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Review

Mind and cancer: do psychological factors cause cancer?

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Abstract

We have reviewed the evidence for an association between major life events, depression and personality factors and the risk for cancer. We identified and included only those prospective or retrospective studies in which the psychological variable was collected independently of the outcome. The evidence failed to support the hypothesis that major life events are a risk factor for cancer. The evidence was inconsistent for both depression and personality factors. Chance, bias or confounding may explain this result, as many of the studies had methodological weaknesses. The generally weak associations found, the inconsistency of the results, the unresolved underlying biological mechanism and equivocal findings of dose–response relationships prevent a conclusion that psychological factors are established risk factors. However, certain intriguing findings warrant further studies, which must, however, be well conducted and large and include detailed information on confounders.

Keywords: Cancer; Risk; Depression; Personality; Psychological stress; Bereavement; Review; Epidemiology

1. Introduction

The hypothesis that there is a causal link between psychosocial factors and cancer has been widely debated in the scientific literature and the public media. Repeated citation of a number of studies [1–6] has nourished the idea of an association between mind and cancer. Since 1969, working groups convened by the International Agency for Research on Cancer (IARC) have assessed the degree of evidence for the carcinogenicity to humans of some 800 biological, physical, chemical and occupational factors and has ranked risk factors for cancer according to the degree of evidence of causality [7]. Psychological factors have never been reviewed in this context; however, a brief review of psychological factors associated with cancer was included in another IARC publication on the 'state-of-the-art' of cancer prevention and control in 1990 [8]. No conclusion was reached about the degree of evidence, but it was stated that future epidemiological studies should include standardised instruments and data on potential confounders in order to be credible.

We have reviewed the scientific evidence for the carcinogenic role of the three psychosocial factors that have been most rigorously investigated: major life events, depression or depressive mood and personality or personality traits. We reviewed only those prospective or retrospective cohort studies and case–control studies in which the information on psychosocial variables was collected independently of the outcome, thereby reducing the possibility of selection and recall bias. In another paper, we review the effect of psychosocial intervention on prognosis and well-being after the diagnosis of cancer [9].

2. Materials and methods

We performed a literature search on the Medline (1966–August 2001) and PsychINFO (1967–August 2001) databases, using the following key words: *neoplasms-aetiology* or *neoplasms-epidemiology* or *neoplasms and risk* in combination with, respectively, *bereavement* or *life events* or *psychological stress* or *personality* or *depression* or *affective states* or *depressed mood*. The strategy of mutually overlapping searches was chosen to ensure the widest possible search for the available evidence on these topics.

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On the basis of a reading of the abstracts, we included only prospective or retrospective studies in which there was no bias in the ascertainment of data on one of the three psychosocial variables, in which cancer incidence was evaluated and which had been published as original articles in a peer-reviewed journal. Additional references were obtained from these articles and review articles. After careful evaluation, we decided not to include the publications describing the Crvenka cohort study in Yugoslavia, by Grossarth-Maticek and colleagues [10–14], which did not contain adequate descriptions of the Materials, Methods and Analyses.

3. Results

3.1. Major life events and risk for cancer

We identified one prospective study [15], six retrospective cohort studies [16–21] and one case–control study [22]. The major characteristics of these studies are summarised in Table 1.

3.1.1. Prospective cohort studies

Jacobs and Bovasso (2000) assessed 1213 women in Baltimore, USA, for depressive or anxious disorder and the death of one or both their parents during their childhood at baseline in 1980. They were further assessed for life events occurring during follow-up for breast cancer through 1995 [15]. An increased risk for breast cancer of 2.56 (95% confidence interval (CI) 1.59–4.35) was observed in adjusted analyses for women whose mother had died during their childhood (only 6 cases), whereas recent life events were not associated with an increased risk (no risk estimates given). The way in which data were collected in this study is problematic as some of the determinants were ascertained at follow-up and the diagnosis of breast cancer was self-reported, leading to a possibility of recall bias; furthermore, there was no adjustment for reproductive factors, which are known to be associated with breast cancer.

3.1.2. Retrospective cohort studies

Jones and colleagues (1984) investigated the risk for cancer after the death of a spouse in a study population that comprised 1% of the population of England and Wales in the 1971 census [16]. After 5 years of follow-up, the risk for cancer at any site was non-significantly increased for men (relative risk (RR), 1.18; 95% CI 0.97–1.41) and was 1.00 (95% CI 0.83–1.20) for women.

Hatch and collegues (1991) studied the cancer risk associated with leakage of radiation from the nuclear power plant on Three Mile Island, USA, in 1979, where the sole health consequence for the neighbouring population was considered to be mental distress [17]. The cancer risk of those living closest to the plant compared with that of people living further away was 1.4 (95% CI 1.3–1.6). The risk was found to be increased for lymphoma (RR 1.9; 95% CI 1.2–3.0), hormonal cancers (RR 1.2; 95% CI 1.0–1.4), lung cancer (RR 1.7; 95% CI 1.3–2.1) and colon cancer (RR 1.7; 95% CI 1.3–2.2). The increase in cancer rate was notable from 1982, persisted for another year and then declined, indicating that improved surveillance may explain the increase in risk observed.

