for all patients, more so than diagnosis with any other disease, and disrupts the patient’s career, socioeconomic status and family life [4]. Cancer is currently a major public health problem in the US and many other countries throughout the world and is one of the four main...
causes of death in the US [5]. Despite the accomplishments in the control and prevention of communicable diseases, the incidence of gynecologic cancer has been increasing in women in recent decades. According to the latest reports, approximately 13% of women all over the world and 11% of those in the US suffer from different types of gynecologic cancer [6]. Cervical cancer (i.e. cancer of the cervix) is especially important because it is the second most common cancer among women in developing countries and the main cause of death from cancer [7, 8]. Based on the World Health Organization, 25% of the cases of female mortality in the world are caused by malignant tumors, with 12% being caused by cervical cancer. Cervical cancer is also the fourth prevalent cancer in Iran [9]. Ovarian cancer accounts for only 5% of all the cases of cancer in women and is the most common cause of death from gynecologic cancers with a 50% mortality rate [10, 11]. Breast cancer also has a high mortality rate that accounts for 25% of the cases of cancer among women in Iran [12] and is considered the second common cause of death after lung cancer [13]. The prevalence of breast cancer in Iran is at a fixed rate of 31 per 100,000 of the population [14]. Studies unanimously agree that breast cancer affects Iranian women a decade earlier than their counterparts in advanced countries [15].

The diagnosis of cancer is a very unpleasant and unimaginable experience for everyone that affects the patient’s life in different ways. It disrupts their career, socioeconomic status, family life and overall quality of life [16]. Physical changes may occur throughout the course of cancer, especially in the treatment phase, due to the side-effects of the treatments administered. These changes can influence the patient’s self-awareness, self-esteem and sense of worth and acceptability. The various physical effects of cancer can also affect the psychological and social aspects of the patients’ life [17]. Cancer patients often experience severe psychological distress after their cancer diagnosis and also throughout the entire course of their treatment. The risk of mental health disorders in cancer patients has been estimated as 30%-40%. Evidence suggests that the psychological distress and mental health consequences experienced by these patients are correlated with the severity of the side-effects of chemotherapy and radiation therapy [18]. Patients with breast cancer experience symptoms such as anger, wrath, depression, anxiety and loneliness [19]. Research suggests that patients with the breast cancer are exposed to psychological stressors that can disrupt their life. For example, they may feel disconnected from their life. The suffering caused by the disease, the concerns about the future of the family, fear of death, the side-effects of the treatments, reduced performances, impaired mental image and sexual problems are among the factors that disrupt the mental health of patients with cancer [20]. Death anxiety (thanatophobia) is one of the main types of anxiety [21], in which the individual experiences confusion and a feeling of horror originating from the reality or from merely conceived perceptions [22]. Death anxiety refers to the constant and abnormal phobia of death or dying [23]. Death anxiety is “a feeling of dread, apprehension or extreme concern when thinking about the process of dying or detaching from life and what happens after death” [24]. This kind of anxiety involves motivational, cognitive and emotional components and varies with the stages of disease development and the events in the individual’s social and cultural life [25]. Death anxiety involves fear of someone’s death, concerns about the pain and suffering leading to death, an imagined closeness to death, death-related fears and death-related thoughts and concerns. Anxiety and death anxiety are two distinct concepts. The level of death anxiety can vary in people due to personal differences and several social factors. The results of previous studies reveal the effect of personal, social, cultural and religious differences on death anxiety. These differences can in return influence the individual’s quality of life. In patients with cancer, the medical team is focused on stabilizing the patient’s physical symptoms (relief from pain, nausea and vomiting), but neglecting their death anxiety as a mental disorder can negatively affect their quality of life [21, 26].

