Should psychological events be considered cancer risk factors?

Existe-t-il un lien entre un événement psychique et le risque de survenue d’un cancer ?

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Received 4 March 2008; accepted 15 December 2008
Available online 2 April 2009

Abstract

Background. – The possibility that life events, personality, or depression can be considered cancer risk factors has been of great interest among the lay public and doctors.

Methods. – A critical review of different publications of meta-analyses, case–control studies, and cohort studies investigating a possible relation between the onset of cancer and life events, personality disorders, or depression is presented. Many studies have methodological limitations with possible bias, which may explain controversial results. We selected 32 studies from which conclusions can be drawn with the least amount of bias.

Results. – Eighteen out of 32 publications whose methodology permits unbiased interpretation show no link between psychological factors and the risk of cancer. Six publications show a significant link only in one or several subgroups and four surveys, three of which were published by the same author, show an inverse relation in gynecological cancers. As for life events and breast cancer, the results are slightly in favor of a positive relation in four studies; four others showed no relation, and one argues in favor of an inverse risk, which means a protective effect for this cancer. For life events and other cancers, studies show no relation, with the possible exception of cancers in women where endogenous estrogens can play a role (colon and endometrial cancers), where there is an inverse relation. No studies showed a significant relation between personality features and the risk of cancer. The studies of a possible relation between depression and cancer are controversial and no conclusion can be drawn.

Conclusion. – It cannot be confidently concluded that life events, personality features, or depression play a role in the onset of cancer.

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Keywords: Cancer; Risk factors; Life events; Psychological stress; Personality disorder; Depression

Résumé

Position du problème. – L’idée d’un lien causal entre un événement psychique et le déclenchement d’un cancer est largement répandue dans le public et parmi les médecins.

Méthode. – Une revue des publications récentes concernant les études épidémiologiques consacrées à ce sujet a été effectuée, avec une analyse des différents types d’études (méta-analyses, cas-témoins, cohortes) sur le rôle des événements difficiles de la vie (stress), des troubles de la personnalité et de la dépression sur l’apparition des cancers du sein et d’autres types de cancers. Il existe en fait une grande hétérogénéité dans les études, avec des biais pouvant expliquer des résultats divergents. Nous n’avons retenu dans cette analyse que les 32 études permettant une interprétation la moins biaisée possible.

Résultats. – Au total 18 études sur les 32 dont la méthodologie a permis une interprétation ne montrent pas de lien entre facteurs psychologiques et risque de cancer, six autres ne montrent une signification que dans certains sous-groupes et quatre enquêtes, dont trois du même auteur, montrent une liaison inverse pour des cancers féminins. En ce qui concerne les éléments stressants de la vie et les cancers du sein, les résultats sont légèrement en faveur d’une augmentation du risque pour quatre études, mais sont contrebalancés par quatre études non significatives et une en sens inverse. Pour les éléments stressants de la vie en relation avec les autres cancers, les diverses études sont plutôt en faveur d’une
absence de lien à l’exception, peut-être, des cancers ayant un lien avec l’environnement estrogénique chez les femmes (cancer du côlon et de l’endomètre) où le stress est protecteur. Aucune des études ne montre de lien significatif entre un trouble de la personnalité et le risque de cancer. Enfin, en ce qui concerne le lien entre dépression et risque de cancer, aucune conclusion ne peut être tirée.

Conclusion. — Dans l’état actuel des connaissances, il apparait difficile de conclure à la responsabilité des événements stressants de la vie, d’une personnalité particulière ou d’une dépression sur l’apparition de certains cancers.

1. Introduction

The idea that there is a relation between a psychological event and later onset of cancer is widely held by the general public, the media, and patients in France. In Australia, 40% of women think that stress can be the cause of breast cancer [1]. The hypothesis of a relation between cancer and a psychological event has been widely debated in the literature since 1701, by Gendron [2] at that time, then in 1846 by Guy [3]. Many scientific studies have attempted to prove this hypothesis through epidemiological, biological, and experimental studies in animals. Several hypotheses have been postulated: can a stressful life event contribute to the onset of cancer as an abnormal reaction to stress? Does a particular personality pattern predispose an individual to cancerous disease? Finally, is depression related to initiating or promoting a tumor?

The animal experiments have shown contradictory results. Depending on the experiment, stress increases the growth of an implanted tumor or accelerates the appearance of spontaneous tumors, with variable results depending on the animal lineage. Animal tumors of viral origin behave differently to stress compared to other types of tumors because of their relation with the animal’s immune functions. In addition, the stresses induced in animals are often acute – electric shocks or confinement to small cages – and are therefore difficult to extrapolate to humans [4–6]. This paper presents a literature review of epidemiological studies selected for their methodological quality so that the least biased interpretations possible could be made.

