

# Psycho-oncology and cancer: linking psychosocial factors with cancer development

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## Introduction

The enthusiasm for the hypothesis that psychosocial factors might have an influence on disease initiation and progression in cancer has been waxing and waning. At present, there is a need to stand still for a while to think about the design of future studies to more effectively test this hypothesis, especially with the knowledge that many studies in the past have yielded negative findings.

The conclusions of an overview of studies in this field will be presented. This overview is restricted to truly prospective studies with adequate design and enough subjects to draw conclusions [1; Garssen B, in preparation]. Seventy-one of such studies have been found; 29 studies focused on breast cancer and the remaining 42 studies were concerned with other types of cancer, several types of cancer or mixed groups. Twenty-one studies investigated the role of psychological variables in the initiation of cancer, while the possible effect of psychological variables on progression of cancer was investigated in 50 studies.

Truly prospective, longitudinal studies on cancer initiation start with healthy people who are given a psychological assessment and are then followed for many years to see who develops cancer and who does not, or who dies of cancer, who is still alive without having cancer and who dies of other causes. Studies on cancer progression start with people who have or have had cancer. These patients are psychologically assessed, often in the period of diagnosis and medical treatment, and then followed-up over a period of months or years. The outcome measure is often a recurrence of cancer after a disease free interval, or it is survival time, i.e. the time from assessment to death.

The reason for only focusing on studies with a truly prospective, longitudinal design is that other designs, especially cross-sectional and group comparison studies, leave us with uncertainty about what cause and effect are. It is theoretically possible that the development of a still unnoticed tumour induces psychological changes, which are then incorrectly considered as causal factors for cancer development. This alternative explanation is, however, not very probable given an interval of years between psychological assessment and assessment of disease outcome, as is applied in longitudinal studies.

An alternative design is followed in so-called 'pseudo prospective studies'. In this design, psychological data are gathered prior to diagnosis, which are then related to the diagnostic outcome obtained (some days or weeks) later, which is often one of three outcomes: cancer, no cancer or benign tumour. These studies are useful in yielding supportive evidence, but are suspect in their design. Schwarz and Geyer [2] demonstrated that many patients somehow know their diagnosis before being told by the doctor. The patient's own assumption about diagnosis often appeared to be correct. This applied to persons who later appeared to have cancer, 65% of whom correctly predicted their diagnosis, and to those who later appeared to be cancer-free, 77% of whom correctly predicted not having cancer. The apparently often accurate assumption of a patient that he or she has cancer may be associated with negative emotions, which is a serious problem when negative emotions, psychological problems or associated concepts, such as hopelessness, are chosen as predicting factors. Thus, a semi-prospective design does not sufficiently protect against drawing the wrong conclusions about cause-effect relationships.

Several excellent reviews have been published on this subject. However, some reviews did not make a clear distinction between truly prospective studies on the one hand, and group comparison, cross-sectional or semi-prospective studies on the other. Other reviews discuss only one specific factor [3, 4] and four other reviews are restricted to the role of psychological factors in the initiation of breast cancer [5–8]. These reviews, along with others [9–11], summarise only a limited number of prospective studies. This review concerns the following domains: (i) stressful life events; (ii) social relationships; (iii) locus of control and personality factors; (iv) coping and adjustment to illness; (v) negative emotional states; (vi) psychiatric diagnoses; and (vii) repression of negative emotions. These domains are primarily chosen because they cover the areas discussed as possible risk factors for cancer in the psycho-oncological literature.

## Review of studies on the role of psychological factors

### Life events

In this line of research, the number of experienced life events over a certain time period before the time of assessment, for instance in the previous 6 months, is determined and related to later disease progression. One study demonstrated a relationship between severity of life stress and disease-free interval or survival. Five other studies, however, failed to find any association between stressful life events and relapse and survival.

