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Research article

# PREDICTING A RISK OF TUMOR EVOLUTION CONSIDERING REGULATORY MECHANISMS OF THE BODY AND ANGIOGENESIS

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*Adverse environmental and lifestyle factors produce considerable effects on occurrence of cancerous tumors, both directly and indirectly through impaired functionality of the body protection mechanisms. Investigation of these effects has practical significance for risk assessment and development of effective cancer preventive strategies. Mathematical modeling is an eligible method for considering complex multicomponent interactions between elements of various systems involved in tumor growth.*

*This article presents an approach to assessing risks of cancerous tumors by using a created predictive model that describes dynamics of abnormal cells considering regulatory mechanisms and angiogenesis. An evolution approach is applied to estimate accumulated functional disorders of the immune system due to natural ageing and chemical environmental exposures. The Monte Carlo simulation is employed to estimate a likely outcome of cancerous tumor evolution given different possible properties of abnormal cells.*

*The article provides the results of accomplished computation experiments aimed at describing dynamics of changes in cell population properties in an analyzed organ tissue. Development of a vessel system is described considering different effects of the most significant factors. Computation results are analyzed within various scenarios that describe cancerous tumor growth in dynamics considering how angiogenesis develops under different parameters of the immune system dysfunction and different properties of abnormal cells. Risks of tumor development are assessed considering parameters that determine the overall state of the body (the immune system) and properties of abnormal cells.*

*This approach makes it possible to develop a system of preventive and sanitary-hygienic activities in areas where environmental conditions are unfavorable in order to reduce cancer incidence.*

***Keywords:*** *mathematical modeling, evolution of functional disorders, angiogenesis, immune system, neuroendocrine regulation, tumor development, risk factors, Monte Carlo simulation.*

Over the last decades, fighting cancer mortality has become a priority in medicine and biomedical research in developed countries [1, 2]. Investigating impacts of adverse environmental and lifestyle factors on tumor initiation is an integral part of cancer research. This research trend is of great significance given growing cancer prevalence worldwide. Adverse environmental and lifestyle factors can lead to a considerable increase in risks of cancer; therefore, it is important to investigate their impacts if we want to create effective strategies for cancer prevention and treatment.

Scientific research indicates that environmental pollution caused by toxicants, heavy metals, and other chemicals can create elevated cancer risks for people. Aluminum can be considered one of such factors. This metal is widely used in various industrial branches. It penetrates the environment due to production processes, waste utilization and from everyday products. In particular, researchers examine a



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potential role aluminum may have in modulation of molecular ways, which participate in colorectal cancer progression such as epithelial-mesenchymal transition and cell death [3]. Some studies report that aluminum bioaccumulation is potentially able to induce breast cancer by making the genome unstable [4].

Adverse environmental and lifestyle factors have substantial influence on cancer initiation both directly and indirectly through weakening the functionality of the body protection barriers. Growing aluminum levels in the human body stimulate dysfunctions and structural disorders of the bone and nerve tissues, reproductive system, hematopoietic system, as well as the immune response.

A key aspect in examining impacts of adverse factors on tumor development is identification of mechanisms, by which these factors affect cells in the body and the body as a whole and induce changes leading to tumor development. This includes investigating genetic aspects, epigenetic mechanisms, influence of the environment on metabolic processes, etc.

Technogenic environmental factors can lead to pathomorphosis, aggravate a clinical course and an outcome of a cancer [5]. These factors also affect regulatory (immune and neuroendocrine) systems; some studies report that technogenic chemical factors produce adverse effects on functioning of these systems [6–8].

Immunity plays a certain role in cancer development. Throughout the life span, abnormal cells occur in the human body; they can grow and develop into cancer but the immune system functioning in most cases is able to prevent this growth. The immune system dysfunctions have been shown to be one of basic reasons for high cancer incidence rates [9, 10].

Experiments *in vitro* and *in vivo* can hardly provide a good insight into interrelations between affecting factors; therefore, it is difficult to explain carcinogenesis considering interactions between different immunity elements given changes in nutrient intake due to angiogenesis. Use of mathematical modeling makes it possible to investigate both internal relations between various elements and interactions between elements in a system as a whole [11–13]. The main issue of mathematical modeling applied to describe how a tumor grows considering angiogenesis is that this process is a multiscale and multi-factorial one.