Kvikstad and colleagues (1994) investigated the risk for cancer after widowhood or divorce in a population-based cohort of more than 600 000 women born between 1935 and 1954 in Norway [18]. A total of 4491 incident cases of breast cancer were identified and compared with 44 910 population controls in a nested case–control design, population-based registries being used to ascertain the change of marital status. The adjusted risk in comparison with married women was 1.13 (95% CI 0.94–1.36) for widowed women and 0.83 (95% CI 0.75–0.92) for divorced women.

Kvikstad and Vatten (1996) studied the risk for cancer after the death of a child [19] in the same cohort as in the previous study [18], again using registry-based data. This nested case–control study comprised 14 669 cancer cases and 29 750 age-matched controls. The adjusted risk for cancer of women who had lost a child was not increased (odds ratio (OR) 0.96; 95% CI 0.87–1.07), nor were the risks for cancers at specific sites.

Johansen and Olsen (1997) conducted a nationwide, register-based follow-up study in Denmark of 11 231 parents whose children had developed cancer [20]. The parents were not at an increased risk for cancer (standardised incidence ratio (SIR), 1.0; 95% CI 0.9–1.0), and they showed no increase in risk during any period of follow-up after the stressful event or for cancer at any particular site.

Levav and collegues (2000) studied the effect of bereavement in 6284 Jewish Israelis who had lost a son in war or in an accident between 1970 and 1977 [21] and found no effect on the risk for total cancer (OR 0.95; 95% CI 0.88–1.04 and OR 1.03; 95% CI 0.90–1.18, respectively). In comparison with the risk for lymphatic and haematopoietic cancers of the Israeli population as a whole, the risk was increased for parents whose sons had been killed at war (OR 1.47; 95% CI 1.13–1.97) or in accidents (OR 2.01; 95% CI 1.30–3.11). In addition, the risk for malignant melanoma was significantly increased in both groups (OR 1.71; 95% CI 1.06–2.76 and OR 4.62; 95% CI 1.93–11.06, respectively), and that for cancers of the respiratory tract were increased in parents of sons killed in accidents (OR 1.50; 95% CI 1.07–2.11).

3.1.3. Case–control studies

Ewertz (1986) conducted a Danish nationwide case–control study of 1792 cases of breast cancer diagnosed in 1983–1984 and 1739 population-based controls on the basis of register data [22]. Divorce did not increase the age-adjusted risk for breast cancer (OR 0.9; 95% CI

Table 1
Characteristics and key findings of studies of *major life events* and cancer incidence by study design

Reference, location	Total sample (% women)	Comparison population	Type of cancer (no. observed)	Follow-up period	Measure of major life event	Adjusted risk estimate (95% CI)	Covariates
Prospective cohort studies							
Jacobs and Bovasso, 2000, USA [15]	1213 (100)	–	Breast (39)	1980–1995	Death of parent in childhood Recent life events	Death of mother in childhood, Breast, 2.56 (1.59–4.35) Recent life events, n.a.	Age, family history of breast cancer, dysthymia, depression, household income
Retrospective cohort studies							
Jones and colleagues, 1984, UK [16]	264 277 (50)	1% of English and Welsh populations	Total (n.a.) Site-specific	1971–1975 1979–1985	Death of spouse[b] Environmental accident	Total (m) 1.18 (0.97–1.41) Total (w) 1.00 (0.83–1.20)	Age Age, sex, urbanicity, social class
Hatch and colleagues 1991, USA [17]	159 684 (n.a.)		Total (3771) Site-specific			Total 1.4 (1.3–1.6) Lymphoma 1.9 (1.2–3.0) Hormonal 1.2 (1.0–1.4) Lung 1.7 (1.3–2.1) Colon 1.7 (1.3–2.2)	
Kvikstad and colleagues 1994, Norway [18]	4491 cases (100) 44 910 controls	~600 000[a]	Breast (4491)	1966–1990	Death of spouse[b] Divorce[b]	Death of spouse, Breast 1.13 (0.94–1.36) Divorce, Breast 0.83 (0.75–0.92)	Age, age at first birth, parity, place of residence
Kvikstad and Vatten, 1996, Norway [19]	14 669 cases (100) 29 750 controls	~600 000[a]	Total (14 669)	1965–1991	Death of child[2]	Total 0.96 (0.87–1.07)	Age, parity
Johansen and Olsen, 1997, Denmark [20]	11 231 (50)	Total Danish population	Total (1665) Site-specific	1943–1992	Cancer in child[b]	Total 1.0 (0.9–1.0)	Age, sex, calendar period
Levav and colleagues, 2000, Israel [21]	6284 (~47)	Total Israeli population	Total (768) Site-specific	1970–1971	Death of son[b]	War-bereaved, Total 0.95 (0.88–1.04) Lymphatic 1.47 (1.13–1.52) Melanoma 1.71 (1.06–2.76) Accident-bereaved, Total 1.03 (0.90–1.18) Lymphatic 2.01 (1.30–3.11) Melanoma 4.62 (1.93–11.06) Respiratory 1.50 (1.07–2.11)	Age, sex, region of origin, period of immigration
Case–control studies							
Ewertz, 1986, Denmark [22]	1792 cases (100) 1739 controls	–	Breast (1792)	1968–1984	Death of spouse[b] Divorce[b]	Death of spouse, Breast 0.8 (0.7–1.0) Divorce, Breast, 0.9 (0.7–1.2)	Age

