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CAN RELAXATION TRAINING AND HYPNOTHERAPY MODIFY THE IMMUNE RESPONSE TO STRESS, AND IS HYPNOTIZABILITY RELEVANT?

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ABSTRACT

A study was carried out with the following aims: (1) to evaluate the psychological and immunological effects of 3 weeks' relaxation practice; (2) to investigate the effects of relaxation training and hypnosis on the modulation of the immune response to an experimental stressor; and (3) to relate changes to hypnotic susceptibility. Twenty-four healthy volunteers were assigned, according to a stratified, permuted blocks, random allocation procedure, to relaxation training with hypnosis or to a control condition. Subjects attended on three occasions: day 1, day 21 and day 22 or 23. Various psychological tests were carried out on each of the occasions and, in addition, samples of urine and blood were collected for immunological and biochemical analysis. Two samples of blood were taken at the second visit, one before exposure to an experimental stressor on day 21 and one immediately thereafter.

Relaxation had several effects including improvement on a number of measures of mental state and a *reduction* in lymphocyte responsiveness and IL-1 secretion. However, on exposure to the stressor, previous relaxation training and pre-exposure hypnotic suggestion led to *increased* lymphocyte responsiveness and IL-1 secretion.

The extent to which IgA increased as a result of relaxation therapy for 3 weeks was positively correlated with Creative Imagination Scale (CIS) scores (changes in the control group during the same period were not correlated with CIS scores). Moreover, immediate changes in IL-1 following exposure to the stressor were *positively* correlated with CIS scores in the experimental group and *negatively* in the control group. Hypnotizability, as assessed by the CIS, may be an important moderator of the psychoneuroimmunological response to relaxation training and exposure to acute stress.

INTRODUCTION

During the last decade, there has been growing interest in the field of psychoneuroimmunology and a number of reviews have been published (Ader, Felton & Cohen, 1991; Lewis, O'Sullivan & Barraclough, 1994; Walker & Eremin, 1995). It is increasingly clear that, in certain situations, environmental and intrapsychic stressors can lead to increased risk of disease due to down-regulation of host defences. The mechanisms involved in the interactions between the central nervous system and the

immune system, and the important mediating role of hormones, have been well reviewed by Black (1994a,b).

The psychoneuroimmunological effects of hypnosis and relaxation training have not been well evaluated and, in particular, little is known about how these intervention modalities might modulate the response to an acute experimental stressor (see Walker, Johnston and Eremin, 1993 for a review).

A study was carried out, therefore, with three aims: (1) to evaluate the psychoneuroimmunological effects of 3 weeks' relaxation practice; (2) to investigate the effects of relaxation training and hypnosis on the modulation of the immune response to an experimental stressor; and (3) to relate the immunological changes to hypnotizability.

METHOD

Design

Twenty-four healthy volunteers were assigned, using a stratified, permuted blocks, random allocation procedure, to an experimental or control condition. Subjects attended on three occasions: day 0, day 21 and day 22 or 23 (half of the subjects attended on day 22 and the remainder the following day). Various psychological tests were carried out at each of the visits and, in addition, blood and urine samples were collected. Two samples of blood were taken at the second visit before exposure to an experimental stressor and one immediately thereafter. Blood was collected via a venflon, which had been *in situ* for not less that 20 minutes, and volunteers collected their urine samples at 8.00 am on the morning of each visit. The subjects attended the Behavioural Oncology Unit in pairs, each pair belonging to the same group (experimental or control).

Visit 1 (day 0) At the first visit, after informed consent had been obtained, subjects were fully briefed about the experiment and a venflon was inserted into the cephalic vein in the antecubital fossa. Various psychological tests and questionnaires were then administered in a specified order and, thereafter, blood pressure, heart rate and respiration rate were recorded. A venous blood sample of approximately 60 ml was then collected into heparinized syringes and the venflon was removed. All subjects then listened to an audio cassette recording containing the hypnotic induction from the Stanford Hypnotic Clinical Scale (Hilgard & Hilgard, 1983) followed by the test suggestions from the Creative Imagination Scale (CIS) (Wilson & Barber, 1978). At the end of the visit, a daily health diary and a container for the next urine sample were given to each subject with verbal and written instructions.