The role of adverse life events as a risk factor has been summarised in a meta-analysis of 15 studies [7]. Before considering these findings, one should realise that this meta-analysis is restricted to breast cancer studies and deals with the role of life events in the initiation of cancer, rather than the course of cancer, as is the case in the studies mentioned above. Moreover, this meta-analysis concerns group comparison and semi-prospective studies which yield less reliable findings than the longitudinal prospective studies, as discussed above. It was found that breast cancer patients reported adverse life events more than twice as often as control subjects. However, if the analysis was restricted to what the authors considered the five highest quality studies, no significant effect was found.

### Social support

Various measures of social support predicted disease progression in five studies, while some indication for the role of support was found in two additional studies. More social support was associated with lower cancer incidence and mortality, and longer disease-free interval and survival. However, five other studies found no such association.

The most impressive study in this area is a Canadian study by Maunsell et al. [12]. They asked 224 women with newly diagnosed breast cancer in an interview whether they had a confidant with whom they had discussed personal problems in the 3 months since surgery. Women were followed with respect to survival data for up to 7 years. Survival rate in women without a confidant and for women who had had at least one type of confidant was 56% and 72%, respectively. Thus the clinical relevance of the social support factor seemed considerable.

A problem with some of these studies is the use of many measures for social support, without predicting in advance which measure would be most strongly related to disease progression.

### Personality/locus of control

Personality is related to many behavioural and biological factors and is stable over time. For these reasons personality is often studied as a potential risk factor for disease, especially type A behaviour as a predictor for coronary heart disease, and may also be of influence on cancer development. Locus of

control is examined in cancer studies more often than any other personality factor. Experiencing control over a stressful situation is a major determinant of the impact of the situation, and one may expect that the possible effect on cancer development of negative factors is dampened in people with an internal locus of control.

Six studies investigated the role of personality, such as introversion and extroversion or neuroticism. Three studies found some indication for a relationship, though for different personality measures. One study found that extroversion was associated with longer survival and the second study demonstrated that a reserved personality was a risk factor for early cancer death. The third study found no effect of type A behaviour on lung cancer mortality, while an increased risk was demonstrated in other types of cancer. Special attention was paid to alcohol use, as this may be a risk factor for some types of cancer, and is possibly associated with type A behaviour. The cancer mortality effect appeared to have occurred mainly in the subgroup of alcohol-related cancers.

Five studies focused on locus of control, which indicates whether a person feels that he or she can influence most situations, or whether most situations in life are experienced as determined by fate, God or powerful others. Of the five studies investigating the role of locus of control, only one found some indication for a relationship. Taken together, personality factors, and especially locus of control, do not seem to play an important role.

### Coping/adjustment

The findings of Greer et al. [13] with the Mental Adjustment to Cancer Interview have been promising. At 15 years follow-up they found longer survival in women with breast cancer who initially reacted with fighting spirit or denial, as opposed to women reacting with helplessness/hopelessness or stoic acceptance. The findings of this study have reached the general public: fighting spirit has become a popular term, and almost a norm to pursue. However, these findings have not been replicated in many other studies (Table 1). For instance, three other studies could not demonstrate a positive relationship between responding to the diagnosis of cancer with fighting spirit and longer survival, and one study even found an opposite relationship. However, one finding still holds: a response style of helplessness and hopelessness, or pessimism is associated with an unfavourable course of the disease in most studies (six of nine studies). Remarkably, most studies also found that denying or minimising the impact of the disease was associated with a favourable prognosis (four of the five studies).

Persons with an active coping style lived longer in one study, but this finding was not confirmed in five other studies.

In general, there is no good evidence that coping style or the way one adjusts to the disease is related to cancer progression, except for the tendency to respond with denial, pessimism or helplessness.