The factors affecting the incidence of death anxiety also include the individual’s internal and external religious orientation, life satisfaction and belief in an afterlife; in fact, some studies have shown that religion is negatively correlated with death anxiety in Muslims [26]. Death anxiety is less perceived in societies, where people practice a religion. The stronger belief in the afterlife reduces the level of death anxiety in these groups [27]. Death anxiety is also negatively correlated with the quality of life [28]. The level of death anxiety varies in different cultures and is higher in developing countries [29].

Otoom et al. (2007) showed that the duration of the disease is a strong predictor of death anxiety and the two are negatively correlated; in their study, the patients who had recently been diagnosed with epilepsy experienced higher levels of death anxiety, since they still had not had ample time to adapt to their disease [30]. One of the main responsibilities of medical teams is to control and modify the outcomes of the disease in the patients, including psychological outcomes, which happen to be less addressed, given the greater emphasis generally placed on physical care. Medical teams use various methods for controlling these outcomes, which are mostly pharmacological. In a study conducted by Sussman et al. (2014), cognitive therapy, acceptance and treatment commitment positively affected death anxiety in patients receiving palliative care [31]. Yaakobi (2015) studied the effect of willingness to work on death anxiety and found that the willingness to work (i.e. perform) acts as a buffer and a panic control mechanism [32]. In another study, Tang et al. (2013) showed that meaning therapy reduces the level of death anxiety in patients with recurrent cancer [33]. Jo et al. (2012) examined the effect of factors such as marital status, religious practices, health status, mental happiness and family unity on death anxiety in older Korean adults and showed that all these factors decrease the degree of death anxiety [34].

Spiritual well-being is the core of human health [35] and constitutes the physical, psychological, and social dimensions of the human being [36] and is identified through characteristics such as stability in life, peace, a sense of close connection with oneself, God, the society and the environment, and meaning and purpose in life [37]. Spiritual well-being refers to the enjoyment of a sense of acceptance, positive emotions and the sense of positive interaction with a governing superior power, others and oneself, and is achieved through a dynamic and coordinated cognitive, emotional and transactional process of a personal nature [38]. Spiritual well-being involves two aspects of the human being, including the existential aspect and the religious aspect. Existential health denotes the attempt to understand the meaning and purpose of life, and religious health refers to the satisfaction resulting from connection to a superi-
or power [39]. Life experiences suggest that spiritual well-being is an important and prominent dimension of a healthy life that makes a meaningful and purposeful living possible [36]. Based on what was discussed, spiritual well-being may be regarded as one of the outcomes of spiritual care that can act as a shield against death anxiety. Based on what was stated, the problem of death anxiety may comprise a major growing problem of human societies in the modern world [40]. The results of previous studies show that the fear of sudden death is a common phenomenon among patients with chronic conditions [26, 41]. Emphasizing the mental dimension of care is therefore very important in chronic conditions. Despite the WHO recommendations to the effect that all nursing practices should focus on the treatment of individuals in all their existential aspects [38], most of the care currently given to patients is focused on the physical aspect and their mental needs are less addressed [42]. Considering the growth in the number of cancer patients and their need for invasive interventions that cause great complications, the level of death anxiety and its relationship with spiritual well-being should be further examined in these patients. This study aimed to identify the factors affecting death anxiety and spiritual well-being in this group of patients. In Iran, several studies have examined psychological problems such as anxiety, depression and stress in cancer patients. Nonetheless, the researchers’ review of the available literature did not lead to any studies on death anxiety and its relationship with spiritual well-being in this group of patients. Given the role of the cultural and religious context in the death anxiety and spiritual well-being of cancer patients, these variables might differ in different countries. The present study was conducted to examine the relationship between death anxiety and spiritual well-being in patients with the gynecologic cancer.

