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Brief report

Depression and serotonin transporter (5-HTTLPR) polymorphism in breast cancer patients

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ABSTRACT

Background: Mixed evidence in the general population and medically ill patients has suggested that homozygous carriers of the short allele (*s*/*s*) of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) may increase the risk of depression in comparison with carriers of the long allele (*l*/*l*) or *s*/*l*. Given the lack of data in oncology, we examined the relationship of depression with the 5-HTTLPR and psychosocial variables among breast cancer patients.

Methods: A sample of 145 breast cancer patients were studied as regards to depression, psychosocial-related variables (coping, Type D-personality, life events, and social support), and the 5-HTTLPR, which was genotyped by using a standard protocol with DNA extracted from the blood.

Results: No difference was found between *s*/*s*, *s*/*l* and *l*/*l* patients on depression and any other psychosocial variable. No gene-by environment (G × E) interactions were observed between the 5-HTTLPR and recent life events.

Conclusions: The study did not provide support of a possible association between 5-HTTLPR polymorphism, alone or in conjunction with life events, and depression in newly diagnosed breast cancer. Further follow-up studies are however necessary to confirm these data.

1. Introduction

Depression is one of the most important psychiatric complication of cancer, affecting between 10 and 58% patients (Massie, 2004), persisting long after cancer therapy and causing remarkable negative consequences (e.g., impairment of quality of life, risk of suicide, increase the level of pain and, reduction of survival) (Chochinov, 2001). Under-recognition and under-treatment of depression in cancer patients is still a problem and this contrasts with the marked needs both diseases have for the health system (Reich, 2008). WHO data (2009) indicate that 30–50 millions of people around the world live with cancer and that cancer incidence will increase by 50% by 2030, with around 16 million new cases in that year. Thus, the exploration of possible risk factors for depression in cancer patients is a priority.

The role of the polymorphism in the gene encoding the serotonin transporter (5-HTTLPR) has been examined as a factor associated with depression and sub-threshold depression. Individuals with two long genotypes (*l*/*l*) were shown to less likely develop depression after exposure to stressful life events (SLE) than individuals with one or two short (*s*) alleles (*s*/*l* and *s*/*s*) (Caspi et al., 2003). These data have been replicated

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in other studies (Kendler et al., 2005), including patients with stroke (Ramasubbu et al., 2006) and myocardial infarction (Otte et al., 2007). Personality traits, such as affective temperament/neuroticism, were found to be associated with the *s* allele (Gonda et al., 2006). Contrasting results emerged in other studies not supporting the role of the 5-HTTLPR genotype and its interaction with SLE on depression in the general population (Gillespie et al., 2005; Chipman et al., 2007; Power et al., 2008), patients with Parkinson disease (Burn et al., 2006), traumatic brain injury (Chan et al., 2008), and Alzheimer disease (Micheli et al., 2006).

In spite of the importance of depression in oncology, very little data are available about the role of 5-HTTLPR polymorphism. In a small study of 34 head–neck cancer patients, Gilbert et al. (2008) showed that the *s* allele was associated with both major depression and general depressive diagnoses.

On this background, the aim of the present study was to explore the relationship between the 5-HTTLPR polymorphism and depression, by including psychosocial variables and the G×E interaction, in breast cancer patients, with the hypothesis that carrying an *l* allele may have a protective role on depression.

2. Patients and methods

The study was carried out at the Department of Clinical Oncology, University Hospital in Ferrara, Northern Italy. A convenience sample of breast cancer outpatients were enrolled in the clinics and day-hospital services of the centre. Criteria for recruitment were: (i) a diagnosis of cancer of within 6 months; (ii) a Karnofosky Performance Status scale >80; (iii) no cognitive impairment; (iv) an age between 18 and 70 years. The study was approved by the ethical committee of the hospital.

Each patient was administered a short clinical semi-structured interview and self-report psychometric instruments. Blood samples were also collected.