**Table 1.** Number of studies demonstrating a positive or negative relationship, or no relationship with disease-free interval and survival

Factor	Positive relationship	No relationship	Negative relationship
Fighting spirit	2	3	1
Denial/minimising	4	1	0
Stoic acceptance/fatalism	1	3	1
Helplessness/hopelessness/pessimism	1	2	6

### Negative emotional states/psychiatric symptoms

The relationship with distress level (anxiety and/or depression) or psychiatric complaints has been investigated in 45 studies with divergent outcomes. The overwhelming impression of these studies, however, is the absence of a relationship (found in 21 studies). So, there seems no good evidence that distress levels or psychiatric symptoms are in themselves important with respect to cancer initiation or progression.

This might seem in contradiction to what was said earlier with respect to the tendency towards helplessness. However, these concepts are theoretically and factually independent. When there is every reason to feel anxious and depressed from time to time, especially during the period of diagnosis and medical treatment and when experiencing distressing symptoms, expressing these feelings may be very adequate, instead of being indicative of response style of helplessness.

### Psychiatric diagnoses

Most of the studies discussed above used a continuous measure in the form of a sumscore to a distress questionnaire. A psychiatric diagnosis is a qualitatively different measure, which may have another relationship with disease outcome than distress. To evaluate whether this distinction would change the conclusions, the next analysis is limited to studies that determined psychiatric 'caseness' by means of a psychiatric interview, or by using a cut-off score on a validated psychological problems scale, sufficiently high to include most psychiatric cases. With respect to course of cancer, a positive relationship (being a psychiatric case predicts longer survival) was found in one study, a negative relationship in three studies and no relationship in two other studies. With respect to cancer initiation, a negative relationship was found in four studies, while no relationship could be demonstrated in four other studies.

To summarise, six of the 14 studies on psychiatric caseness could not demonstrate a relationship, and the evidence seems too weak to support the suggestion that being a psychiatric case has an effect on the initiation and development of cancer. However, the finding of one remarkable study warns against a rejection of this suggestion too easily. Chronic depression was defined in this study [14] as scoring above a cut-off value on a depression questionnaire on three separate occasions over a 6 year period. The authors did not find a relationship with depression if a single measurement was used. However,

long-lasting depression, determined over a 6 year period, predicted later cancer development. Therefore, as all other studies used single measurements, we are still uncertain about the role of chronic depression.

### Repression

It has been suggested that many cancer patients are characterised by emotional non-expression (repression), especially with respect to anger and other dysphoric emotions, and by the tendency to present to the world a facade of contentment. A direct and valid measure of repression is the combination of low reported anxiety combined with high defensiveness. Using this measure, the expected relationship with cancer progression was demonstrated in two studies: repressors had an unfavourable prognosis. Instead of using a combination of two questionnaires, one for anxiety and one for defensiveness, the next series of studies measured 'emotional repression' or 'emotional control' with single questionnaires or an interview. More expression and less suppression of emotions predicted longer survival in one study. However, three other studies found no association between repression and relapse and survival. 'Cognitive avoidance' and 'having a reserved personality' are conceptually related to repression of negative emotions, and these measures appeared also to be related to an unfavourable course of disease. So the role of repression in cancer progression is demonstrated in five of these eight studies.

The role of repression is, however, questionable with respect to the initiation of cancer: more repression was related to later development of cancer in one study, but not in three other studies.

### Discussion and conclusions about the role of psychological factors

Fifty-three (75%) of the 71 studies showed an association between psychological variables and disease outcome. One might consider the number of positive studies promising, but the problem is that a relationship found in one study for a particular psychological variable was not systematically confirmed in other studies. In fact, there is no psychological factor whatsoever for which an influence on the initiation or progression of cancer has been convincingly demonstrated in a series of studies. Some evidence has been found for a role of lack of social support, denial, the tendency towards helplessness and

repression of negative feelings. Even the role of these factors is not beyond doubt. These meagre findings force us to wonder whether the role of psychological factors is very modest or even non-existent, or whether inadequate research methods have been used.

