Scholars LITERATURE

Neurological Sciences and Neurosurgery

Review Article

DOI: https://doi.org/10.47275/2692-093X-143
Volume 5 Issue 2

A Systematic Review on Relationship Between Head and Neck Cancer Associated to Parkinson's Disease

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Abstract

A general inverse association between Parkinson's disease (PD) and cancer development has been found in epidemiological studies. A growing body of eclectic evidence, however, points to an association between PD and cancer in different ethnic groups and across different time periods. Head and neck cancers (HNC) are frequently associated with neurodegeneration. The relationship between HNC and PD remains unclear. It was the aim of this study to clarify the relationship between HNC and subsequent PD. The review included different papers which screened 4365 individuals without HNC and 1054 individuals with HNC who were matched on sociodemographic factors. HNC are more likely to develop PD in the future. People with HNC and oral cavity cancer who were middle-aged had a higher risk of PD. We found that middle-aged patients with HNC are more likely to develop PD, especially those with oral cavity cancers. Reviewing recent epidemiological and biological findings regarding the association between PD and cancer, we offer insight into the sometimes-contradictory findings.

Keywords: Cancer, Parkinson's disease, Head and neck cancer

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Citation: Nori A, Gowda SU, Chandra VVRV, Hema E (2024) A Systematic Review on Relationship Between Head and Neck Cancer Associated to Parkinson's Disease. Neurol Sci Neurosurg, Volume 5:2. 143. DOI: https://doi.org/10.47275/2692-093X-143

Received: August 25, 2024; **Accepted:** October 28, 2024; **Published:** November 01, 2024

Introduction

In industrialized countries, PD affects 0.3% of the population and nearly 2% of those over 65 years of age, making it one of the most common and well-studied of all age-related neurodegenerative disorders. As a result of dopaminergic neurons being lost in the substantia nigra pars compacta, PD consists of four cardinal motor symptoms: resting tremor, rigidity, hypokinesia, and postural instability. Because of its elusive mechanisms, this slowly debilitating disease remains incurable and irreversible [1]. Cancer is another chronic disease that has a devastating impact on human health and is a significant research focus [2]. The inverse association between PD and cancer has been reported in a number of epidemiological studies, and a positive association has been found recently in some cancers, including the skin, breast, and brain. In molecular genetics and cell biology, genetic mutations that alter cell cycle control, protein turnover, and mitochondrial function have been revealed to be associated with this positive association [3]. Biologically similar cancers originate in many parts of the body, including the oral cavity, the pharynx, the larynx, the paranasal sinuses, and the neck. Across different nations in the world, HNC has a lower incidence rate than other cancers, at 7 - 8 per 100,000 person-years [4-9]. At 2.2 per 100,000 person-years, HNC remains a significant cause of death. As cancer diagnostic technologies and therapeutic interventions like surgical resection, radiation therapy, and chemotherapy have improved, patients with HNC have had a significantly longer survival rate [10]. The increased survival rates have led to an increase in late-onset complications despite these improvements. In particular, long-term adverse effects, including neurodegenerative diseases, are a growing concern. In many cases, this condition develops months or years after treatment for the malignancy or its treatment. In addition to affecting patients' quality of life, HNC can also impose a significant burden on the healthcare system due to its neurodegenerative consequences [11, 12]. HNC and its treatments have long-term neurodegenerative effects, which is crucial for improving patient outcomes and addressing healthcare challenges. It is a neurodegenerative movement disorder caused by the premature death of dopaminergic neurons in the substantia nigra of the midbrain. Patients with this disease experience tremors, rigidity, bradykinesia, and postural instability. Neuronal death is well defined in its pathological characteristics, but its underlying causes and mechanisms are unclear [13-16]. In addition to providing a new perspective on the well-known opposing fate of post-mitotic neurons, the intriguing link between PD and cancer provides an intriguing explanation of cancer cells' uncontrolled division and enhanced resistance to death. Combining these processes provides new avenues for studying age-related conditions and addressing an urgent need for therapeutic options [2, 17].