Adjusted risk estimates, risk estimates listed for total cancer and for cancer at sites with increased risk adjusted for covariates listed. CI, confidence interval; m, men; w, women; n.a., not assessed/published; hormonal, cancer sites associated with hormones including cancers of the breast, ovary, prostate and testis; Lymphatic, cancers of lymphatic and haematopoietic tissue (ICD-9 200–209); Respiratory, cancers of the respiratory tract (ICD-9 140–149, 161–162).

[a] Nested case-control study in a cohort of Norwegian women born between 1935 and 1954 [18,19].

[b] Register-based information.

0.7–1.2), and widowhood was associated with a reduced risk of 0.8 (95% CI 0.7–1.0). The risk for breast cancer after 15 or more years of widowhood or divorce was 0.7 (95% CI 0.4–1.2) and 1.3 (95% CI 0.8–2.0), respectively.

In summary, large population-based studies based on information from administrative registers, in which information is collected independently of scientific hypotheses, failed to support the proposal that major life events are associated with an increased risk for cancer [16,18–20,22]. Furthermore, some of the studies that did find an association had basic methodological problems [15] or were based on information on exposure of aecological character and may have suffered from surveillance bias [17]. One study showed an increased risk [21]; however, the high degree of consistency among five of the six presumably unbiased studies [16,18–20,22] indicates that explanations for the elevated risk may include selection bias or chance.

3.2. Depression and risk for cancer

We identified 10 prospective cohort studies [15,23–31] and two retrospective studies [32,33]. The major characteristics are shown in Table 2.

3.2.1. Prospective studies

Persky and colleagues (1987) studied a cohort of 2018 middle-aged men who had been employed at a factory in Chicago, USA, in 1957–1958. Depression was measured on the Minnesota Multiphasic Personality Inventory (MMPI) [23]. Follow-up for cancer through to 1979 resulted in an adjusted risk estimate of 1.38 (95% CI 1.00–1.89) for men with a high score when compared with men with a low score. When stratified by follow-up time, however, the risk was increased only during the first 10 years of follow-up.

Hahn and Petitti (1988) examined the effect of depression in a cohort of 8932 women who completed the MMPI in California, USA, between 1969 and 1972 [24]. Follow-up for breast cancer through to 1982 showed an insignificantly increased adjusted risk of 1.5 (95% CI 0.9–2.5) for women with a high score compared with those with a low score.

Kaplan and Reynolds (1988) measured depression on the Human Population Laboratory scale in a cohort of 6848 adults in California, USA, in 1965 and followed them up for cancer through to 1982 [25]. The age-adjusted risk estimates were 0.97 for men and 1.27 for women ($P > 0.05$ for both).

Zonderman and colleagues (1989) measured depression on the Center for Epidemiological Studies Depression scale (CES-D) in a nationally representative sample of 6913 Americans between 1971 and 1975 [26]. A subsample of these persons also completed the 'cheerful versus depressed' subscale of the General Well-being schedule. Follow-up for cancer through to 1981 yielded an adjusted risk for cancers at all sites of 1.1 (95% CI 0.9–1.4).

Linkins and Comstock (1990) reported on a study of 2264 persons in Washington, USA, who had completed the CES-D between 1971 and 1974 and who were still free of cancer at the start of follow-up 1–4 years later in 1975 [27]. After 12 years of follow-up, the age-adjusted RR for cancer at any site was 1.09 (95% CI 0.69–1.71). However, the risk for smoking-related cancers was higher in depressed heavy smokers than in heavy smokers who were not depressed, indicating that depression may have modified the effect.

Vogt and colleagues (1994) studied the effect of depression, assessed from answers to questions that allowed for an approximation of depression according to Diagnostic and Statistical Manual of Mental Disorders, third revision, in home interviews, in a random sample of 1529 persons in Portland, USA, in 1970–1971 [28]. It was unclear, however, how many persons actually participated. After 15 years of follow-up, the adjusted risk for cancer at any site was 1.08 (95% CI 0.77–1.52).

Knekt and colleagues (1996) used the General Health Questionnaire and Present State Examination to assess depression in a nationally representative sample of 7018 persons in Finland in 1978–1980 [29]. Follow-up for cancer through to 1991 resulted in age- and sex-adjusted estimates of risk for cancer at any site of 0.99 associated with psychiatric depression (95% CI 0.68–1.44) and 1.22 associated with a high score for depression (95% CI 0.91–1.63). However, the risk for lung cancer among men with a high score for depression was 3.32 (95% CI 1.53–7.20). Furthermore, a strong interaction was found between smoking status and depression, indicating a possible modification of the effect by depression, in line with the results of Linkins and Comstock [27].

