

## RETROSPECTIVE ANALYSIS

# Effect of the nervous system on cancer: Analysis of clinical studies

Mravec B<sup>1,2\*</sup>, Dubravicky J<sup>3\*</sup>, Tibensky M<sup>1</sup>, Horvathova L<sup>2</sup>*Institute of Physiology, Faculty of Medicine, Comenius University in Bratislava, Slovakia.***boris.mravec@fmed.uniba.sk****ABSTRACT**

Preclinical data have shown that neurotransmitters released in peripheral tissues from nerve endings may influence carcinogenesis, affect the tumor microenvironment, and directly potentiate both proliferation and migration of cancer cells. This stimulatory role of the nervous system in cancer initiation and progression has also been documented by clinical studies investigating the effect of attenuated signaling from nerves innervating cancer tissue. However, compared to preclinical studies, clinical studies are rarer and some of them have ambiguous results. In this retrospective analysis, to assess the effect of the nervous system on cancer, we analyzed published clinical studies investigating the incidence of cancer in patients with spinal cord injury or pheochromocytoma. Our findings support a concept of the neurobiology of cancer based on the assumption that the nervous system affects cancer initiation and progression (Ref. 60). Text in PDF [www.elis.sk](http://www.elis.sk).

**KEY WORDS:** cancer, neurobiology of cancer, norepinephrine, sympathetic nervous system, spinal cord injury, pheochromocytoma.

**Introduction**

Several factors and mechanisms participate in the initiation and progression of cancer (1, 2). Preclinical and clinical studies have demonstrated that the nervous system plays a significant role in these processes, as well. These studies create a basis for the concept of cancer neurobiology. This concept is based on several findings: a) the nervous system modulates the reaction of the immune system to cancer (3–5), b) tumor tissue is innervated (6–8), c) cancer cells express receptors for neurotransmitters (9, 10), d) neurotransmitters affect the proliferation and migration of cancer cells (7, 11, 12), and e) psychological factors may affect the incidence and progression of cancer (13–15).

In addition to the above-mentioned facts, it has been demonstrated that either surgical or pharmacological interventions of the nervous system could affect cancer initiation and progression. For example, preclinical studies showed that elimination of sympathetic nerve endings in rats reduced azoxymethane-induced experimental colon carcinogenesis (16) as well as the incidence of fibrosarcoma (7). Compared to preclinical studies, clinical studies

investigating the role of interventions affecting the nervous system in cancer incidence and survival of oncological patients are rarer. Furthermore, the majority of these clinical studies were focused on determining the effect of psychotherapy on the survival and quality of life of oncological patients and report ambiguous results (17–20). The most encouraging (and still occasionally ambiguous) data were obtained from retrospective clinical studies investigating the effect of concomitant treatment of oncological patients with  $\beta$ -blockers for hypertension (21). Importantly, the first prospective study employing the non-selective  $\beta$ -blocker propranolol as an adjuvant therapy achieved a 80% reduction in the risk of melanoma recurrence in patients treated with propranolol (22). These findings indicate the efficiency of cancer treatments based on attenuating the signalization from nerves to cancer tissue.

Even if the results from preclinical and some clinical studies indicate that reduction of signalization between the nervous system and cancer tissue exerts a beneficial effect for oncological patients, additional proofs are necessary before introducing this approach as a new adjuvant therapeutic modality into daily oncological treatment. Therefore, the goal of this paper is to provide analysis of published clinical studies, particularly those investigating the effect of spinal cord injury or pheochromocytoma in cancer incidence. Our analysis shows the participation of the nervous system in cancer incidence and as such may enrich our knowledge in the field of cancer neurobiology.

**Incidence of cancer in patients with spinal cord injury**

In preclinical studies, it is possible to investigate whether tumorigenesis or progression of cancer is affected by selective destruction of sympathetic, parasympathetic, or sensory nerve

<sup>1</sup>Institute of Physiology, Faculty of Medicine, Comenius University in Bratislava, Slovakia, <sup>2</sup>Biomedical Research Center, Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia, and <sup>3</sup>Department of Urology, University Hospital, Bratislava, Slovakia

**Address for correspondence:** B. Mravec, MD, PhD, Institute of Physiology, Faculty of Medicine, Sasinkova 2, SK-813 72 Bratislava, Slovakia. Phone: +421.2.59357527, Fax: +421.2.59357601