METHODS

This descriptive correlational study was conducted at the oncology ward of Shohada-e Tajrish Teaching Hospital on a statistical population consisting of all the women visiting this hospital for the treatment of gynecologic cancer. The willing candidates who had the necessary skills to communicate effectively and exchange information were included in the study (n = 230). Definitive diagnosis with a gynecologic cancer of any grade and stage was another inclusion criterion of the study. The patients were selected through convenience sampling. Data were collected using a questionnaire in three parts. The demographic part inquired about participants’ age, marital status, education, and economic status, main source of income and duration of the disease. The validity of this part of the questionnaire was evaluated using the content validity method. For this purpose, the questionnaire was distributed among nursing professors at Tehran and Shahid Beheshti universities of medical sciences and the final version of the questionnaire was drafted based on the majority opinion. Templer’s 15-item Death Anxiety Scale (1970) was used in the second part of the questionnaire, which has previously been used in different studies in Iran for the evaluation of death anxiety and is in line with Iran’s value structures and culture. The answer to each item in this scale is scored on a 5-point Likert scale with the options including completely disagree (1), disagree (2), no comments (3), agree (4), and completely agree (5). Items 2, 3, 6, 7 and 15 are reverse scored. The minimum and maximum scores obtainable were 15 and 75, and lower scores indicated less and higher scores more death anxiety in the patients. Scores of 15-35 showed low death anxiety, 36-55 moderate and 56-75 severe death anxiety [42-44]. Previous studies have evaluated and confirmed the validity and reliability of this scale [45, 46]. The present study also used the qualitative and quantitative content validity methods to confirm the validity of the Death Anxiety Scale. For the qualitative content validity assessment, Templer’s scale was distributed among 15 specialists (ten midwifery PhDs, three psychologists and two psychiatrists) and they were asked to provide their feedback on the scale after its careful qualitative examination in terms of grammar, proper wording, proper phrasing and proper scoring. The quantitative content validity of the scale was determined by calculating the content validity ratio (CVR) and content validity index (CVI) of its items. Considering that the value obtained from the Lawshe’s table for the CVR (to determine the minimum value of the index) was greater than 0.49 for all the items (based on the 15 specialists’ evaluation), the level of statistical significance was set at P < 0.05 for all the items [47]. The CVI was used to measure “simplicity,” “relevance” and “clarity,” which were scored on a 4-point Likert scale. Given that the score of every item was greater than 0.79 [48], all the items were kept in the scale. The internal consistency coefficient or Cronbach’s alpha were also used to examine the reliability of the Death Anxiety Scale (0.83).

The third part of the questionnaire assessed the patients’ spiritual well-being. This study measured spiritual well-being using the Spiritual Well-Being (SWB) scale designed by Paloutzian and Ellison in 1982. The SWB scale is a general indicator of perceived well-being that is used to evaluate personal and social spiritual well-being, the quality of spiritual life and the subscales of religious and existential well-being. Religious well-being indicates the individual’s self-assessment of her relationship with God, and existential well-being is the individual’s self-assessment of her feelings about the purpose of life and life satisfaction. The SWB scale consists of 20 items scored on a 6-point Likert scale with responses from strongly agree (6 points) to strongly disagree (1 point). The items with negative verbs (items 1, 2, 5, 6, 9, 12, 13, 16 and 18) are reverse scored. The SWB scale is divided into two subscales, including religious well-being and existential well-being. Each subscale has ten items and is scored from 10 to 60. The odd items examine religious well-being and the even items existential well-being. The total score is obtained by calculating the sum of the scores of these two subscales and ranges from 20 to 120, indicating low (scores 20-40), moderate (scores 41-99) and high (scores 100-120) spiritual well-being [49]. Allah Bakhshian et al. (2010) confirmed the reliability of the scale with a Cronbach’s alpha of 0.82 [50]. After obtaining an ethics approval from the Ethics Committee and presenting an official reference letter from the Research Deputy of the Faculty of Nursing and Midwifery of Shahid Beheshti University of Medical Sciences (SBMU) to the officials of the teaching hospital affiliated to SBMU and obtaining their consent, the researcher visited the oncology ward of the hospital on different days and hours of the week (in the morning, evening and night shifts) in order to increase the number of participants, and selected any patients who met the eligibility criteria. The researcher described the objectives of the study to the patients and those who were willing to participate were entered after signing an informed consent form. All the questionnaires were completed by the
researcher through interviews with the participants.