Penninx and colleagues (1998) studied 4825 Americans aged 71 years or older with depression, measured by the CES-D prospectively three times, 6 and 3 years before baseline and at baseline in 1988 [30]. Thus, the effect of chronic depression on cancer risk could be assessed after a mean follow-up of 3.8 years. An increased risk for cancer at any site was found for persons with chronic depressed mood of 1.88 (95% CI 1.13–3.14), but no increased risk was observed for persons who were depressed only at baseline (hazards ratio (HR), 1.02; 95% CI 0.73–1.42).

Gallo and colleagues (2000) measured depression by the Diagnostic Interview Schedule (DIS) in 3109 persons in Baltimore, USA, in 1981 [31]. Follow-up for cancer through to 1994 yielded an adjusted odds ratio for cancer at any site of 1.3 (95% CI 0.6–2.8) for persons with major depression and 1.3 (95% CI 0.9–1.9) for persons with dysphoric episodes. An increased risk of borderline significance of 3.8 (95% CI 1.0–14.2) for breast cancer (based on 25 cases) was observed. Cancer

Table 2
Summary of characteristics and key findings of studies of *depression* and cancer incidence, by study design

Reference, location	Total sample (% women)	Type of cancer (no. observed)	Follow-up period	Measure of depression	Adjusted risk estimate (95% CI)	Covariates
Prospective cohort studies						
Persky and colleagues, 1987, USA [23]	2018 (0)	Total (212)	1959–1979	MMPI	Total 1.38 (1.00–1.89)	Age, smoking alcohol, family history, occupation, body mass index, cholesterol
Hahn and Petitti, 1988, USA [24]	8932 (100)	Breast (117)	1969–1982	MMPI	Breast 1.5 (0.9–2.5)	Age, nulliparity, obesity, hysterectomy
Kaplan and Reynolds, 1988, USA [25]	6848 (n.a.)	Total (476) Site-specific	1965–1982	HPL	Total (m), 0.97; $P > 0.05$ Total (w), 1.27; $P > 0.05$	Age
Zonderman and colleagues, 1989, USA [26]	6913 (n.a.)	Total (569)	1971–1981	GWB-D CES-D	Total 1.1 (0.9–1.4)	Age, sex, smoking, family history, marital status, hypertension, cholesterol
Linkins and Comstock, 1990, USA [27]	2264 (58)	Total (169) Site-specific	1975–1987	CES-D	Total 1.09 (0.69–1.71)	Age
Vogt and colleagues, 1994, USA [28]	1529 (n.a.)	Total (n.a.)	1970–1985	Questionnaire in survey (DSM-III appr.)	Total 1.08 (0.77–1.52)	Age, sex, smoking, socioeconomic status, length of health plan membership, subjective health status
Knekt and colleagues, 1996, Finland [29]	7018 (54)	Total (605) Site specific	1978–1991	PSE GHQ	Psychiatric depression Total 0.99 (0.68–1.44) Heavy depression Total 1.22 (0.91–1.63) Lung (m), 3.32 (1.53–7.20)	Age, sex
Penninx and colleagues, 1998, USA [30]	4825 (65)	Total (402)	1988–1992	CES-D	Baseline depression Total 1.02 (0.73–1.42) Chronic depression Total 1.88 (1.13–3.14)	Age, sex, smoking, alcohol, race, disability, hospital admissions
Gallo and colleagues, 2000, USA [31]	3109 (61)	Total (203) Site-specific	1981–1994	DIS	Major depression, Total 1.3 (0.6–2.8) Breast 3.8 (1.0–14.2) Dysphoric episode, Total 1.3 (0.9–1.9)	Age, sex, smoking, alcohol
Jacobs and Bovasso, 2000, USA [15]	1213 (100)	Breast (29)	1980–1995	DIS	Major depression plus dysthymia, Breast 14; $P < 0.001$	Age, sex, smoking, familiy history, race, sociodemographic factors, other psychiatric diagnoses, life events, somatisation
Retrospective cohort studies						
Friedman, 1994, USA [32]	923 (n.a.)[a]	Total (70)	1969–1988	Psychiatrically diagnosed depression	Total 1.21 (0.95–1.53)	Age, sex
Hjerl and colleagues, 1999, Denmark [33]	66 648 (100)[b]	Breast (1270)	1969–1993	Hospitalisation with affective disorder (ICD-8)	Breast 1.02 (0.97–1.08)	Age, sex, calendar period

Adjusted risk estimates, risk estimates listed for total cancer and for cancer-sites with increased risk adjusted for covariates listed; MMPI, Minnesota Multiphasic Personality Inventory; HPL, Human Population Laboratory; GWB-D, General Well-being-Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, Third Edition; PSE, Present State Examination; GHQ, General Health Questionnaire; DIS, Diagnostic Interview Schedule; ICD-8, International Classification of Diseases, 8th revision; CI, confidence interval; n.a., not assessed/or published; m, male; w, women; appr., approximation.

