The Role of Psychological Factors in Cancer Incidence and Prognosis

By Bernard H. Fox, PhD [3]

The relationships between psychological variables and the presence of cancer, its prediction, and the prediction of cancer mortality and course of disease have been studied extensively. From a limited list of about 50 such

Introduction

This article reviews the literature regarding the possible effects of various psychological factors on cancer incidence and prognosis. For a clear understanding of the findings in the literature, a number of terms need to be defined. The term "psychological factors" refers to personality or behavior traits or reactions. In studies of psychological factors and cancer, these are the independent variables, with one restriction: If a psychological factor is associated with a physical carcinogen, it will not be considered an acceptable independent variable, although it may be regarded as a possible confounder. For example, it is claimed that certain traits predispose a person to smoking. Those traits will not be of interest insofar as they affect smoking and its carcinogenic consequences, but only insofar as they may affect cancer independently of smoking.

The dependent variables are cancer incidence, mortality, and prognosis (disease-free interval and survival time). Possible confounders, cofactors, or primary etiologic agents that may act in conjunction with psychological factors include familiar factors such as radiation, genetic attributes, viruses, smoking, and exposure to chemicals, as well as some less familiar factors. Incidence of cancer is determined in two ways, either by clinical diagnosis or at autopsy. In both cases, the malignancy has had to grow to the point of detection. That is, if it is a blood or lymphatic cancer, enough cells have been transformed to be detected, and if a solid tumor, it has grown large enough to be detected by x-ray, palpation, sonogram, visualization, or some other method. The first actual mutation of a cell to malignancy, however, has taken place long before—in rare cases months before, and in most cases years before [1,2]. For example, the median time to detection of leukemia incidence after the atomic bomb was dropped on Hiroshima was between 6 and 7 years [3]. The estimated median growth time to detection for breast cancer is 7 to 11 years, depending on the researchers [1,4]. According to Steel [1], in a mix of several cancers, with lung heavily represented, the median was about 5.5 years. Thus, all incidence statistics are a combination of the first mutation of a cell to cancer and the progression of that cancer to detectable size.

Another issue is type of study. The two classic types of epidemiologic studies are case-control, sometimes called retrospective, and cohort, sometimes called prospective. In case-control studies, a group of cancer patients, cancer survivors, or patients with recurrence is selected, together with a control group, and the researcher measures some putatively discriminating attribute in both groups to see whether they differ in respect to that attribute. In cohort studies, an attribute is measured in all members of the cohort before the outcome of disease, death, or recurrence, and the researcher waits to see who gets cancer or not, survives or not, or suffers a recurrence or not. The pair of groups being tested is examined for differences in outcome that may have emerged, given the existence of differences in the attributes originally measured. For example, if the pair of groups in the population is defined as "those who are stressed" and "those not stressed," the risk factor is the condition of being stressed, and the control condition is not being stressed. The proportion who get cancer during the given follow-up period in the group with the risk factor is compared with the proportion who get cancer during this period in the group without the risk factor.

This distinction between types of study is important, because the case-control type, when used only on a sample and not the population, is subject to a number of possible biases. Such potential biases make it difficult to decide which case-control studies to accept, doubt, or reject. Cohort studies, which are also subject to some biases, but not nearly so many or so damaging as those.
characterizing many case-control studies, are more trustworthy and involve less risk of a false conclusion.

**The Variety of Psychosocial Factors**

A variety of psychosocial factors have been used as independent variables in the past. These include not only directly measured variables but also those inferred from results on an instrument that provides an indirect measure (e.g., the Rorschach test). In most case-control studies, the authors imply that because they found a relationship, the factor existed before the tumor was discovered, and they seldom remark on whether it existed before malignant transformation. The analyst is left hanging in the air because the researchers had not learned enough about the disease to know the meaning or implication of their finding. The Table lists a number of psychosocial factors (with the most important items discussed below). Each of them has been examined at least once as a risk factor in some study in the literature (see Fox [4] for a bibliography). Very few mention the possibility that the factor, e.g., depression or suppression of emotions, may have arisen from the biologic effects of the cancer itself or from the patient's knowledge that he or she had the disease. Personally, I do not think that such a possibility was ignored; I think the possibility never even occurred to the researchers in the first place because of their narrow disciplinary focus. Most of those researchers were psychologists or psychiatrists, although a few were somatic physicians, e.g., Kissen [5] and Thomas [6]. More recently, both psychologists and psychiatrists have become more aware of the need to examine the effects of cancer on the psyche, as well as the potential interference by a number of possible confounders, both demographic and biologic, with proper research methods. Nonetheless, such confounders still receive limited attention.