**In this study, our aim was** to assess risks of tumor evolution using a predictive mathematical model to describe dynamics of abnormal tissue cells considering influence of angiogenesis and reactions of the immune system under exposure to chemical environmental factors.

**Materials and methods.** Dynamics of tumor progression is determined by outcomes of competition between cell subpopulations to get access to glucose, which is the key energy source and basic building material for tumor cells. Effects produced by elements of the immune system considering regulatory influence of the endocrine system are examined within the context of mechanisms that protect the body from uncontrolled growth of abnormal cells. Rate of cell division, cell life span, maximum density of a created tissue, antigenicity, and a level of glucose consumption are taken as basic features necessary to describe mechanisms of tumor initiation.

The study uses several hypotheses and assumptions due to complexity of processes involved in the immune response considering neuroendocrine regulation. One of the main hypotheses is that cell populations are distributed evenly in a representative area of an organ tissue at any time moment [14]. In addition to that, changes in any variable in the model are assumed to be dependent on current values of all variables; this means the latter contain some relevant information about history of an analyzed process.

Another assumption is that the immune response is regulated by signal proteins present in three basic tissue volumes: the brain (hypophysis and hypothalamus), abdominal cavity (adrenals), and a target organ. Interaction between organs that are located at a cer-

tain distance from each other is considered with introducing a time lag. Regulatory impacts of the immune and neuroendocrine systems are delayed since transfer of signals from source organs to a target one takes some time.

Protection mechanisms are activated after macrophages contact tumor cells born by mutation of normal cells. Elimination of abnormal mutated cells is accompanied with synthesis of information molecules such as cytokine interleukin-1 [15].

Changes in interleukin-1 levels lead to changes in the rate of interleukin-2 production by T-helpers and this induces changes in the rate of corticoliberin synthesis by effects on the hypothalamus. Corticoliberin affects the front lobe of the hypophysis thereby changing the rate of adrenocorticotropic hormone (ACTH) secretion. In its turn, ACTH, while circulating in blood, influences the activity of adrenals and thus regulates cortisol production. Changes in cortisol levels induce an inverse reaction in ACTH and interleukin-1 secretion [16].

Interleukin-2 stimulates production of NK-cells [17], cytotoxic T-lymphocytes [18] and B-cells [19, 20]. NK-cells are produced by the bone marrow; they destroy abnormal cells at the initial stage in the immunity fight against tumors. NK-cells are non-specific as regards abnormal cells and their functional activity relies on using the 'friend or foe' mechanism.

Most occurring abnormal cells are neutralized at the initial stage in the body protection without activation of the specific immune response. The model developed in this study considers inhibiting effects by cortisol [21, 22] and stimulating effects by interleukin-2 on the intensity of NK-cells production [23]. Specific adaptive immunity is mostly related to production of antibodies by B-cells that block vital activities of abnormal cells as well as to elimination of abnormal cells by cytotoxic T-lymphocytes [23, 24]. These immune cells start to reproduce actively after a signal has been received about an existing population of abnormal cells due to stimulating effects by interleukin-2. When numbers of specific cells reach a certain level, B-cells start to produce antibodies [25] and cytotoxic T-lymphocytes enter the circulatory and lymphatic systems. Immune cells ability to fight abnormal cells is inhibited by cortisol [26]. Presence of a permanent stressor (cortisol) weakens the activity of natural killers, slows down reproduction of T-lymphocytes made to eliminate abnormal cells and hampers normal production of antibodies.

The vascular system plays a key role in supply of nutrients (carbohydrates) necessary for maintaining adequate vital activity of all tissues in the human body. New vessels are formed by angiogenesis; they spread steadily thereby creating a new local vascular system. Use of anti-angiogenic therapy is being investigated actively in medical oncology [27, 28]. This therapy reduces the nutrient supply to the tumor thereby slowing down its growth. Some recent studies indicate that angiogenesis may be influenced by various factors [29], which are able to induce structural changes in the vascular network.

