

CAN SARS-COV-2 CHANGE INDIVIDUAL RADIATION SENSITIVITY OF THE PATIENTS RECOVERED FROM COVID-19? (EXPERIMENTAL AND THEORETICAL BACKGROUND)

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R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Science of Ukraine has been studying the mechanisms and specificities of individual radiation sensitivity (IRS) formation in professionals who work in the field of ionizing radiation, cancer patients and representatives of other population groups. Our data based on the use of G_2 -test in *in vitro* irradiated blood lymphocytes in late G_2 -period of cell cycle indicated an increased carcinogenic risk in professionals with high IRS. We suggest that the COVID-19 pandemic could make significant adjustments in the formation of IRS in professionals who have survived the disease and continue to work with ionizing radiation (IR). Increased systemic inflammatory activity, which persists for a long time in COVID-19 patients, in combination with low-dose range irradiation (professionals who continue to work with IR) and with local irradiation in the high-dose range (radiation therapy for cancer patients) may affect IRS. Repeated determination of IRS in professionals who have had COVID-19 infection, using chromosomal G_2 -radiation sensitivity assay will answer the question: can SARS-CoV-2 coronavirus affect the IRS? The proposed hypothesis of the radiosensitivity evolution needs further experimental validation using a set of radiobiological indices to clarify the mechanism of IRS formation following COVID-19 infection. The detected changes (increase) of human IRS after COVID-19 must be taken into account for personalized planning of radiotherapy of COVID-19 cancer patients.

Key words: ionizing radiation, coronavirus SARS-CoV-2, professionals, cancer patients, individual radiosensitivity.

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Late in 2019, an outbreak of a new highly contagious coronavirus infection with an epicenter in Wuhan occurred in the People's Republic of China. In February 2020, the World Health Organization named the new coronavirus infection as COVID-19 and its causative agent as SARS-CoV-2 [1, 2]. To date, tests have been developed to detect the pathogen. However, oropharyngeal and nasal swabs detect the virus in 30–60% of cases only [3]. Clarification of the long-term consequences in COVID-19 survivors (re-convalescents), including those that may develop under conditions of exposure to ionizing radiation (IR), is of paramount importance for the preservation of life and health of the world's population. At the same time, a well-founded question arises: how “dangerous” can the radiation safety of a human being be in the setting of a COVID-19 pandemic, taking into account the post-radiation distant consequences of a nuclear catastrophe of man-made origin (the accident at the Chernobyl nuclear power plant, 1986) and mixed genesis (the accident at Fukushima, 2011 as a result of a powerful tsunami)? This also applies to medical personnel, who are the largest cohort of professionals working in the field of IR and one of the social groups, which is the most affected by the coronavirus disease.

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of IR [4], cancer patients [5] and representatives of other population groups. Individual sensitivity to IR is known to be genetically determined and various factors, including biological factors (e.g. viruses), can significantly modify it. An informative approach for IRS assessment is the use of chromosomal G_2 -radiation sensitivity assay, which we modified based on classical provisions of human radiation cytogenetics [6]. The essence of this test is the estimation of cytogenetic effect induced by test irradiation (1.5 Gy dose) in the most radiosensitive late G_2 -period of cell cycle — at 46 h of cultivation of blood lymphocytes of examined persons. It should be noted that the chromosomal G_2 -test is performed with use of the mitogen (phytohemagglutinin) of the T-lymphocytes, which are the most radiosensitive cells and the biomarkers/biodosimeter of the human body's irradiation. An increase in the IRS of professionals as compared to the median level in population is the risk factor of the development of radiation carcinogenesis.

The data we obtained in the chromosomal G_2 -test (irradiation test of the lymphocyte blood culture using the dose of 1.5 Gy) in our examination of professionals (radiation oncologists, radiologists) suggest the following. The median rate of chromosome aberrations was 36.6 aberrations/100 metaphases among professionals who had been working in the radiation field for up to 1.5 years. The range of variability of the total number of chromosome aberrations in this group of professionals was from 19 to 67 aberrations/100 metaphases. Chromatid deletions are a major contributor to genetic instability (Figure, a).