At the end of visit 1, subjects in the experimental group were given a relaxation tape and asked to listen to one of the two recordings once daily for the next 21 days. The first recording contained instructions for progressive muscular relaxation (22 minutes). After subjects had been asked to tense a particular muscle, they were to think the key words 'one, two, three relax' and, as they thought the word 'relax', they were to relax the muscle in question (cue-controlled relaxation). The second side of the recording contained instructions for relaxation based mainly on mental imagery and other cognitions (16 minutes).

Visit 2 (day 21) Twenty-one days later, subjects returned to the Unit and their health diary, mood rating scales, diet sheet and urine samples were collected. A venflon was inserted and subjects were then asked to complete in sequence various tests and questionnaires. Physiological measurements were again taken. Subjects in the experimental group then listened to an audio cassette recording, which lasted 12.5 minutes. The

hypnotic induction used at the first visit was repeated and, thereafter, subjects were told that, during the procedure that was to follow, they would continue to feel relaxed and at ease. Control subjects spent the equivalent length of time sitting and reading quietly. In pairs, subjects were then exposed to the experimental stressor, namely two doctor-patient role plays, which were recorded on video and then played back with feedback. Each subject did two role plays, one as the doctor and another as the patient. Prior to playing the latter role, subjects were given a written brief of the patient's presenting problems.

Immediately following the role-play, further psychological tests were carried out, blood was taken and physiological parameters assessed. Each subject was then given a diet sheet and a container for an early morning urine sample to be used on the day of visit three.

Visit 3 (day 22 or 23) The third visit took place either 24 or 48 hours later (day 22 or 23). Documentation and urine samples were collected and a venflon inserted. Subjects then completed various psychological tests. Physiological parameters were assessed and, thereafter, a venous sample of blood was removed.

Immunological and Biochemical Assessments

Mitogen response to Phytohaemagglutinin (PHA) was assessed at four concentrations of PHA (0.25, 1, 4 and 16 μg ml^{-1}) using tritiated thymidine uptake, measured in duplicate, in a beta counter and expressed as counts per minute (cpm). Natural killer (NK) cell activity was assessed using ^{51}Chromium release. A standard target cell line was used (K562) from a chronic myelogenous leukemia line. Radioactivity was measured in a γ-counter using standard techniques at four effector:target cell ratios (5:1, 10:1, 20:1 and 40:1). Interleukin 1 (IL-1) and γ-interferon concentrations were assessed using ELISA methods. Immunoglobulin A (IgA) was measured using a turbidometric immunoassay. Urinary free cortisol (UFC) concentrations were measured by specific radio-immunoassay and the results were expressed as nmol/mmol of urinary creatinine, a measure independent of urinary flow rate. Thyroxine (T_4) was assessed by immunoassay using a specific monoclonal antibody; Prostaglandin E_2 (PGE_2) was also measured by immunoassay (Biotrack, Amersham International).

Physiological Assessments

With subjects seated, systolic and diastolic blood pressure (BP) were assessed using a Takeda Medical Digital Blood Pressure Meter (UA-751).

Psychological Assessments

At Visit 1, subjects completed the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975), the Courtauld Emotional Control Scale (CECS) (Watson & Greer 1983), the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) and the Creative Imagination Scale (Wilson & Barber, 1978). At Visit 2 (pre-stress) and at Visit 3 the Profile of Mood States (Bipolar version) (Lorr & McNair, 1984) was administered. Before and after exposure to the stressor at Visit 2, the subjects completed an *ad hoc* Mood Rating Scale MRS (six visual analogue scales (relaxation, happiness, energy, confusion, easy-goingness and confidence) each of which has five defined anchor points).

Subjects

Twenty-four healthy volunteers, all of whom were members or students of the helping

professions, were recruited and randomized. Inclusion criteria were as follows: male or female, aged 18–65 years, willing to accept venous catheterization, and able to attend in the evening. Exclusion criteria were: suffering from acute or chronic illness likely to affect the immune response, a history of major psychiatric illness (e.g., schizophrenia), currently suffering from clinically significant anxiety or depression, currently taking medication known to affect the immune system (except an occasional analgesic or oral contraceptive), and a clinically significant result on biochemical screening. Data for at least three of the four time points were available for 20 subjects (10 experimental and 10 control). Statistical analysis showed that the two groups were well matched in terms of age, gender ratio, hypnotizability (CIS), personality (EPQ, CECS) and mood (HADS).