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\*Both authors participated equally

endings, transection of nerves, or administration of drugs that interfere with neurotransmission. However, clinical studies are significantly limited with several factors. Therefore, in the field of cancer neurobiology, retrospective clinical studies generally only evaluate the effect of commonly used interventions approved for the treatment of other diseases. For example, patients treated by vagotomy for peptic ulcers represent a population in which the interconnection between the vagus nerve and cancer can be assessed by retrospective studies. These studies investigating the incidence of cancer in vagotomized patients showed a significant increase in the incidence of gastric cancer (23–26). However, vagotomy profoundly affects the gastrointestinal system and in addition, there was also a higher prevalence of smoking in these patients. Therefore, the reported increased prevalence of gastric cancer in patients that have undergone vagotomy may not unambiguously reflect a direct causality between the parasympathetic nervous system and stomach cancer (25–28). Because treatment of gastric ulcers by vagotomy has been replaced by pharmacotherapy, other approaches for investigating the nervous system's effect on the incidence of cancer in humans needs to be found. One such example may involve patients with chronic spinal cord injury (SCI).

In patients with SCI, signal transmission between the brain and peripheral tissue is severely disturbed. The extent of nervous dysregulation of peripheral tissues depends on the location, where the spinal cord injury occurred. Whereas parasympathetic innervation by the vagus nerve is usually preserved, sympathetic and sacral parasympathetic nervous activity is disrupted, allowing the role of the nervous system in the cancer incidence of these patients to be investigated. As such, a relationship between SCI and cancer risk has been reported in several retrospective clinical studies (29–31). However, it is necessary to take into consideration the fact that chronic complications of SCI and autonomic dysfunction may also represent indirect factors affecting the development of cancer (32).

One of the most consistent findings from clinical studies on SCI patients is a reduced incidence of prostate cancer (33–35). Based on these data, Rutledge et al. suggested that tumorigenesis in prostate depends significantly on proper function of the autonomic nervous system (36). This assumption is supported by pre-clinical data showing that both sympathetic and parasympathetic nerves play an important role in the development of prostate cancer (37). Rutledge et al. hypothesized that prostate cancer might be both prevented and treated by approaches attenuating the effect of nerves on the prostate (e.g. administration of BOTOX or antibodies against neurotrophic factors). We suggest that an administration of  $\beta$ -blockers may represent a suitable preventive and therapeutic strategy. Furthermore, these drugs are approved for clinical use and therefore can be easily employed as an experimental adjuvant therapy of prostate cancer in humans.

In contrast to a reduced incidence of prostate cancer, the risk for urinary bladder cancer is increased in SCI patients (38, 39). Whereas originally it was believed that the use of indwelling catheters in SCI patients was responsible for this phenomena, more recent clinical studies indicate that other factors, such as

neurogenic bladder may also play an important role (40, 41). We suggest that except factors such as indwelling catheters, recurrent urinary tract infections, and bladder calculi; nervous factors, such as particularly increased parasympathetic activity, may also participate in an increased incidence of urinary bladder cancer in SCI patients. This assumption is supported by an in vitro study showing that nicotine stimulates proliferation of bladder epithelial cells via activation of intracellular pathways (42).

In a population-based cohort study, Kao et al. evaluated the risk for non-genitourinary cancers in patients with SCI. They found that patients with SCI exhibited higher risks for esophageal, liver, and hematologic malignancies, but had a lower risk of colorectal cancer compared to the patients without SCI. Kao et al. suggest that the diverse patterns of cancer risk among the patients with SCI might be related to complications of chronic SCI (30). Interestingly, it is possible to find a pattern that indicates that there is a correlation between the extent of reduced signal transmission from the nervous system to particular organs and the incidences of specific types of cancer. Additionally, whereas esophageal and liver innervation is intact in the majority of SCI patients, the reported increase in the incidence of cancer of these organs may reflect an increased activity of the sympathetic nerves innervating their tissues. This increased activity of sympathetic nerves may occur as a consequence of autonomic dysreflexia (43). On the other hand, nervous signalization to the colon and rectum is severely affected in the majority of SCI patients (44). Therefore, we suggest that the data of Kao et al. may reflect “nerve dependency” of colorectal cancer, as similarly suggested in prostate cancer by Rutledge et al (see above).

