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CANCER IN THE CURRENT CONTEXT OF THE COVID-19 PANDEMIC

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ABSTRACT

The new coronavirus disease (Covid-19) emerged in December 2019 in Wuhan, China, and quickly spread around the world. Cancer is regarded to be one of the leading causes of premature death in most countries and correlated with an increased risk for complications in patients infected with Covid-19. Thus, the aim of this study was to inform whether cancer is a predominant factor in the mortality rate from SARS-CoV-2 infection. This study is a narrative review based on a bibliographic survey in the databases PubMed, SCOPUS, Web of Science and Cochrane. The results show that Covid-19 is a public health problem that can aggravate cancer due to its association with worsening of prognosis of the pathology. Randomized clinical trials and large population studies should be conducted in order to better elucidate this issue and show the relationship of cancer in complications and mortality rate in patients with Covid-19.

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INTRODUCTION

In December 2019, the first case of coronavirus disease 2019 (Covid-19), caused by a new viral infection identified as Serious Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), arose. The new disease emerged in Wuhan, China, and quickly spread worldwide, thus being declared as a public health emergency of international importance by the World Health Organization (WHO) (Ferreira, Lima, Oliveira, Cancela, & Santos, 2020; Gosain *et al*., 2020). The most frequent symptoms in evidence of the new pandemic are fever (above 37.8 °C), difficulty and/or respiratory discomfort, cough, headache, diarrhea, muscle pain, anosmia, and ageusia (Wang & Zhang, 2020). As the new coronavirus pandemic has a high potential for transmissibility, control strategies have been adopted in several countries, which enable the prevention of contagion and the maintenance of population health. These strategies include social distance, hygiene instructions, and the use of protective face masks(World Health Organization, 2020a).

Although 80% of infected patients are asymptomatic in terms of prognosis, patients with weakened immune system, older adults, and with chronic diseases, including cancer, are more susceptible to higher severity of the Covid-19 outcomes (Pan *et al*., 2020). These complications include worsening of the acute respiratory syndrome and possible evolution to multiple organ dysfunction syndrome (Ferreira *et al*., 2020; J. Zhang, Xie, & Hashimoto, 2020). Among cancer patients, those who had a higher risk of complications due to coronavirus infection were those with lung cancer, in view of the relationship with previous smoking (Xia, Jin, Zhao, Li, & Shen, 2020). In addition, patients who underwent bone marrow transplantation or who underwent chemotherapy treatment were also more affected to Covid-19 infection, mostly because of the action of immunosuppressants in the cancer treatment protocol (Gosain *et al*., 2020; Ma, Yin, Qian, & Wu, 2020). Given the above, this review aims to inform whether cancer is a predominant factor in the mortality rate from SARS-CoV2.

MATERIALS AND METHODS

This narrative review used a bibliographic search in the databases PubMed, SCOPUS, Web of Science, and Cochrane. The search was conducted during the months of May and June 2020. The keywords were used: cancer, Neoplasm, SARS-CoV-2, and Coronavirus, selected from the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MESH). The descriptors were used in combination with the Boolean operators AND and OR. The inclusion criteria were: studies that presented relevant information about cancer, Covid-19, and the correlation between them. We used studies available in Portuguese and English. Classic and more recent articles were preferred for this publication, with originality and relevance.

RESULTS AND DISCUSSION

Physiopathology of cancer: Cancer is regarded as a group of more than 100 diseases that have in common the disordered (malignant) growth of cells that invade tissues and organs, and can spread (metastasize) to other regions of the body other than the initial site of the pathology(Instituto Nacional de Câncer, 2012). Cancer is the leading cause of premature death in most countries, responsible for 29.8% of premature deaths worldwide in 2016 (World Health Organization, 2020b). In Brazil, it is estimated that there will be over 800,000 new cases of cancer up until 2020 (Instituto Nacional de Câncer, 2019b). The etiology of this disease is complex and involves several factors that can contribute to the triggering of carcinogenesis, such as: genetic factors, lifestyle (alcohol and tobacco consumption, diet, obesity, and physical inactivity), infectious agents (papilloma virus), reproductive and hormonal factors, radiation, pollution, pharmaceutical drugs, and exposure to carcinogens substances (Instituto Nacional de Câncer, 2019a; World Health Organization, 2014).

