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Mind as a risk factor for cancer—some comments†

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Introduction

It is striking how often psychological factors are included in conversations about life in general and illness in particular. We ascribe the occurrence of disease to certain personality traits, recent episodes of stress or major life events. In our understanding of illness, we consider that psychology plays a role in all aspects of the risk, contributes to healing and influences the outcome.

With better understanding of the causes of infectious diseases and the availability of treatment strategies for many of them, the role of psychological factors has narrowed down to chronic disease. Most chronic conditions do not appear to be associated with infectious agents, and psychological factors became an obvious target in the search for explanations. In the early studies, it was suspected that chronic diseases such as gastric ulcer, cardiovascular disease, diabetes and asthma were completely or partly associated with mind factors. As the factors that play the major role in the causation of these illnesses became clear, however, psychological factors were largely abandoned as targets for preventive action, although, in relation to cardiovascular disease for instance, it was argued that stress in daily life might be one causal factor.

Cancer has regularly been reported to be associated with depressive mood, genuine clinical depression, personality traits and exposure to severe stress such as major negative life events [1]. Perhaps the main reason for suspecting that the mind is associated with the risk for cancer is the lack of other hypotheses with regard to the agents responsible. Despite growing knowledge about cancer risk factors, we do not know the causes of about one-third of the incident cases. The idea that the mind causes cancer also arose from individual experiences of the interactions between stress in the broadest sense and physiological reactions, including heart palpitations, extrasystoles, sweating and a general feeling of dysfunctional homeostasis. The somatic system reacts to psychologically stressful exposures, and these well-known, well-characterized psychosomatic interactions have been accepted as proof of concept.

The prevailing hypothesis is that exposure to mind-associated factors, including major life events, depression and personality traits, impairs the immune function and subsequently predisposes people to the initiation or promotion of cancer. Thus, patients with well-defined disorders of the immune system are at increased risk for non-Hodgkin lymphoma [2]. As mind factors may also influence lifestyle in general, any association observed might, however, be due to tobacco smoking, alcohol drinking, inadequate physical activity or a poor diet [3]. An adverse lifestyle affects the ability to cope of people suffering from depression, experiencing a major negative life event or living with odd personality traits, which can be difficult in a society that does not accept deviations from the norm.

Many different types of study have been conducted to investigate whether there is an association between mind and cancer and, if so, whether it is physiological or indirectly causal. This paper addresses some methodological considerations in studies of the mind as a risk factor for cancer, stressing the advantages of registry-based investigations. The paper does not contain a lengthy and detailed discussion of advantages and limitations of other methodological approaches in this area of research. However, this is the focus in the review [1] by Dalton *et al.*

Material and methods

In Denmark, as in the other Nordic countries, society is organized and financed from the highest to the lowest administrative unit (from state to municipality) by public and company paid tax, so that most educational, social and health services are funded by tax from all residents and most businesses in the country. This system was instituted to establish a welfare state, with equal access of the entire population to all these public services. The system is administered by the use of two key identifiers: a personal identification number (PIN) for residents, which came into operation in 1968, and an individual tax number for companies, for establishing the income level and thereby deciding the level of taxation. The PIN is also used for registering individuals in numerous administrative and health databases and in all encounters between residents and the public administration, such as visits to a general practitioner, schooling and the social welfare system [4].

The Danish Cancer Registry was established in late 1942 and came into nationwide, population-based operation in 1943. Today, it represents the world's oldest, most reliable source of data on cancer incidence and mortality for an entire country. Several other unique national databases on health and disease are also used to investigate associations, such as between the mind and cancer.

Register-based information is useful, as it was usually obtained independently of any hypothesis, thereby almost completely excluding any risk for either recall or interviewer bias. The objective character of the data in these administrative registries excludes recall bias, as there are no study participants to provide information on determinants, exposure, confounders or outcomes. Interviewer bias is obviated, as there is no direct communication between people and the administrative database: all information is obtained electronically or, earlier, on paper forms, such as tax declarations from citizens, information provided by educational institutions and information from hospital administrations. Finally, there is no selection bias as all residents are notified to the registries by their individually assigned unique PIN, so that each person provides information as soon as he or she interacts with the public administration. It must be recognized, however, that these advantages also result in limitations, as information cannot be obtained directly from the people under study. Therefore, studies based on access to these sources lack data on lifestyle variables, occupational exposures and biological characteristics. In addition, there is a possibility for misclassification, which is almost always non-differential, thereby resulting in estimates that are lower than the true values. As a consequence, the results of studies based on these data may be more conservative.