Since the association between 5-HTTLPR and depression has been shown to be similar for self-reported and interview-based measurements (Caspi et al., 2003), the 7-item Depression subscale of the Hospital Anxiety–Depression Scale (Zigmond and Snaith, 1983) (HAD-D) was used. Cut-off scores >8<11 and >11 were recommended in oncology to identify "borderline cases" and "cases", respectively (Carroll et al., 1993).

Two main sub-factors of the Mini-Mental Adjustment to Cancer scale (Mini-MAC) (Watson et al., 1994), namely Anxious Preoccupation (8 items), and Hopelessness (8 items), were used to assess maladaptive coping.

The Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet et al., 1988), a 12-item questionnaire, was used to investigate social support in the dimensions of Family (4 items), Friends (4 items), Others (4 items), and Total Support.

The occurrence of SLE over the time since the diagnosis of cancer was evaluated by means of the Life Events Scale (Paykel, 1997). Sixty-four possible events covering several areas (e.g. work, education, finance, health, bereavement, family and social) are inquired by the scale. For statistical analysis SLE were considered as a dichotomous variable (i.e. absence/presence of SLE events = yes/no).

The Type D-Scale (DS) (Denollet, 2005) was used to measure personality traits, specifically Negative Affectivity (NA), (the tendency to experience negative emotions across times and situations) and Social Introversion (SI) (the tendency to inhibit the expression of emotions and behavior in social interactions), with recommended cut-off scores of both NA and SI >10 for Type-D.

3. Genotyping

Genomic DNA was obtained from whole blood cells, using standard procedures (GenEluteTM blood Genomic DNA Kit, Sigma). Polymerase chain reaction (PCR) amplification of 5-HTTLPR was performed using the primers described by Gelernter et al. (1997), and with the GC-Rich PCR System (Roche Molecular Biomedicals) in a 50-μL reaction containing 20–100 ng of DNA; 100-μm deoxyribonucleoside triphosphate (dNTPs), 20 pmol for each primer, and 1.5 mM MgCl2. DNA was denatured at 95 °C for 10 min and subjected to 40 cycles of 40 s of denaturation at 94 °C, 45 s of annealing at 56 °C, 40 s of extension at 72 °C, and 10 min of final extension at 72 °C. The products of PCR amplification were separated on a 2% agarose gel, and were visualised in ultraviolet light after ethidium bromide staining.

4. Statistical analysis

All statistical analyses were carried out using the SPSS 16.0 package. The data were analyzed according to genotype (*ss*, *sl* and *ll* genotypes; additive model), and phenotype groupings (subjects carrying and not carrying the *s* allele; dominant model). ANOVA, with post hoc LSD tests, Student's *t* test, chi-square test, Pearson's *r* coefficient test and binary logistic regression were used when appropriate. Statistical significance was set at $p<0.05$.

5. Results

5.1. Socio-demographic, clinical and genotype characteristics of the sample

Socio-demographic and clinical characteristics of the 145 patients (mean age 55.87 ± 8.98) in the study are presented in Table 1. The frequencies of the three 5-HTTLPR genotypes were: *ll*, 31.3% ($n=45$); *sl*, 45.5% ($n=66$); and *ss*, 23.4% ($n=34$), comparable with previous reported frequencies in similar samples (Hardy–Weinberg equilibrium: $\chi^2=0.90416$; $p=$ ns).

There was no significant difference in age between the three genotype groups ($F=0.67$, $p=0.93$) and the two phenotype groups ($F=0.67$; $p=0.79$). No difference were found with regard to medical variables, such as stage (genotype: $\chi^2=5.87$, *df*, 4, $p=0.2$; phenotype: $\chi^2=4.7$, *df*, 2, $p=0.09$) and treatment (genotype: $\chi^2=6.3$, *df*, 4, $p=0.1$; phenotype: $\chi^2=5.1$ *df*, 2, $p=0.08$).

