

Psychological Response to Cancer: Role of 5-HTTLPR Genetic Polymorphism of Serotonin Transporter

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Abstract. *Background:* 5-HTTLPR genetic polymorphism of serotonin transporter (SERT) and stressful life events facilitate depression. The aim of this investigation was therefore to determine the correlations between SERT polymorphism and mental adjustment to cancer. *Patients and Methods:* Breast cancer patients early after surgery, and subjects with various advanced tumours were recruited, evaluated using the Mini Mental Adjustment to Cancer Scale and Hospital Anxiety and Depression Scale (HADS), and genotyped. *Results:* In early breast cancer patients (n=53), hopelessness-helplessness (HH) and anxious preoccupation (AP) significantly correlated with depression and anxiety; avoidance (AV) correlated with anxiety. Advanced cancer patients (n=73) displayed similar correlations, and a negative correlation of HADS depression with fighting spirit (FS) and AV. The stratification for 5-HTTLPR showed that early breast cancer carriers of the L/L variant displayed a significant correlation between HH and depression. *Conclusion:* Among early breast cancer patients, a specific set, characterized by their 5-HTTLPR variant, display differential correlations between HH and depression, with possible implications for treatment options.

A significant proportion of cancer patients, ranging from 10% to 40%, affected by the disease in various stages of progression, are diagnosed as having a depressive disorder

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(1). Moreover, mood disorders such as depression, have been shown to interfere with mental adjustment to cancer, influencing the adaptive coping styles of the patients (2).

A crucial methodological issue encountered in psycho-oncological research is the difficulty of evaluation of the mental condition of the cancer patients. Indeed, the majority of the existing psychometric instruments available have been developed and validated outside oncology for psychopathological conditions, including mood disorders, and coping strategies different from those of cancer patients. There are still issues regarding the methodological difficulties of the psychometric evaluation of cancer patients that deserve further clarification (3).

Among the various specific standardised psychometric scales developed, the Mini Mental Adjustment to Cancer (Mini-MAC) and the Hospital Anxiety and Depression Scale (HADS) are widely used in psycho-oncology. The available evidence indicates that HADS is a valuable instrument for qualitatively and quantitatively assessing anxiety and depressive conditions in individuals with somatic, non-neoplastic and neoplastic diseases (4). The Mini-MAC scale has been similarly shown to be suitable for the evaluation of the cognitive and behavioural responses displayed by cancer patients who adjust to the communication of the diagnosis (5).

The existence of correlations between HADS and Mini-MAC scales appears to have been examined particularly in studies aimed at validating these psychometric instruments for use in specific nationality versions, in relation to the construct validity (6-10).

The 5-hydroxytryptamine transporter gene-linked polymorphic region (5-HTTLPR) polymorphism of the serotonin transporter (SERT) has been widely examined in relation to the difficulties of adaptation to stressful life events and to the possible consequently increased risk of developing depressive mood disorders (11-17).

Table I. Correlations between the scores of Hospital Anxiety and Depression Scale (HADS) and Mini Mental Adjustment to Cancer Scale (Mini-MAC).

Mini-MAC	Patients with early breast cancer (N=53)		Patients with advanced cancer (N=73)	
	HAD-D	HAD-A	HAD-D	HAD-A
Hopelessness-helplessness	0.490**	0.612**	0.689**	0.612**
Anxious preoccupation	0.493**	0.779**	0.536**	0.672**
Fighting spirit	-0.208	-0.219	-0.517**	-0.286
Fatalism	0.147	0.050	0.175	0.099
Avoidance	0.223	0.326*	-0.352*	-0.029

The values reported in the table are the Pearson's correlation coefficient (** $p < 0.001$; * $p < 0.05$). HAD-D: HADS depression; HAD-A: HADS anxiety.

Table II. Correlations coefficients of the scores of Mini-MAC Hopelessness-Helplessness (HH) and HADS Depression (HAD-D) in relation to 5-HTTLPR polymorphism in cancer patients.

	Patients with early breast cancer 5-HTTLPR variant		Patients with advanced cancer 5-HTTLPR variant	
	L/L	S/L, S/S	L/L	S/L, S/S
Correlation coefficients of HH and HAD-D	0.700*	0.326	0.728*	0.662*

The values reported in the table are the Pearson's correlation coefficient (* $p < 0.001$).

The aim of the present investigation was therefore to determine, in cohorts of patients either with early breast cancer or with advanced cancer, the magnitude of the correlations between HADS and Mini-MAC and to characterize the correlations obtained according to the specific SERT genotypic variant of the patients.

Materials and Methods

Study sample. This study included a cohort of 53 consecutive early breast cancer patients, who were referred to the Centro Sociale Oncologico, Azienda Servizi Sanitari 1 (Trieste, Italy) after having received the communication of cancer diagnosis. A second cohort comprised 73 consecutive terminally ill cancer patients affected by different types of advanced cancer who were admitted to the hospice of the Casa di Cura Pineta del Carso (Trieste, Italy). The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, after having been approved by the relevant institutional Ethical Committee. Informed consent was obtained from all the participants of the study.