One important question is whether psychological factors are only active in some types of cancer, or in some stages of the disease. In trying to answer these questions, the number of studies finding a relationship between psychological factors and disease progression was counted and divided by the total number of studies. In breast cancer, 62% of the studies on non-metastatic disease showed a relationship. This number was 83% in metastatic breast cancer. So, stage of the disease seemed not an important factor; at least not in the case of breast cancer. Slightly more evidence has been found for effects of psychological factors on progression of cancer, rather than on cancer initiation: 76% of the studies on cancer progression showed a relationship, compared to 71% for studies on cancer initiation.

It is sometimes suggested that types of cancer with poor prognosis, such as lung cancer, may be less adequate for studying the possible effects of psychological factors. Medical prognostic factors may be so prominent in these types of cancer, that there is no role for psychological factors. On the other hand, some types of cancer may be preferred in this field of study, because they are sensitive to hormonal and immunological factors, and may be influenced via the neuro-hormonal-immunological pathway by psychological factors. Cancers that fall into this category include breast cancer, malignant melanoma and virally-induced cancers, such as cancer of the cervix.

In proportion to the total number of studies, the number of studies that found a relationship for different cancer types is as follows: breast cancer, 73%; malignant melanoma, 75%; haematological malignancies, 67% and lung cancer, 75%. Given the small number of studies on types of cancer other than breast cancer, one can only conclude that no remarkable differences are found for these types of cancer. That is to say, the expected substantial difference between breast cancer and malignant melanoma on the one hand, and lung cancer on the other, was not found.

Probably the most important reason for not finding a relationship is not having studied interactive effects. Instead of concentrating on one factor at a time, the interaction between several factors should be studied. This may be decisive for the conclusions drawn. An interactive effect was in fact demonstrated in five studies. In the first study, depression predicted cancer mortality in men, but not in women [15]. The second study found that number of social ties and experienced social isolation was related to cancer incidence and mortality from cancer in women, but not in men [16]. In the third study the largest effect of bereavement on cancer incidence was found in the youngest group of widowers, while being absent in the oldest group [17]. The fourth study found no direct effect for pessimism on death from cancer. However, there was an effect

of pessimism, depending on age. In the younger group pessimism was predictive for later mortality, while such an effect did not occur in the older group [18]. The last study found an effect of both social support and emotional expression on survival, but the effect of lack of emotional expression was strongest if social support levels were low [19].

Medical factors have often been treated as confounding variables, which are 'controlled away'. However, one should also study the possibility of interactive effects of medical and psychological factors. There are several examples of study findings showing that medical risk factors increased or decreased the influence of psychological variables. Degree of adjustment had an effect on cancer progression in a subgroup of malignant melanoma patients with relatively few positive lymph nodes, but not in patients with many positive nodes [20]. In the presence of receptors for estrogen and/or progesterone, life events were related to recurrence in women with breast cancer, while such a relationship did not occur in women with receptor negative breast cancer [21]. The effect of depression on development of cancer was only seen in heavy smokers [22, 23]. Relationships with psychosocial variables were found in patients with breast cancer, but not in patients with colorectal or lung cancer; and were found in patients with localised cancer, but not in patients with more advanced cancer [24]. The effect of 'stress' on death from lung cancer was much larger in the presence of other risk factors, such as cigarette smoking, than in their absence [25].

It is not certain whether these specific interactive effects will hold in new studies. There is, however, enough evidence to assume that the role of psychological factors has not been adequately studied until now.