In order to address these limitations, Nordic researchers on mind and cancer, who initially used only register-based information gradually included more and more data, either from patients or from clinical databases. This was the case in four studies by our group within the past 25 years [3,5–7].

Results

This section briefly describes a few studies conducted with the methods outlined earlier. The section does not cover all the literature in this area; although other studies are included, it highlights studies by my Danish research team.

The first Danish study published in this dive into the mind and cancer was one in which we hypothesized that a diagnosis of cancer in a child was a major stressor and a major negative life event for the parents. The overall experience of the diagnosis and the long treatment, including multiple hospital stays, and the consequent psychological and social consequences for the parents was anticipated to increase their risk for cancer. We identified all 5807 children in Denmark in whom cancer was diagnosed between 1943 and 1985 and used their PINs to identify their parents ($N = 11\ 231$). We then observed the number of cases of cancer in these parents and compared it with the numbers expected in corresponding sex and age groups from the date of diagnosis of cancer in the child. In up to 50 years of follow-up, we did not observe an increased risk for cancer overall or for cancers at sites that might be suspected of an association with the psychological stress of having a child with cancer including immune associated or hormone-related cancers. We obtained similar results when we included 8042 parents who also experienced the death of their child [5].

The second study, which is of particular interest, included all Danes admitted to a psychiatric ward with a clinical diagnosis of major depression ($N = 89\ 491$) between 1969 and 1993. The Central Psychiatric Register contains information on all admissions to psychiatric wards since 1969, with coverage of 95–100%. We observed a 5% overall increased risk, which was, however, confined to tobacco-associated cancers. Further stratifications confirmed this overall result, which probably reflects an increased prevalence of smoking among depressed persons. In addition, 17% of the patients had been admitted for an alcohol-related psychiatric disorder, which probably contributed to the observed increased risk for tobacco-associated cancers, as alcohol drinking is a risk factor for some of these cancers. The results of this large cohort study do not support the hypothesis that depression *per se* increases the risk for cancer [3].

The third paper from my group reported an investigation of classic personality traits and the risk for cancer in a small cohort of 1031 people who had participated in a health survey. At inclusion between 1976 and 1977, the cohort members filled in a questionnaire on alcohol consumption, tobacco smoking, marital status, social class and the Eysenck personality inventory, which is based on the notion of the famous British psychologist Hans Eysenck that smoking is

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significantly correlated with personality and specifically with extraversion. In addition, the interviewing doctor rated the existence of psychiatric illness in all the cohort members. The observed number of cases of cancer was not higher than that expected during the 20 years of follow-up. Further multivariate regression analysis did not indicate that people with cancer-prone personality traits according to the Eysenck personality inventory were at increased risk. This paper illustrates use of a combination of personal information and register-based information in a linkage system, providing almost complete follow-up with regard to the outcome under study and vital status [6].

As a follow-up to these three studies, a number of new cohorts and ideas were pursued in order to further examine the question of mind and cancer. Studies were carried out to address in particular the timing of exposure in a life perspective (young, middle-aged and old), the latency (time from first exposure) and the duration (e.g. schizophrenia).

One study of particular interest for the discussion of an association between mind and cancer was conducted within a large prospective, population-based cohort of 59 548 Swedish and Finnish twins, who completed a questionnaire eliciting information for the Eysenck personality inventory and on health behaviour at baseline. To analyse the association between the personality traits extraversion and neuroticism and risk for cancer, 4631 cancer cases with a maximum of 30 years of follow-up were identified. In multivariate analyses, extraversion and neuroticism were not significantly associated with the risk for cancers at any site (extraversion: hazard ratio, 0.99; 95% confidence interval [CI], 0.98, 1.01; neuroticism: hazard ratio, 1.00; 95% CI, 0.99, 1.02). This study is interesting because of its large size, the long follow-up and the availability of detailed information on the exposures of interest [7]. Still, no overall increase in risk for cancer was detected.

Discussion

Taken together, these four studies [3,5–7] appear to confirm the general impression that mind factors do not increase the risk for cancer. Additional studies by our group also do not, in general, support the hypothesized association [3,5–17].