Nutrition is delivered from arterioles to cells due to diffusion of nutrients through the intercellular space. In case nutrients are in deficiency, organ cells start to produce vascular endothelial growth factor (VEGF), which stimulates growth of capillaries from arterioles [30, 31]. Capillary presence in a tissue considerably increases its permeability for nutrients thereby eliminating their deficiency. In our model, capillary growth is described by local changes in tissue porosity.

Figure 1 shows a graphic scheme to describe basic interrelations between the model variables. It includes a set of interrelated elements of the immune and endocrine systems and organs cells that form a vascular network.

Relying on the presented interaction scheme, the mathematical model can be represented by a system of 19 ordinary first order differential equations with retarded argument.

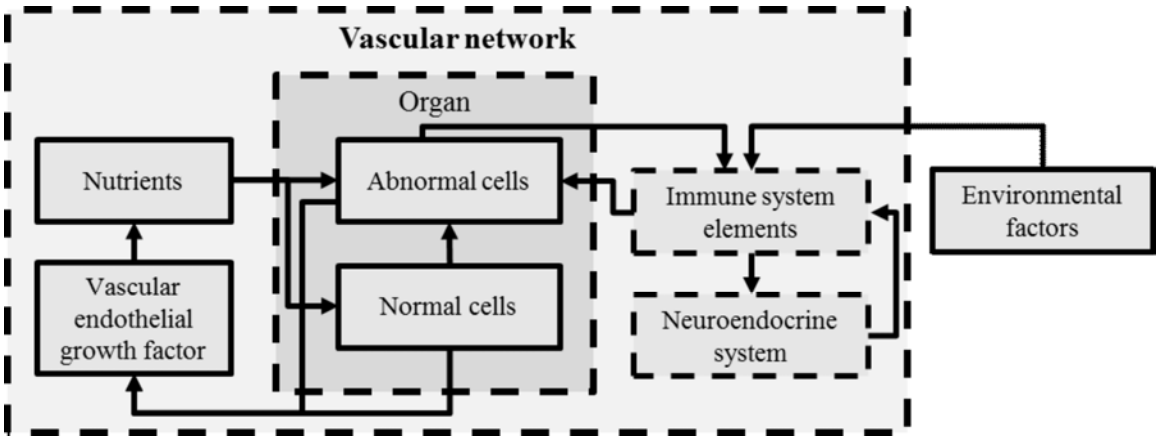



Figure 1. The scheme to describe how the immune and endocrine systems function when a tumor develops in the body

The equation (1) describes changes in abnormal cells concentration considering immune regulation; it also takes into account antigenicity parameter and how well different immunity cells are able to see abnormal cells (the equation coefficients are determined when the model is identified by using data derived by *in vivo* and / or *in vitro* experiments):

$$\begin{aligned}&\frac{dC_c^m}{dt} = k_1^m\left(C_c^m + \tilde{C}_c^m\right)\left(1-\frac{\rho}{k_2^m+\rho}\right)-\\&-k_3 C_c^m C_M H\left(S^m-k_4\right)-\\&-k_5 C_A C_c^m H\left(S^m-k_6\right)-k_7^m C_c^m-\\&k_8 C_{NK} C_c^m\left(1-k_9\frac{C_K\left(t-T\right)}{1+C_K\left(t-T\right)}\right)H\left(S^m-k_{10}\right)-\\&-k_{11} C_{CTL} C_c^m\left(1-k_{12}\frac{C_K\left(t-T\right)}{1+C_K\left(t-T\right)}\right)H\left(S^m-k_{13}\right)-\\&-k_{14}\left\langle C_p^{Nm}-C_p\right\rangle,\end{aligned} \quad (1)$$

where $\rho$ is the total density of organ cells, [cells/ml];

$\tilde{C}_c^m$ is the concentration of abnormal cells in an organ near the calculation point, [cells/ml];

$S^m$ is visibility of abnormal cells in an organ for the immune system elements (antigenicity) (zero value means a cell is normal), [sizeless];

$C_M$ is the level of macrophages (monocytes), [cells/ml];

$C_A$ is the level of antibodies, [mIU/ml];

$C_{NK}$ is the level of NK-cells (natural killers), [cells/ml];

$C_K$ is the cortisol level, [nanogram/ml];

$C_{CTL}$ is the level of cytotoxic T-lymphocytes, [cells/ml];

$C_P$ is the nutrient concentration, [mg/ml].