**Stress**

Stress will be defined here as the psychic and physiologic disequilibrium caused by some event, which will be called a stressor.

**Stress in Animals**

The earliest work on the effect of psychological factors on cancer dealt mainly with humans. But soon afterwards, a number of studies appeared in which the relationship of stress and cancer in animals was explored. Important early work on this topic was done by Riley [7], who carried out extensive studies on the topic, and Seifert et al [8]. They and others who followed found clear evidence that stress in rodents led to faster growth of transplanted tumors or those caused by injection of oncogenic viruses, and shorter survival times than in nonstressed control animals. This was also true for development and growth of spontaneous tumors. It is of note that Riley's early work on spontaneous tumors was done in animals with virus-infected milk, like the mammary tumors caused by the Bittner virus.

On the other hand, some researchers, e.g., Newberry and Sengbusch [9], found stress to inhibit tumor development and growth in animals under some conditions. In a thorough review of these and other findings, Justice [10] presented an extensive list of variables that stimulate and inhibit tumor development. The most important inference he drew, now well confirmed, was that viral tumors in animals are adversely affected by stress, while those induced by chemical carcinogens are favorably influenced by stress.

In view of the role attributed to the immune system in protecting against cancer growth and possibly initiation, one might be tempted to transfer these animal findings to humans. Yet several facts suggest caution.

1. Humans, guinea pigs, and certain other animals are considerably less sensitive to corticosteroid proliferation than the major rodent species used in the laboratory, [11] and, indeed, even among these rodent species, various strains differ in their sensitivity to glucocorticoids. Thus, the major finding of Riley [7], Seifert [8], and others that stress-induced high glucocorticoid levels in rodents led to increased tumor growth might not be duplicated in humans, even if human cortisol levels did rise with stress.

2. Humans are outbred, with a variety of responses to many physiologic stimuli; mice and rats used in laboratories historically have been inbred to produce cancer-prone strains. While there are now more varied strains, overall that history cannot be ignored.

3. Tumor transplants or heavy doses of carcinogens introduce strong antigens, that is, stimuli to immune recognition and response, with consequent greater protection against the tumor. Spontaneous human tumors take a long time to develop and probably involve relatively weak or
even absent antigen proliferation, and hence limited or even absent immune recognition of and response to antigens.

4. When animals are immunosuppressed, they develop tumors in excess of normal at many sites, each strain being susceptible to tumors at the site peculiar to that strain, eg, liver, lung, testes. When humans are immunosuppressed, they also develop tumors in excess of normal, but most frequently lymphoreticular tumors; that is, the focus of the immunosuppressive stimulus is the immune system itself. The incidence of reticulum cell sarcoma in immunosuppressed individuals, for example, is 150 times that of the population, whereas the incidence of other tumors (except other lymphomas, which is also very high) is about twice that of the population.

5. Justice reported [10] that stress inhibited growth in chemically induced animal tumors. While many stress experiments in animals involve viral tumors, with associated stimulation of tumor growth, in humans, the proportion of viral tumors is small, on the order of 3% to 4% of all tumors. Thus, if one extrapolated directly and incautiously to humans from animal findings, one would conclude that overall, stress is a depressant of tumor development and growth, as found by Newberry [9] and others in animals, rather than a stimulant to tumor growth, as many researchers suggest. For a number of reasons, such a conclusion should not be drawn. Although the animal findings are important, they should form the bases for hypotheses, not conclusions, about the effects of stress on human cancers.