An overview of common cancers and PD

The risk of developing cancer is inversely related to PD, according to a number of epidemiological studies. According to several studies we reviewed, PD was associated with a 30% overall decrease in cancer risk, and a 36% decrease after melanoma and other skin tumors were excluded [3, 18]. A few studies have also found that PD patients have a 25% lower risk of cancer. The number of cancers has been reported to be reduced in PD patients, including prostate, lung, bladder, stomach, colorectal, and blood cancers. All smoking-related cancers, including

lung, bladder, and colorectal cancer, are significantly lower in PD patients, but stomach, leukemia, and uterine cancer fail to achieve significance in some studies for a clear inverse relationship [19]. There is also evidence linking PD to a higher prevalence of certain cancers, including non-melanoma skin cancer. PD is associated with breast and brain cancer, but there is conflicting evidence regarding the timing of these associations [20-23]. In some studies, researchers like Olsen found significant risks of non-melanoma skin cancer before PD diagnosis; however, other researchers like Wirdefeldt showed an increase in risk of 40% after one year following PD diagnosis. There is also a difference in direction and statistical significance between cancer risks before and after PD diagnosis, according to other studies [24-27].

There is a difference between ethnicities as well as between Eastern and Western populations in terms of trends [28-31]. There was a positive association between brain, kidney, and uterine cancers after diagnosis in two Taiwanese and British cohort studies, but stomach and lung cancers were negative according to researchers in England, whereas they were positive according to Taiwanese researchers [32, 33]. According to the Taiwan study, PD patients have no negative cancer risks. These differences have validity, regardless of whether they are caused by genetics, the environment, or technical differences. There is a need for further research into cancer in PD patients [34-39].

Materials and Methods

PD was eliminated from the dataset during the first year as a washout period. The authors tried to study research papers of patients diagnosed with HNC during the index period of 2015-2023 [40]. The papers studied cancer groups were defined based on the presence of HNC diagnostic codes. Individuals who had these diagnostic codes more than twice or had inpatient hospitalizations with these diagnostic codes were included [41]. Those diagnosed with dementia before the cancer diagnosis, those under 40 years of age, and those who died during the index period were excluded from the studies in order to enhance the accuracy of the outcome [42]. For each patient with cancer, on average ten control participants were selected using a propensity score-matching methodology [43-48]. The researchers matched participants based on independent variables and cancer diagnosis year during propensity score matching. Several independent variables were controlled in the target and comparative cohorts to refine the results. As a result, age, sex, residence, household income, and comorbidities were selected as independent variables. Patient comorbidities were adjusted using the Charlson comorbidity index, a weighted index. Most of the studies defined the primary endpoint as PD events until the dataset's final date. Following the follow-up period, the patients were censored if they had not experienced these events [49]. The authors gathered papers published with healthcare data on adults from different healthcare claims databases as part of our nationwide representative cohort study, which spans from 2015 to 2023. In addition to capturing inpatient and outpatient visits, medical procedures, and prescription records, this dataset contains a wide array of healthcare information. This dataset adheres to the international classification of diseases and clinical modification standards to ensure consistency and accuracy. Individuals within this dataset are assigned unique identification numbers at birth [50]. Healthcare claims data are protected by this unique identifier to prevent omissions or duplications. This ensures that the paper represents the entire population over the study period with a high degree of accuracy and reliability, minimizing the potential for selection bias [51].