The first summand is employed to describe formation of new abnormal cells. An additional characteristic is introduced to establish the upper limit of abnormal cells division, which is the maximum density of a created tissue. The second summand describes elimination of abnormal cells by macrophages accompanied by production of interleukin-1 signal protein. The third summand is employed to describe how abnormal cells are neutralized by specific antibodies.

The fourth summand describes natural death of abnormal cells; the coefficient value is determined relaying on a life span of an abnormal cell. The fifth summand is employed to describe how abnormal cells are destroyed in a target organ by NK-cells. Destruction takes place when an infected cell contacts a NK-cell. Cortisol inhibits NK-cells activity and their effects are delayed since it takes time to transfer it from the adrenals to a target organ.

The sixth summand in the right part of the equation describes how abnormal cells are eliminated by cytotoxic T-lymphocytes. An abnormal cell is eliminated after its contact

with a cytotoxic T-lymphocyte. Cortisol inhibits its activity of such lymphocytes as well. Accumulation of these cells in lymph nodes until a certain level is reached is described by using the Heaviside function. The last summand describes abnormal cells death due to lack of nutrients.

Changes in immunological and neuroendocrine elements are described using the following balance equations:

$$\frac{dC_x}{dt} = \sum_i k_{x,i}^{+} C_{y,i} - \sum_j k_{x,j}^{-} C_{y,j}\,, \quad (2)$$

where $k_{x,i}^{+} C_{y,i}$ is the summand describing a growing rate at which the concentration of the $C_x$ indicator changes due to effects by the influencing factors $C_{y,i}$;

$k_{x,j}^{-} C_{y,j}$ is the summand describing a declining rate at which the concentration of the $C_x$ indicator changes due to effects by the influencing factors $C_{y,i}$.

The structure of the equations (2) and values of their parameters are provided in an article that describes how a tumor grows considering effects of regulatory systems [32].

Changes in nutrient concentrations are described by the following equation; the ratio considers a decrease in a concentration due to nutrients being absorbed by both normal and abnormal cells:

$$\frac{dC_P}{dt} = -k_{15} C_C^m - k_{16} C_{ST}\,, \quad (3)$$

where $C_{ST}$ is the concentration of healthy cells in an organ, [cells/ml];

$C_c^m$ is the concentration of abnormal cells in an organ near the calculation point, [cells/ml].

Changes in levels of vascular endothelial growth factor (*VEGF*) are described by the following ratio that considers production of the protein by abnormal and healthy cells in an organ when nutrients are in deficiency as well as the natural clearance:

$$\frac{dC_{VEGF}}{dt} = k_{17} C_C^m \left\langle C_P^{Nm} - C_P \right\rangle - \\ -k_{18} C_{ST} \left\langle C_P^N - C_P \right\rangle - k_{19} C_{VEGF}\,, \quad (4)$$

where $C_c^m$ is the concentration of abnormal cells in an organ near the calculation point, [cells/ml];

$C_{ST}$ is the concentration of healthy cells in an organ, [cells/ml];

$C_p$ is the nutrient concentration, [mg/ml];

$C_p^N$ is the lowest nutrient concentration necessary to maintain vital activity of cells, [mg/ml].

Changes in tissue porosity that model capillary growth due to effects produced by vascular endothelial growth factor are described by the following equation; the ratio describes stimulation by vascular endothelial growth factor and natural degradation of a vascular network:

$$\frac{dD}{dt} = k_{20} C_{VEGF} - k_{21},\ \tilde{\mathrm{D}} > \mathrm{D_N}\,, \quad (5)$$

where $C_{VEGF}$ is the concentration of vascular endothelial growth factor *VEGF*, [IU/ml];

$D$ is tissue porosity associated with capillaries in a tissue and tissue fluid, [sizeless];

$D_N$ is such a level of tissue porosity above which we can suspect a capillary network able to induce growth of new capillaries, [sizeless];

$\tilde{\mathrm{D}}$ is tissue porosity near the calculation point, [sizeless].