Human Stress
This discussion will focus on cohort studies, as there are several reasons for giving little emphasis to case-control studies. First, cancer can and does produce physical, psychological, and attitudinal changes, mostly negative, that can bias conclusions [12]. Second, these changes in patients are known to increase reports of stressful events when compared with controls [13]. Third, and perhaps most important, one can never be sure that the patient group sample is unbiased, and that the control group is matched to the patient group in regard to variables that might lead to erroneous conclusions. A very limited list of such variables would include the tumor's site, stage, histologic grade, depth of invasion, and size; the degree of lymphocytic invasion at the tumor site; the degree of microvascularization; the patient's age, sex, socioeconomic level, race, smoking status, prior tumor history, alcohol habits, body mass index, status of certain genes (eg, p53), compliance with treatment regimen, and, for breast cancer, age at menarche, age at menopause, oral contraceptive use, estrogen-receptor level, and menstrual stage at operation. In a large cohort study, one hopes that the sheer size of the sample will cause most of these variables to even out among the groups with and without the risk factor.

Case-Control Studies--Several early workers, using the case-control model, reported a greater number of stressful events occurring earlier in life in patients with cancer than in the noncancer groups, eg, Greene [14], and LeShan and Worthington [15]. But most later case-control studies showed no excess of traumatic events among patients, eg, Schonfield [16] and Greer [17] (a short review of his studies).

Among the more recent case-control studies, we find similar contradictory results. Ramirez et al [18] compared frequency of traumatic events between diagnosis of breast cancer and first recurrence among 50 patients with recurrence with the frequency of such events during a similar period in 50 patients without recurrence. They found an excess of reported stressful events among those patients with recurrence.

In contrast, Priestman et al [19], who studied 300 women, 100 with malignancy, 100 with benign tumors, and 100 controls, found that the severity and nature of the stressors did not differ among the groups. In fact, the controls experienced more stressful events than did the benign group, and the benign group experienced more than those with cancer.

Early Cohort Studies--The earlier cohort studies found no more cancers among stressed than unstressed members of the cohort. For example, Keehn et al [20] found no greater cancer mortality among 9,813 soldiers of World War II discharged for psychoneurosis than among 9,942 controls over the period January, 1946, to December, 1969.

Keehn [21] studied cancer mortality among prisoners of war in World War II from 1946 through 1975, and the Korean conflict from 1954 through 1978. No excess cancer mortality was found for either Pacific or European World War II veterans (n = 6,023), or for Korean veterans (n = 3,959) over their respective controls (n = 5,223 and n = 3,953).

Joffres et al [22] looked at 4,581 Japanese men in Hawaii and found no more stressful events among cancer patients than among controls. While this is a case-control analysis, it should be noted that if such an analysis is done on all the cases and all the controls in a population, the results are no more biased than those in a cohort study, in which all the later cases and later controls are similarly
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Recent Cohort Studies--There have been relatively few recent cohort studies. An example is a study by Barracough et al [23], who found no relationship between stressful events and breast cancer survival. In a widely cited series of studies, Grossarth-Maticek et al [24] did find a relationship between stressful events and later cancer, but this work has been criticized most severely [25] and will not be further dealt with here.

Readers should be aware of a demonstrated bias that may affect these studies [4]. It appears that, on the whole, cancer patients tend to recall more stressful events than noncancer controls, even though some studies report otherwise [26]. A few defining studies have shown that cancer patients' reports of stressful events do not reflect actual events experienced. In a thorough review of memory as it is influenced by affect (that is, emotion, mood, or feeling), Blaney [27] concluded that people with negative affect report more negative events than people with average or positive affect. Studies reflecting his conclusions are those of Brett et al [13] and Cohen et al [28]. Almost all patients who have cancer and know it have negative affect to varying degrees. Even if not all but a substantial number had negative affect, their excessive recall of negative events would be enough to bias the average recall level of the whole cancer group.

These three sets of findings lead us to the following conclusions:
1. Case-control studies yield mixed results but are subject to biases.
2. Most cohort studies show no excess stressful events associated with cancer incidence, mortality, or survival.
3. People with negative affect report having experienced more stressful events than those with average or positive affect, when the true frequencies are alike.

The last fact explains many, if not all, of the case-control findings. It is also the basis for predicting that in the absence of such bias, there will be no excess of stressful events among the cancer group.

The prediction is confirmed by the findings of the cohort studies, in which that particular bias cannot exist. Thus, it is almost certain that stressful events do not occur more often among those who later get cancer, die of it, or survive a shorter time than among controls.