## References

1. Garssen B, Goodkin K. On the role of immunological factors as mediators between psychological factors and cancer progression. *Psychiatry Res* 1999; 85: 51–61.
2. Schwarz R, Geyer S. Social and psychological differences between cancer and noncancer patients: cause or consequence of the disease. *Psychother Psychosom* 1984; 41: 195–199.
3. Sanderman R, Ranchor AV. The predictor status of personality variables: etiological significance and their role in the course of disease. *Eur J Personality* 1997; 11: 359–382.
4. Denollet J. Personality and cancer. *Curr Opin Psychiatry* 1999; 12: 743–748.
5. McGee R, Williams S, Elwood M. Are life events related to the onset of breast cancer? *Psychol Med* 1996; 26: 441–447.
6. Bleiker EMA, van der Ploeg HM. Psychosocial factors in the etiology of breast cancer: review of a popular link. *Patient Educ Couns* 1999; 37: 201–214.
7. Petticrew M, Fraser JM, Regan MF. Adverse life-events and risk of breast cancer: a meta-analysis. *Br J Health Psychol* 1999; 4: 1–17.
8. Butow PN, Hiller JE, Price MA et al. Epidemiological evidence for a relationship between life events, coping style, and personality factors in the development of breast cancer. *J Psychosom Res* 2000; 49: 169–181.

9. Cwikel JG, Behar LC, Zabora JR. Psychosocial factors that affect the survival of adult cancer patients: a review of research. *J Psychosoc Oncol* 1997; 15: 1–34.
10. Faller H. Beeinflussen psychologische Faktoren die Überlebenszeit bei Krebskranken? Teil 1: Literaturübersicht. *Psychother Psychosom Med Psychol* 1997; 47: 163–169.
11. De Boer MF, Ryckman RM, Pruyt JFA, Van den Borne HW. Psychosocial correlates of cancer relapse and survival: a literature review. *Patient Educ Couns* 1999; 37: 215–230.
12. Maunsell E, Brisson J, Deschenes L. Social support and survival among women with breast cancer. *Cancer* 1995; 76: 631–637.
13. Greer S, Morris T, Pettingale KW, Haybittle JL. Psychological response to breast cancer and 15-year outcome. *Lancet* 1990; 335: 49–50.
14. Penninx BWJH, Guralnik JM, Pahor M et al. Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst* 1998; 90: 1888–1893.
15. Whitlock FA, Siskind M. Depression and cancer: a follow-up study. *Psychol Med* 1979; 9: 747–752.
16. Reynolds P, Kaplan GA. Social connections and risk for cancer: prospective evidence from the Alameda County study. *Behav Med* 1990; 16: 101–110.
17. Martikainen P, Valkonen T. Mortality after the death of a spouse: rates and causes of death in a large Finnish cohort. *Am J Public Health* 1996; 86: 1087–1093.
18. Schulz R, Bookwala J, Knapp JE et al. Pessimism, age, and cancer mortality. *Psychol Aging* 1996; 11: 304–309.
19. Reynolds P, Hurley S, Torres M et al. Use of coping strategies and breast cancer survival: results from the Black/White Cancer Survival Study. *Am J Epidemiol* 2000; 152: 940–949.
20. Rogentine GN, Kammen DPV, Fox BH et al. Psychological factors in the prognosis of malignant melanoma: a prospective study. *Psychosom Med* 1979; 41: 647–655.
21. Ramirez AJ, Richards MA, Gregory W, Craig TKJ. Psychological correlates of hormone receptor status in breast cancer. *Lancet* 1990; 335: 1408.
22. Linkins RW, Comstock GW. Depressed mood and the development of cancer. *Am J Epidemiol* 1990; 132: 962–972.
23. Knekt P, Raitasalo R, Heliovaara M et al. Elevated lung cancer risk among persons with depressed mood. *Am J Epidemiol* 1996; 144: 1096–1103.
24. Ell K, Nishimoto R, Mediansky L et al. Social relations, social support and survival among patients with cancer. *J Psychosom Res* 1992; 36: 531–541.
25. Eysenck HJ. Synergistic interaction between psychosocial and physical factors in the causation of lung cancer. In Lewis CE, O'Sullivan C, Barraclough J (eds): *The Psychoimmunology of Cancer. Mind and body in the fight for survival*. Oxford: Oxford Medical Publications 1994; 163–178.