2. Methods

A general review of the literature was carried out in 1987 [5]. Since then, a number of general reviews have been published, including reviews by MacGee [7], Butow et al. [8], Reynaert et al. [9], and Nielsen et Gronbaek [10] as well as meta-analyses in 1999 and 2003 [11,12], which for the most part examined epidemiological data.

We selected articles in journals that were referenced in the Medline database. Given the two meta-analyses already published, stressful events were searched for only from 2003 on, with the following criteria: [“neoplasms” AND “causality” AND “stressful events”]. For the relations between personality disorders or depression and the onset of cancer, the search did not specify a time frame and was done based on the following criteria: [“neoplasms” AND “causality” AND “personality disorders”] and [“neoplasms” AND “causality” AND “psychologic depression”].

The main epidemiological studies conducted were classical case–control studies, short case–control studies where the cases and controls were patients who were questioned on stresses experienced in the past while they were waiting for confirmation of the malignancy or benignity of their biopsies, or cohort studies.

In our review, we did not retain the classical case–control studies in which memory bias results in an ill patient having a greater tendency to remember particular stressful events than a healthy control subject. Similarly, we did not select studies presenting insufficiently defined stress measurements (vague questions, absence of scored results). Likewise, studies with small populations (fewer than 100 cases) and studies that did not adjust for the main cancer risk factors were not considered. For breast cancer, for example, we did not take into account the studies that did not adjust for reproductive or hormonal factors. We retained a total of 32 studies out of the 51 reviewed: the two meta-analyses cited above as well as the cohort studies and the case–control studies responding to the criteria outlined above.

This paper will successively examine the epidemiological studies on stressful events and breast cancer risk, then the studies of the same type investigating other forms of cancer, then the relations between personality and cancer, and finally the possible relations between depression and cancer. We excluded from this review all studies on changes in the progression of cancer as influenced by the effect of psychological stress or supportive intervention.

3. Results

3.1. Stressful life events and breast cancer risk

We present here two meta-analyses, one by Petticrew et al. [11] on difficult life events and breast cancer risk published in 1999 and the other by Duijts et al. [12], published in 2003, which reviewed the research published before these dates (Table 1).

Petticrew et al. reviewed the studies on this topic up to 1997, classifying them according to the type of stress: bereavement or other stressful life events. After having selected all types of epidemiological studies, for all levels of research quality, they noted that the 29 studies found varied greatly in terms of methodological quality.

In cases of bereavement and the relation with breast cancer, the meta-analysis carried out on 11 quality-selected case–
Table 1
Relation between stress and risk for breast cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years studied</th>
<th>Type of study</th>
<th>Number of cases</th>
<th>Criterion studied</th>
<th>Results OR# or RR## [95% CI]</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petticrew 1999 [11]</td>
<td>1966–1997</td>
<td>Meta-analysis 11 case–control, 1 cohort</td>
<td>58 787 females</td>
<td>Bereavement</td>
<td>OR = 1.06 [0.95–1.18]</td>
<td>Studies selected for the meta-analysis out of 29 reviewed</td>
</tr>
<tr>
<td>Petticrew 1999 [11]</td>
<td>1966–1997</td>
<td>Meta-analysis on 5 studies: 4 case–control and 1 cohort</td>
<td>Not mentioned</td>
<td>Adverse life events other than bereavement</td>
<td>OR = 0.8 [0.61–1.06]</td>
<td>Selection of 5 studies of sufficient quality of 15 reviewed</td>
</tr>
<tr>
<td>Lillberg 2003 [13]</td>
<td>1981–996</td>
<td>Cohort of twins and case–control study embedded in this cohort Follow-up: 15 years</td>
<td>10 808 females 180 cases</td>
<td>Stressful life events occurring before entering study (number of events and score obtained by weighting events on Holmes and Rahe scale)</td>
<td>RR = 1.07 [1.00–1.15] for each additional adverse event RR = 1.35 [1.09–1.67] for each additional adverse event among the 5 major stresses only</td>
<td>Overall and one subgroup significant and dose-response relation Adjusted</td>
</tr>
<tr>
<td>Lambe 2004 [15]</td>
<td>Females born between 1925 and 1976</td>
<td>Case–control in population cohort</td>
<td>27 571 cases 141 798 controls</td>
<td>Bereavement (death of a child)</td>
<td>OR: 1.05 [0.96–1.15]</td>
<td>Overall NS⁰, One subgroup significant</td>
</tr>
<tr>
<td>Kroenke 2004 [16]</td>
<td>1992–2000</td>
<td>Cohort Follow-up: 8 years</td>
<td>69 886 females 46–71 years 1700 cases</td>
<td>Stress declared and hours of nursing work Estradiol rate</td>
<td>Work-related stress NS⁰ Caregiving duration &gt; 15 h/week: decrease in estradiol level S⁰</td>
<td>Adjusted Protection hypothesis?</td>
</tr>
<tr>
<td>Nielsen 2005 [17]</td>
<td>1981–1999</td>
<td>Cohort Follow-up: 18 years</td>
<td>6689 females 251 cases</td>
<td>Stress declared (daily self-questionnaire)</td>
<td>Low level/high level: RR = 0.60 [0.37–0.97]</td>
<td>Adjusted</td>
</tr>
</tbody>
</table>