Data Analysis

The Kolmogorov-Smirnov test was used to examine the normal distribution of the main variables of the study. Descriptive statistics, including the mean (± standard deviation) and frequency (percentage) were used to describe the qualitative/nominal variables (gender and education). Pearson's correlation coefficient was used to evaluate the correlation between death anxiety and spiritual well-being in the patients. The two groups of patients (females/males) were compared in terms of their mean death anxiety and spiritual well-being using the independent t-test. The ANOVA was performed to compare more than two groups of patients. The predictors of death anxiety and spiritual well-being were evaluated using the linear regression model. The level of statistical significance was set at P < 0.05 for all the tests. Then, the data were analyzed using the IBM SPSS 22 software.

RESULTS

The mean age of the patients was 40.17 years with a standard deviation of 11.82 years. Most of the patients participated in this study were married (56.6%) and illiterate (63.5%). The most prevalent type of cancer was breast cancer (57%). The majority (50%) of the patients used combination therapy (surgery, chemotherapy and radiation therapy). The economic status of most of the patients (62.2%) was moderate and the main source of income in the majority (86%) was personal and familial. Their mean duration of disease was 15.71 with a standard deviation of 9.73 months. The mean and standard deviation of death anxiety and spiritual well-being were 48.57 ± 12.55 and 95.27 ± 14.40, respectively. Pearson's correlation coefficient showed a negative correlation between death anxiety and spiritual well-being in the women with cancer (r = -0.35, P = 0.001). The results of the same test showed a significant correlation between age and death anxiety (r = -0.300, P = 0.001) and between age and spiritual well-being (r = 0.302, P = 0.001).

Table 1 presents the results of the linear regression model used to predict death anxiety in the patients with gynecologic cancer. As shown, age (b = -0.23, P = 0.001) and stage of cancer were the only predictors of death anxiety. This model explains 40.3% of the variance in death anxiety.

Table 1: The Predictors of Death Anxiety in the Patients with Gynecologic Cancer

<table>
<thead>
<tr>
<th></th>
<th>Non-Standard Regression Coefficient</th>
<th>Standard Error</th>
<th>Standard Regression Coefficient</th>
<th>P-Value</th>
<th>Collinearity Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.23</td>
<td>0.07</td>
<td>-0.21</td>
<td>0.001</td>
<td>0.618</td>
</tr>
<tr>
<td>Marital Status</td>
<td>-0.51</td>
<td>1.08</td>
<td>-0.02</td>
<td>0.635</td>
<td>0.828</td>
</tr>
<tr>
<td>Education</td>
<td>-1.08</td>
<td>0.94</td>
<td>-0.07</td>
<td>0.249</td>
<td>0.670</td>
</tr>
<tr>
<td>Type of Cancer</td>
<td>0.34</td>
<td>0.99</td>
<td>0.01</td>
<td>0.730</td>
<td>0.987</td>
</tr>
<tr>
<td>Stage of Cancer</td>
<td>-5.17</td>
<td>0.52</td>
<td>-0.05</td>
<td>0.001</td>
<td>0.895</td>
</tr>
<tr>
<td>Type of Treatment</td>
<td>1.38</td>
<td>0.75</td>
<td>0.09</td>
<td>0.068</td>
<td>0.950</td>
</tr>
<tr>
<td>Economic Status</td>
<td>-2.25</td>
<td>1.16</td>
<td>-0.10</td>
<td>0.054</td>
<td>0.876</td>
</tr>
<tr>
<td>Main Source of Income</td>
<td>1.32</td>
<td>1.00</td>
<td>0.07</td>
<td>0.187</td>
<td>0.879</td>
</tr>
<tr>
<td>Living with</td>
<td>-1.62</td>
<td>1.08</td>
<td>-0.07</td>
<td>0.135</td>
<td>0.966</td>
</tr>
</tbody>
</table>