Statistical Analysis

Due to the relatively small sample size, and the markedly non-normal distribution of some of the immunological parameters, the data were analysed using non-parametric methods. Between-group comparisons were carried out with the Mann-Whitney U-test and within-group comparisons by means of the Wilcoxon Matched Pairs Signed Rank test. Kendall's correlation coefficient (τ) was used. Alpha was set at 0.05 (two-tailed). Data were analysed using SPSS MS for Windows.

RESULTS

Changes induced by relaxation and the stressor

The medians and ranges for the two groups for most of the parameters studied are shown in Table 1. Statistically significant within-group changes, and their direction, are shown in the extreme right hand column.

Immunology Although none of the between-group differences at any of the four time points studied were statistically significant, a number of significant within-group differences were observed for IL-1β, PHA, NK activity and IgA (Table 1).

Biochemistry Volunteers in the experimental group had higher PGE_2 levels than control subjects at trial entry ($z = 2.08$, $P<0.04$). Additional between group analyses, even after adjusting for baseline differences, revealed no further differences, and no significant within-group differences were obtained for this or the other biochemical parameters.

Physiology There were no significant between-group differences in blood pressure. However, the pattern of within-group changes was different for the two groups (Table 1). For example, only volunteers in the experimental group showed a reduction in diastolic BP 24–48 hours post-stress.

Psychology Following relaxation training (Visit 2 pre-stress), experimental subjects, but not control subjects, scored lower on HADS anxiety than at Visit 1.

The POMS bipolar was administered at Visit 2 (pre-stress) and at Visit 3 (not shown in Table 1). At Visit 2, experimental subjects were more composed ($z = 2.14$, $P < 0.03$) and clearheaded ($z = 1.99$, $P < 0.05$) than control subjects. At Visit 3, between-group comparisons of the six POMS variables revealed that the experimental subjects were significantly more elated ($z = 2.22$, $P < 0.03$), more confident ($z = 1.97$, $P < 0.05$), more clearheaded ($z = 2.33$, $P < 0.02$) and more energetic ($z = 2.33$, $P < 0.02$) than control subjects. At Visit 3, experimental subjects were more clearheaded ($z = 2.14$, $P < 0.03$) and more composed ($z = 1.99$, $P < 0.05$) than they had been at Visit 2.

Table 1. Medians (and ranges) for the experimental and control groups.