Bereavement
Bereavement is an important category of stress that has been studied for its possible effects on later cancer incidence and mortality. Holmes and Rahe [29] ranked loss of spouse as the most stressful among 43 possible stressful events. Yet, several writers have observed that bereavement is not always accompanied by sadness, distress, or regret. For example, the death of a spouse with a fatal and painful disease can produce relief rather than sadness or distress. Although the number of such cases is quite probably relatively small, I know of no studies on this matter.

An overall measure of the effects of bereavement combines data from those who are distressed by the death and those who are relieved. The result is conservative, since the possible effect of distress in producing cancer will be diminished overall by the lack of reported stress among those experiencing relief. The result will be even more conservative if the bereaved who are relieved at a close person's death do, in fact, have reduced susceptibility to later cancer.

Some of the earlier case-control studies reported increased cancer incidence among widowed persons. These have been intensively analyzed, as have prospective studies up to 1986, and their problems and difficulties have been carefully delineated [30].

In the cohort studies, as before, the bias that may exist in case-control studies has been removed. None of the large cohort studies carried out over an extended period have shown excess cancer deaths in bereaved spouses, compared with still-married spouses. In the exceptions, the excess lasted 6 months, a year, or, in one study, as long as 2 years. Since the development time to diagnosis of most cancers is on the order of years--3, 10, 15--those findings could not have referred to cancer initiation. One such large cohort study, a 1987 Finnish study of 95,647 persons widowed in 1972 [31], showed no excess deaths during the subsequent 4 years among 7,600 cancer cases. One can ignore the excess mortality seen among widows in the first week following death and in the first month among widowers as not being attributable to cancer.

Another study, conducted in Washington County, Maryland, of 4,032 white persons widowed between 1963 and 1974 and followed for approximately 12 years [32] showed no excess of cancer deaths. A third large cohort study looking at this question [30] reported a similar lack of excess cancer deaths over 10 years among persons widowed in 1971. Here, the sample was 1% of the whole population of England and Wales, observed from 1971 to 1981. The authors write, "No peak of postbereavement mortality from malignant disease is clearly established in either sex." [30]. In a
fourth such study of 1,782 breast cancer patients--all those diagnosed in Denmark from March 1, 1983, to February 29, 1984--and 1,738 controls, Ewertz [33] found no difference in the death rates of married and widowed patients.

In summary, while some studies have reported a short-term excess of cancer following bereavement, large cohort studies have not, in general, found excess cancer incidence or death over the long term. This conclusion is consistent with the previous one that stress other than bereavement cannot be said to increase later cancer incidence or death.

A few studies have looked at cancer survival among widows, eg, Neale [34], and one or two have included widowers' survival. Also, one or two studies have looked at disease-free interval. However, the results have been mixed, some finding reduced survival among the widowed and some not. In either case, those results cannot be applied to the current issue—bereavement as a psychological factor—since none of the studies on survival even mention the time of bereavement in respect to the cancer diagnosis. Only one thing can be certain in these studies: the marital status of the patient at the time of cancer diagnosis. Thus, the cancer could have been detected 1 day after bereavement or 20 years after bereavement. This fact allows no conclusions to be drawn from the marital status studies with regard to bereavement as a psychological factor.

**Psychosis, Especially Schizophrenia**

Many studies have reported a clear reduction of cancer incidence or mortality among psychotics, especially schizophrenics. Investigations by several researchers [35-37] have shown a fundamental error of calculation in those studies. The faulty studies estimated cancer deaths by proportional mortality. That is, they asked what proportion of deaths in a mental patient cohort were due to cancer when compared with the proportion who died of cancer in an age-equivalent population. The properly done studies, however, compared the absolute cancer death rate in a mental patient cohort with the age-equivalent population's absolute cancer death rate.

It is quite clear in these studies that the death rates in the hospital sample due to noncancer causes, eg, alcoholism, neurologic disease, accidents, or suicide, were in excess of the population rate. Thus, the proportion of deaths in the remaining patients due to other causes, especially cancer, was less than that of the population. Fortunately, eight of the studies that were analyzed by the proportionate mortality method reported enough data so that absolute mortality rates could also be determined. The newly analyzed data showed either no deficiency of cancer deaths, or even a slight, though nonsignificant, excess among the hospitalized samples [35,36,37]. Thus, one can lay to rest the view—often repeated, even today—that psychotics, especially schizophrenics, have fewer cancer deaths than normal.