The diffusion equation (6) can be used to describe rate of changes in a concentration of abnormal cells determined by cell division in any arbitrary point of an organ. The main growth direction is oriented towards an area with the lowest tissue porosity:

$$\frac{dC_C^m}{dt} = -k_{22} D \frac{\partial C_C^m}{\partial x}, \qquad (6)$$

where $C_c^m$ is the concentration of abnormal cells in an organ near the calculation point, [cells/ml].

Glucose diffusion in a tissue is described with the following differential equation in partial derivatives; the description considers movement both due to dissolution in a tissue fluid and through a capillary network:

$$\frac{dC_P}{dt} = -k_{23} D \frac{\partial C_p}{\partial x}, \qquad (7)$$

where $C_P$ is the nutrient concentration, [mg/ml].

Vascular endothelium growth factors tend to diffuse from an area with a higher concentration to an area with a lower one. Tissue permeability has a significant role in *VEGF* diffusion. Diffusion of vascular endothelial growth factors is given with the following equation that describes how *VEGF* protein moves from cells with insufficient nutrition to capillary walls aiming to stimulate their growth:

$$\frac{dC_{VEGF}}{dt} = -k_{24} D \frac{\partial C_{VEGF}}{\partial x}, \qquad (8)$$

where $C_{VEGF}$ is the concentration of vascular endothelial growth factor *VEGF*, [IU/ml].

The model identification relied on using experimental data available in literature and obtained by investigating how abnormal cells occur and grow in kidney tissues. Values of the model parameters are provided in the Table.

Use of the model to describe carcinogenesis in other organs requires identification of the outlined coefficients based on empirical data that reflect specific features of a given organ.

Interaction between cell populations and information molecules of the body is based on the clonal selection theory, law of mass action as well as use of interaction characteristics and Markov birth-death processes.

Table

Parameters of the mathematical model that describes dynamics of abnormal cells growth in a tissue considering influence of angiogenesis and the immune system reaction

| Parameter | Value | Source |
|---|---|---|
| $k_1$ | $2.35 \cdot 10^{-11}$ (1/cells·day) | [33] |
| $k_2$ | $1.2 \cdot 10^{7}$ (cells/ml) | – |
| $k_3$ | $10^{-14}$ (ml/cells·day) | – |
| $k_4$ | 0.85 (sizeless) | – |
| $k_5$ | $8.6 \cdot 10^{-10}$ (ml/mIU·day) | [34] |
| $k_6$ | 0.7 (sizeless) | – |
| $k_7$ | 0.0043 (1/ cells·day) | [35] |
| $k_8$ | $2.5 \cdot 10^{-17}$ (ml/cells·day) | [36] |
| $k_9$ | 0.5 (sizeless) | – |
| $k_{10}$ | 0.5(sizeless) | – |
| $k_{11}$ | $6.6 \cdot 10^{-18}$ (ml/cells·day) | [36] |
| $k_{12}$ | 0.5(sizeless) | – |
| $k_{13}$ | 0.8 (sizeless) | – |
| $k_{14}$ | 0.046 (ml·cells/mg·day) | [37] |
| $k_{15}$ | $3.6 \cdot 10^{-3}$(mg/ cells·day) | [37] |
| $k_{16}$ | $1.5 \cdot 10^{-3}$ (mg/ cells·day) | [37] |
| $k_{17}$ | $8.3 \cdot 10^{-7}$ (ml·IU/cells·mg·day) | [38] |
| $k_{18}$ | $6.5 \cdot 10^{-7}$ (ml·IU/cells·mg·day) | [38] |
| $k_{19}$ | 0.0019 (1/day) | [38] |
| $k_{20}$ | 0.0135 (ml/IU·day) | [38] |
| $k_{21}$ | $7.13 \cdot 10^{-3}$ (1/day) | [38] |
| $k_{22}$ | 0.02 (mm/day) | – |
| $k_{23}$ | 0.83 (mm/day) | – |
| $k_{24}$ | 1.2 (mm/day) | [39] |

Functional disorders of the immune system are considered by using the bone marrow as an example. This organ is responsible for producing immune elements and its dysfunction can be caused by aluminum contamination.