[a] Comparison population was 143 574 members of a health plan [32].

[b] Compared with the total Danish female population [33].

cases were ascertained from self-reports or death certificates for only 2017 persons, resulting in a loss to follow-up of 35%.

Jacobs and Bovasso (2000) studied 1213 women in the same cohort for depressive and anxious disorders as well as for life events (this study is further described in the section on major life events) in 1980 and followed them up for breast cancer through to 1995 [15]. The adjusted risk for breast cancer was 14 ($P < 0.001$) for the 11 women with both dysthymia and major depression, of whom two reported developing a breast cancer. The authors concluded that cancer is associated with the combination of chronic and severe depression. As noted in the section on major life events, the diagnosis of cancer was based solely on self-reporting, and there was no adjustment for reproductive factors.

3.2.2. Retrospective cohort studies

Friedman (1994) identified 923 persons without cancer, but with a psychiatric condition related to depression between 1969 and 1973 among members of a health plan in San Francisco, USA, and followed them up for death from cancer through to 1988 in the local cancer registry (Surveillance, Epidemiology, and End Results (SEER)) [32]. The standardised morbidity ratio was 1.21 (95% CI 0.95–1.53) and was increased to 1.38 (95% CI 1.06–1.76) when the first 2 years of follow-up were excluded.

Hjerl and colleagues (1999) studied a nationwide, population-based cohort comprising all 66 648 Danish women who had been hospitalised with an affective or neurotic disorder (as defined in the ICD-8) between 1969 and 1993, following them up for cancer in the national cancer registry [33]. No increased risk for breast cancer was found overall (SIR 1.02; 95% CI 0.97–1.08), or when the analysis was stratified by a number of characteristics of the cohort.

Of the studies showing an effect of depression on cancer risk, most found increased risks for cancers at specific sites, such as breast [15,31], lung [29] and all smoking-related cancers [27]. In several studies, the risk for selective inclusion of patients with symptoms of depression due to an unrecognised cancer was minimised by stratifying for time since baseline [33] or by excluding the first few years of follow-up [27,29,32], but in only one study did this support the association [32], underlining the need for a prospective design in this type of study. The duration of depression was related to cancer in two studies [15,30], but this aspect was not evaluated in most studies. The inconsistency of the results, most of the studies that assessed total cancer risk finding no statistically significant increase or increased risks in only some strata, use of different measures and definitions of depression, the relatively small samples and the fact that some of the studies that found an association used flawed case ascertainment, were subject to loss of follow-up and controlled for confounding only inadequately [15,31] raise the possibility that the positive findings could just as well have been due to chance as to depression.

3.3. Personality factors and risk for cancer

We identified 11 studies of the effect of personality factors on the development of cancer in a total of 10 cohorts (Table 3). Most of the studies were inspired by the notion of a 'cancer-prone personality'. In order to provide an overview, we grouped the studies into three broad categories: those of the effect of a cancer-prone personality, in an exploratory design or to test an *a priori* theory [34–37]; those of the effect of repression or expression of emotions [23,24,38–40]; and those of the effect of hopelessness and related traits [41,42].

3.3.1. Cancer-prone personality

Hagnell (1966) studied a population-based sample of 1869 persons in Sweden [34] by measuring capacity, stability, solidity and validity at baseline in 1947 in a structured interview developed by Sjöbring [43]. After 10 years of follow-up, no association was found between validity, capacity or solidity and the incidence of cancer at any site. However, a significantly higher proportion of women who were sub-stable had cancers. 'Stability' referred to the degree of emotional control, in the sense of coolness (as opposed to warmth and heartiness [34]), and the degree of abstract thinking and of precision and elegance of thought and movement [34]. Thus, the 'personality factors' appear to include assessment of different aspects of neuropsychological functioning judged by the clinician.

Dattore and colleagues (1980) tested the hypothesis of a cancer-prone personality by studying approximately 3000 male US Army veterans, all of whom completed the MMPI on entering a veterans' home in Kansas, USA, between 1969 and 1978 [35]. The 75 cancer patients identified were compared with 125 controls without cancer (100 with other diseases and 25 healthy controls) in a nested case–control study. All were free of disease 1 year prior to the MMPI test except for alcohol-related disorders. The two groups were found to be significantly different, those with cancer having greater repressive tendencies, fewer self-reported depressive symptoms and less denial of hysteria.