The study offers insight into the prevalence of various diseases, the effectiveness of treatments, and the healthcare behaviors of people. It contributes to the improvement of public health strategies and interventions across countries by incorporating a diverse and representative sample for epidemiological studies and health policy assessments [52]. Furthermore, because the dataset is longitudinal, researchers can examine changes over time in health status and healthcare utilization. Informed predictions about future healthcare needs can be made using this information [53, 54]. Based on NIH-collected national health claims data, the studies we analyzed mentioned a nationwide population-based dataset. De-identification was performed on the dataset before it was obtained. During a particular period, the incidence rate was calculated to determine the frequency of disease or other incidents reported per 1000 person-years. For three scenarios, person-years were calculated: for death cases, the period between the initial cancer diagnosis and the date of death; for specific events, the period between the initial cancer diagnosis and the first occurrence of these events; if no events occurred, the period from the initial cancer diagnosis until the study was over [3, 55]. A cox proportional hazards regression analysis was conducted to determine whether patients with cancer are at an increased risk of developing specific diseases after adjusting to other independent variables (Table 1).

Diseases associated with neurodegeneration, including cancer

Studies have shown a negative association between Alzheimer's disease (AD) and cancer, although the epidemiological evidence is not as strong as that for PD [57]. According to a study, cancer risk decreased by 69% among those 65 and older. Romero et al. estimated that those with dementia had a 0.5 risk ratio for cancer mortality. Epithelial and lung cancer risks are reduced by 40%, and colorectal cancer risks are reduced by 57% in people with AD. They found an inverse association between cancer and AD not only among women, but also among tumors related to the endocrine system, with odds ratios of 0.5. It appears that AD and cancer are bidirectional [2, 58]. A hazard ratio of 0.67 was calculated by comparing study participants with and without cancer. Researchers have found that people without non-melanoma skin cancer who have a history of skin cancer are 85% less likely to develop AD [59-61]. According to a study conducted by the AD neuroimaging initiative, skin cancers, but not breast or prostate cancer, are associated with a decreased risk of AD, contrary to PD. There is an apparent reverse relationship between cancer survivors and AD, but reduced cognitive function and cerebral gray matter density have also been found in cancer survivors pre- and post-treatment, complicating the apparent reduction in AD risk.

Although there is no biological evidence to support this theory,

Table 1: Distribution based on NIHSS and MoCA-Ina.

Mutation/polymorphism	Type of neoplasm
MC1R polymorphism p.R151C	Melanoma
LRRK2 G2019S mutation	Skin cancer and breast cancer
R1441C/G mutation	Colon cancer and hematological malignancies
LRRK2-PD	Non-skin cancer, hormone-related cancers, breast cancer, and leukemia
PARK1, PARK4	Lung, intestine, prostate, and ovarian cancers; melanoma; and non-Hodgkin's lymphoma
PARK2	Lung, ovary, kidney, and pancreatic cancers; glioma; and melanoma
PARK6	Glioma and ovarian cancer
PARK7	Breast, lung, pancreatic, stomach, and prostate cancers
PARK1/4, PINK1, PARK9 (ATP13A2)	Brain tumors
DR polymorphisms increased expression of dopamine D2 receptors	Gastric, colorectal, and non-small-cell lung cancers; gastric cancer; breast cancer; neuroendocrine tumors; and glioma

it is believed that the Phosphatase and tensin homolog (PTEN) gene and protein are important in advancing AD. There is a significant reduction in PTEN expression in AD neurons, which may explain the importance of its downstream targets. The phosphorylation of Tau by glycogen synthase kinase regulates neuronal survival in experimental models of AD. There have been PD genes associated with almost all biological mechanisms studied, but this does not mean that the list is exhaustive. In this article, we also reviewed the genes that play a role in neurodegenerative diseases. Several overlapping molecules have been associated with the pathophysiology of cancer and neurodegenerative diseases, including p53, cyclin D, cyclin E, cyclin F, peptidyl-prolyl cis–trans isomerase, never in mitosis A-interacting 1 (Pin1), and protein phosphatase 2A (PP2A) (Figure 1) [62, 63].