5.2. Association of 5-HTTLPR genotypes (ss, sl and ll groups) and phenotypes with depression and psychosocial variables

HAD-D scores were comparable among the 3 genotype and phenotypes groups. The genotype and phenotype distribution was comparable among depressed ($n=16$; 11.03%), borderline/sub-threshold depressed ($n=20$; 13.8%) and non-depressed patients ($n=109$; 75.1%) (genotype: $\chi^2=1.6$, *df*, 4, $p=0.89$;

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Table 1
Socio-demographic and clinical characteristics of the sample.

Age	55.87 ± 8.98	Stage	
Education (years)	9.76 ± 4.34	Local	123 (84.8%)
		Loco-regional	22 (15.2%
Marital status		Surgery	
Married	110 (75.8%)	Quadrantectomy	93 (64.1%)
Separated/divorced	15(10.3%)	Mastectomy	43 (29.6%)
Never-married	11 (7.6%)	Conservative intervention (lumpectomy and sectoriectomy)	9 (6.2%)
Widow	9 (6.2%)		
Job		Treatment	
Employed	65 (44.8%)	No therapy	70 (48.3%)
Housewife	29 (20%)	Chemotherapy	33 (22.7%)
Retired	44 (30.3%)	Combined therapy (hormone therapy + radiotherapy; hormone therapy + chemotherapy + radiotherapy)	21 (14.5%)
Unemployed	7 (4.8%)	Hormone therapy	21 (14.5%)
		No therapy	70 (48.3%)
Psychiatric history			
Yes	50 (34.5%)		
No	95 (65.5%)		

Table 2
Binary logistic regression analyses for predictor variables of 5-HTTLPR genotype, stressful life events, Type D and social support on depression.

	HAD-D>8 *			HAD-D>11 **		
	β	S.E.	p	β	S.E.	p
5-HTTLPR	1.07	0.44	0.87	0.8	0.44	0.87
Life events	0.28	1.21	0.01	2.91	1.26	0.01
Type D	0.68	0.44	0.005	1.25	0.44	0.005
Social support	0.45	0.55	0.15	0.79	0.55	0.15

* Patients with mild to high levels of depression HAD-D>8 depression.
** Patients "cases" of depression (HAD-D>11).

phenotype $\chi^2 = 0.34$, *df*, 2; $p = 0.84$). No difference emerged between the 3 genotype/phenotypes groups on any psychosocial variables.[1]

The distribution of *s/s*, *s/l* and *l/l* carriers were comparable among patients with and without previous psychiatric episodes (genotype: $\chi^2 = 0.84$, *df*, 2, $p = 0.65$; phenotype: $\chi^2 = 0.27$, *df*, 1, $p = 0.61$), and those with and without stressful life events (genotype: $\chi^2 = 1.72$, *df*, 3, $p = 0.18$; phenotype: $\chi^2 = 0.96$, *df*, 2, $p = 0.62$).

5.3. Effects of 5-HTTLPR, stressful event, personality and social support on depression

Patients not reporting SLE ($n = 102$; 70%) had lower HAD-D scores (4.66 ± 3.96) than patients reporting 1 event ($n = 37$; 25.85%; HAD score = 5 ± 3 5.24) or 2 or more events ($n = 6$; 4.1%; HAD-D score = 9.5 ± 4.84) ($F = 3.49$; $p = 0.03$).