Carcinogenic agents

The psychosocial scientific literature on mind and cancer rarely discusses what a carcinogenic agent actually is. In 1969, the World Health Organization established an international cancer research institution (the International Agency for Research on Cancer [IARC]). One of its activities, launched in 1971, is to evaluate the carcinogenicity of various agents to humans. Almost 1000 physical, biological and chemical agents have been evaluated by numerous independent experts groups convened by IARC in Lyon, France, to support governments and public agencies in the prevention of cancer. As illustrated in Table 1, agents are classified into one of five categories. The numbers assigned to each category illustrate the distribution of judgements by these expert groups up to 2012.

Confounding and bias

The same strict rules as used by the IARC working groups can be used in reviewing the literature on the extent to which mind factors cause cancer. This has not always been the case, as there has often been a lack of discussion of potential confounding and other methodological issues. The first reports indicating that the mind could cause cancer did not provide detailed clinical information or did not take into account the age, gender or lifestyle of the participants but nevertheless anticipated that the 'mind factor' operated independently as a causative agent. Many of the early reports also relied solely on interviews with cancer patients after their diagnosis, with no consideration of recall bias as a problem in constructing the data set. To the best of my knowledge, selection bias was not discussed in any of the early studies, as it was not anticipated that patients who refused to participate might differ on crucial parameters from those who accepted the invitation to participate.

Mechanism

This paper does not cover all the mechanistic studies or those conducted in experimental animals, which are useful for evaluating the mind as a risk factor for cancer. To the best of my knowledge, however, the evidence obtained in epidemiological, clinical, experimental and mechanistic studies has never been reviewed overall in order to reach a balanced consensus about the mind as a risk factor for cancer. As this paper illustrates, authors tend to use their own data in their argumentation for one or another position regarding causality in the question of mind and cancer.

From a biological point of view, it was assumed in the early studies that the mind affects human physiology without having a physiological mechanism. For instance, it was assumed that brain activity (thinking) could cause mutations. In some papers, mind was isolated from brain activity. Understanding of human physiology entered the mind–cancer discussion only with the proposal that certain psycho-neuro-immunological mechanisms might explain the associations observed [18].

In some of the register-based epidemiological studies described earlier, the overall risk for cancer was close to unity, whereas the risk for some lifestyle-associated

Table 1. Agents classified by the IARC Monographs, Volumes 1–102

Carcinogenic to humans	107
Probably carcinogenic to humans	59
Possibly carcinogenic to humans	267
Not classifiable as to its carcinogenicity to humans	508
Probably not carcinogenic to humans	1

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cancers, mainly those associated with tobacco smoking and alcohol drinking was actually increased. One may speculate that the increase in risk of people who are depressed or have a certain personality trait is increased because they smoke and drink more in order to cope with these conditions than people who do not suffer from depression or deviate from the norm. This argument leads to consideration of whether the mind factor causes cancer through certain lifestyles or whether the lifestyle itself is the causative agent. The *IARC Monographs* do not take into consideration why exposure to a given agent takes place but only whether the exposure occurs. In this simplistic model, mind does not increase the risk for cancer. The evidence rather suggests that it is lifestyle that causes cancer.

Advocates of an association between mind and cancer have not concluded that lifestyle-associated cancers are caused by mind factors. Rather, they argue that mind factors influence the risk for cancers associated with dysfunction of the immunological system, and therefore, populations at risk are at increased risk for leukaemia and lymphoma. In addition, most of the register-based studies did not confirm this hypothesis. Further, although it has been proposed that the risk for hormone-associated cancers would increase in response to stress, as the hormonal system can be influenced by mind factors, no increase in the risk for such cancers, for example, of the breast or prostate, was observed in our Danish register-based studies.

Exposure

An issue of interest is the length of exposure (short, chronic or lifelong) and whether it is related to life in general or to work. In the studies described earlier, exposure was to a stressor such as a cancer diagnosis in a child, which by nature is acute but, as pointed out in the literature, also has a chronic character. The period around diagnosis and initial treatment can be considered acute. After several years of treatment, the children are followed up in childhood cancer survivor clinics, a service that ensures that any relapse or secondary cancer will be diagnosed but is also a reminder of a life-threatening condition. Thus, follow-up procedures are clinically relevant but are also a stressor for both the patient and close relatives. In addition, kindergarten, school and social life not only are positive experiences but also have negative aspects for the parents of a childhood cancer survivor. Every time the child is exposed to an infection, the symptoms and disease periods may raise fears of a relapse from the cancer. Thus, surviving diagnosis and treatment of cancer has both positive and challenging aspects.