Results and Discussion

For sample matching, all covariates used for HNC, and non-cancer groups were similar. Furthermore, the researchers and their papers found no significant differences in any of the independent variables. An appropriate match was also confirmed using a balanced plot. An analysis of non-cancer person-years and multiple HNC person-years was conducted to investigate the incidence rate of PD [64]. There was a noticeable difference between the incidence rates in the two groups, according to our findings. PD was diagnosed in 12 out of 1000 people. By contrast, the incidence rate for the non-cancer group was 8 per 1000. In contrast to individuals with no cancer history, those with a history of HNC have a higher incidence of PD. Considering this significant disparity, further research is needed to identify possible links between HNC and increased risk of PD. We can better understand HNC's health outcomes and risks by analyzing these incidence rates, which will help guide future research and potential interventions [65-71].

Most of the results in the paper revealed a significant association between HNC and the onset of PD, with an adjusted risk after adjusting for all covariates. Based on the results, individuals with HNC are more likely to develop PD than those without HNC. Furthermore, our evaluation of PD risk throughout the follow-up period revealed critical insights. Following a diagnosis of HNC, the risk increased particularly in the seventh year. Even after the seventh year, there was still a significant risk ratio for developing PD. PD patients with a history of HNC need ongoing monitoring and preventive strategies for this prolonged elevated risk [72]. HNC patients must be followed up long-term and managed comprehensively, according to the findings of this study. Researchers are investigating potential mechanisms linking HNC to neurodegenerative processes based on the increased risk of PD observed in these patients. Identifying these mechanisms could lead to improved prevention and treatment approaches. The risk ratio for developing PD was higher for patients aged above 50 with HNC than for those aged 75 years or older [73].

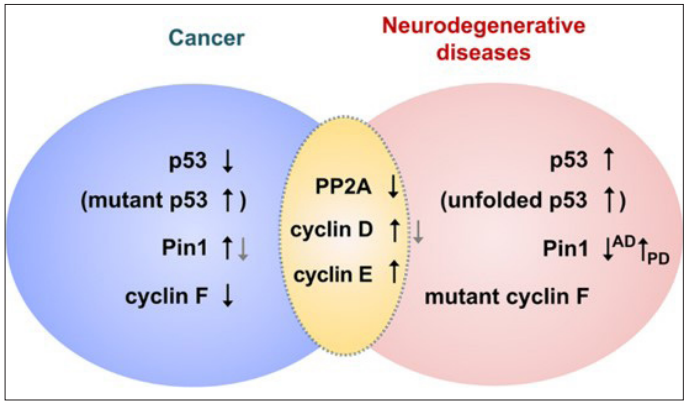

Figure 1: Changes in overlapping molecules in cancer and neurodegenerative diseases [62].

Mutations or DNA damage disrupt normal cell growth and division, contributing to the development of various diseases via multiple pathways. Recent research has shown that cancer may be associated with neurodegenerative diseases that can affect patients' quality of life and cause psychosocial problems. Cancer and neurodegenerative movement disorders such as PD have been studied extensively. A number of studies have examined the relationship between PD and various types of cancer, such as colorectal, skin, lung, and prostate cancers, with conflicting results. As of yet, there is no evidence that HNC and PD are associated [74]. The study is the first to use a representative national cohort dataset to analyze the risk of developing PD in patients with HNC. The incidence of PD was significantly higher in patients with HNC than in non-cancer patients. The hazard ratios (HR) of PD after adjusting for sex, age, residence, income level, and comorbidities was significantly higher in the HNC group. Furthermore, the risk of developing PD was significantly higher in the oral cavity cancer group than in the non-cancer group when analyzed by HNC subtype. Other cancer types had too few patients to draw significant results, but oropharyngeal and nasopharyngeal cancers had higher HRs. It is unclear how HNCs play a role in the pathogenesis of PD. In spite of this, accumulating evidence from numerous studies suggests that HNC and PD may be related in various ways. PD and HNC may have a significant genetic component [75]. Parkin gene mutations are known to cause PD, mainly through their role in the ubiquitin-proteasome system, which degrades misfolded proteins preventing neurodegeneration. HNC treatment methods can also influence PD development. Radiation therapy alone, postoperative radiation therapy, and surgery alone are the primary treatment strategies for HNC. The survival rate of most cancer patients is improved by radiotherapy. Due to the close proximity of the treatment site to the brain, oral cavity cancer, which showed a significantly higher HR among HNCs, poses an increased risk of radiation-related brain damage. PD may be a result of radiation-induced brain damage resulting from this close anatomical relationship. Radiation near the substantia nigra can damage and degenerate dopaminergic neurons, as described in one case report of a patient who underwent chemotherapy and radiotherapy for a low-grade astrocytoma [76].