Binary logistic regression analysis was conducted with the dependent variable dichotomized according to the cut-off for depression (first analysis 0 = HAD-D score < 11 and 1 = HAD-D score ≥ 11; second analysis 0 = HAD-D score < 8 and 1 = HAD-D score ≥ 8). The predictor variables for the models were 5-HTTLPR genotype (0 = *s/s*, 1 = *s/l*, 2 = *l/l*), SLE (from 0 = no event up to 2 or more events), social support (0 = no; 1 = yes) and Type-D personality (0 = no; 1 = yes). No effect and no interaction of the 5-HTTLPR on depression was found (Table 2). In the univariate ANOVA, with only SLE and 5-HTTLPR as fixed factors and HAD-D scores as the dependent variable, there was a significant main effect of SLE on the HAD-D score ($F = 4.38$, *df*, 2, $p = 0.014$), while SLE and 5-HTTLPR genotype did not show a significant interaction ($F = 1.59$, *df*, 4, $p = 0.18$). By using multiple regression analysis with HAD-D score as a dependent variable, of all the psychosocial variables examined, only Mini-MAC-AP ($B = 0.24$; SE = 0.07, $\beta = 0.29$, $t = 3.23$, $p = 0.02$), Mini-MAC-H ($B = 0.27$; SE = 0.07; $\beta = 0.31$; $t = 3.45$; $p = 0.001$), and Type-D-NA ($B = 0.15$; SE = 0.05; $\beta = 0.22$; $t = 2.82$; $p = 0.005$) entered the equation explaining 51% of the variance.

6. Discussion

In this study we investigated the association of the 5-HTTLPR genetic polymorphism, SLE and a series of psychosocial variables with depression in breast cancer patients.

No difference was found between "*s/s*", "*l/l*" and "*l/s*" allelic variants of 5-HT with respect to depressive symptoms. Furthermore, 5-HTTLPR genetic polymorphism was not related to maladaptive styles of coping with cancer, SLE in the previous year, social support and Type-D personality. We also were not able to find any G × E interaction on depression.

Our data are in contrast with studies showing a relationship between depression and the s allele, including the small study by Gilbert et al. (2008) on head–neck cancer patients. However, our findings are in agreement with other studies not confirming an association between 5-HTTLPR genotypes, or the presence of the s allele, or G × E interaction, and depression. Recently, Phillips-Bute et al. (2008) found that the 5HTTLPR *l/l*, and not the *s/s* genotype was associated with increased depressive symptoms one year after coronary artery bypass graft surgery, and that the presence of the *l* allele, in combination with baseline depression, was associated with increased incidence of adverse cardiac events.

There are limitations that should be taken into account in this study. First, the sample size does not allow generalizability of our results. Second, since depression was assessed by the HAD-D, we cannot ascertain that patients with a formal

[1] Complete results are available upon request from the authors.

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(e.g. DSM-IV) diagnosis of major depression were more vulnerable to depression if they were carrying an *s* allele. Some authors (Caspi et al., 2003; Otte et al., 2007), however, found that 5-HTTLPR genotype and the G × E interaction was not exclusively related to major depression, but also to depressive symptoms as assessed by psychometric instruments, as we did. A third limitation is that the evaluation of stressors regarded only the previous year and this might be too short to result in significant G × E interactions. Caspi et al. (2003) and Wilhelm et al. (2006), suggested in fact that G × E interaction might be conditional on the duration of exposure to the stressors prior to the onset of depression. However, other data indicated that *s*/*s* homozygous subjects may require minimal exposure to SLE to acquire a level of risk for depression found among *l*/*s* or *l*/*l* subjects after higher exposure to SLE (Cervilla et al., 2007; Verhagen et al., 2009). Moreover, Taylor et al. (2006) showed that *s*/*s* individuals had greater levels of depression if they had experienced early or recent adversity, but significantly lower levels if they reported a supportive early environment or recent positive experiences. Fourth, the patients were recruited after a short period of time from the diagnosis of cancer and this might have biased the analysis of the data. Prospective studies are necessary for a more comprehensive understanding of the role of genetic factors in patients facing the major stressful event of cancer. We also did not study other possible genetic factors, such as functional variants in the 5-HT transporter gene that may influence the interaction between the 5-HTTLPR polymorphism and depression (Lazary et al., 2008). Furthermore, all participants were women and the triallelic system of 5-HTTLPR was not used, suggesting caution should be taken in interpreting the results.