F = 16.528, P < 0.001; R² = 0.403, adjusted R² = 0.379, Durbin-Watson: 1.045

Table 2: The Predictors of Spiritual Well-Being in the Patients with Gynecologic Cancer

<table>
<thead>
<tr>
<th></th>
<th>Non-Standard Regression Coefficient</th>
<th>Standard Error</th>
<th>Standard Regression Coefficient</th>
<th>P-Value</th>
<th>Collinearity Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>0.09</td>
<td>0.18</td>
<td>0.021</td>
<td>0.618</td>
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<td>Marital Status</td>
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<td>1.46</td>
<td>0.13</td>
<td>0.043</td>
<td>0.828</td>
</tr>
<tr>
<td>Education</td>
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<td>0.581</td>
<td>0.670</td>
</tr>
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<td>Type of Cancer</td>
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<td>1.34</td>
<td>-0.01</td>
<td>0.766</td>
<td>0.987</td>
</tr>
<tr>
<td>Stage of Cancer</td>
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<td>0.70</td>
<td>0.24</td>
<td>0.001</td>
<td>0.859</td>
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<tr>
<td>Type of Treatment</td>
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<td>1.01</td>
<td>-0.04</td>
<td>0.462</td>
<td>0.950</td>
</tr>
<tr>
<td>Economic Status</td>
<td>0.30</td>
<td>1.56</td>
<td>0.01</td>
<td>0.845</td>
<td>0.876</td>
</tr>
<tr>
<td>Main Source of Income</td>
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<td>1.34</td>
<td>-0.07</td>
<td>0.252</td>
<td>0.879</td>
</tr>
<tr>
<td>Living with</td>
<td>-0.82</td>
<td>1.46</td>
<td>-0.03</td>
<td>0.572</td>
<td>0.966</td>
</tr>
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</table>

F = 5.349, P < 0.001; R² = 0.180, adjusted R² = 0.146, Durbin-Watson: 1.439
Table 2 presents the results of the linear regression model used for predicting spiritual well-being in the patients with gynecologic cancer. As shown, age (b = 0.220, P = 0.021), marital status (b = 2.985, P = 0.043) and stage of cancer (b = 2.649, P = 0.001) were the predictors of spiritual well-being. This model was able to explain 18% of the variance in spiritual well-being.

DISCUSSION

This study was conducted to examine the correlation between death anxiety and spiritual well-being in patients with gynecologic cancer. The results showed a significant negative correlation between death anxiety and spiritual well-being in these patients. Other studies have also revealed a significant reverse correlation between death anxiety and spiritual well-being [30, 50, 51]. The personal and cultural views of each society about the experience of death and its subsequent anxiety may contribute to this relationship. Differences in terms of the acuteness or chronic nature of the disease may also play a role in the relationship between these two important constructs. The degree of death anxiety was moderate in the studied patients, which is consistent with the results obtained by Motvasselian et al. in 2008 [52] Sadeghi et al. (2014), however, reported a high level of death anxiety in hemodialysis patients [21]. It appears that time gives people more opportunity to adapt to their disease and its unexpected consequences. Immediately after diagnosis with a chronic disease, people tend to not picture a bright future for them and therefore experience greater death anxiety at the beginning of their diagnosis. Over time, the patients return to their previous routine and even resume their working life in some cases [23].