In classic aetiological research, several aspects of time are crucial: latency, for example, the time from first exposure to date of diagnosis; duration, for example, length of exposure in minutes, hours, months or years; temporality, for example, exposure prenatally, in childhood, in adolescence or in adult life; and timing, for example, before menarche, before menopause or after the birth of a first child. Exposure can also be categorized by type of agent, which may initiate the carcinogenic process in a given cell or may promote cancer cells to divide more rapidly. The role of these aspects of exposure in the mind–cancer association has not been determined, but it has been the focus of my group, as illustrated in our published studies [3,5–17].

Mind factors can also be separated into those related to a person's life and those related to exposure at the workplace. Some studies have investigated whether work-related stress increases the risk for cancer. In the Nurses' Health Study of 26 936 postmenopausal women aged 46–72 years in the USA who were in paid employment and who had no previous history of cancer, multivariate-adjusted regression analysis provided no evidence for a relation between job strain and risk for breast cancer or tumour size, even though job strain was associated with less frequent breast cancer screening [19]. Likewise, in a study of 10 519 Finnish women who appraised their own daily stress in 1975 and 1981, multivariate-adjusted analysis gave hazard ratios for breast cancer risk of 1.11 (95% CI, 0.78–1.57) for those with medium stress and 0.96 (95% CI, 0.53–1.73) for those with the highest stress as compared with women with no stress. Neither shifting the stress cut-off points nor restricting the analysis to women who reported the same level of stress in 1975 and 1981 materially altered the results [20].

Differentiation of acute and chronic exposure may therefore be artificial, as the effect of depression, stress or the experience of the death of a spouse might have either a lifelong or only a short effect, depending on the individual. The Danish data, however, not only are nationwide and population-based but also include extensive follow-up over different calendar periods, various forms of cohabitation, various relationships between parents and children and various family structures. Studies based on these data therefore include many aspects of how stress, depression and personality traits are observed, treated and experienced. The results are therefore relatively robust and inclusive.

Positive epidemiological studies

Some studies have found that mind factors cause cancer. In a cohort of 6284 Jewish Israelis who lost an adult son in the Yom Kippur War or in an accident between 1970 and 1977, increased incidences of lymphatic and haematopoietic malignancies and of melanoma were found among the parents of accident victims (odds ratio [OR], 2.01; 95% CI, 1.30, 3.11; and OR, 4.62; 1.93, 11.06) and among war-bereaved parents (1.47; 1.13, 1.92; and 1.71; 1.06, 2.76, respectively). Accident-bereaved parents also had an increased risk for respiratory cancer (OR, 1.50; 95% CI, 1.07, 2.11) [21]. In a Swedish cohort of 4 687 073 parents, 2% (101 306 parents) lost a child during follow-up; of these, 1608 subsequently had an

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infection-related cancer. After adjustment for age, sex, calendar year, educational level and civil status, the overall relative risk for cancers at the 14 sites studied was 1.07 (95% CI, 1.02, 1.12). Parents who lost a child were at a particularly high risk for cancers associated with human papilloma virus (HPV) infection, such as cervical cancer (relative risk, 1.46; 95% CI, 1.17, 1.80). Higher risks for most cancers were observed within 5 years after loss of a child, and excess risks for liver and stomach cancers were confined to that period. No association was observed with lymphoma or non-melanoma skin cancer at any time after loss of a child. The authors concluded that, although potential confounding by unmeasured factors could not be ruled out, their findings lent support to the hypothesis that severe life stressors raise the risks for several, chiefly HPV-related, cancers [22].

Conclusion

Mind does not appear to have the capacity to increase the risk for cancer; however, mind factors may change the way in which we live and may alter our exposure to lifestyle factors, such as smoking, alcohol drinking, poor diet and inadequate physical activity. These exposures can subsequently increase the risk for cancer. It must be stressed that this paper covers only a small part of the literature. It was not intended to be objective but to present one viewpoint in the discussion.

In view of the body of literature published so far, IARC may soon decide that mind, especially stress in the broadest sense, should be evaluated as a carcinogenic agent in the *Monographs* programme. In the minds of many people around the world, cancer is ascribed at least partly, to mental factors. A conclusion is needed on the extent to which this is fact or fiction.

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