OR: odds ratio, RR: relative risk.

⁰ S: test significant p ≤ 0.05.

⁰⁰ NS = Test not significant, p > 0.05.
control studies concluded in an odds ratio (OR) of 1.06 with the following 95% confidence interval (95% CI) equal to 0.95 – 1.18, i.e., a nonsignificant relation. The only cohort study investigated 4905 widows: the risk of death from breast cancer was not higher in widows than in population controls, and the study observed a trend toward decreasing breast cancer risk with increasing time as a widow.

Considering the influence of a stress other than bereavement, Petticrew et al. retained only five studies (five selected case–control studies and one cohort study) that were considered to be sufficiently high standard in terms of methodological quality (quality score greater than the mean). The resulting meta-analysis showed an OR of 0.8 (95% CI = 0.61 – 1.06), which led him to conclude that there was no relation between stress and breast cancer.

Duijts et al.’s meta-analysis [12] reviewed 27 studies published between 1966 and 2002, including a certain number of publications in Petticrew’s meta-analysis. Duijts et al. also noted several biases in a large number of studies, showing up as heterogeneity in the results (except for the “death of spouse” category). His meta-analysis did not argue in favor of an overall association between stressful life events and breast cancer, except for death of a spouse, for which there appeared to be an association that he qualified as modest: OR = 1.37 (95% CI = 1.10 – 1.71).

We analyzed the data published in the literature since this last publication by Duijts et al. until February 2008.

The Lilberg study [13] was a cohort study of female twins followed from 1981 to 1996 with a case–control study. The cases of breast cancer were collected from the cancer registry. A questionnaire on stressful life events was filled out by these women upon their inclusion in the study. The results were adjusted on the known risk factors for breast cancer. The relative risk (RR) was 1.07 (95% CI = 1.00 – 1.15) for the adverse life events combined, regardless of their importance. If only the five major adverse events are taken into account, the overall relative risk was 1.35 (95% CI = 1.09 – 1.67). More specifically, for a divorce or a separation, it was 2.26 (95% CI = 1.25 – 4.07); for death of the spouse, it was 2.00 (95% CI = 1.03 – 3.88), and for death of a close relation, it was 1.36 (95% CI = 1.00 – 1.86). Although multiple subgroup analyses do not provide sufficient confidence in partial results, the overall significance should be retained, with an increase, although modest, in risk.

Helgesson et al. [14] studied a cohort of 1462 Swedish women between 38 and 60 years of age. The stress experienced had been reported by the women at the beginning of the study between 1968 and 1969 and the cancers collected until 2002. The incidence of breast cancer in these women who had declared a high level of stress was compared to the incidence in women who declared no stress. After adjustment for confounding factors, the relative risk was 2.1 (95% CI = 1.2 – 3.7) for women who presented a high level of stress.

Lambe et al. [15] conducted a case–control study nested in a national cohort study in Sweden, researching whether the loss of a child (corresponding to a severe adverse event) predisposed patients to breast cancer after adjustment for age, parity, age at the birth of the first child, and education level. The relative risk was 1.05 (95% CI = 0.96 – 1.15). The authors noted a significantly increased risk if the woman had lost her only child between the ages of one and four years. Given the number of comparisons made, the authors believed that this latter result was random and concluded in the absence of an increased risk after the death of a child.

