Explaining inconsistent results in cancer quality of life studies: the role of the stress–response system

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Abstract
This study tests the hypothesis that avoidance and intrusion play different roles in health-related quality of life (QoL) in women who have undergone breast cancer surgery. We assessed QoL (RAND-36), avoidance, intrusion, and total cancer-related distress (Impact of Event Scale) in 83 women at 3, 6, 9, and 12 months after mastectomy. Social functioning and role limitations improved over time; physical functioning, general health, and mental health did not change; vitality initially improved followed by a decrease to a below initial level; physical pain initially improved followed by a decrease to an above initial level. Cancer-related distress remained high during follow-up. Individual variation in QoL as assessed across the four measurement times was associated with individual variation in intrusion but not with individual variation in avoidance. Baseline intrusion did not predict the subsequent course of QoL but high initial avoidance was associated with an unfavourable time course in physical functioning, social functioning, and general health. Hence, variation in intrusion over time explains variation in QoL while baseline avoidance predicts the subsequent course of QoL. The findings provide new insight into the relationship between the stress–response system in QoL and women with breast cancer.

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Keywords: oncology; breast cancer; quality of life; stress–response; prospective study

Introduction
There are remarkable inconsistencies in the outcomes of quality of life (QoL) research within the field of psycho-oncology. For example, a number of studies in women with breast cancer (the most widely studied group of cancer patients) found decreased QoL (e.g. [1,2]), while other studies found no differences in QoL between breast cancer patients and healthy women (e.g. [3,4]) or between cancer survivors and healthy women (e.g. [5,6]). QoL studies that compared women who had undergone radical mastectomy with women who had partial mastectomy or breast-sparing treatments also showed inconsistent results. Some studies have indicated that different treatments result in comparable QoL (e.g. [7,8]), while others found that women treated with breast-sparing surgery report better QoL than women who have undergone mastectomy (e.g. [9]). In gynaecological cancer patients consistently higher QoL scores, including sexual functioning, have been found in patient groups than in matched control populations [10,11]. These inconsistent results are often considered to be the result of a phenomenon called ‘response shift bias’, i.e. when a person’s situation changes dramatically, so do his/her values [12]. As Sprangers and Schwartz [13] put it: ‘This variability may reflect informative shifts in an individual’s internal standard, in values and priorities, or in the conceptualization of perceived QoL, in addition to actual health state’.

Although this explanation contributes to our understanding of inconsistent outcomes in a methodological way, it contributes little to our understanding of the underlying psychological processes that regulate change in values. An explanation that has been offered lies in the psychological adjustment process to cancer [10,14–16]. A central issue in this adjustment process is the mental counterpart of the more instrumentally oriented adjustment process. In psychotraumatology this is referred to as the stress–response system (SRS [17,18]). Distinctive characteristics of a stress–response that occurs after a traumatic event include intrusive, unwanted negative thoughts (in this case about cancer) accompanied and/or alternated by efforts to avoid these thoughts. In terms of intensity of emotions, the SRS can be described as an oscillating pattern, in which phases of intrusion alternate with phases of avoidance [18–20]. Intrusion is characterized by reliving the traumatic event and by feelings of intense helplessness, powerlessness, sadness, anger, and fear. Intrusion is alternated by avoidance, i.e. a period of relative rest, in which a person is able to distance him or herself from fear, anger, etc. The two phases are functionally complementary. During the intrusion phases, restoration of basic cognition takes place, which is essential for
tested the following hypotheses:

In order to investigate SRS theory, we assessed health-related QoL, and avoidance and intrusion have different associations with health-related QoL. Moreover, in line with the suggestion by Horowitz, it has been shown that their avoidant coping styles are associated with persistently high levels of distress and avoidance, but not high levels of intrusion, to be associated with poor prognosis (e.g., [24] but see also [25,26]). Oscillation between the phases of intrusion and avoidance may attenuate over time until the adjustment process has been completed and a new coping baseline is achieved. Completion on an emotional level means that the patient is no longer overwhelmed by fears and memories and that he or she no longer has the tendency to repress the trauma; on a cognitive level this means that new cognitions (in terms of control, meaning, etc.) are formed. At the end of the adjustment process, the difference between intrusion and avoidance is negligible.