Shaffer and colleagues (1987) reported on a cohort of 1337 male medical students at the Johns Hopkins Medical School, MD, USA, who had filled out a Family Attitude Questionnaire, and a Habits of Nervous Tension Questionnaire and undergone a Rorschach test between 1948 and 1968 [36]. Five personality types were established in a hierarchical analysis of 972 men. Those classified as 'acting out/emotional' were at a lower risk of developing cancer than men characterised

Table 3
Characteristics and key findings of prospective studies examining *personality variables* and cancer incidence, by broad categories of personality factors investigated

Reference and location	Total sample (% women)	Type of cancer (no. observed)	Follow-up period	Measure of personality	Adjusted risk estimate (95% CI)	Covariates	Other findings
Cancer-prone personality							
Hagnell, 1966, Sweden [34]	1869 (48)	Total (42)	1947–1957	Personal structured interview	n.a.	Age	Lower degree of stability
Dattore and colleagues, 1980, USA [35]	75 cases (0) 125 non-cancer controls[a]	Total (75)	1969–1978	MMPI Byrne's R-S	n.a.	Alcohol-related disorder	Higher mean score on repression Lower mean score on depressive symptoms and denial of hysteria
Shaffer and colleagues, 1987, USA [36]	972 (0)	Total (n.a)	1948–1978	FAQ HNTQ	n.a.	n.a.	Cumulative cancer-free proportion: acting out/emotional: 99.3%; bland/normal: 96%; interpersonal conflict: 93%; healthy/sensitive: 89.9%; loners: 88.9%; log rank $P=0.045$
Schapiro and colleagues, 2001, Denmark [37]	1031 (52)	Total (113)	1976–1996	EPI-Q	High extraversion, Total 0.96 (0.65–1.42) Low neuroticism, Total 1.28 (0.79–2.05) High extraversion + low neuroticism Total 1.36 (0.72–2.59)	Age, sex, calendar period, smoking, alcohol, personality score, psychiatric disease, marital status, social class	–
Repression and expression of emotions							
Persky and collegues, 1987, USA [23]	2018 (0)	Total (212)	1958–1979	MMPI Welsh's R scale Form A of C-16F	n.a.	n.a.	No difference on mean score for repression
Hahn and Petitti, 1988, USA [24]	8932 (100)	Breast (117)	1969–1982	MMPI	n.a.	Age, nulliparity, obesity, hysterectomy	Higher mean score on lying
Kavan and colleagues, 1995, USA [38]	61 cases (0)[b] 61 controls	Colon (61)	1977–1988	MMPI	n.a.	Age, education, referral source	Higher mean score on aggressive hostility
Bleiker and colleagues, 1996, Holland [39]	131 cases (100)[c] 771 controls	Breast (131)	1989–1994	SAQ-Nijmegen	High anti-emotionality, Breast 1.19 (1.05–1.35)	Age, family history, parity	–
Tijhuis and collegues, 2000, Netherlands [40]	590 (0)	Total (119)	1985–1994	CECS	Intermediate depression control, Total 1.7 (1.0–2.8)	Age, smoking, alcohol, socioeconomic status, marital status, life events, loneliness, subjective health, body mass index, physical activity, diet	–

(*continued on next page*)

Table 3 (*continued*)

Reference and location	Total sample (% women)	Type of cancer (no. observed)	Follow-up period	Measure of personality	Adjusted risk estimate (95% CI)	Covariates	Other findings
Hopelessness and related factors							
Greenberg and Dattore, 1981, USA [41]	58 cases (0)[d] 104 non-cancer controls	Total (58)	1969–1978	MMPI	n.a.	Age, alcohol-related disorder, latency, intelligence	No difference on mean score for repression
Everson and colleagues 1996, Finland [42]	2428 (0)	Total (73)	1984–1992	Two-item scale of hopelessness	High-to-moderate hopelessness, Total 1.42 (0.83–2.41)	Age, systolic blood pressure, body mass index, lipids, education, income, behavioural factors, subjective health, MMPI depression, social support, disease history	–

Adjusted risk estimates, risk estimates listed for total cancer and for cancer-sites with increased risk adjusted for covariates listed in the covariate column. Other findings: Difference in mean scores between groups. Listed according to direction of score in persons with subsequent cancer. EPI-Q, Eysenck Personality Inventory; FAQ, Family Attitude Questionnaire; MMPI, Minnesota Multiphasic Personality Inventory; Byrne's R-S, Byrne's Repression-Sensitization scale; CECS, Courtald Emotional Control Scale; SAQ-Nijmegen, Self-Assessment Questionnaire-Nijmegen; HNTQ, Habits of Nervous Tension Questionnaire; MBHI, Millon Behavioral Health Inventory (Pessimism-scale); HHPQ, Heart Patients Psychological Questionnaire (Social inhibition scale); Form A of C-16F, Form A of the Cattell 16 Factor Personality Questionnaire; CI, confidence interval, n.a., not assessed/published; latency, time from assessment to diagnosis.

[a] Case–control study nested in cohort of 3000 men [35].
[b] Case–control study nested in cohort of 9500 men [38].
[c] Case–control study nested in cohort of 9705 women [39].
[d] Case–control study nested in cohort of men, cohort size not specified [41].

as 'bland/normal', 'healthy/sensitive', 'loners' or having an 'interpersonal conflict personality', on the basis of a Kaplan–Meier analysis.