The development of PD can also be influenced by complications associated with HNC surgery. As compared with other cancers, HNC can significantly impair patients' ability to speak and eat, causing significant inconvenience in daily life and severe cosmetic problems, adding to their stress. As a result, patients with HNC are more likely to experience anxiety and depression than patients with other types of cancer. A number of studies have shown that depression is associated with the development of PD. There was a significant increase in the risk of developing PD for patients diagnosed with depression, with a relative risk of 6 [77]. There was a higher risk during the first year following diagnosis. According to some studies, peripheral inflammatory agents that are increased by depression can penetrate the blood–brain barrier and activate glial cells, causing neuroinflammation that, in turn, causes neurodegeneration and contributes to PD pathogenesis through oxidative stress and glutamate excitotoxicity. Researchers found a link between depression and chronic stress in patients with HNC, suggesting that chronic stress and depression play a role in the pathogenesis of PD.

Limitations

The results of studies need to be interpreted with caution. The

diagnosis of HNC and PD was based solely on international classification of diseases 10th revision (ICD-10) codes. Medical records, including pathological reports and medical history, are not provided by these codes. Due to this, it was impossible to analyze important clinical details such as cancer stage, pathology, and PD. Due to this lack of granularity, we are unable to fully understand the diseases under investigation. In addition, we could not access information about the treatment methods for HNC in our study. Consequently, we were unable to assess how chemotherapy and radiotherapy, as well as their duration, might affect PD risk. Considering the fact that treatment methods can have varying effects on patient outcomes and the progression of comorbid diseases, this represents a significant problem. It is less likely that our findings regarding the relationship between HNC and PD will be comprehensive without this data [2, 78]. Due to the de-identification protocols, the database did not provide specific ages but rather grouped categories. We matched the two groups by categorizing their ages, but this method may have introduced residual bias. In the absence of precise age information, some subtle but significant differences could have been missed because age influences disease progression and onset. Since most of the studies were retrospective, the pathological mechanisms underlying HNC and PD could not be directly examined. It is important to conduct prospective clinical studies that can collect a wider range of factors in a real-time manner in order to fully understand these mechanisms. This limitation can be overcome by incorporating detailed medical records, including patient histories and pathology reports, into future research. It is necessary to conduct prospective studies on the effects of various treatment methods on the risk of panic disorder severity scale. Additionally, age-related analyses would be more accurate if precise data were obtained instead of grouped categories. To understand the underlying biological interactions between HNC and PD, clinical studies investigating pathophysiological mechanisms in greater detail are essential [79, 80].

Conclusion

Despite the emerging overlap between PD and cancer, several concerns arise from contradictory epidemiological and laboratory results. As evidenced by the discrepancy in cancer risk and prevalence between different populations, there are undoubtedly differences in genetic mutations across ethnicities and races. Clinically relevant genetic or pharmacological models should identify which groups are most likely to be relevant.

The authors tried to highlight whether HNC is associated with the onset of PD. PD is particularly common in patients with oral cavity cancer, which has a strong association with HNC. There may be valuable perspectives and new therapeutic options for the two traditional disparate but pathologically converging groups of diseases if further investigations of these links and genetic factors are undertaken. A new understanding of the relationship between HNC and PD is provided by these results. In this regard, clinicians should monitor any movement disorders and physical symptoms in patients with HNC and refer them to a neurologist as needed.

Acknowledgements

None.

Conflict of Interest

None.

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