Studying a sample in the cohort of 69 886 American nurses aged 46 – 71 years, Kroenke et al. [16] analyzed the stress experienced by the nurses as well as the number of hours of care giving (considered an occupational stress). The stress experienced and a high number of hours of care giving were not predictive of a higher incidence of breast cancer. This author also studied the variations in estradiol rates as related to stress and found that these rates were significantly lower in nurses who had felt stressed and worked more. This observation could explain a relation with a reduction in the risk for breast cancer in women who were highly stressed, as observed by Nielsen [17].

Nielsen et al. analyzed a cohort study initiated in 1976 in Copenhagen, the Copenhagen City Heart Study [17]. In this study, conducted between 1981 and 1983, 70% of 7018 women responded to a questionnaire on daily stressful events in terms of both intensity and frequency. The author took into account other risk factors except family history and age at menstruation onset and at first pregnancy. During the follow-up period (16 – 19 years), 251 had breast cancer. The relative risk of presenting breast cancer was lower in highly stressed women (in intensity and frequency), with an overall RR of 0.60 (95% CI = 0.37 – 0.97) and a dose-response effect: the higher the stress was, the more risk decreased.

Problems at work as an indicator of stress were correlated with breast cancer incidence in a cohort of 36 332 Swedish women aged 30 – 50 years. After a 12-year follow-up, women working full time, who had a job over which they exercised no control and that was very demanding, had a higher incidence of breast cancer (RR = 1.4; [95% CI = 1.1 – 1.9]) than those who had control over their job and were subjected to less pressure [18].

All in all, of the nine studies that we selected, including three meta-analyses, one case–control study nested within a cohort, four cohort studies, and one mixed study, four showed no significant results (two of which were meta-analyses on a selected group); four others showed an increase in the risk of breast cancer with stress, with a dose-response effect in two of them. A single study showed stress to have a protective effect.

### 3.2. Stressful life events and risk for other cancers

Studies of other cancers than breast cancer show results that are quite incongruent (Table 2).

#### 3.2.1. All cancers

Keehn conducted a study on ex-World War II and Korean War prisoners and did not observe that captivity, a substantial stress, increased cancer mortality [19].
<table>
<thead>
<tr>
<th>Study</th>
<th>Years studied</th>
<th>Type of study</th>
<th>Number of cases</th>
<th>Criterion studied</th>
<th>Type of cancer</th>
<th>Results or #OR or RR## [95% CI]</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keehn 1980 [19]</td>
<td>1940–1965</td>
<td>Case–control Prisoners</td>
<td>5201 cases 3257 controls</td>
<td>Captivation</td>
<td>All cancers</td>
<td>SMR all causes: 0.99 (NS)</td>
<td>Comparison of mortality</td>
</tr>
<tr>
<td>Levav 2000 [20]</td>
<td>1970–1990</td>
<td>Cohort</td>
<td>6 284 exposed 1 019 255 nonexposed</td>
<td>Bereavement for death of a child</td>
<td>All cancers + specific cancers</td>
<td>Overall: war RR = 0.95 [0.88–1.04]</td>
<td>Not adjusted for specific risks of cancer locations</td>
</tr>
<tr>
<td>Johansen 1997 [21]</td>
<td>1943–1992</td>
<td>Cohort of parents</td>
<td>11 231 parents 1665 cancers in children</td>
<td>Child with cancer</td>
<td>All cancers</td>
<td>SIR = 1.0 [0.9–1.0]</td>
<td>Study on population registry</td>
</tr>
<tr>
<td>Li 2002 [22]</td>
<td>1980–1996</td>
<td>Cohort of parents</td>
<td>21 062 parents</td>
<td>Death of a child</td>
<td>All cancers</td>
<td>Increase only for tobacco-related cancers: SIR = 1.65 [1.04–2.59]</td>
<td>Continuation of previous study</td>
</tr>
<tr>
<td>Bergelt 2006 [23]</td>
<td>1991–2002</td>
<td>Cohort</td>
<td>8736 eligible 1011 cancers</td>
<td>Number of stressful events (list of 12 stressful events)</td>
<td>All cancers</td>
<td>1 stressful event: RR = 0.95 [0.81–1.11]</td>
<td>Adjustment for risk factors</td>
</tr>
<tr>
<td>Nielsen 2008 [25]</td>
<td>1981–2000</td>
<td>Cohort</td>
<td>6488 females: 162 cases</td>
<td>Stress declared, intensity and frequency</td>
<td>Colorectal</td>
<td>Females, moderate stress: RR = 0.60 [0.37–0.68] and high: RR = 0.52 [0.23–1.14]</td>
<td>Adjusted risk factors</td>
</tr>
<tr>
<td>Nielsen 2007 [27]</td>
<td>1981–2000</td>
<td>Cohort Follow-up: 19 years</td>
<td>6760 females cases</td>
<td>Stress declared, intensity and frequency</td>
<td>Endometrium</td>
<td>RR = 0.88 [0.76–101] per 7 points on stress scale</td>
<td>Adjusted for other factors</td>
</tr>
<tr>
<td>Nielsen 2007 [28]</td>
<td>1981–2000</td>
<td>Cohort Follow-up: 19 years</td>
<td>5496 males 328 cases</td>
<td>Stress declared</td>
<td>Prostate</td>
<td>RR = 0.99 [0.90–1.09]</td>
<td>Adjusted for other risk factors</td>
</tr>
</tbody>
</table>