Schapiro and colleagues (2001) tested the hypothesis of a cancer-prone personality as defined by Kissen and Eysenck [44], characterised by a high degree of extraversion and/or a low degree of neuroticism, in a cohort of 1031 persons in Denmark, aged 40 years, who filled out an Eysenck Personality Inventory in 1976–1977 and were followed-up for 20 years [37]. The overall adjusted risk for cancer at any site was 0.96 (95% CI 0.65–1.42) for highly extraverted people, and was non-significantly increased for persons with a low degree of neuroticism (RR 1.28; 95% CI 0.79–2.05) and for persons with a combination of high extraversion and low neuroticism (RR 1.36; 95% CI 0.72–2.59).

3.3.2. Repression and expression of emotions

Persky and colleagues (1987) assessed personality factors with the MMPI and form A of the Cattell Personality Inventory and repression with the Welsh R-scale in 2018 middle-aged men (described in detail in the section on depression) [23]. No differences among men who did and did not develop cancer were found in the mean scores, apart from those for depression.

Hahn and Petitti (1988) examined repression, sensitisation and lying as assessed in the MMPI in relation to the development of breast cancer in a cohort of 8932 women who were followed-up for 14 years (also described in the section on depression) [24]. The difference in the mean scores of women with cancer and healthy women did not reach significance for repression or sensitisation and was only just significant for the lying scale. However, no risk estimates were given.

Kavan and colleagues (1995) tested the hypothesis of a positive association between depression and a negative association between aggressive hostility or assertiveness and subsequent development of colon cancer in a cohort of male US Army veterans in Minneapolis, USA, who were given the MMPI in 1947–1975 and followed-up between 1977 and 1988 [38]. In a nested case–control design, aggressive hostility was the only factor found to differ between the cases and controls, and contrary to the hypothesis, men with cancer scored higher for this factor.

Bleiker and colleagues (1996) investigated whether personality factors, and especially the expression and control of (negative) emotions, affected the risk for breast cancer in 9705 women invited for mammography screening in The Netherlands in 1989–1990 and asked to fill out the Nijmegen Self-Assessment Questionnaire [39]. After 6 years of follow-up in a matched case–control study, the only personality factor that was associated with the development of breast cancer was 'anti-emotionality' (adjusted OR 1.19; 95% CI 1.05–1.35). In order to rule out the possibility that positive

results were found simply because 11 traits were analysed, the authors replicated the finding in comparison with another matched control group, which minimised the likelihood of a chance finding.

Tijhuis and colleagues (2000) studied emotional control, as measured on the Courtald Emotional Control Scale, and the subsequent risk for cancer during 10 years of follow-up in a sample of 590 men in The Netherlands in 1985 [40]. The adjusted risk for cancer at any site was increased with borderline significance for men with intermediate levels of emotional control of depression (RR 1.7; 95% CI 1.0–2.8), whereas men with a high level rather than a low level of control of depression had a relative risk of 1.5 (95% CI 0.9–2.5). All levels of control of anxiety were only insignificantly related to cancer risk, whereas no changes in risk were found with degree of overall control and control of anger.

3.3.3. Hopelessness and related factors

Greenberg and Dattore (1981) used the same cohort of US Army veterans as studied by Dattore [35] to examine the effect of dependence before illness, as measured by MMPI scores, in 58 men with cancer and in 67 controls with other diseases and 37 who were free of disease [41]. No differences in the mean score were found, and the MMPI scores for dependence were similar for the veterans and the background population.

Everson and colleagues (1996) examined the relationship between hopelessness, measured on a two-item scale, and the incidence of cancer at any site in a cohort of 2428 men aged 42–60 years between 1984 and 1989 [42]. Follow-up through to 1992 (mean 6 years) yielded 73 cases of cancer. A moderate-to-high degree of hopelessness was associated with an age-adjusted risk of 1.8 (95% CI 1.11–3.92), whereas the risk adjusted for multiple variates was non-significantly increased (RR 1.42; 95% CI 0.83–2.41). The rather short follow-up indicates that the results may be explained by the presence of occult disease.

In summary, the prospective studies of the effect of personality factors on the risk for cancer provide conflicting results. The hypothesis of a cancer-prone personality, described as cooperative, unassertive, patient, suppressing negative emotions and accepting external authority [45,46], was supported only in part by the exploratory studies of Dattore and colleagues [35] and Shaffer and colleagues [36]. The early results of Hagnell [34] must be interpreted with caution, as the conceptualisation of personality included intelligence and clinical judgement [34], and the early hypothesis of a highly extrovert, un-neurotic cancer-prone personality was not supported by the results of Schapiro and colleagues [37].

With regard to repression and control of emotions, four studies showed no association [23,24,38,39], whereas in one study control of depression appeared to affect the cancer risk [40], albeit with no convincing dose–response effect, in that intermediate control of depression was associated with a higher risk rather than high control of depression. In one study, hopelessness was found to be related to cancer risk [42], whereas in another study dependence was not [41].

