

REVIEW ARTICLE

The Importance of a Biopsychosocial Approach in Melanoma Research Experiences from a Single-center Multidisciplinary Melanoma Working Group in Middle-Europe

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The biopsychosocial model represents a very important theoretical framework developed in the 21st century. According to a body mind unity theory, it postulates that research must focus not only on biomedical but also on other aspects in order to understand complex interactions occurring on different system levels. With regard to the occurrence of melanoma, both immunologic surveillance and a lack of cancerogenic factors are crucial in the suppression of tumor development. In addition, a reduction in mental stress (employing effective strategies for coping with stress) in cases of malignant disease seems to prolong life. Focusing on these theories, examples of studies that followed an interdisciplinary, biopsychosocial approach to melanoma research conducted at one center are given to emphasize the multi-dimensional and interdisciplinary aspects of the biopsychosocial model. Key words: melanoma; stress; biopsychosocial melanoma research.

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Stimulation of the immune system is widely used in melanoma treatment, capitalizing on aspects of immunogenicity. After a long period where only interferons or interleukin 2 were available, novel therapies such as ipilimumab, nivolumab and pembrolizumab and combinations thereof have yielded impressive results, even in patients with widespread metastatic disease (1–4). The immune system, however, is sensitive and involves both humoral and cellular defense mechanisms. Interactions among cytokines, chemokines, and lymphocytes result in complex reactions and counter-reactions within the system. Cytokines (Greek κύτταρο “cell” and κινειν “creep”) are substances that are produced by different cells that have pro- and/or anti-inflammatory effects. Chemokines (Greek χημεία “chemistry” and κινειν “creep”) are cytokines that exert chemotactic effects on a variety of cells. Subsets of lymphocytes vary in multiple diseases and lead to enhanced or suppressed immunologic responses. Thus,

the cytokines, chemokines and immune cells of the innate and adaptive immune system have been shown to influence tumorigenesis and tumor progression, but are also susceptible to modulation by melanoma cells (5–7). Hallmarks of the carcinogenic process include the sustenance of proliferative signaling, evasion of apoptosis and acquisition of the ability to invade tissues and evoke metastasis (8). The work by Cavallo et al. (9) highlights the immune hallmarks of cancer by stating “immune hallmarks consist of the ability of cancer cells to thrive in a chronically inflamed micro-environment, ability to evade immune recognition and ability to suppress immune reactivity”. However, the immune system is not only influenced by pathogenic organisms or tumors but also by stress (10) and thus, is an important focus of biopsychosocial research.

THE BIOPSYCHOSOCIAL MODEL

The biopsychosocial model may be considered as the most significant theoretical framework in human medicine (11). Georg Engel pointed out the need for a new medical model in human medicine. In the year 1977, he published “The Need for a New Medical Model: A Challenge for Biomedicine” (12, 13). In his article he criticized the biomedical model, arguing that it leaves no room for the complex dimensions of illness (13). Engel pointed out the limitations of the biomedical model and, instead, recommended the biopsychosocial model as a new model that “*is based on a systems approach, a development in biology hardly more than 50 years old, the origin and elaboration of which may be credited chiefly to the biologists Paul Weiss and Ludwig von Bertalanffy*” (14, p. 535). In the same article he emphasized the importance of the understanding of hierarchy and the nature of a continuum in natural systems. Thus, “*each level in the hierarchy represents an organized dynamic whole, a system of sufficient persistence and identity to justify being named*” (14, p. 536). Furthermore, he revealed another important aspect by considering complex interactions among system levels: “*Each system is at the same time a component of higher systems...In the continuity of natural systems every unit is at the very same time both a whole and a part*” (14, p. 537).

The biopsychosocial model can now be described as a “body mind unity theory” and should not be considered as acting in opposition to the biomedical model (15). According to J.W. Egger “*Every event runs – due to the vertical and horizontal networks – more or less simultaneously on the different system levels. This phenomenon may be technically described as parallel interface*” (15, p. 46). Thus, taking the biopsychosocial approach, encourages us to focus on interdisciplinary and multidimensional research (International Society of Biopsychosocial Medicine: Venice Declaration) (16).

Based on the theories expressed in these models, our interdisciplinary team of experts, consisting of dermatologists, psychologists, psychiatrists, immunologists and sport scientists from the Medical University of Graz, in Austria, conducted biopsychosocial melanoma research with support from Austrian Cancer Aid/Styria. Results of this research are summarized here.

EXERCISE-INDUCED MELANOMA IN MARATHON RUNNERS

Endurance exercise such as marathon running may be associated with an increased risk of severe illness (17). Based on observations made at the Department of Dermatology (Medical University of Graz) of 8 young- to middle-aged ultra-marathon runners with high, weekly training intensities and with malignant melanoma, a study on marathon runners was consequently carried out to investigate this type of coincidence. Two-hundred and ten marathon runners were included in this observational study, conducted during an annual Graz marathon. Subjects were recruited at random voluntarily on the day before the race and compared to age- and sex-matched control subjects, who were not marathon runners and were recruited during the skin cancer screening campaign “*sun.watch.*” run by Austrian Cancer Aid/Styria (18). In this study, marathon runners were shown to present significantly more atypical nevi, which were particularly pronounced in the subgroup of runners with the highest training intensity, as compared to the controls. The authors speculated that an association might exist between exercise-induced immunosuppression and the occurrence of melanoma.