According to SRS theory large differences in QoL can be expected during this period of adjustment, depending on whether the patient is assessed during the avoidance or the intrusion phase. These differences in phasing may explain the inconsistencies in QoL outcomes, but they may also form an even better explanation for the inconsistencies in QoL outcomes, but they may also form an even better explanation for the consistencies in outcomes, because according to SRS theory, patients show a non-linear, oscillating pattern of QoL outcomes. In order to investigate this theory, we assessed health-related QoL, avoidance, and intrusion at four time points during a 12-month period following mastectomy. We tested the following hypotheses:

1. Health-related QoL increases over the 12-month follow-up.
2. Avoidance and intrusion decrease over the 12-month follow-up.
3. The two phases of adjustment, i.e. intrusion and avoidance, have different associations with self-reported QoL:
   a) For intrusion we expect that variation in the levels correspond with variation in health-related QoL.
   b) For avoidance we expect that high initial levels predict an unfavourable subsequent course of health-related QoL.

Methods

Participants

One hundred and twelve women diagnosed and treated for breast cancer entered the study. In the present paper we focus on 83 women (74% of the original sample) who completed all four assessments. The 29 women who did not complete the four assessments did not differ in baseline QoL and avoidance (ANOVA’s) from those who completed all assessments but they did show higher baseline intrusion (ANOVA, p = 0.012). Mean age was 53.55 years (SD: 9.83, range 36–76); 84% were married (for an average of 27.97 years), three women were co-habiting, and the rest were single; 40% were religiously affiliated; 38% had completed a relatively low education (elementary school or lower vocational training), 17% were highly educated (higher vocational training and advanced university) and 46% had completed an education level in between.

Procedure

Patients were recruited between 2002 and 2003 from five regional hospitals in the Netherlands. Of the women who met the inclusion criteria 90% agreed to participate in the study. Inclusion criteria were: unilateral mastectomy 2–3 months prior to the study entry; localized disease; and sufficient healing of the surgical wound to exclude complications that might interfere with the (QoL) outcome. All patients gave written informed consent. Participants were invited to fill in a questionnaire at the out-patient clinic on four successive occasions: at 3, 6, 9, and 12 months after surgery. All women received chemotherapy and eight women had an indication for radiotherapy.

Measures

Quality of life

The RAND-36 [27], the Dutch version of the MOS 36-item Short Form Health Survey (New England Medical Center Hospitals, 1991), was used to measure generic health-related QoL. The RAND-36 has good psychometric properties [27,28]. It consists of the following eight sub-scales: physical functioning (10 items), role limitations due to physical (four items) and to emotional (three items) problems, social functioning (two items), physical pain (two items), mental health (five items), vitality (four items), and general health perception (five items). All sub-scale outcomes vary between 0 and 100. High scores indicate good functioning and less pain. We did not include the single item on change in health status in our analyses.

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DOI: 10.1002/pon
Stress–response symptoms

The Dutch version of the Impact of Event Scale (IES) [17,18,29,30] was used to assess levels of stress–response. The list has been well validated in the Dutch language and it has good psychometric properties [18,29,31–33]. The list consists of 15 questions that are scored on a 4 point Likert scale (assigned the values 0, 1, 3, and 5). From the list two sub-scales can be calculated: avoidance (eight items, range 0–40) and intrusion (seven items, range 0–35). In addition, a total score can be calculated by summing the two sub-scales (total IES, range 0–75). Higher scores indicate greater distress. A total score of between 8 and 26 form a reason to perform more thorough diagnostics whereas a total score of 26 or more is considered to be a strong indication of serious psychological risk [18] and may indicate post-traumatic stress disorder (PTSD) [31].

Data analysis

Creation of intrusion/avoidance subgroups

A median split procedure was used to classify participants into those who suffer from relatively high or low intrusion (median = 11) and high or low avoidance (median = 8).

Assessment of oscillation patterns

To investigate the oscillation patterns in avoidance and in intrusion we calculated the standard deviation (SD) of the avoidance and intrusion scores across the four assessments of each participant individually. The stronger the oscillations in intrusion and avoidance the higher the SDs will be. Likewise, for each participant we assessed the SD of the QoL dimensions. High SDs within subjects may result not only from an oscillating pattern but also from large declines or increases over time. To investigate whether the observed SDs reflect a decline or increase over time rather than an oscillating pattern, we calculated Pearson correlations between: (1) change in intrusion (12-month assessment minus 3-month assessment) and SD in intrusion and (2) change in avoidance (12-month assessment minus 3-month assessment) and SD in avoidance. Non-significant correlations support our assumption that the SDs reflect the hypothesized oscillating pattern.

Statistical analyses

To avoid multiple testing we applied multivariate analyses of variance to investigate: (1) the time course of health-related QoL and of avoidance and intrusion (MANOVAs with time as within-subject effect) and (2) the predictive quality of avoidance and intrusion on the course of QoL (MANOVA with initial intrusion or initial avoidance as between-subject factor (median splits) and with the QoL dimensions and time as within-subject factors). To investigate the association between variation in avoidance and in intrusion on one hand and variation in the QoL dimensions on the other, partial correlations (corrected for baseline levels of the QoL) were calculated. Fisher Z tests were performed to compare the correlations between variance in avoidance and variance in QoL with the correlations between variance in intrusion and that in QoL. All tests were two-tailed with α set at 0.05.