Diagnosis with life-threatening diseases is a major factor exacerbating death anxiety. Given that chronic diseases threaten people’s life and do not have any definite treatments, some degree of death anxiety is expected in this group of people compared to others [47]. Humans are consciously aware of their death [53], and patients with high-risk diagnoses are inevitably faced with death [53]. Death is a biological, psychological and inescapable reality [54] that can be considered the only definitive phenomenon in life [55]. Cultures differ with one another in terms of the framework in which they define death and some of these definitions are more effective in reducing the side-effects associated with the awareness of death. Western societies often condemn hiding illness and aging and therefore protect their members of the awareness of death; however, some acts may actually increase death anxiety in these societies [56]. The results of this study showed a rather favorable spiritual well-being in the cancer patients. This spiritual well-being appears to have arisen from religious well-being. Similarly, the results of other studies conducted in Iran show a moderate and high spiritual well-being in patients [51, 57, 58]. Human beings are more likely to turn to religion for adapting to crises, and considering the significant correlation between religious beliefs and spiritual well-being in the patients examined in the present study, religion may be said to have a role in improving spiritual well-being [51]. The results of the regression model revealed the stage of cancer as a negative predictor of death anxiety in the patients. Environmental factors may affect the experience of death anxiety in spite of the experience of unpredictable situations filled with stress, although it may not always be the case. A sudden diagnosis, hospitalization and specialized interventions such as radiation therapy and chemotherapy can impose great mental stress on the patients and even their family caregivers. Researchers have studied the positive association between life-threatening diseases and death anxiety. For instance, a qualitative analysis of a set of data collected through interviews revealed that the family members of patients with the brain tumor experience death anxiety. The authors then concluded that patients living with a persistent feeling of threat try to avoid thoughts of death during the day, although symptoms of the disease trigger their death anxiety [57]. These results suggest that, in the face of stressors, the conscious manifestations of death anxiety may differ from one patient to another based on their type of disease, background and duration of experiencing environmental damages and death-related stressors. Long-term habituation to a stressful and insecure environment may greatly reduce the level of death anxiety [59]. Moreover, the fear of death gradually decreases in hospitalized patients at end-stages of their disease [60]. Underlying issues related to the severity of the disease, such as worries about coming face to face with death and leaving loved ones behind are also associated with an increase in death anxiety [61]. Otoom et al. (2007) showed that the duration of the disease is a strong predictor of death anxiety and has a negative correlation with it. They also found that patients who have recently been diagnosed with a disease experience higher levels of death anxiety as they still have not had enough time to adapt to their disease. Being diagnosed with high-risk diseases also disrupts cognitive functions and life skills [30]. The results of another study showed that young men treated for testicular cancer or Hodgkin’s disease and men who have recently been diagnosed with the disease have a higher death anxiety [61]. Although no significant correlations were observed between the duration of the disease and death anxiety, other demographic characteristics may affect this relationship.

The results of the regression model revealed marital status as a strong predictor of spiritual well-being in the patients, since the married patients enjoyed higher spiritual well-being compared to the other group. The results of other studies conducted on this subject are also in line with these findings. For instance, Rezaei et al. showed that married patients with cancer undergoing chemotherapy have a higher spiritual well-being compared to single or divorced patients [62]. The results of this study further showed that patients with lower levels of education have a higher spiritual well-being compared to the more educated patients. The results of the study by Rezaei et al. (2008) on cancer patients also showed a significant correlation between spiritual well-being and the level of education [62]. Nonetheless, Habibi et al. reported that spiritual well-being and the level of education are not correlated in patients with cancer [35]. In the present study, although the patients with breast cancer had a higher spiritual well-being than the patients with other types of cancer, the difference was not statistically significant. Rezaei et al. showed a high spiritual well-being in cancer patients undergoing chemotherapy. Moreover, the patients’ religious well-being was higher than their existential well-being [62].

The present study showed a significant correlation between death anxiety and spiritual well-being in patients with cancer. Age and stage of cancer were the only predictors of death anxiety in this group of patients. Age, marital status and stage
of cancer were also significant predictors of spiritual well-being in patients with gynecologic cancer. Healthcare providers should therefore pay attention to the demographic variables that can affect death anxiety and health in this group of patients.

ETHICAL CONSIDERATION
This research was approved by ethics committee of Shahid Beheshti University of Medical Sciences.

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There was no conflict of interest to be declared.

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All authors contributed equally to this project and article. All authors read and approved the final manuscript.

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