The average rate of chromosome aberrations was 80.2 aberrations/100 metaphases for professionals (radiation oncologists, radiologists) with longer work-

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Abbreviations used: IR – ionizing radiation; IRS – individual radiation sensitivity.

ing experience in the field of radiation exposure. The range of variability of the total number of chromosome aberrations in the professionals of this group was from 45 to 140 aberrations/100 metaphases. The spectrum of radiation-induced genetic changes, in addition to deletions, was characterized by chromatid and chromosome type exchanges. This significantly complicates the genomic instability of the examined professionals and potentially increases carcinogenic risk (Figure, *b*).

Using the GTG-method of differential staining of chromosomes, we showed that the largest number of genetic disorders was registered in radiologists with high IRS [7]. Professionals with the detected long-arm deletion of chromosome 5 have an increased risk of developing myeloid leukemia [8], translocation of chromosome 14 — involves the q32 segment of multiple myeloma [9], and translocation of chromosome 3 is associated with an increased risk of kidney cancer [10]. Our data indicate an increased carcinogenic risk in professionals with high IRS. This applies not only to radiologists, but also to persons operating X-ray machines, employees of nuclear power plants, miners of uranium mines and others.

The obtained data suggest that the pandemic caused by the COVID-19 could make significant adjustments in the formation of IRS in professionals who have survived the disease and continue to work in the IR field.

There exists an observation that irradiation of the thoracic organs in the low-dose range can attenuate inflammatory processes in the lungs [11]. This may be relevant to COVID-19, as its most dangerous complication is pneumonia [12]. Although the effect of IR in the low-dose range does not appear to be specifically antiviral, in this situation, SARS-CoV-2 “may compensate for an overreaction of the immune system known as a cytokine storm” [13, 14]. This interpretation is based on the assumption that the different lesions caused by COVID-19 are explained by the three-stage mechanism of action of the SARS-CoV-2 virus [15]. At the first step, the virus binds to the enzyme ACE2, which is expressed on multi-organ cells, infects and damages these cells and thus causes a cytokine “storm”. In what we believe to be the second key step of the viral action, cytokines increase vascular permeability, which causes the progression of inflammatory processes. The main enzyme responsible for the development of inflamma-

tion and the cytokine “storm” is bradykinin. The use of ACE2 as a receptor for SARS-CoV-2 to penetrate the cell results in the increased levels of this enzyme causing tissue inflammation. At the third step, the virus crosses the blood encephalitis barrier. This pathway of the events in the cells of COVID-19 patients extensively reviewed by Komisarenko [13] is recognized as one of the key components of the pathogenesis of COVID-19 disease.

Several clinical trials have now begun in the US and other countries using COVID-19 therapeutic irradiation of patients in the low-dose range to treat viral pneumonia. The possible effect of SARS-CoV-2 on the radiosensitivity of normal cells of cancer patients during local therapeutic irradiation in the high-dose range is currently overlooked.

We shall look in more detail at the formation of IRS in cancer patients, which correlates with the frequency of normal tissues’ adverse radiation reactions from the environment of the irradiated tumor. It should be noted that radiation therapy, which is prescribed in 50–70% of cases, either as an independent method or in combination with chemotherapeutic and surgical methods, remains one of the main and effective methods of treatment [16, 17].

Despite the conformal “strategy” of radiation oncology, cells of normal tissues inevitably enter the irradiation zone that includes the tumor. These are tissue structures that are located at the entry and exit of the therapeutic IR beam, blood vessels that are exposed to the IR at the same dose as the tumor, and finally, microscopic tumor infiltrates in healthy tissues [16]. Sections of initially normal tissues surrounding tumors undergo a number of changes as a result of the therapeutic irradiation, including inflammation. Therefore, the irradiated tissue substantially differs from the original normal tissue by the end of the treatment course [18]. The emergence of secondary tumors after irradiation of prostate cancer by the IMRT method is explained by the use of a large number of irradiation fields and linear accelerators with a higher power, which increases collimating and phantom scattering [19]. After the irradiation of radiosensitive forms of tumors, their destruction occurs without significant damage to the surrounding healthy tissues (the tumor bed). The effective action on radioresistant tumors requires a dose of IR that causes a certain degree of destruction of healthy tissues. Therefore, the risk