Results

Hypothesis 1: QoL increases over time

Table 1 presents the means and SDs on the QoL dimensions at the four assessments. A MANOVA (with QoL dimensions and time as within-subject factors) revealed a significant main effect of time (F3, 246) = 20.19, p < 0.001) and a significant interaction effect of dimension and time (F(21, 1722) = 129.18, p < 0.001). Planned comparisons revealed that physical functioning, mental health, and general health did not change over the 12-month follow-up. Social functioning and role limitations in physical and emotional functioning improved over the 12-month follow-up. For vitality and physical pain quadratic effects best described the time course. Planned comparisons revealed that vitality and pain followed an inverted U-shaped course over the follow-up period with improvement during the first 6 months and deterioration during the following 6 months. At the 12-month assessment the mean pain score was higher than baseline (F(1, 82) = 33.27, p < 0.001) but the mean vitality score was lower than baseline (F(1, 82) = 9.69, p = 0.003). Hence, our first hypothesis received partial support.

Hypothesis 2: avoidance and intrusion decrease over time

Additionally, Table 1 presents the means and standard deviations of intrusion and avoidance and of the total IES for the four assessments. At the different time points the Pearson correlation between intrusion and avoidance varied between r = 0.599 and 0.677 (p-values all below 0.001). A MANOVA (with IES sub-scales and time as within-subject factors) showed neither a significant main effect of time (p = 0.900) nor a significant interaction effect of sub-scales and time (p = 0.153). At 12-months the mean total IES score was 20.6. Twenty-three women (28%) reported a total IES score below 9. Twenty-eight women (33.6%) met the criteria for serious psychological risk (a total IES score of 26 or higher) of whom 27 women (33%) had scores on the total IES of 26 or higher at...
all four assessments. Thus, in contrast to our second hypothesis, cancer-related distress remained high over the 12-month follow-up.

Hypothesis 3a: variation in intrusion but not in avoidance is associated with variation in QoL

Lastly, Table 1 presents the mean SDs of intrusion, avoidance, and health-related QoL as calculated across the four time points for each participant individually. To investigate our assumption that variation scores reflect oscillations in intrusion and avoidance we first considered whether the SD scores were associated with the observed change over time. Change in intrusion was not correlated with variation in intrusion (Pearson’s $r = 0.13, p = 0.255$). Also, change in avoidance was not correlated with variation in avoidance (Pearson’s $r = 0.08, p = 0.474$). These findings underscore our assumption. Further support for our assumption comes from the finding that variation in intrusion and in avoidance is inter-related (Table 2).

Table 2 presents the partial correlations between the variation in intrusion and avoidance on one hand and the variation in the QoL dimensions on the other (corrected for baseline levels of the QoL dimension). Women with high variation in intrusion also showed high variation in mental

| Table 2. Partial correlation between variation in intrusion and avoidance (corrected for baseline levels of intrusion and avoidance) and between variation in intrusion and avoidance on the one hand and in health-related QoL dimensions on the other (corrected for baseline health-related QoL dimensions). |
|---------------------------------|-----------------|-----------------|
| SD Fisher Z significance (p-value) |
| Intrusion Avoidance |
| Partial r p | Partial r p |
| Intrusion $^a$ | 0.33 | 0.002 | 0.44 | <0.001 |
| Avoidance $^b$ | 0.33 | 0.002 | 0.44 | <0.001 |
| Physical functioning | 0.14 | 0.220 | 0.05 | 0.629 | 0.0566 |
| Social functioning | 0.09 | 0.403 | 0.03 | 0.781 | 0.704 |
| Role limitations (physical) | 0.01 | 0.899 | -0.07 | 0.519 | 0.613 |
| Role limitations (emotional) | 0.02 | 0.881 | -0.02 | 0.838 | 0.800 |
| Mental health $^c$ | 0.49 | <0.001 | 0.08 | 0.506 | 0.004 |
| Vitality | 0.20 | 0.073 | 0.04 | 0.725 | 0.305 |
| Pain | 0.15 | 0.175 | 0.29 | 0.008 | 0.353 |
| General health | 0.40 | <0.001 | 0.08 | 0.466 | 0.031 |

The last column presents the p-values of the Fisher Z tests (significant p-values indicate different correlation coefficients). Significant findings are presented in bold.