**Depressed Mood**

A considerable number of case-control studies have reported more cancer cases in people with depressed mood than in controls, although a few have not. It is surely curious that the researchers paid little or no attention to the possibility that the knowledge of having cancer might have induced depressed mood (as Holland and Zittoun [38] warned) or that paraneoplastic syndromes might have produced some cases of depressed mood [39], enough to give an average finding of an excess among cancer cases. That possibility could easily be eliminated in cohort studies.

The first such cohort study was done by Shekelle et al [40] in a group of 2,018 male workers at an electric plant in Chicago. Those workers whose highest scale score among the nine scales of the MMPI (Minnesota Multiphasic Personality Inventory) was depressed mood showed a cancer death rate 2.3 times higher than the remainder of the cohort over a 17-year period (that is, the relative odds were 2.3). This finding (1981) stood alone for several years, but in 1988 and 1989, a series of further cohort studies appeared. First, colleagues of Shekelle's, Persky et al [41], after following the same cohort for another 3 years, observed a substantial decline in the relative risk of cancer deaths, but the overall risk of those with depressed mood was still in excess of that of the remainder of the cohort.

Four other cohort studies have since appeared, all with cohort size greater than that of Shekelle et al. None of these showed an excess of cancer deaths among people with depressed mood. A review of these findings in an editorial in the *Journal of the American Medical Association* concluded that "the combined evidence is consistent with a null or weak relationship, the relative risks being distributed around a value of 1.0 or slightly more. It is clearly not consistent with a strong relationship between depressive symptoms and cancer among major segments of the population" [42]. Special circumstances in the electric plant where the Shekelle et al cohort worked could have
biased their results, ie, the presence of ubiquitous electric fields in the plant and widespread
distribution of PCB vapors from condenser and transformer manufacture, both of which have been
shown to yield neurologic symptoms and to stimulate cancer in animals and probably humans.

_Suppression of Emotions, Especially Anger_

A number of researchers have described cancer patients as nice, accommodating, and, especially,
not prone to express anger. This was interpreted as anger suppression, not unconscious repression,
although that view is not universally accepted. The major work on this issue was done by Greer and
Morris [43], with similar findings reported by several other investigators, eg, Jansen and Muenz [44].
In a number of these studies, the cancer group was substantially older than the control group.
Temoshok [45] presented an interesting concept in her studies of melanoma patients. She reported
that those with what she called a type C personality (opposite in character to the better known type
A) had a worse survival experience than others. The term "type C" was first used by Morris and Greer
Temoshok described people with this personality as "cooperative and appeasing, unassertive,
patient, unexpressive of negative emotions (particularly anger), and compliant with external
authorities "[45].

A further set of data, however, is very intriguing, and casts considerable doubt on the concept that
cancer patients have a type C personality both before and after diagnosis. Several such studies point
to two conditions that would negate the personality hypothesis: (1) prior strong belief by the patient
as to the future benign or malignant biopsy result and (2) attitude change among those diagnosed
with cancer upon learning of the outcome, that is, increased emotional suppression and
defensiveness. The first condition was shown by Schwarz [47] in a 1993 German language article,
presented in English at a 1990 conference (English version available on request from the author).
Schwarz reported that out of 195 patients scheduled for a breast biopsy, 124 (80%) of the 156 later
shown by the pathologist to have a benign condition had guessed their diagnosis correctly
beforehand. Further, of the 39 later shown by the biopsy to have cancer, 26 (67%) had guessed their
diagnosis correctly beforehand. Adding the judgment of the patient's physician to that of the patient
did not change the proportion of correct benign predictions she made alone, but improved somewhat
her predictions of malignancy. If we combine the weighted proportions of predictions of benignity
and malignancy, 76.9% of the patients predicted their diagnoses correctly, and 81.5% of the joint patient-physician
predictions were correct.