Cell growth and maturation are normal events in development during embryogenesis, growth and repair, and remodeling of injured tissues. An error or deregulation of these processes can lead to the emerging of neoplasms, which cause abnormal cell growth (Hammer & McPhee, 2016). Therefore, cancer arises from changes in the cell's DNA, which starts to receive wrong instructions for its functional activities (Instituto Nacional de Câncer, 2019a). Carcinogenesis can start spontaneously or be caused by the action of carcinogenic agents (chemical, physical or biological). In all cases, mutagenic, non-mutagenic or epigenetic changes are induced in the cells. The cell growth control mechanism seems to depend on stimulating and inhibitory factors. This mechanism is normally in balance, until an effective growth stimulus appears, without activating the inhibitory mechanism (Instituto Nacional de Câncer, 2008). Neoplasms can be malignant or benign, which have proliferation in an organized manner, usually with slow, expansive growth, and very clear limits. Malignant (cancerous) neoplasms are formed by anaplastic cells, have rapid and disordered growth, do not have a well-defined mass, and are capable of invading close tissues and causing metastasis (Instituto Nacional de Câncer, 2012). Proto-oncogenes and tumor suppressor genes (TSG) seem to play a crucial role in the carcinogenesis processes, as they are involved in the coding of several proteins. Some of these proteins present the function of regulating the cell cycle, mediating growth factor signal transduction pathways, and regulating programmed cell death (Hammer & McPhee, 2016). The activation of proto-oncogenes and/or inactivation of TSG can lead to changes favorable to carcinogenesis, for example the loss of TSG p53, which is responsible for recognizing DNA damage and inhibiting the continuation of the cell cycle, inducing cell death, which can lead to continued cell replication despite DNA damage (Hammer & McPhee, 2016; Olivier *et al*., 2016). Proto-oncogenes are naturally inactive. However, when activated, they become oncogenes, which causes the malignancy of normal cells. The oncogenesis process has three stages: 1) the initiation stage (genes are affected by cancerous agents, altered cell can still be destroyed or remains latent), 2) promotion stage (oncogenic agents act on the already altered cell increasing the alteration), 3) and progression stage (characterized by the uncontrolled and irreversible multiplication of the cancer cell) (Instituto Nacional de Câncer, 2012). Once consolidated, the cancer can metastasize, characterized by the formation of secondary tumors at a distance from the primary site of the original neoplasm (Martin, Ye, Sanders, Lane, & Jiang, 2013). Cancer cells spread to the organism by lymphatic, hematogenous, or transcavitary dissemination (Instituto Nacional de Câncer, 2008). Invasive and mobile cancer cells can enter the circulation long before the tumor is diagnosed. Most of these cells perish, but a small proportion are able to infiltrate and survive in distant organs as disseminated seeds for eventual relapse (Massagué & Obenauf, 2016). Even small tumors can release millions of cancer cells (circulating tumor cells), but many cancer patients never relapse or do so after a long latency period without clinically manifesting the disease. Many of these cells have to go through several stages that hinder their survival, such as escape from the immune system, adaptation to support niches, and obtaining inputs and growth factors (Massagué & Obenauf, 2016). However, despite the difficulties, after the establishment of metastases, small tumors are the main cause of death in individuals with cancer (Robert, 2013).

Immune Response to Covid-19 and Cancer: The mortality rate for cancer-infected patients is higher than the mortality rate for patients infected with Covid-19. In countries like China, death from cancer reaches 28.6% compared to 2,3% from the new coronavirus disease (L. Zhang *et al*., 2020). Many of these problems are due to the interaction between the new SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) and the renin-angiotensin-aldosterone system (RAAS), which facilitates infection by Covid-19 (Ferreira *et al*., 2020; Gosain *et al*., 2020). The SARS-CoV-2 interaction with RAAS through ACE2activity is a key factor for infection (Russell *et al*., 2020). ACE2 acts as a receptor for theSARS-CoV-1 and SARS-CoV-2. The binding to the ACE2 receptor requires a viral surface unit called a protein spike (S-spike). The entry of the virus into cells also depends on the serine protease TMPRSS2 (transmembrane protease, serine 2). SARS-CoV-2 also uses this receptor to infect cells. Therefore, the entry of SARS-CoV-2 into cells can be blocked both by neutralizing antibodies to protein S and by inhibitors of TMPRSS2 (camostatemesylate) (Danser, Epstein, & Batlle, 2020; Vaduganathan *et al*., 2020). Although ACE and ACE2 are similar in structure, their active enzymatic sites are different. Unlike ACE, ACE2 does not convert angiotensin I into angiotensin II. Similarly, ACE inhibitors do not inhibit this activity. ACE2 is the most potent of the 3 enzymes that convert angiotensin II vasoconstrictor to angiotensin-(1-7), which antagonizes the effect of angiotensin II. Angiotensin-(1-7) is well-known for having organ-specific properties that

oppose and counterbalance the properties of angiotensin II. ACE2 is a membrane-bound enzyme and its blood-soluble portion is very low. The type 1 AT receptor (AT1)of angiotensin 2 activates metalloprotease 17 (ADAM17), that cleaves ACE2 in the membrane, thus increasing soluble ACE2 levels(Danser *et al*., 2020; Vaduganathan *et al*., 2020). As a result, ACE inhibitors do not directly affect ACE2 activity. Theoretically, ACE inhibitors can partially reverse the cleavage of angiotensin II, increasing the expression of this enzyme in the cell membrane, therefore, this is unlikely to affect the entry of SARS-CoV-2, which depends on membrane-bound ACE2. During acute lung injury, alveolar ACE2 appears to be under-regulated. This would decrease the metabolism of angiotensin II, resulting in higher local levels of this peptide, which increases alveolar permeability and promotes lung injury (Danser *et al*., 2020).