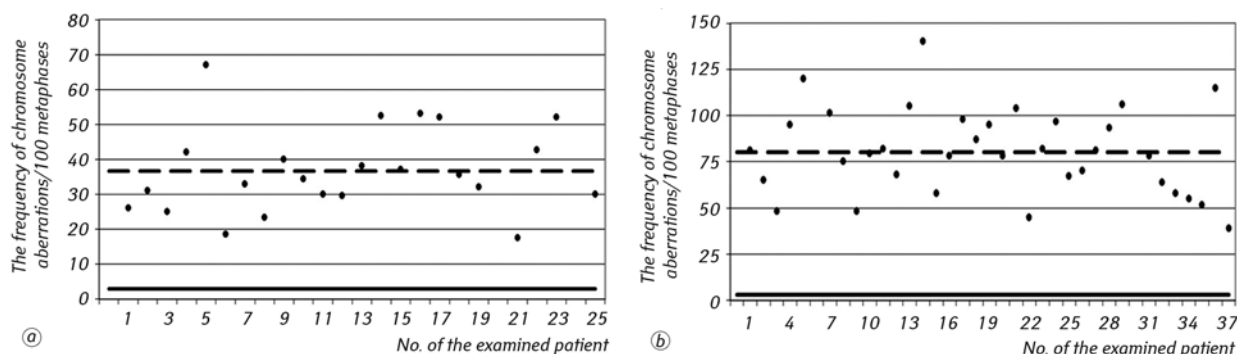


Figure. Individual radiosensitivity of professionals with up to 1.5 years (*a*) or more than 1.5 years (*b*) of work experience in the field of radiation exposure based on cytogenetic data of G_2 -test. Designations: straight line — the average population chromosome aberration rate; dotted line — the individual chromosome aberration rate

of developing adverse radiation reactions from normal tissues can be quite high [20].

Early radiation reactions occur in tissues with rapid cellular renewal, which include the skin, bone marrow, epithelium of the stomach and intestines, etc. Early reactions are often caused by the damage to stem cells and predecessor cells that lead to a temporary or permanent lack of mature functional cells. In some tissues, for example, lymphoid and salivary glands, the rapid loss of cells is due to their apoptosis. Early tissue reactions are inflammatory responses because of changes in cell permeability [21]. Because of irradiation, the endothelial cells lose the ability to proliferate, the capillaries become desolated, and the growth of new vessels is inhibited. To this are added damages of lymphatic vessels. The common defeat of the vascular network, which nourishes various tissues, leads to the development of fibrosis and radiation ulcers. Late radiation damage can develop on the bridgehead of early effects, including secondary tumors of radiation genesis.

Recently the attention of radiation oncologists and clinical radiobiologists has been concentrated on the problem of assessing the IRS of the body of cancer patients, the understanding of the role of IRS in the personification of radiotherapy [5, 22, 23]. Solving this problem will help to reduce the frequency of adverse reactions from healthy tissues during therapeutic irradiation of tumors of various locations.

Given that the growth of tumors of different genesis is accompanied by the development of profound disorders in the immune system, additional radiation exposure aggravates immunosuppression and may contribute to the development of secondary tumors.

According to the own data [22], more than 10% of persons in a cohort of healthy individuals have elevated radiosensitivity at the chromosomal level of peripheral blood lymphocytes (assessed with lymphocyte G₂-test). It is important to note that a “hidden” chromosomal instability among cancer patients induced by a “provocative” radiation in peripheral blood lymphocytes *in vitro* is much more common, as it occurs in 30% to 60% of patients having the sporadic malignancies, including breast, stomach, prostate cancer etc [5, 23–26].