	(1) Day 0	(2) Day 21 (pre-stress)	(3) Day 21 (post-stress)	(4) Day 22 or 23	Significant within group differences
EXPERIMENTAL GROUP					
Immunology					
IL-1β (pg/ml)	2.8 (0.0-4.6)	2.0 (0.0-3.5)	2.9 (0-4.1)	3.2 (2.0-6.1)	(1)>(2),(2)<(3),(2)<(4),(3)<(4)
PHA (cpm @ 2 μg/ml)	29615 (5186-127097)	15252 (53-29502)	22307 (38-73873)	28199 (197-102366)	(1)>(2),(2)<(3),(2)<(4)
NK 10:1 (% Cr release)	14.1 (5.4-46.8)	11.0 (5.4-23.2)	14.2 (4.7-27.7)	9.9 (5.7-20.0)	(2)>(4)
20:1 (% Cr release)	19.1 (7.0-54.7)	19.2 (5.5-42.7)	21.8 (5.9-44.9)	16.4 (5.7-37.7)	
IgA (g/l)	1.6 (0.5-2.0)	1.5 (0.5-2.8)	1.5 (0.6-2.9)	1.4 (0.5-2.7)	(3)>(4),(1)>(2)
Biochemistry					
T4 (nmol/l)	97 (69-113)	93 (67-190)	98 (73-249)	103 (68-71)	
UFC (nmol/mmol)	11 (5-19)	9 (3-41)	-	11 (5-15)	
PGE_2 (ng/mmol)	30 (8-93)	17 (5-74)	-	31 (6-91)	
Physiology					
Systolic BP (mm/Hg)	122 (96-145)	112 (90-164)	116 (101-161)	109 (92-139)	(1)>(4)
Diastolic BP (mm/Hg)	78 (66-99)	76 (60-92)	85 (64-96)	74 (64-95)	(1)>(4),(2)<(3),(3)>(4)
Psychology					
HADS-depression	3 (0-5)	2 (0-6)	-	-	
HADS-anxiety	6 (5-10)	5 (4-8)	-	-	(1)>(2)
CONTROL GROUP					
Immunology					
IL-1β (pg/ml)	2.2 (0.2-3.4)	1.4 (0.0-6.5)	3.0 (0.2-5.5)	3.9 (0.4-5.0)	(1)<(4)
PHA (cpm @ 2 μg/ml)	34408 (10938-80186)	20977 (4779-58364)	31402 (2104-57112)	13289 (4989-54001)	(1)>(2),(1)>(3),(1)>(4)
NK 10:1 (% Cr release)	15.1 (8.5-24.3)	15.5 (7.5-22.7)	13.4 (6.5-39.6)	12.15 (5.9-27.2)	
20:1 (% Cr release)	26.0 (11.1-41.2)	20.1 (10.7-34.8)	24.3 (8.7-51.8)	19.9 (8.4-44.4)	(1)>(2)
IgA (g/l)	1.3 (0.6-1.9)	1.2 (0.6-1.8)	1.4 (0.7-2.0)	1.2 (0.6-1.7)	(2)<(3),(3)>(4)
Biochemistry					
T4 (nmol/l)	107 (75-215)	100 (65-145)	87 (70-169)	103 (66-188)	
UFC (ng/mmol)	10 (2-24)	20 (3-53)	-	12 (7-27)	
PGE_2 (ng/mmol)	10 (5-97)	12 (3-85)	-	23 (3-83)	
Physiology					
Systolic BP (mm/Hg)	120 (108-150)	119 (108-144)	120 (110-136)	112 (105-132)	(1)>(4),(3)>(4)
Diastolic BP (mm/Hg)	79 (70-102)	76 (69-86)	84 (67-97)	74 (66-87)	
Psychology					
HADS-depression	1 (1-5)	2.5 (1-9)	-	-	(2)>(1)
HADS-anxiety	5 (3-15)	5 (2-15)	-	-	

The MRS was administered before and after exposure to the stressor at Visit 2 and again at Visit 3. Compared with the control subjects, the experimental subjects were more relaxed than control subjects immediately before being stressed ($z = 2.23$, $P < 0.03$)

The Health Diaries revealed that, during each of the first 3 weeks of the study, there were no significant differences between the two groups in the number of hours of exercise or hours slept. However, the control subjects drank significantly more units of alcohol than the experimental subjects during the first week of the study ($z = 2.35$, $P < 0.02$).

Changes related to hypnotizability (CIS scores)

During the first 3 weeks of the study, the extent to which IgA levels increased was positively correlated to CIS scores only in the experimental group (Figure 1).

Immediately after exposure to the stressor, a positive correlation between IL-1 β levels and CIS scores were observed for the experimental subjects ($\tau = 0.571$, $P < 0.04$) and a negative correlation was obtained for control subjects ($\tau = -0.551$, $P < 0.04$) (Figure 2).

DISCUSSION

Despite the demands made on the volunteers, compliance with study procedures was good. Twenty of the 24 volunteers satisfactorily completed the study. Apart from the recordings made in their health diaries, there is reason to believe that the subjects in