$^a$ Corrected for baseline intrusion.

$^b$ Corrected for baseline avoidance.

$^c$ Corrected for baseline health-related QoL dimensions.
health and in general health. A tendency was found that variation in intrusion was also associated with variation in vitality. Variation in avoidance was significantly associated with variation in pain. Fisher Z tests revealed that the correlation coefficients found between variation in mental health and general health on the one hand and variation in intrusion on the other differed from those between variation in these QoL dimensions and variation in avoidance. These findings support our hypothesis that variation in QoL is associated with variation in intrusion rather than with variation in avoidance.

Hypothesis 3b: high initial avoidance but not initial intrusion predicts a poor QoL

Table 3 presents the results of the MANOVA’s with high and low initial intrusion (median split) or initial avoidance (median split) as between-subject factors and the eight dimensions of QoL and time as between-subject factors. The results showed a main effect on QoL of both intrusion and avoidance. Planned comparisons revealed that throughout the follow-up period women who scored low on initial intrusion or initial avoidance reported higher mental health, higher role limitations due to emotional functioning, and higher vitality than women who reported high intrusion or avoidance. In addition, women with low initial avoidance reported better general health than women with high avoidance. Of interest here is that the interaction effect between avoidance, QoL dimensions, and time reached significance. This indicates that avoidance has predictive quality with respect to the subsequent course of at least some dimensions of QoL. Indeed, planned comparisons revealed that compared to women with low initial avoidance, women with high initial avoidance reported a less favourable course of physical functioning, social functioning, role limitations due to physical impairments, and general health reports over the following 9 months. Figure 1 displays the time course of the QoL dimensions for women with high and low avoidance at 3 months after surgery. The significant interaction effect between intrusion, QoL dimensions, and time was not significant. Hence, in line with our hypothesis, the findings indicate that initial avoidance, rather than initial intrusion, has predictive quality with respect to the subsequent course of QoL.

Discussion

This paper presents an observational study of the time-dynamic aspects of health-related QoL and the SRS in a Dutch sample of women who underwent mastectomy. The findings provide support for two of our three hypotheses. In line with our first hypothesis improvement over time in QoL was found for social functioning and role limitations due to physical and to emotional functioning. However, no changes were found in physical functioning, mental health, and in general health whereas an initial improvement in vitality and physical pain was followed by a deterioration over the following 6 months. At 12-months, vitality was reported to be decreased while less pain was reported when compared to baseline. Our second hypothesis was not supported: avoidance and intrusion did not decline over the follow-up period. The study supports our third and main hypothesis that avoidance and intrusion are differently associated with the QoL of women who have undergone breast cancer surgery. Variation in QoL, in specific general health and mental health,

<table>
<thead>
<tr>
<th>Effect</th>
<th>F (df)</th>
<th>p</th>
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<tbody>
<tr>
<td>(a) Intrusion</td>
<td></td>
<td></td>
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<tr>
<td>Main effect of intrusion</td>
<td>F(1, 81) = 6.04</td>
<td>0.016</td>
</tr>
<tr>
<td>Main effect of time</td>
<td>F(3, 243) = 20.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Main effect of QoL sub-scales</td>
<td>F(7, 567) = 32.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction intrusion x time</td>
<td>F(3, 234) = 0.18</td>
<td>0.911</td>
</tr>
<tr>
<td>Interaction intrusion x sub-scales</td>
<td>F(7, 567) = 2.49</td>
<td>0.016</td>
</tr>
<tr>
<td>Interaction time x sub-scales</td>
<td>F(21, 1701) = 19.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction avoidance x sub-scales</td>
<td>F(21, 1701) = 5.21</td>
<td>0.025</td>
</tr>
</tbody>
</table>

| (b) Avoidance                 |         |      |
| Main effect of avoidance      | F(1, 81) = 5.21  | 0.025 |
| Main effect of time           | F(3, 243) = 20.36 | <0.001 |
| Main effect of QoL sub-scales | F(7, 567) = 33.31 | <0.001 |
| Interaction avoidance x time  | F(3, 234) = 1.80  | 0.149 |
| Interaction avoidance x sub-scales | F(7, 567) = 3.77  | 0.001 |
| Interaction time x sub-scales | F(21, 1701) = 19.42 | <0.001 |
| Interaction avoidance x time x sub-scales | F(21, 1701) = 2.01 | 0.004 |

Significant effects are presented in bold.
Figure 1. Time course of quality of life domains (as assessed with the RAND-36) for women with scores below and above the median on avoidance at 3 months. MANOVA (high and low avoidance groups as between-subject factor and time and QoL domains as within-subject factors: interaction effect groups × time: p = 0.037. Presented statistics in the figures refer to planned comparisons (groups as between-subject factor and time as within-subject factor). (a) Physical functioning; (b) social functioning; (c) role limitations due to physical problems; (d) role limitations due to emotional problems; (e) mental health; (f) vitality; (g) pain; and (h) general health.
was associated with variation in intrusion rather than with variation in avoidance. Furthermore, women with initial high levels of avoidance reported a poorer time course in physical functioning, social functioning, and general health over the 12-month follow-up as compared to women with initial low levels of avoidance. Women with initial high levels of intrusion did not differ in the subsequent QoL course from those with low initial levels.