#OR: odds ratio, RR##: relative risk, SMR: standardized mortality ratio, SIR: standardized incidence ratio.

a NS: p > 0.05.
b S: p ≤ 0.05.
In the meta-analysis on case–control studies retained by Petticrew on all types of cancer, he calculated an OR of 1.06 (0.95 – 1.18) for stress related to bereavement.

In 2000 in Israel, Levav et al. [20] studied the effect of losing a child (war-related death or accidental death) on the parents. He found no overall relation for “all cancers” but a significant increase in certain cancers: leukemias, lymphomas, and melanomas for either cause of death. These risks were adjusted for age but not for the specific risk factors for these types of tumor.

The cohort study conducted by Li et al. [22] follows an identical study by the same authors [21]. In the first study using the Denmark cancer registry, the authors studied the incidence of cancers in the parents of all the children with cancer. They observed a standardized incidence ratio (SIR) of 1.0 (95% CI = 0.9 – 1.0), identical in mothers and fathers. The second study (22) investigated a larger population and cancers in parents who had lost a child. In multivariate analysis, only a RR of 1.18 (95% CI = 1.01 – 1.37) was noted in mothers who had lost a child, but the investigators observed that this risk was related to the increase in cancers related to tobacco. There was not an increase in breast cancers or cancers related to alcohol, virus, or hormone intake. The authors concluded that the increase in risk may be related to general life stress, leading to an increased consumption of tobacco.

Still in Denmark, Bergelt et al. [23] studied the same Copenhagen cohort assembled in 1976 from a sample of subjects entered in the cohort between 1991 and 1994 and analyzed the relation between stress and incidence of all cancers. The subjects responded to a list of 12 stressful events. They were then classified into four groups according to the number of stressful events they reported. Cancer cases were identified using the Denmark cancer registry. An adjustment was made on the relevant variables. The median duration of follow-up was 9.3 years. Of the 8736 persons studied, 1011 developed cancer. The results after adjustment do not argue in favor of an increase in cancer incidence, whatever the number of stressful events.

### 3.2.2. Colorectal cancers

Kojima’s cohort study [24] in Japan, with follow-up lasting nine years, sought to determine whether there was a relation between stress and colorectal cancer death. The results were not homogeneous: the relative risk was high (RR = 1.64; [95% CI = 1.01 – 2.66]) for the colon in women if the stress was very intense, but it was not high in women for rectal cancer or in men for cancers of the colon or rectum.

Nielsen et al. [25] studied the incidence of colorectal cancers in 6488 women and 5426 men in the Copenhagen cohort, questioned between 1981 and 1983 on the level of perceived stress in terms of intensity and frequency. Patients were followed up until 2000 and cancer incidence was obtained from the Denmark cancer registry. The relative risk for women was 0.52 (95% CI = 0.23 – 1.14) and 0.60 (95% CI = 0.37 – 0.98) for a high and moderate levels of stress, respectively, compared to women who had experienced no stress. It should be noted that only moderate stress was significantly protective here. No association was noted in men.

### 3.2.3. Cervical cancer

Coker’s short case–control study [26] investigated women with in situ cervical cancers compared to women presenting cervix dysplasias and controls with a normal cervix from a population with a low socioeconomic level. The study sought to identify a relation between uterine cervical lesions and the number of stresses in white and African-American women. Because of the differences in the prevalence of uterine lesions and the number of stresses in the two populations, the analysis was carried out separately in the two groups. After adjusting for known risk factors, including HPV infection, the authors noted an OR of 1.20 (95% CI = 1.04 – 1.38) only in white women and for certain types of stress (relations with the partner: divorce, infidelity, or violence).