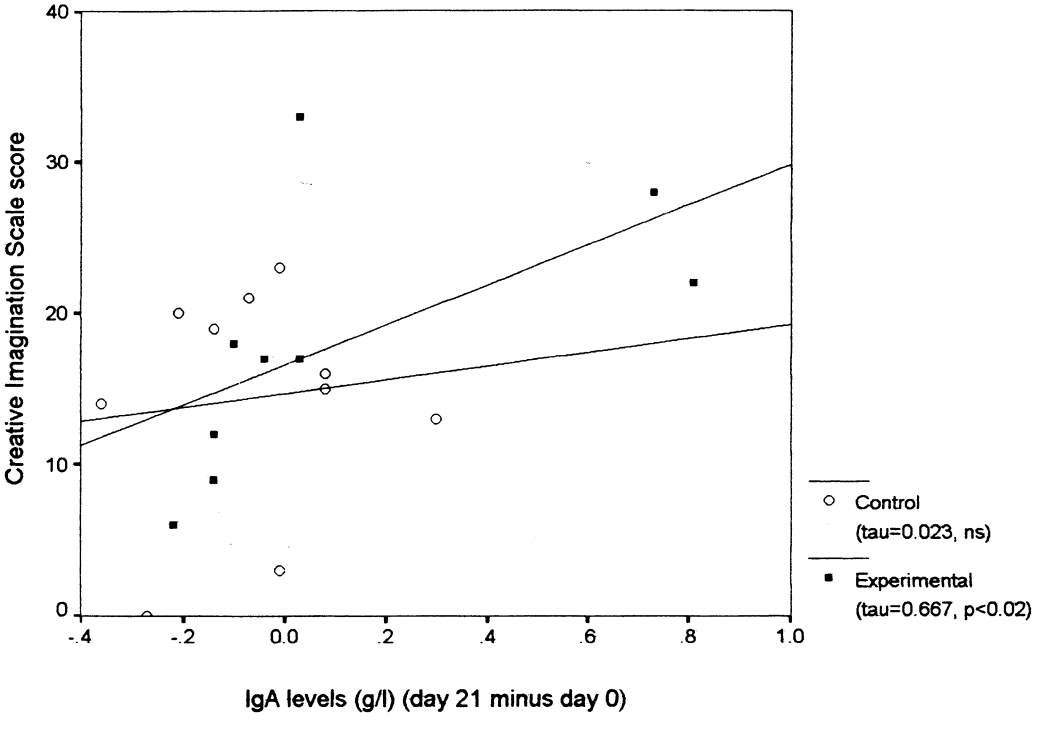

Figure 1. Changes in IgA following relaxation training.

the experimental group did practise the relaxation exercises. The anxiolytic effects of relaxation therapy are well known: following relaxation training for 3 weeks, experimental subjects were less anxious as measured by the HADS whereas this was not the case for control subjects who actually scored significantly higher on HADS depression at Visit 2. Moreover, subjects in the experimental group were significantly more relaxed (MRS) prior to exposure to the stressor.

Effects of relaxation

IL-1 β levels fell significantly between day 0 and day 21 in the experimental group only. This suggests that relaxation training for 3 weeks reduces secretion of this key cytokine. In both groups, mitogen response to PHA fell significantly during the first 3 weeks of the study. Although not statistically significant, this reduction was more marked in the experimental subjects for whom the reduction was statistically significant for all four concentrations of PHA (cf. only one significant result in the control group). At Visit 2, control subjects, but not experimental subjects, showed lower NK cell activity; this is consistent with the findings of Kiecolt Glaser, Glaser, Williger *et al*, (1985) who found an increase in NK cell activity in geriatric residents who learned relaxation techniques. Following relaxation training, IgA levels (an important component of host defences) were increased significantly only in the experimental group.

On day 21, a between-group analysis showed that the experimental subjects were significantly more composed and more clear-headed than control subjects. This suggests that even 3 weeks of relaxation training can produce significant changes in mood. This is further supported by the reduced anxiety on day 21 observed only in the experimental group.

