Review Article

The Mythical Carcinogenesis Potential of COVID-19 Vaccination: *Perspectives*

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Abstract

In the era of COVID-19, vaccination is the most powerful shield for new-normal living. Although developed rapidly, the two leading vaccines, whole virus vaccines and viral component vaccines, have proven efficacy. However, risk of cancer from the COVID-19 vaccines is a concern despite only minor effects on DNA repair enzymes. There is a hypothesis that COVID-19 infection impairs RB protein and p53 protein, a tumor suppressor and gatekeeper to functions of the cell. Also, the disease causes inflammation leading to the propagation of carcinogenesis. With the benefit of immunization, COVID-19 vaccination might have the least potential effect of carcinogenesis. As one crucial piece of the jigsaw, a cohort study must prove whether the COVID-19 vaccine can safely reduce lifetime cancer risk in upcoming decades and not eventually increase cancer risk.

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Introduction

In 2019 the SARS-CoV-2 outbreak started in Wuhan and spawned the notorious COVID-19 pandemic.[1] SARS-CoV-2 is the 7th discovered coronavirus that caused fatal illness. SARS-CoV-2 is an enveloped virus that is comprised of single-strand RNA. Pathogenesis of SARS-CoV-2 infection occurs when the virus enters a cell by binding with the angiotensin-converting enzyme 2 (ACE2) receptor of an epithelial cell, followed by endocytosis. The viral genome is replicated, transcribed and translated, into protein-inducing cytokines that cause inflammation of vital organs and eventually lead to severe systemic inflammation as a cytokine storm.[2] The acute phase of SARS-CoV-2 infections leads to acute respiratory distress syndrome.

There is an interesting medical hypothesis about the oncogenic potential of persistent infection of SARs-CoV-2 because of the ability of RNA viruses to shed to evade host immunity eradication. The theoretical implication is derived from other RNA viruses, e.g., the Flaviviridae family RNA-virus (HCV) to the SARS-CoV-2. The shedding of RNA viruses, such as HCV and the Borna disease virus, alters host genetic material via epigenetics such as microRNA,[3] leading to blinding the innate immune detection.[4] At the same time, being uncensored from host immunity, the virus possibly deregulates the tumor-suppressor protein pRb.[5]

Another important mechanism of carcinogenesis is oxidative stress. Reactive oxygen species (ROS) damage mitochondria functions, which account for increasing destructive cytokines such as Tumor-necrosis factor (TNF). The event leads to immortality of the cell. Viciously, the cell mutates and never ends with apoptosis.[6]

One of the hallmarks of cancer is inflammation that can enforce other hallmarks of cancer, including (i) evading apoptosis, (ii) self-sufficiency in growth signals, (iii) insensitivity to anti-growth signals, (iv) tissue-invasion and metastasis, (v) limitless replicative potential, (vi) sustained angiogenesis, (vii) genome instability, (viii) inflammation, (ix) resisting cell death, (x) deregulating cellular mechanism, (xi) unlocking phenotypic plasticity, (xii) non-mutational epigenetic reprogramming, (xiii) polymorphic microbiomes, and (xiv) senescent cell.[7-9]

As mentioned, SARS-CoV-2 enters a cell via the ACE2 and causes inflammation, as does treatment such as using a mechanical ventilator for ARD, both of which produce a lot of ROS.[10] This complication of late treatment is a cause of cancer risk. However, consequences of the infection, complications, and life-saving intensive treatment are associated with the hallmarks of cancer. Thus, COVID-19 vaccination might be the best approach to protect against acute symptoms and unknown long-term consequences of SARS-CoV-2 infection. Despite the scarcity of time, the vaccines have proven efficacy and safety to reduce the virulence of SARS-CoV-2 and limit the accelerating outbreak. Although the effectiveness has been established, there are still concerns about mysterious adverse events, especially the risk of cancers.

There are two main types of vaccines: whole virus vaccines and viral component vaccines (including genetic materials).