### 3.2.4. Endometrial cancer

Nielsen et al. [27] analyzed data from 6781 women from the above-mentioned Danish cohort followed up until 2000. There was no positive relation between stress and endometrial cancer. The nonsignificant RR was 0.88 (95% CI = 0.76 – 1.01) for a seven-point increase on the stress scale. The association became significant, in the sense of reducing risk, in women on hormone replacement therapy and in women who were not overweight. The author hypothesized a stress-related reduction of estrogen synthesis, decreasing estrogen’s promoter effect.

### 3.2.5. Prostate cancer

Using the same Copenhagen cohort, Nielsen et al. [28] studied the possible relation between stress and prostate cancer risk in 5496 men followed up until 2002. No relation was noted between stress and prostate cancer (RR = 0.99; [95% CI = 0.90 – 1.09]).

We analyzed 11 studies here: one meta-analysis, two case–control studies, and eight cohort studies. Five studies were not significant, four other studies did not produce significant results in the overall group but showed an increase in cancer risk in one or several subgroups, and two cohort studies had significant results with an inverse association for female subgroups (colorectal and endometrial cancers).

### 3.3. Personality disorders and cancer risk

The personality and psychological disorders are the source of another hypothesis that has been postulated as possibly predisposing to or being the source of cancer, particularly breast cancer. Problems expressing emotions, inhibition of anger, a hopeless attitude, suppression of one’s own needs in preference to the needs of others have all been advanced as cancer promoting. As early as the 1950s, authors have hypothesized a relation between diseases and this personality type, described as a type C personality [29–31] contrasting with the type A personality, competitive, willful, and ambitious. Another psychological trait was studied as predisposing to cancer: the inability to cope (Table 3).

Keehn et al. [32] analyzed the causes of death in American soldiers reformed in 1944 for neurosis and observed no differences in cancer frequency with the control group.
In 1966 in Sweden, Hagnell [33] studied a cohort of subjects in good health followed for 10 years. They filled out a personality questionnaire at the beginning of the study. Overall, no significant association was demonstrated. Only a subgroup of women characterized by emotional instability showed an increase in cancer risk ($p < 0.005$).

Price et al. [34] conducted a study on the personality of women recalled for assessment after routine mammography in a breast screening program. Different validated questionnaires measuring defense mechanisms and conflict resolution were used. The study also included a scale of expression and control of emotions, a self-esteem and depression scale, and an anxiety score. A multivariate analysis showed no differences on the various personality traits ($p = 0.28$).

Over seven years, Nakaya [35] studied a cohort with 30,277 subjects who had taken personality tests. The relative risk, adjusted for sex, age, education, tobacco and alcohol consumption, body mass index (BMI), and family history of cancer, showed no association between the different types of personality and cancer.

Bleiker’s case–control study [36] investigated women living in Nijmegen, the Netherlands, who were participating in a study on breast cancer mammographic screening. These women were part of a cohort who had initially responded to a questionnaire on personality and factors predisposing to breast cancer. Overall, expression or suppression of emotions, adjusted for risk factors for breast cancer, was not correlated with tumor risk. However, the authors indicated an association with the absence of emotional reactivity or with the lack of confidence in one’s own feelings ($OR = 1.19; [95% CI = 1.05 – 1.35]$). In a recent publication [37] on the same cohort, but where the time to recruitment of cases and controls after the initial questionnaire was longer (a mean seven additional years), the same authors no longer found a significant relation between personality traits and the increase in breast cancer risk, after adjustment for risk factors. All five studies retained – three case–control studies and two cohort studies – were nonsignificant. In only a single case did a transitory relation appear in a subgroup of women characterized by an extraverted personality that did not control stress well.

### Depression and cancer risk

Depression is also a condition that has been proposed to predispose to cancer. Persky and Shekelle [38] studied a cohort