The second condition was shown by Kreitler et al [48] in a study of breast cancer patients pre- and
postsurgery. Kreitler's experiment was impressive. The researchers examined three groups of
women, two possible breast cancer groups and a group with surgery unrelated to cancer. All three
groups were tested pre- and postsurgery on anxiety and suppression of emotions. The possible
cancer patients were told their cancer status after surgery. None of the groups-cancer patients,
benign patients, and noncancer surgical patients-differed in their test results before surgery. After
surgery, the three groups did not differ on the anxiety measure, but in the cancer group,
defensiveness and number of those suppressing emotion increased significantly. Kreitler and
colleagues summed up the probable state of affairs as follows: "Our results suggest that cancer
patients probably do not have an intrinsic tendency for suppression, at least not for suppression as
defined and assessed in terms of the new conceptualization based on anxiety defensiveness" [48].
It is still too early to take a firm position on the matter. While several studies confirm the findings of
Schwarz, those of Kreitler et al need further confirmation before we can be confident that they are
reliable.

_Helplessness and Hopelessness_

Many researchers believe that the helplessness and hopelessness coping reaction among patients
diagnosed with cancer presages shorter survival than other coping responses. Many very early
researchers observed that cancer patients in general displayed such a response. Greer and Morris
[43] performed the first good clinical trial to examine relapse and survival statistics among patients
with various coping styles. They reported longer survival among breast cancer patients (mostly stage
I, some stage II) who showed either denial or a fighting spirit, and shorter survival with either a
helpless-hopeless attitude or stoic acceptance. Earlier research had shown that many cancer
patients had such an attitude, but did not examine their prognosis in a controlled study.
Since Greer and Morris's report, other studies have been performed with varied results. Cassileth et
al [49] measured attitude, among other things, in two cancer groups. Group 1 was a mixed-site
group of 100, who were followed for survival for up to 3 years. Group 2, made up of 60 stage II
breast cancer patients and 40 intermediate- or high-risk melanoma patients, was followed from
diagnosis to first recurrence. No relationship was found between degree of helplessness-hopeless-
ness and either survival in group 1 or disease-free interval in group 2. The median survival among
those who died in group 1 (75% of the sample) was 7 months. In group 2, the median disease-free
interval was 12.3 months.

In a follow-up study of the two groups 3 to 8 years after diagnosis, Cassileth et al reported that no
psycho-
social factor, including helplessness-hopelessness, was consistently associated with the length of
survival or remission [49]. They did report that people who scored in the middle third of the range of
scores on the hopelessness scale experienced longer disease-free intervals than those whose scores
were higher or lower. The meaning of this is obscure and cannot be held to support the Greer and
Morris finding, but is consistent with Cassileth's finding of no consistent association. The tentative
hypothesis of Cassileth et al is certainly possible, namely, that survival and hopelessness are related
as a function with an inverted U shape. A more recent longitudinal study [50] showed no relation
between three coping styles (depressive coping, self-encouragement and distraction, and
problem-tackling) and 3-year course of disease (metastasis or death).

Social Support

The presence of social support is known to be inversely related to overall disease mortality.
However, most of these studies involved primarily cerebrovascular and cardiovascular disease, with
cancer mortality only occasionally mentioned. Some studies, however, have been aimed specifically
at cancer incidence or mortality. They report inconsistent results, but when a significant finding is
reported, the researchers have found that poor social support accompanies shorter survival.
The measures of social support in these studies differ considerably, which may be one reason for the
inconsistent findings. Some of the measures examined include number of social contacts, number of
supportive friends, number of support persons, employment status, size of social network, frequency
of contact with friends, frequency of contact with relatives, level of need for social support, and
difference between level of need and level of received support. In addition, different studies
controlled for different possible confounders affecting survival. Ell et al [51] called attention to this
problem in their study: "Findings showed different factors related to survival for those with breast vs
lung or colorectal cancer and for those with localized vs non-localized cancers. Results provide
important evidence that social relations and social support may operate differently depending on
cancer site and extent of disease"[51].