COVID-19 Vaccination

There are various approaches to inventing COVID-19 vaccines. Two main approaches are whole virus vaccines and viral component vaccines. The whole virus vaccines include inactivated vaccines, e.g., CoronaVac(Sinovac), BBIBP-CorV/HB02 (Covilo, Sinopharm [Beijing]), and Covaxin(Bharat Biotech). The action mechanism is multiple viral targeting of the immune response. A weakened live vaccine has also been produced. However, the live vaccine is not appropriate for immunocompromised hosts and could potentially recombine wild-type viruses.

There are two main types of viral component vaccines. The first type is mRNA vaccines ((BNT162b2 (Pfizer-BioNTech vaccine) and mRNA-1273 (Moderna vaccine)). A strength of mRNA vaccines is their low carcinogenesis potential. The mRNA does not enter the nucleus and does not fuse with the DNA of the host. It translates into a spike protein which provides immunity. The efficacy is 90 - 95% against death and hospitalization for seven doses after the second.[11-13] The effectiveness has been proven in various special population groups such as cancer patients, the elderly, children, and adolescents. Common adverse effects of mRNA vaccines are fever, fatigue, and local reactions at injection sites.

The second main type of viral component vaccines is viral vector vaccines (both replication-incompetent and competent). This article will

discuss only replication-incompetent vector vaccines, e.g., (Ad26.COV2.S (Janssen/Johnson & Johnson), ChAdOx1 nCoV-19/AZD1222 (AstraZeneca), Gam-COVID-Vac Sputnik V (Gamaleya Institute), Ad5-nCoV (CanSino)).[15] The viral vector has been engineered not to replicate, so there is less risk of cancer from viral integration into the host's DNA.

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There is no evidence that the COVID-19 vaccine can cause cancer or carcinogenesis.[16] The writer would like to propose two main ideas. Firstly, infection, inflammation, and genetic alteration are more proximate causes of carcinogenesis. Secondly, an imbalance of the immune system (both innate and adaptive immune system) can cause cancer to evade it. In this era of cancer treatment, immunotherapy, immune checkpoint inhibitors, and CAR-T cells, cancer vaccines are being developed for cancer treatment. Altogether, precision medicine's big data enlighten oncologists that "one size does not fit all." Some cancers have an excellent response to immunotherapy treatment, and others respond to targeted therapy or even to chemotherapy.

Timing is a critical issue of therapy; for example, cancer patient immunity drops to nadir when they have systemic treatments, including polychemotherapy or biological agents. Even though the period of lower white blood cell count is a concern, the ASCO/ASH-ASCTC/CDC/ESMO/NIH/TSCO recommendations state that vaccine administration for cancer patients should not be delayed significantly during pandemics. Additionally, both immunocompromised hosts and immunocompetent hosts who were previously infected with SARS-CoV-2 and treated with immunotherapy should be aware of vaccination timing due to the lower efficacy of vaccines.[17-20]

T-cell function supports the theory of cancer risk reduction with vaccination. Since the COVID-19 infection elicits cytokines which lead to T-cell depletion, the immune system will become dysfunctional and cancer cells can escape from the dysfunctional T-cells. Consequently, viral clearance will be ineffective.[22,23]

Our knowledge about cancer, the disruptive environment, and accelerated treatment innovation have been improving. During the pandemic era, we are moving into the new normal. Our response to COVID-19 is trending in two directions: aggressive countermeasures and acceptance of epidemic disease. Meanwhile, we continue to live with threat of infection and cancer. Thus, a cancer screening program should address different individual risks.

A further observational study should answer the mythical question of whether COVID-19 vaccination will increase the risk of cancer or lower the risk of cancer. The strong recommendations will be updated upon entering the data.

Conclusion

The concerning carcinogenesis potential of the COVID-19 vaccine contradicts the oncolytic possibility of SARS-CoV-2. Correlation between SARS-CoV-2, COVID-19 vaccination, and carcinogenesis is under investigation. Based on the actual evidence, once again, we will "fly to the moon" with the evolution of knowledge from the pandemic era to a new approach to cancer treatments, infection treatment, and inflammatory disease treatment. Meanwhile, the following up-to-date studies and recommendations will also save people's lives from cancer and SARS-CV-2 infections.

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