In conclusion, our study failed to find that variation in the *s*/*l* allele in the 5-HTTLPR was associated with depression among breast cancer patients. Also we did not find any significant G × E interaction on depression. Further research taking into account the possible relationship between the 5-HTTLPR and other biological mechanisms hypothesized to be related to depression in cancer patients, such as cytokine production and the HPA axis functioning (Jehn et al., 2006; Soygur et al., 2007), is needed for a more comprehensive understanding of this complex area.

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Conflict of interest

The authors declare no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, the work.

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References

Burn, D.J., Tiangyou, W., Allcock, L.M., Davison, J., Chinnery, P.F., 2006. Allelic variation of a functional polymorphism in the serotonin transporter gene and depression in Parkinson's disease. Parkinsonism Relat. Disord. 12, 139–141.

Carroll, B.T., Kathol, R.G., Noyes Jr, R., Wald, T.G., Clamon, G.H., 1993. Screening for depression and anxiety in cancer patients using the Hospital Anxiety and Depression Scale. Gen. Hosp. Psychiatry 15, 69–74.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.

Cervilla, J.A., Molina, E., Rivera, M., Torres-González, F., Bellón, J.A., Moreno, B., Luna, J.D., Lorente, J.A., Mayoral, F., King, M., Nazareth, I., PREDICT Study Core Group, Gutiérrez, B., 2007. The risk for depression conferred by stressful life events is modified by variation at the serotonin transporter 5HTTLPR genotype: evidence from the Spanish PREDICT-Gene cohort. Mol. Psychiatry 12, 748–755.

Chan, F., Lanctôt, K.L., Feinstein, A., Herrmann, N., Strauss, J., Sicard, T., Kennedy, J.L., McCullagh, S., Rapoport, M.J., 2008. The serotonin transporter polymorphisms and major depression following traumatic brain injury. Brain Inj. 22, 471–479.

Chipman, P., Jorm, A.F., Prior, M., Sanson, A., Smart, D., Tan, X., Easteal, S., 2007. No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: results from two community surveys. Am. J. Med. Genet. B Neuropsychiatr. Genet. 5 (144B), 561–565.

Chochinov, H., 2001. Depression in cancer patients. Lancet Oncol. 2, 499–505.

Denollet, J., 2005. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosom. Med. 67, 89–97.

Gelernter, J., Kranzler, H., Cubells, J.F., 1997. Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. Hum. Genet. 101, 243–246.

Gilbert, J., Haman, K., Yarbrough, W.G., Dietrich, M.S., Chung, C.H., Cmelak, A.J., Pham, M., Muldowney, N., Blakely, R.D., Murphy, B.A., 2008. Head and neck cancer (HNC), depression, and genetic polymorphism. J. Clin. Oncology 26 (15S), 6017 (May 20 Supplement).

Gillespie, N., Whitfield, J., Williams, B., Heath, A., Martin, N., 2005. The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. Psychol. Med. 35, 101–111.

Gonda, X., Rihmer, Z., Zsombok, T., Bagdy, G., Akiskal, K.K., Akiskal, H.S., 2006. The 5HTTLPR polymorphism of the serotonin transporter gene is associated with affective temperaments as measured by TEMPS-A. J. Affect. Disord. 91, 125–131.

Jehn, C.F., Kuehnhardt, D., Bartholomae, A., Pfeiffer, S., Krebs, M., Regierer, A.C., Schmid, P., Possinger, K., Flath, B.C., 2006. Biomarkers of depression in cancer patients. Cancer 107, 2723–2729.

Kendler, K.S., Kuhn, J.W., Vittum, J., Prescott, C.A., Riley, B., 2005. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch. Gen. Psychiatry 62, 529–535.