Major Studies--Some major studies should be mentioned. In a cohort study, Reynolds and Kaplan
[52] examined survival and incidence over 17 years among 154 men and 185 women with cancer
from an initial cohort of 6,848 adults. They measured the following social support elements: social
network index level (four levels, from least connected to most connected), number of contacts,
feeling of isolation, marital status, friend/relative contacts, church and other group member- ships,
and church attendance. Controlled variables were age at diagnosis and stage at diagnosis.
The researchers found that men who were least connected (level 1 of the social network index)
survived a significantly shorter time than those at other levels, but that women showed no such
relationship. None of the other social support variables were related to survival duration. The degree
of men's social support showed no relationship to their subsequent cancer incidence, but among
women, those reporting social isolation had a greater cancer incidence than those who were not
isolated. Those women who reported not only the fact of isolation but also the feeling of social
isolation were at especially high risk of later cancers, particularly hormone-related cancers. Since
Reynolds and Kaplan did a multivariate Cox regression analysis, the issue of chance significance did
not arise.

Funch and Marshall [53] studied 208 white female breast cancer patients, measuring social support
in an interview at diagnosis that covered the 5 previous years. After 20 years, the survival pattern of
the cohort was determined for all patients. Social support (except involvement in organizations) was
not related to survival when the group as a whole was examined, but based on theoretical grounds,
asubanalysis by age group was undertaken. Those in the youngest and oldest groups
(premenopausal = 15 to 45 years and postmenopausal = 61 to 90 years) survived longer when their
social involvement was high than when it was low. Those in the perimenopausal group (46 to 60
years) showed no difference in survival in regard to social involvement. These findings are not
impressive, but show the variability one finds in these studies. Of the eight studies examined on this topic, I found three showing a clear relationship, four with mixed or uncertain relationships, and one [44] showing no relationship.

I am inclined to the position that there is a low relationship between cancer survival and social support, but that it probably stems from more basic cancer variables, eg, diet, spouse's or own occupation, and level of exposure to various carcinogens. I believe that if there is a relationship, the population relative risk is small—perhaps on the order of 1.1 or 1.2. Such a risk ratio in the population will produce just the mixed results observed in the various samples examined in the studies.

**Psychotherapeutic Interventions**

Several studies report on the success of psychotherapeutic intervention in extending cancer survival and disease-free interval. Those that seem to have followed good procedure have been prominently disseminated throughout the scientific community. Yet results of these studies differ, possibly due to procedural differences. The best known study is that of Spiegel et al [54] at Stanford University. These investigators studied 86 patients with metastatic breast cancer, offering group therapy weekly for a year to 50 treatment patients, and administering routine oncologic care both to the 50 treatment patients and to the 36 control patients. At 10-year follow-up, three treatment patients were alive, and death records were examined for the remaining 83 patients. Mean survival for the intervention patients from time of randomization, which was also the beginning of treatment for those alive at that point, was 36.6 months, compared with 18.9 months for the controls. Divergence in survival did not begin until 20 months after entry, or 12 months after the end of the group therapy sessions.

This study has been widely cited, but Spiegel properly said that it must be replicated, and as of early 1995, he is well into the conduct of such a study. It is of interest that from the time of randomization in their initial study, 14 intervention patients had either died, were too ill to participate, or had moved away, leaving 36 who were actually treated. Similarly, only 24 of the 36 controls could participate in the testing phase of the study, so the actual comparison of living subjects at the time of intervention was 36 vs 24, not an impressive number. However, to be clear, their survival data analysis dealt with the full 50 intervention patients and 36 control patients.

Fawzy et al [55] reported positive results in melanoma patients using 6-week series of group therapy sessions, rather than a year's series. The death rate over 5 to 6 years was 10 of 34 for the controls and 3 of 34 for the treatment group, a significant difference. Neither of the death frequencies is particularly large, and one hesitates to give much weight to these findings.

A study using individual counseling was done on 120 end-stage male cancer patients, 62 randomly assigned to the counseling group and 58 to the control group. Treatment patients improved in quality-of-life measures, but did not differ from controls in survival over a year's time [56]. Gellert et al [57] examined the effectiveness of Bernie Siegel's group therapy sessions at Yale University on breast cancer patients in a follow-up study to an earlier trial that showed practically no improved survival for the therapy group, compared with a control group. The earlier result had emerged after correcting for a difference in the intervals between diagnosis and treatment between the two groups. Gellert et al improved the selection of controls by using historical controls matched with the treatment patients on several important variables, and extended the observed survival time by 10 years. Three controls were matched to each of the 34 treatment patients, and their survival was monitored from the treatment dates (1971 through 1980) until March, 1991. No difference in ultimate survival could be observed after matching the duration of survival of the two groups at the time of entry into therapy. Without this matching, the treatment group spuriously showed longer survival.