In a subsequent study conducted by the same group, the investigation focused on the influence of training parameters on the development of nevi and lentigines, which are known as melanoma markers (19). One-hundred and 50 white volunteers were enrolled in this study. For each volunteer, physiological parameters such as the basic heart rate, training heart rate, training velocity, and physical strain index (defined as velocity multiplied by mean training heart rate) were assessed and combined with data from a total body skin examination that was performed by experienced dermatologists. During the total body skin examination, volunteers

were screened for melanoma, atypical melanocytic nevi and lentigines. Runners who reported higher training heart rates had significantly more nevi, as did runners exercising with a higher training velocity and a higher physical strain index. These findings were found to be independent of the weekly running time. No statistically significant correlations could be drawn between physiologic parameters and the numbers of lentigines. Again, the authors speculated that sun exposure and lifetime sunburn history alone could not explain the increased melanoma risk observed for marathon runners, but that immunosuppressive effects due to excessive exercise might play a key role (19).

STRESS AND MELANOMA

Immunologic parameters are not only influenced by physical stress factors such as marathons, but also by psychological stress factors. Studies on this topic contain conflicting data on the effects of stress on the immune system. Both up-regulations of cytokines and down-regulations of various cellular components have been observed (20, 21). In a recent study, psychophysiological parameters such as heart rate and heart rate variability were used to assess psychological and psychovegetative strain in adolescents with atypical pigment nevi (22). Fifty-one students from a secondary school in Graz, Austria, completed a defined test procedure consisting of a standardized mental stress task, a questionnaire and intermittent periods of rest. Psycho-physiological data were recorded continuously, and the number of atypical nevi was assessed by dermatologists. With regard to the physiological and psychological parameters, adolescents with atypical nevi displayed higher levels of vegetative strain and more stress-related symptoms. Thus, the authors concluded that stress might be a confounding factor for the early onset of atypical nevi, which are a known risk factor for melanoma. Subsequently, a pilot study was performed to examine the immunological response of 19 patients with early-stage melanoma and a matched control group that underwent a stress test before surgery. Cytokine and chemokine levels as well as numbers of lymphocyte subpopulations were measured at baseline and at post-stress test time-points. The authors demonstrated that, when exposed to stress, melanoma patients (even in the early stages of the disease) had different immunological reaction patterns than members of the control group (23).

COPING STRATEGIES IN MELANOMA PATIENTS

Higher levels of social support seem to be associated with a higher quality of life, better prognosis and better

outcome in patients with malignant diseases. A positive correlation between coping styles and quality of emotional adjustment has been described in patients with melanoma in terms that high social support and active coping strategies seem to be associated not only with positive adjustments (24, 25), but also with better outcomes (26). On the basis of these findings Trapp et al. (27) investigated coping strategies among melanoma patients. Twenty-five melanoma patients and 21 control patients were recruited, and their coping strategies were assessed using the German stress-coping questionnaire SVF 120 (Stressverarbeitungsfragebogen 120). The item "situation control" was significantly associated with a decrease in the risk of a melanoma diagnosis, whereas the items "resignation" and "trivialization" were associated with increased risk. Patients with higher levels of education showed a tendency towards greater resignation, leading the authors to speculate that such patients might feel more helpless when facing the diagnosis of malignancy. Interestingly, higher values for positive coping strategies were associated with reductions in melanoma thickness and, thus, with a better prognosis. The authors concluded that "the possibility of an early intervention, focused on psychological risk factors of coping profiles of patients with melanoma suggests a beneficial effect on further disease development, if such interventions are able to provide sufficient "relief" for the immune system" (27).

CONCLUSION

Following the biopsychosocial model, illness and health are considered to be dynamic processes and health must consciously be "created" in every second of our lives (28). Pathogenic and constitutional hereditary dispositions influence the wellbeing of the individual as do environmental influences and lifestyles. Immunosuppression is not only caused by drugs (e.g. after organ transplantation), but can also be caused by a number of physical or psychological stressors, which seem to be co-factors in the development of illness. For this reason, every intervention that leads to an enhancement of the immune system can potentially benefit the patient. The development of resilience may lead to suppression and modification or even remission of an illness, but risk factors may contribute to development, progression and perpetuation of pathologic processes (29). The examples of studies given, conducted by the biopsychosocial melanoma working group of the Medical University of Graz, may contribute to small pieces of knowledge that can help to solve the huge puzzle of cancerogenesis and immunologic surveillance. It would seem to be beneficial for the patient not only to take into account the mutational status of the tumor, but also to focus on possible resilience factors that can enhance the immune system, even during an early stage of disease. In

2007, based on the knowledge that physical activity can influence inflammatory diseases, Schedlowski (30) postulated that interventional programs that focus on inducing behavioral changes after the diagnosis of such diseases should be implemented. It is necessary to consider salutogenic approaches and the influences of the working environment, as well as help patients build and maintain psychosocial networks. Additionally, the individual stress tolerance level of each person needs to be considered. In recent decades, changes in patients' behavioral patterns have been observed: the "domineered patient" of the 1960s has given way to the "informed patient" and, gradually, the "mature patient" of today. Shared decision-making, which can only be effected by an "autonomous type of patient", has led to the presence of the "competent patient" type, currently well known (31). Physicians are considering increasing numbers of personalized treatment options for melanoma patients and should focus not only on the patient's tumor and immune system but also helping their patients develop empowerment strategies. It is necessary to take interdisciplinary and multidimensional approaches to reach this goal, and these should be implemented as early as possible, and ideally when primary tumor is diagnosed. There is excessive demand of individual coping strategies and therapy should include the enhancement of positive coping strategies that is consistent with a reduction in the number of risk factors.

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