According to modern concepts, the inflammasomes containing caspase-1 are the key components of the stress-induced inflammatory response to radiation exposure. Inflammasomes activated by radiation and the release of caspase-1 play a major role in both the development of inflammatory processes and cell death: apoptosis, necrosis and pyroptosis [27]. Increased systemic inflammatory activity, which persists for a long time in COVID-19 patients [28, 29], in combination with low-dose-range irradiation (professionals who continue to work in IR) and with local irradiation in the high-dose range (radiation therapy for cancer patients) may affect IRS. At the same time, it is known that in immunodeficiency virus-infected individuals the IRS is elevated [21]. Taking into account our previous studies and partially presented in this paper as well as the above theoretic-

cal and experimental background, we proposed a hypothesis of evolution of individual human sensitivity to radiation exposure in post-COVID-19 syndrome — virus-infected systemic inflammation [30]. The evolution of IRS of COVID-19 patients who are subsequently exposed to radiation for different reasons may follow the following pathway: combined virus-induced systemic and radiation-induced inflammation → increased blood supply to cells and tissues of the body → expansion of the microvessel network → increased cell oxygenation → increased IRS with accompanying lymphocytopenia → increase in IRS and carcinogenic risk.

Repeated determination of IRS in professionals (Figure) who have had COVID-19 infection, using chromosomal G₂-radiation sensitivity assay will answer the question: can SARS-CoV-2 coronavirus affect the radiation sensitivity of the human body?

The proposed hypothesis of the evolution of human body radiosensitivity needs further experimental validation using a set of radiobiological indices to clarify the mechanism of IRS formation following COVID-19 infection. If our hypothesis will be confirmed, it would be relevant to revise certain statements of radiobiology and radiation oncology concerning IRS, dose-effect relationships, and the effects of low-dose IR, etc.

We believe that the detected changes of human IRS after COVID-19 must be taken into account:

- for the development of the algorithm of long-term follow-up examination of COVID-19 exposed professionals working in the area of IR for the primary prevention of radiogenic diseases; an obligatory part of the algorithm should be G₂-radiation sensitivity assay;
- for personalized planning of radiotherapy of COVID-19 cancer patients with the aim of tertiary prevention of the development of post-radiation complications in healthy tissues from the environment of the irradiated tumor.

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ЧИ МОЖЕ КОРОНАВІРУС SARS-COV-2 ЗМІНИТИ ІНДИВІДУАЛЬНУ РАДІОЧУТЛИВІСТЬ ПАЦІЄНТІВ, ЩО ПЕРЕХВОРИЛИ НА COVID-19? (ЕКСПЕРИМЕНТАЛЬНО-ТЕОРЕТИЧНІ ПЕРЕДУМОВИ)

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В Інституті експериментальної патології, онкології і радіобіології ім. Р.Є. Кавецького виконуються дослідження, що спрямовані на з'ясування механізмів і особливостей формування індивідуальної радіочутливості (ІРЧ) професіоналів, які працюють у сфері дії іонізуючої радіації (ІР), онкологічних хворих, яким призначена променева терапія, та ін. Використано хромосомний G2-тест, модифікований нами на основі класичних положень радіаційної цитогенетики людини. Одержані дані свідчать про підвищений канцерогенний ризик у професіоналів з високою ІРЧ. Підвищена системна запальна активність, яка зберігається тривалий час у реконвалесцентів після COVID-19 у поєднанні з опроміненням в діапазоні низьких доз (професіоналів, які продовжують працювати у сфері дії ІР) та з локальним опроміненням в діапазоні високих доз (променева терапія онкологічних хворих) можуть модифікувати їх ІРЧ. Запропонована гіпотеза еволюції ІРЧ реконвалесцентів після COVID-19. Повторне визначення ІРЧ у професіоналів, які перехворіли на COVID-19, із залученням хромосомного G2-тесту дасть обґрунтовану відповідь на питання: чи може SARS-CoV-2 впливати на ІРЧ організму людини? Визначення ІРЧ первинних онкологічних хворих забезпечить персоналізований підхід до планування променевої терапії і таким чином зменшення променевих ускладнень з боку здорових тканин, що оточують пухлину.

Ключові слова: іонізуюча радіація, коронавірус SARS-CoV-2, професіонали, онкологічні хворі, індивідуальна радіочутливість.