4. Discussion

This review of studies of psychological factors and cancer does not indicate that these factors play a major role in cancer causation, when the possible roles of bias, confounding and chance are taken into account. Although we carefully excluded all quasi-prospective studies and case–control studies in which the information on psychological factors was based on personal memory, leading to the possibility of, especially, recall and observation bias, other sources of systematic error could apply to the studies that were reviewed. Insufficient sample size and length of follow-up and use of large numbers of analyses make it hard to rule out a role of chance in many of the studies. Furthermore, loss to follow-up and inadequate ascertainment of cancer cases limit the interpretation, especially of those studies finding the strongest effects [15,31].

Adjustment for confounding factors is essential. Although in most studies adjustment was made for age and sometimes for other confounding factors, either by matching or by statistical analysis, it is questionable whether the adjustment was adequate in most studies. Some of the intriguing findings reviewed above were for tobacco-related cancers [21,27,29]. As smoking is a very strong risk factor for certain cancers, the possibility of residual confounding due to inadequate control for smoking remains.

The lack of convincing evidence from well-conducted studies for a role of major life events as risk factors for cancer may be due to the fact that none of the studies took into account how the individuals perceived those life events. In addition, psychological stress as a risk factor for cancer may not be adequately assessed by measuring major life events, but could alternatively be assessed by a less specific measure that was more likely to reveal stable, intra-individual aspects of stress rather than the acute stress caused by external factors. However, two large prospective studies of daily job strain, as measured by the Karasek Job Content Questionnaire among 26 936 women in the American Nurses Health Study [47] and of perceived stress of daily activities in a Finnish cohort study of 10 519 women [48], showed no increase in the risk for breast cancer.

In the studies of depression as a risk factor for cancer, depression was defined as a continuous variable in some of the prospective studies [24–27,30] and as a psychiatric

diagnosis in others [15,28,29,31]. Hence, cancer incidence was either expressed as a function of the degree of depression or compared with that of the general population. The information may not be comparable. The two retrospective studies, one of which showed a slight increase in risk [32] and the other showing no increase [33], both relied on psychiatric diagnosis and comparison with the general population, thereby attenuating the risk estimates, as all persons with depression, diagnosed and undiagnosed, are included in the background rates. Another explanation for the disparate results regarding depression as a risk factor for cancer could be the lack of specificity in classifying the study participants; no fewer than 10 different instruments, eight standardised scales and two personal interviews, were used to assess the degree of depression or depressed mood in the prospective studies. Only two studies categorised persons according to chronicity of depression [15,30], and these studies indicated that only chronic depression increased the risk for cancer.

Defining personality is complex, because no one theory of personality is universally accepted. The prospective evidence reviewed here is characterised by diverse construct and measure definitions. There appears to be little support for the cancer-prone personality described by Temoshok [46]. Studies of some of the discrete traits or combinations of traits that constitute this personality type have yielded contrasting results. Furthermore, they must be viewed in the light of the wide variety of conceptualisations of similar theories, making interpretation almost impossible.

In the discussion of cause and effect, several criteria must be taken into consideration. With regard to the studies reviewed: (i) The association between the selected psychological variables and the risk for cancer, if any, must be considered to be weak; (ii) the lack of consistency of associations weakens the possible causal link between psyche and cancer; (iii) although several biological mechanisms whereby psychological factors might lead to an increased risk for cancer have been suggested [49] the plausible biological explanations are unclarified. A common, underlying biological susceptibility could determine both personality and the response to psychological stress, as well as the risk for developing cancer [49]. Another possible explanation is that psychological factors lead to impaired immune function, which would predispose the organism to the initiation and progression of neoplastic disease [49,50]. Indeed, increased risks of the immune-related cancer forms, lymphomas and malignant melanoma [51], were observed [17,21], but no other studies have replicated these intriguing findings. Furthermore, certain behavioural and lifestyle factors linked to the psychological factors in question may affect the risk for cancer [49]; and (iv) dose–response relationship was observed in two studies with the length of exposure and severity of depression [15,30], but no clear dose–response relationship was observed with regard to personality [40]. According to these criteria, therefore, the available evidence does not indicate that psychological factors are established risk factors. The strict criteria for excluding a risk factor as carcinogenic in studies in which the methods are considered sound also include a requirement that the relative risk in all the studies should be around unity for all levels of exposure. This criterion is also not fulfilled, leaving the field open to further investigation.

Future studies might benefit from better-articulated hypotheses, prospective design and large study populations to ensure adequate statistical power. They should also allow less ambiguous interpretations of the data by including detailed information about possible confounders. In addition, we must consider carefully whether health behaviour should be regarded as an intermediate rather than a confounding factor, as this would have wide implications for our understanding of the possible association between psychological factors and the risk for cancer. In this intriguing area of research, high scientific quality can be achieved only by taking into account the fact that psychological factors are closely related to the biological, physiological and behavioural characteristics of individuals. Psyche cannot be separated from soma.

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