In our opinion the present study contributes to the discussion on inconsistencies in results in health-related QoL research. We focussed on the time-dynamic aspects of both health-related QoL and cancer-related distress. Our findings show that different dimensions of health-related QoL take a different course over the months following mastectomy. Hence, improvement in health-related QoL is not simply a linear process. Furthermore, in line with the theoretical framework on SRS (e.g. [17]) we found that patients’ levels of intrusion and avoidance fluctuate during the time following mastectomy. Adaptation to severe stress (in this case breast cancer and mastectomy) is characterized by variation in intrusion and in avoidance of emotionally upsetting thoughts and feelings. High levels of intrusion are associated with upsetting feelings and thoughts that can negatively affect health-related QoL. Thus, depending on whether the patient is assessed in the avoidance phase or in the intrusion phase one would expect differences in QoL. Moreover, based on SRS, one can hypothesize that the two phases of adjustment, i.e. intrusion and avoidance, are differently associated with QoL. Our findings support our hypothesis: on the one hand, variations in mental health and in general health over time are associated with fluctuations in intrusion but not with fluctuations in avoidance. On the other hand, high baseline levels of avoidance but not of intrusion are associated with an unfavourable course of health-related dimensions of QoL, in particular with respect to reports of physical functioning, social functioning, and general health.

A significant percentage of the patients under study showed cancer-related distress for which professional psychological support is recommended. Even after 12 months 34% of the women met the criteria for serious psychological disturbance whereas only 28% of the women showed IES scores within the low range. This finding is in line with other studies that report high psychological stress in patients who have been diagnosed with and treated for breast cancer (e.g. [20,26,32–37]). All women but one who displayed high levels of distress at the 12-month assessment showed high levels of distress at all four assessments. The observed persistently high levels of distress fit within results from other studies showing that high initial levels of distress following a diagnosis of cancer predicts PTSD at follow-up (e.g. [38]).

Our results show that improvement in health-related QoL is not a linear process in all aspects of QoL. Initial improvement in vitality and in physical pain during the first 6 months of the follow-up was followed by deterioration during the following 6 months. Possibly, this decrease of vitality and increase in pain during the second half of the follow-up can be explained by side effects of chemotherapy and/or the development of lymph oedema. However, we cannot exclude other explanations such as a negative change in disease status. From a clinical perspective, the non-linear developments in QoL justify more attention from medical specialists and medical psychologists for the psychological and physical well-being of women who have undergone mastectomy for longer periods after surgery. Our findings may be useful in the screening of women who may benefit from early psychological interventions that help improve coping. In line with other studies (e.g. [21,22]) our findings indicate that such early interventions may be particularly helpful to women with high initial avoidance. Furthermore, the relationship between the variation in QoL and in intrusion may be used for screening women who may benefit from additional psychological interventions during follow-up periods. These interventions may be more helpful to women who demonstrate poor QoL in combination with low levels of intrusion than to women with poor QoL and high levels of intrusion.

Some limitations of the present study need to be addressed. First, little information on the patients’ medical condition was available. Second, the present findings provide no information on the direction of the relationship between the variation in intrusion and QoL. Future studies may address the question whether variation in painful intrusive thoughts impacts on QoL or whether a decrease in QoL brings up intrusive memories and worries about the cancer, or both.

To the best of our knowledge this is the first study that has focussed on the dynamic aspects of QoL and cancer-related distress over time. The findings stress the importance of such an approach by showing that intrusion and avoidance have different effects on the course of health-related QoL. In concordance with other studies (e.g. [21,22]), we found that avoidant strategies in coping with cancer are associated with a negative subsequent course of QoL. Stanton et al. [21,22], argue that avoidant coping styles constrain patients from taking an active approach to making adjustments and to treatment that bolsters recovery and adaptation (see also [23]). In addition, we found that oscillations in the levels of QoL are associated with oscillations in intrusive thoughts. Taken together, the present results underscore the need to incorporate the SRS in future oncological QoL research.
References