Lazary, J., Lazary, A., Gonda, X., Benko, A., Molnar, E., Juhasz, G., Bagdy, G., 2008. New evidence for the association of the serotonin transporter gene (SLC6A4) haplotypes, threatening life events, and depressive phenotype. Biol. Psychiatry 64, 498–504.

Massie, M.J., 2004. Prevalence of depression in patients with cancer. J. Natl. Cancer Inst. Monogr. 32, 57–71.

Micheli, D., Bonvicini, C., Rocchi, A., Ceravolo, R., Mancuso, M., Tognoni, G., Gennarelli, M., Siciliano, G., Murri, L., 2006. No evidence for allelic association of serotonin 2A receptor and transporter gene polymorphisms with depression in Alzheimer disease. J. Alzheimers Dis. 10, 371–378.

Otte, C., McCaffery, J., Ali, S., Whooley, M.A., 2007. Association of a serotonin transporter polymorphism (5-HTTLPR) with depression, perceived stress, and norepinephrine in patients with coronary disease: the Heart and Soul Study. Am. J. Psychiatry 164, 1379–1384.

Paykel, E.S., 1997. The interview for recent life events. Psychol. Med. 27, 301–310.

Phillips-Bute, B., Mathew, J.P., Blumenthal, J.A., Morris, R.W., Podgoreanu, M.V., Smith, M., Stafford-Smith, M., Grocott, H.P., Schwinn, D.A., Newman, M.F., 2008. Perioperative Genetics and Safety Outcomes Investigative Team. Relationship of genetic variability and depressive symptoms to adverse events after coronary artery bypass graft surgery. Psychosom. Med. 70, 953–959.

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Power, T., Stewart, R., Ancelin, M.L., Jaussent, I., Malafosse, A., Ritchie, K., 2008. 5-HTTLPR genotype, stressful life events and late-life depression: no evidence of interaction in a French population. Neurobiol. Aging Jul 18, [Electronic publication ahead of print].

Ramasubbu, R., Tobias, R., Buchan, A.M., Bech-Hansen, N.T., 2006. Serotonin transporter gene promoter region polymorphism associated with post-stroke major depression. J. Neuropsychiatry Clin. Neurosci. 18, 96–99.

Reich, M., 2008. Depression and cancer: recent data on clinical issues, researchchallenges and treatment approaches. Curr. Opin. Oncol. 20, 353–359.

Soygur, H., Palaoglu, O., Akarsu, E.S., Cankurtaran, E.S., Ozalp, E., Turhan, L., Ayhan, I.H., 2007. Interleukin-6 levels and HPA axis activation in breast cancer patients with major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 1242–1247.

Taylor, S.E., Way, B.M., Welch, W.T., Hilmert, C.J., Lehman, B.J., Eisenberger, N.I., 2006. Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. Biol. Psychiatry 60, 671–676.

Verhagen, M., van der Meij, A., Janzing, J.G., Arias-Vásquez, A., Buitelaar, J.K., Franke, B., 2009. Effect of the 5-HTTLPR polymorphism in the serotonin transporter gene on major depressive disorder and related comorbid disorders. Psychiatr. Genet. 19, 39–44.

Watson, M., Law, M., dos Santos, M., Greer, S., Baruch, J., Bliss, J., 1994. The Mini-MAC: further development of the Mental Adjustment to Cancer Scale. J. Psychosoc. Oncol. 12, 33–46.

Wilhelm, K.A.Y., Mitchell, P.B., Niven, H., Finch, A., Wedgwood, L., Scimone, A., Blair, I.P., Parker, G., Schofield, P.R., 2006. Life events, first depression onset and the serotonin transporter gene. Br. J. Psychiatry 188, 210–215.

World Health Organization: Cancer. www.who.int/cancer/en/. 2009

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.

Zimet, G.D., Dahlem, N.W., Zimet, S.G., Farley, G.K., 1988. The multidimensional scale of perceived social support. J. Person. Ass. 52, 30–41.

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