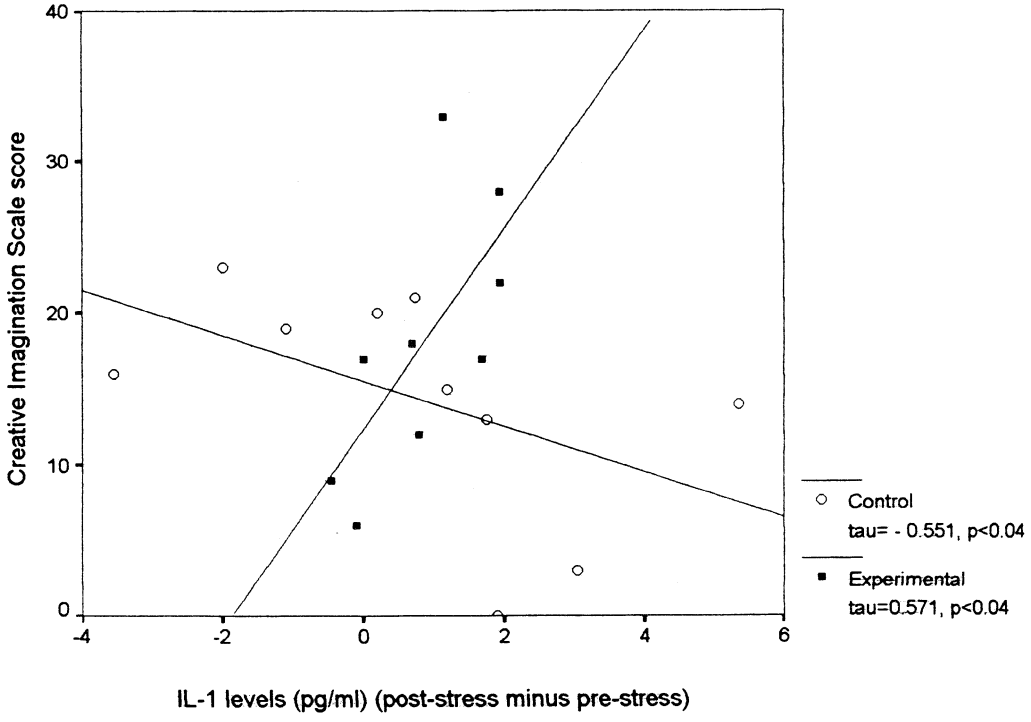

Figure 2. Modulation of IL-1 levels in response to stress.

Modulation of response to stress by relaxation and hypnotic induction

On exposure to the stressor, previous relaxation training and hypnotic suggestion led to increased lymphocyte responsiveness to PHA, both immediately and 24–48 hours later. This is in marked contrast to control subjects whose responsiveness was significantly reduced at both these time-points compared with trial entry. Similarly, only experimental subjects showed a significant increase in IL-1 β immediately after stressing and 24–48 hours later.

The experimental procedure (relaxation training and hypnotic induction at Visit 2) appeared to modulate the effects of the stressor on mood. At Visit 3, experimental subjects were significantly more elated, more confident, more clear-headed and more energetic than control subjects. Also at Visit 3, experimental subjects were more clear-headed and more composed than they had been at Visit 2.

Despite the fact that all subjects were healthy, experimental subjects showed significantly lower diastolic blood pressure at Visit 3 compared with Visit 1. The control subjects did not show any significant changes in this parameter during the study.

Relevance of Hypnotizability

Creative Imagination Scale (CIS) scores moderated the effects of 3 weeks' relaxation practice: when IgA concentrations at day 21 (before exposure to the stressor) were subtracted from concentrations on day 0, a positive correlation with CIS scores was obtained for subjects in the relaxation group but not the control group (Figure 1). In a randomized study with children, Olness, Culbert and Uden (1989) found that self-hypnosis with specific suggestions to enhance salivary immunoglobulin led to an increase in IgA. However, in their study, hypnotizability was unrelated to changes in IgA.

When levels of IL-1 obtained immediately after exposure to the stressor were subtracted from immediate pre-exposure levels, these change scores were positively correlated with CIS scores in the experimental group and negatively in the control group (Figure 2). IL-1 is thought to play a fundamentally important role in the modulation of psychoneuroimmunological processes (Black *et al.*, 1994b). To the best of our knowledge, this is the first time that stress induced changes in IL-1 have been related to hypnotizability.

These findings indicate that hypnotizability, as assessed by the CIS, may be an important moderator of the psychoneuroimmunological response to relaxation training and exposure to an acute stressor.

Although this study was considerably larger than a number of those previously reviewed (Walker *et al.*, 1993), some of the immunological parameters show considerable variability. Accordingly, for these variables, the study would have benefited from more subjects. This may have produced more significant between-group differences. Another limitation is the number of comparisons which were made. This increases the risk of a Type I error (that is, rejecting the null hypothesis when it is true). However, given the sample size and variability of the data, setting a more stringent criterion of significance by adjusting the level of alpha would have greatly increased the probability of a Type II error. The findings should be interpreted with these considerations in mind.

The diagnosis and treatment of cancer are stressful experiences and stress may impair host defences in a way that is significant in patients with malignant disease. Increased understanding of the effects of such interventions in healthy subjects could ultimately prove useful in the management of cancer patients and further large-scale studies would be helpful.

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