<table>
<thead>
<tr>
<th>Study</th>
<th>Years studied</th>
<th>Type of study</th>
<th>Number of cases</th>
<th>Criterion studied</th>
<th>Type of cancer</th>
<th>Results or #OR RR## [95% CI]</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keehn</td>
<td>1974–1969</td>
<td>Case–control</td>
<td>9813 cases of neurosis 9942 controls</td>
<td>Neurosis</td>
<td>All cancers</td>
<td>Mortality all causes OR: 1.21 ($p &lt; 0.001$) Mortality per cancer OR: 0.95 (NS)</td>
<td>Comparison of mortality</td>
</tr>
<tr>
<td>Hagnell</td>
<td>1947–1957</td>
<td>Cohort</td>
<td>2250 people</td>
<td>Sjöbring personality questionnaire</td>
<td>All cancers</td>
<td>Extroverted women have more cancers ($p &lt; 0.005$)</td>
<td>Overall NSa</td>
</tr>
<tr>
<td>Price</td>
<td>1994–1997</td>
<td>Case–control in screening cohort</td>
<td>298 cancer</td>
<td>Psychometric questionnaires (DSQ 40, LCR, EEC, Spielberger, etc.)</td>
<td>Breast cancer</td>
<td>No difference between different personality traits in multivariate analysis ($p = 0.28$)</td>
<td>A single subgroup significant Adjusted for risk factors</td>
</tr>
<tr>
<td>Nakaya</td>
<td>1990–1997</td>
<td>Cohort</td>
<td>947 negative 999 benign 30 277 people</td>
<td>Personality questionnaire Eysenck</td>
<td>All cancers and specific sites</td>
<td>No association between personality traits, all cancers, or with certain sites: stomach, colorectal, breast, lung</td>
<td>Adjusted for other risk factors</td>
</tr>
<tr>
<td>Bleiker</td>
<td>1989–1994</td>
<td>Case–control in screening cohort</td>
<td>986 cases 131 cancer 771 controls</td>
<td>Personality questionnaire (SAQ-N)</td>
<td>Breast cancer</td>
<td>Anti-emotional personality test values in cancers OR = 1.19 [1.05–1.35].</td>
<td>Overall NSb, not adjusted</td>
</tr>
<tr>
<td>Bleiker</td>
<td>1995–2003</td>
<td>Case–control in screening cohort</td>
<td>217 cancer 868 controls</td>
<td>Personality questionnaire (SAQ-N)</td>
<td>Breast cancer</td>
<td>No differences between diverse personality traits</td>
<td>One subgroup significant Continuation of preceding study</td>
</tr>
</tbody>
</table>

#OR: Odds ratio, ##RR: relative risk.

a NS: not significant $p > 0.05$. 

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Table 3
Relation between personality and risk for cancer.
### Table 4. Relation between depression and risk for cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years studied</th>
<th>Type of study</th>
<th>Number of cases</th>
<th>Type of cancer</th>
<th>Results or #OR: RR## 95% CI</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn 1988 [39]</td>
<td>1968–1988</td>
<td>Cohort</td>
<td>8932 females</td>
<td>Personality score (MMPI)</td>
<td>Breast cancer: Comparison of scores</td>
<td>Adjusted for risk factors. Follow-up: 20 years 117 cases RR = 1.4 [0.8–2.4]</td>
</tr>
<tr>
<td>Kaplan 1988 [40]</td>
<td>1965–1982</td>
<td>Cohort</td>
<td>6848 subjects</td>
<td>Depression score</td>
<td>All cancers: Males: RR = 0.97 NS a</td>
<td>Adjusted for education and income. Follow-up: 7 years 476 cancer deaths from cancer. Females: RR = 1.27 NS a</td>
</tr>
<tr>
<td>Dalton 2002 [42]</td>
<td>1969–1993</td>
<td>Cohort</td>
<td>89491 subjects</td>
<td>Hospitalized for depression</td>
<td>All cancers: SIR of 1.05 (95% CI = 1.03 – 1.07) related to an excess in cerebral tumors the first year. If this first year is excluded from the analysis (because of a possible confusion between neurological, psychiatric, and oncological symptoms), the overall SIR for cancers not related to tobacco was 0.99 (95% CI = 0.95 – 1.02). Using the Copenhagen cohort analyzed above for the relations between stress and cancer, Bergelt et al. [44] studied the relation between depression and cancer. He showed that in cases with a high depression score, the risk of developing cancer was lower (RR = 0.80; [95% CI = 0.66 – 0.96]). This result is also valid for cancers related to tobacco, alcohol consumption, and viral infection (Table 4). Of the seven cohort studies retained, only two argued significantly in favor of an increase in the risk of cancer in depressive subjects. In contrast, a third showed a lower risk in depressive subjects, and four other cohorts did not demonstrate a relation.</td>
<td></td>
</tr>
</tbody>
</table>

#### 4. Discussion

This review of 32 studies only included studies that a priori did not present major biases, bringing out the following points.

For stressful life events and breast cancer, the results are slightly in favor of an increase in risk in four studies, but this conclusion is not totally conclusive because of four studies with nonsignificant results and one showing an opposite trend.

For stressful life events and other cancers, the diverse studies tend toward a conclusion of no relation between the two, with the possible exception of a relation with the estrogenic environment in women: colon and endometrium cancers where, surprisingly, stress appears to be a protective factor.
None of the five studies showed a significant relation between personality disorder and cancer risk, with the exception of a particular subgroup.