Based on the available evidence and despite theoretical concerns and uncertainties about the effect of RAAS on ACE2 and the way these drugs can affect the propensity or severity of COVID-19, RAAS should be continued in patients in a stable condition. In addition, physicians need to be aware of the unintended consequences of early interruption of proven therapies in response to hypothetical concerns that may be based on incomplete experimental evidence(Vaduganathan *et al*., 2020). In cancer patients, higher expressions of ACE2 and comorbidities are associated with increased age. Therefore, older adults with cancer have a higher risk of adverse outcomes when infected with SARS-CoV-2. Moreover, data showed that the use of tobacco significantly increases the gene expression of ACE2, binding to the severe acute respiratory receptor, which could explain the high susceptibility to Covid-19 infection in smokers(Prompetchara, Ketloy, & Palaga, 2020). After the initial innate response, a specific adaptive immune response is required to eliminate SARS-CoV-2 from the body. Persistent release of cytokines (probably mediated by lymphocytes in addition to T lymphocytes) can lead to a "cytokine storm" and cause significant lung damage. In addition, the below-average specific immune response allows for viral spread, tissue destruction, and progression to severe stages, especially in tissues rich in ACE2, for example, lung, intestine, and kidneys (Wang & Zhang, 2020). Therefore, strategies that increase the immune response at this stage, for example, immunoadjuvant therapies (IFNα or convalescent plasma), block cytokines (Interceulin-6 Interleukin-1), tumor necrosis factor alpha (TNFα), or the administration of antiviral agents can be beneficial (L. Zhang *et al*., 2020).

Cancer epidemiology during Covid-19 outbreak: Covid-19 is considered, in the current scenario, the public health problem with the fastest transmission rate in the world and cancer is among the comorbidities that can aggravate its clinical picture, as isassociated with the worst prognosis of the pathology (Ferreira *et al*., 2020). This is probably due to the immunosuppressive state of the disease evolution or acquired during its treatment (Liang *et al*., 2020). A retrospective study showed that, of the 28 cancer patients admitted to the hospital, 53.6% developed serious events, 21.4% had to be admitted to the Intensive Care Unit (ICU), 35.7% had complications with high risk, and 28, 6% passed away. It is worth mentioning that 83% of individuals who received antitumor treatment within 14 days before being infected with Covid-19 significantly increased the risk of developing serious events, which is justified by the reduction in blood cell count that occurs in between 10 to 14 days after the start of chemotherapy. This is known by oncologists as nadir, which makes patients more predisposed to the infectious process by decreasing the number of immune defense cells (Wang & Zhang, 2020). Data indicate that breast cancer is not an aggravating factor for Covid-19. In fact, the mortality of breast cancer patients was mainly associated with clinical cases that had other pathologies contributing to the severe progression of Covid-19 (Vuagnat *et al*., 2020). However, lung cancer had greater clinical complications regarding the SARS-CoV-2. it is understood that previous surgical treatment with resection of part of the organ most compromised by the infectious condition, as well as some comorbidities such as chronic obstructive pulmonary disease and smoking, were determinant for increasing the severity of the disease (Liang *et al*., 2020; Luo *et al*., 2020). It is important to emphasize the relationship between smoking and endothelial dysfunction and the increase in the concentration of free radicals, in the same way as microbial infections such as COVID-19. Among them, the high levels of C-reactive protein (CRP) and dimer- D, diagnostic markers of thrombosis, already altered in smokers. One study observed a picture of disseminated intravascular coagulation in 71% of deaths by COVID-19 compared to 0.4% of survivors. Thus, it is warned that higher levels of D-dimer (above 1μg / L) increase the chance of death by 18 times. This reveals that smokers are 3.25 times more likely to develop more serious symptoms than non-smokers (Da Silva, Moreira, & Martins, 2020).

Conclusion

Although the effects caused by the virus in cancer patients are still poorly known, the saturated health system makes it still unknown the survival or mortality of this population due to the delay or discontinuity of treatment. There is still no scientific evidence for changes in the treatment protocol during the pandemic, which leads us to believe that preventive measures, early diagnosis, cure, and rehabilitation should be coupled with cancer care. Therefore, there is a need for studies that assess the characteristics and physiological parameters of cancer patients. This can clarify the relationship between cancer mortality and complications in patients with COVID-19, in order to contribute to clinical interventions aimed at controlling this disease.

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