### **Incidence of secondary cancer in patients with pheochromocytoma**

In vitro studies showed that administration of either agonists or antagonists of neurotransmitter receptors might significantly affect the proliferation and migration of cancer cells (45, 46). For example, it has been found that norepinephrine significantly potentiates the proliferation of cancer cells and this affect can be blocked by administration of  $\beta$ -blockers (7, 47, 48). Additionally, several clinical studies determined that there is an effect of  $\beta$ -blockers on both cancer incidence and the survival of oncological patients. The majority of these studies included patients that were treated by  $\beta$ -blockers for hypertension and this treatment started before the diagnosis of cancer. Importantly, it was found that blockade of  $\beta_2$ -adrenergic receptors prolongs the survival of patients with mammary carcinoma (21). If the blockade of  $\beta_2$ -adrenergic receptors reduces cancer progression, then it can be hypothesized that overactivation of these receptors may induce the opposite effect. It is known that increased activation of these receptors may be found in individuals exposed to intensive chronic stressors (49). Because reactivity to stressors significantly varies between individuals (50), there are several difficulties in investigating the effect of stress on cancer development and progression. However, in patients with pheochromocytoma, plasma catecholamine levels are enormously increased (51). These cate-

cholamines may profoundly stimulate  $\beta_2$ -adrenergic receptors and therefore pheochromocytoma may represent a clinical model of exaggerated sympathetic nervous system activity. Based on these facts, we suggest that the effect of overactivation of  $\beta_2$ -adrenergic receptors on cancer initiation should be studied in the patients with pheochromocytoma.

Khorram-Manesh et al investigated the mortality rates associated with pheochromocytoma in a retrospective study. They found 4-times higher tumor-related mortality than in the controls. In the cohort, liver/biliary tract and central nervous system tumors were increased in men, while malignant melanoma and uterine cervical cancer were significantly over-represented in women (52). These data indicate that catecholamines play an important role in the development of these cancers. We hypothesize that administration of  $\beta$ -blockers may reduce the incidence of secondary cancers in pheochromocytoma patients. In support of this hypothesis, an in vitro study has shown that propranolol suppresses proliferation and induces apoptosis, when administered to medium nourishing liver cancer cells (53). In addition, the first prospective clinical study using  $\beta$ -blockers as an adjuvant cancer treatment has shown that administration of propranolol results in an 80 % reduction to the risk of melanoma recurrence (22).

#### Transplantation-related denervation of organs in recipients

Transplanted solid organs, such as kidneys, hearts, or lungs are denervated in recipients (54–56). Even if the re-innervation of transplanted organs does eventually develop (57), recipients of transplanted organs may represent another population of patients enabling us to study cancer incidence in individuals with disconnections between the nervous system and peripheral tissues. In these patients, a 3-fold excess risk of cancer, relative to the age- and sex-matched general population was found. However, they developed types of tumors that affect various organs and that are frequently of viral etiology. Furthermore, the most important factor responsible for the increased incidence of cancer in transplantation patients is iatrogenic immunosuppression (58). Therefore, it seems that data from transplantation patients are not appropriate for the study of cancer neurobiology.

#### Neurostimulation in the treatment of neurological and somatic diseases

In the last decades, significant progress has been made in the development of various neurostimulatory devices called electroceuticals. For example, vagus nerve stimulation (VNS) is widely used for the treatment of epilepsy. Electroceuticals have also been developed for the treatment of urinary incontinence, constipation, and chronic pain. In addition, both preclinical and clinical data showed the efficiency of VNS in the treatment of depression, heart failure, and rheumatoid arthritis (59). Looking towards the future, smaller and more precise electroceuticals that can stimulate selected nervous fibers of certain nerves are currently under development for the treatment of various other somatic diseases (60).

The action of electroceuticals is based on inducing the release of neurotransmitters in peripheral tissues. Therefore, the question arises as to whether these devices may influence cancer incidence and progression. To answer this, we investigated the effect of VNS in rats injected with tumor cells. We have found that VNS slightly reduced tumor incidence, without effecting the survival of tumor-bearing rats (9). However, because of the lack of other preclinical and clinical data, further preclinical studies, along with retrospective and prospective clinical studies will be necessary to determine the safety of electroceuticals in affecting the incidence of cancer.

#### Conclusions

Evidences accumulated from preclinical studies indicate that the nervous system plays an important role in cancer initiation and progression. However, even if some data from clinical studies involving patients with altered signalization between the nervous system and peripheral tissues support findings from preclinical studies, further preclinical and clinical data will be necessary to get a more detailed understanding of the role of the nervous system in cancer initiation and progression. Only then it will be possible to introduce new adjuvant therapeutic and preventive interventions in oncology that will be based on neurobiological view of cancer.

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