Finally, no conclusion can be drawn on the relation between depression and risk for cancer.

All in all, 18 studies out of 32 whose methodology made interpretation possible showed no relation between psychological factors and risk for cancer, six others showed a significant relation only in one or several subgroups, and four studies, three by the same author, showed an inverse relation in female cancers. Moreover, the interpretation of these studies remains delicate. For example, the time from the adverse life event and the appearance of cancer, when it is mentioned, varies from one study to another. Johansen segmented his study according to the time passed since the adverse event and found no modification in risk for any period. However, Li [22] analyzed his cohort with two time periods: 1 – 6 years, showing a RR of 1.10 (95% CI = 0.9 – 1.34), and 7 – 18 years, with a RR that became significant (RR = 1.18; [95% CI = 1.01 – 1.37]). For the five major stressful events that occurred in the five years preceding the inclusion in the cohort, Lilberg [13] also found a different result depending on the time period: the RR was 1.69 (95% CI = 1.13 – 2.51) for the 1982 – 1988 time period and the results were nonsignificant (RR = 1.22; [95% CI = 0.96 – 1.56]) for 1989 – 1996. These results change if major stressful events occurring over the entire period preceding inclusion are taken into account (RR = 1.23; [95% CI = 0.85 – 1.78]), nonsignificant for the first period and significant (RR = 1.27; [95% CI = 1.04 – 1.56]) for the second.

Another problem concerns the variation in the criterion considered from one study to another. It can be a well-defined event such as the death of a loved one representing a major event on the Holmes and Rahe scale [45]; in other studies it is a questionnaire developed specifically for the study [13,24] or a list of stressful events (Bergelt [23]). This variability in the evaluation criterion may well modify the results as well as the power of the tests, which depends on the variance of this criterion.

Another point concerns the pathology studied: nearly all the studies looked into breast cancer and few examined other types of tumors. Breast cancer was chosen because of its frequency and the biological hypotheses on the role of steroidal hormones in both the genesis of these cancers and on the psyche. Nielsen [27] explains the inverse relation between daily stress and breast cancer risk that she observed through a lower endogenous estrogen rate in supposedly stressed women. Moreover, she observed that this protection related to stress was only significant (RR = 0.83; [95% CI = 0.72 – 0.97]) in women with a normal weight or in those taking hormone replacement therapy.

In contrast, the defenders of the theory that stress is the source of cancer claim that stress works through the immune system. It has indeed been observed that intense and long-lasting immunodepression predisposes patients to the appearance of certain cancers such as lymphomas, Kaposi sarcoma, and skin cancers in AIDS patients or in transplantation patients given immunosuppressor treatments. Relations have also been demonstrated between stress and hypothalamic neurohormones, hypophysial hormones, secretion of cortisone, adrenaline, and sex hormones, which may play a role in initiating or promoting certain cancers [46,47].

The existence of a possible relation clearly is not equivalent to demonstration of a causal relation. The decrease in immunocompetent cells in subjects under stress or other aggressions has been described, but these are not severe and long-lasting deficiencies. A number of studies have been conducted on the modification of biological immune parameters after a stressful event, or even after the benefit of social support, but nearly all of these studies were conducted on patients, particularly women, who already had cancer at the time of the study, notably breast cancer. The possibility of stress and immune changes playing a role in carcinogenesis remains an interesting hypothesis deserving future research, as does the hypothesis suggesting a relation between the rate of steroid sex hormones, adverse life events, and cancer.

Finally, the demonstration of a causal relation between stress, personality disorder, depression, and cancer risk in epidemiological studies of a good level of quality require that a certain number of criteria be combined:

- the majority of the studies should provide significant and concordant results with risks on the same scale;
- the observation of a dose-response relation should support the causal hypothesis;
- solid underlying biological hypotheses should support the study results.

Yet in this review, none of these points was totally verified. As for the meaning of the studies, we found that of the group of studies retained, 23 provided globally nonsignificant results with varying power, five of which found significant results in one or several subgroups; five showed a significant increase in risk related to the variables studied (four of which investigated stress and breast cancer); and four studies with significant results (three of which were conducted by the same author, in female cancers) where stressful events had a protective effect. The dose-response relation was only observed in one study [13]. The biological hypotheses are not verified to a sufficient degree.

This review has shown that with today’s knowledge and in agreement with the majority of the studies reviewed, it seems difficult to conclude in the responsibility of stressful life events, a particular personality, or depression in the induction or even the promotion of certain cancers.

### 5. French version


### References