Measures. All patients were evaluated psychometrically at enrolment by using the following instruments: (i) HADS (18), consisting of 14 items measuring, on a 4-score Likert scale (0-3), anxiety (HAD-A) and depression (HAD-D), the sum of which yields a total HADS score; (ii) Mini-MAC (1, 6), a 29-item scale measuring coping with cancer in five dimensions, namely Hopelessness-helplessness (HH), fighting spirit (FS), anxious preoccupation (AP), fatalism (FS) and avoidance (AV).

Each patient was also genotyped for the 5-HTTLPR polymorphism by analysing genomic DNA obtained from buccal

epithelial cells using standard laboratory procedures (19). Polymerase chain reaction (PCR) amplification of 5-HTTLPR was performed using the primer described by Gelernter *et al.* (20) and with the GC-rich PCR System (Roche Molecular Biomedicals, Milano, Italy).

Data analysis. The data were analysed by conventional descriptive analytical procedures using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at the 5% level.

Results

The correlations between the scores of HADS and Mini-MAC subscales are reported in Table I. In the cohort of patients with early breast cancer, both the Mini-MAC HH and AP significantly correlated with HADS HAD-D and HAD-A; AV significantly correlated with HAD-A. In terminally ill cancer patients, similar correlations were found for HH and AP with HAD-A and HAD-D; a significant negative correlation was found between HAD-D and FS and AV.

When the 5-HTTLPR genotype was examined, 75 patients (60%) were carriers of a variant with one S allele (15 S/S and 60 S/L variants) and 51 were homozygous for the L/L allele (40%). The cohort of patients with early breast cancer comprised 30 cases (57%) with one S allele (4 S/S and 26 S/L variants) and 23 homozygous for the L/L allele (43%). Among the patients with advanced cancer, 45 had one S allele (62%) (11 S/S and 34 S/L variants) and 28 were homozygous for the L/L allele (38%). The genotypic distribution for the

5-HTTLPR polymorphism did not significantly differ from the Hardy–Weinberg equilibrium in both instances ($\chi^2=0.84$; $p=0.36$; $df=1$, and $\chi^2=0.017$; $p=0.90$; $df=1$, respectively).

The data reported in Table II indicate that when the patients with early breast cancer were stratified for their allelic variant, the correlations between Mini-MAC HH and HAD-D were significant only in those carriers of the L/L variant.

Discussion

The correlation between the Mini-MAC and HADS sub-scales was examined in patients with early breast cancer. Significant positive correlations were identified considering the scores of Mini-MAC HH and AP on one hand and the sub-scales of HADS on the other, in agreement with the findings of Bredal *et al.* (10). Positive correlations between the Mini-MAC and HADS scales have also been reported for patients with other types of cancer (21, 6-9), whereas the existence of similar correlations does not appear to have been explored for cancer patients in the terminal phase of the disease. When terminally ill cancer patients were considered during the present investigation, significant negative correlations were identified for HADS depression, in relation to the Mini-MAC FS and AV scores, in addition to the significant positive correlations which were observed also for early breast cancer patients. The patients enrolled in this study were also stratified for the genotype according to the 5-HTTLPR polymorphism. Early breast cancer patients which were homozygotes for the L allelic variant, unlike those carrying at least one S allele, displayed a significant positive correlation between the scores of Mini-MAC HH and HAD-D. This observation indicates that the highly functional SERT activity corresponding to the 5-HTTLPR L/L genetic polymorphism variant (22) may have a role in modulating the association of depressive symptoms with HH coping styles in women with early breast cancer.

These results appear of interest, since they may lead to the characterization of a sub-group of patients homozygous for the L/L variant which are more prone to depression and to the coping style of HH than the carriers of the S allele. A specific intervention may thus be envisioned for these patients, either based on psychoeducational or other psychotherapeutic approaches (23-28), or on the use of antidepressant drugs. In this connection, pharmacogenetic data concerning SSRI antidepressant drugs are available (29-30), indicating that their effects are more pronounced in patients with depressive mood disorders carrying the L/L 5-HTTLPR polymorphism in comparison with those carrying at least one S allele. This result has been confirmed for citalopram and sertraline in small groups of terminally ill cancer patients in whom mental adjustment to cancer also

appeared to be related to L/L 5-HTTLPR polymorphic variant (31). The use of antidepressant drugs with a mechanism of action different from that of SSRIs may thus be considered for the treatment of patients who, according to their 5-HTTLPR genetic polymorphism, would not be expected to provide a complete response to SSRIs.

The laboratory examination of this SERT polymorphism thus appears of interest for the identification of the individual specific needs for support and/or intervention for early breast cancer patients. A deeper examination of a larger cohort of patients is currently in progress, and may be extended to include those with different types of cancer and at different stages of progression, contributing to the clarification of the difficulties in adjustment to cancer and the possible intervention.

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