In a very recent study by Ilnyckyj et al [58], 96 cancer patients were randomly assigned to receive weekly group psychotherapy, and 31 to a control group. One treatment group (n = 31) was led by a professional social worker for 6 months; a second (n = 30) was led for 3 months, then continued to meet for 3 months without a leader; a third met for 6 months without professional leadership. Controls had no treatment other than normal oncologic care, which all groups received. Mean survival from time of randomization was 70.7 months in the professionally led group, 62 months in the unled groups, and 82.4 months in the control group. None of these means differed significantly from any other. This study suffers from some design problems.

Whether psychotherapeutic intervention extends life in cancer patients is an unsettled issue. The many differences in procedures, samples, disease types, stages, experimental designs, approaches to therapy, and especially durations of treatment do not allow a clear conclusion.
Some Considerations

How confident can one be about the status of any of the psychological factors discussed above or, indeed, about any of the much larger number of factors that have been associated with cancer in various studies? In regard to initiation of cancer, we have very little information. Stress in rats and mice stimulates initiation of viral tumors but inhibits that of chemically induced tumors. In humans, only a few cancers, perhaps 3% to 4%, seem to be virus-related, the most prominent being Burkitt’s lymphoma and cancers of the cervix, liver, and nasopharynx. But the body reacts to stress by producing corticosteroids, which seems to depress immune competence to various degrees. Rats and mice react strongly to their corticosteroid, corticosterone, while humans react considerably less strongly to their hormone, cortisol. Together with other factors, these facts suggest that we should not extrapolate to humans the tumor-stimulating findings regarding stress in animals.

As for other possible cancer-initiating psychological factors, there is evidence from a Russian study [59], confirmed in an American study [60], that sister-chromatid exchange is increased in mice under stress. Other studies have suggested that increased sister-chromatid exchange might increase cancer susceptibility. Finally, one study (Kiecolt-Glaser et al [61]) has shown that in humans, one of the DNA repair enzymes falls off under stressful conditions. Theoretically, unrepaired mutated DNA in cancer-inhibiting genes might increase the cancer risk, or reduce it in cancer-stimulating genes. But if gene mutation is random, as seems to be the case, and unrepaired DNA is likewise random, the risk of cancer from failure to repair DNA is quite small, since current theory says that the number of cancer-prone or cancer-inhibiting genes is a tiny fraction of the total number of genes.

As for prognosis, the theory espoused in most of the recent papers on presumably negatively acting psychological factors is that immune system activity may be depressed in people with such factors, and hence the cancer tends to grow faster. Positively acting psychological factors would tend to do the opposite. But things are not so simple. The few studies looking at both immune system activity and survival have reported that even if there is a decline in responsiveness of one or several immune system elements (eg, T4 cells, T8 cells, T4/T8 ratio, natural killer cells, mitogen-responsive mononuclear cells in general), there is no corresponding reduction in survival time [55]. To my knowledge, among the few studies of psychological intervention, none of the psychological factors measured have predicted survival differences [54,55]!

It has been suggested [4] that the influence of psychological factors might ride on top of the known influence of various carcinogens, selectively causing certain people to get cancer among all those exposed to the risk factor (eg, which smokers get lung cancer?). It seems to me that such an interaction is very difficult to justify across the large array of psychological factors; the equally large array of known-and unknown-carcinogens; and the more than 100 types of cancer, each peculiar to the cytologic, hormonal, and other characteristics of particular cancer patients. Such a notion must remain a speculation at present, but should not be discarded out of hand.

Thus, in regard to the basic question of possible influence of psychological factors on cancer, it seems fairly certain that for a few factors, there is no influence (or at most, very little influence), while for the remaining factors, the influence is uncertain. In my opinion, some people, under some conditions, for some cancer types, may well be affected by psychological factors such that cancer is more likely or less likely to occur in them than in other individuals, or, if the disease is already present, that it may progress faster or slower in them than in other patients. I feel, moreover, that such cases are probably quite rare, and it would be impossible, at present, to identify them singly.

References:


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