Impaired functionality of the bone marrow has adverse effects on how fast different cells of the innate and adaptive are produced, which later on leads to both quantitative (changes in quantities of immune and accessory cells of the immune system) and quali-

tative changes in the immunity (lower functional activity). Evolution of the immune system dysfunctions is described with the following equation given the accepted hypothesis that rates of changes in the functionality are additive depending on chemical factors:

$$\frac{dF}{dt} = aF + b\left\langle \frac{x}{x^N} - 1 \right\rangle, \qquad (9)$$

where $a$ is the coefficient that describes how fast functional disorders $F$ grow in the immune system due to natural mechanisms, [1/year];

$b$ is the coefficient that describes intensity of impacts exerted by an adverse factor (aluminum) on the immune system dysfunction $F$, [1/year];

$x$ is the aluminum dose taken by the body;

$x^N$ is the standard (maximum permissible) level of an adverse factor (aluminum);

$\langle x \rangle$ are Macaulay brackets: $\langle x \rangle = \max(x, 0)$.

The equation system (9) makes it possible to provide approximate description of evolution of functional disorders and considers macro-levels processes including natural ageing, recovery, accumulating disorders of the productive function due to chemical exposures exceeding their safe levels. Studies [40, 41] provide an example how the evolution approach can be used to consider impacts of aluminum oxide on accumulation of functional disorders in the immune system.

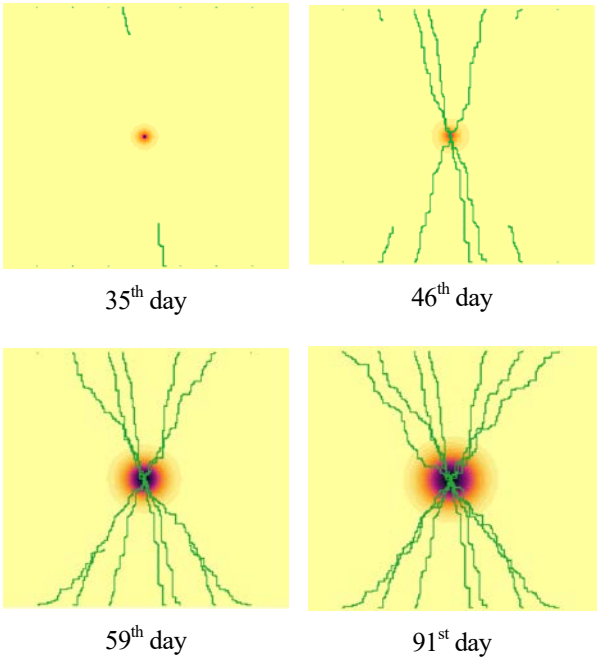
The formulated Cauchy problem was solved by using the implicit numerical 3rd order Runge – Kutta method (RadauIIA); this algorithm is one of those algorithms used to solve stiff systems of differential equations with retarded argument. Since rates as characteristics of the described indicators have different orders of magnitude, the computation process was divided into three time-different stages in order to optimize it. The stages follow the ascending order in rates: evolution of the vascular system, occurrence of new abnormal cells, regulation of the immune and neuroendocrine systems. The modeling area was divided into 1000 × 1000 meshes.

Numeric modeling was accomplished in a two-dimensional setting on a test sample of kidney tissue. The kidneys are one of target organs for aluminum accumulation in the body, following the bone and nerve tissue; they are also the main organ that excretes the chemical from the body. Aluminum damages not only cellular structures but cells themselves since it can produce direct cytotoxic effects inducing necrosis of epithelial cells in the renal tubules. Impaired excretory function of kidneys leads to elevated aluminum levels in the body and its stronger effects on the immune system.

The Monte Carlo simulation was employed to quantify a risk of tumor evolution. A series of computations was accomplished for the selected values of the immune system dysfunctions; the following parameters that describe abnormal cell properties were randomly set during these computations: division rate, life span, maximum density of a created tissue, antigenicity, and glucose consumption.

**Results and discussion.** Dynamics of changes in abnormal cells quantity is largely determined by random initiation and properties of abnormal cells that occurred due to mutations. Results of accomplished studies indicate that a tumor may evolve following different scenarios. The suggested model is able to describe different types of carcinogenesis in dynamics considering angiogenesis; for example, it can describe tumors with different rates of abnormal cell division. Figure 2 provides dynamic of changes in concentrations of cancer cells for a ‘solid’ tumor with a low rate of abnormal cell division.

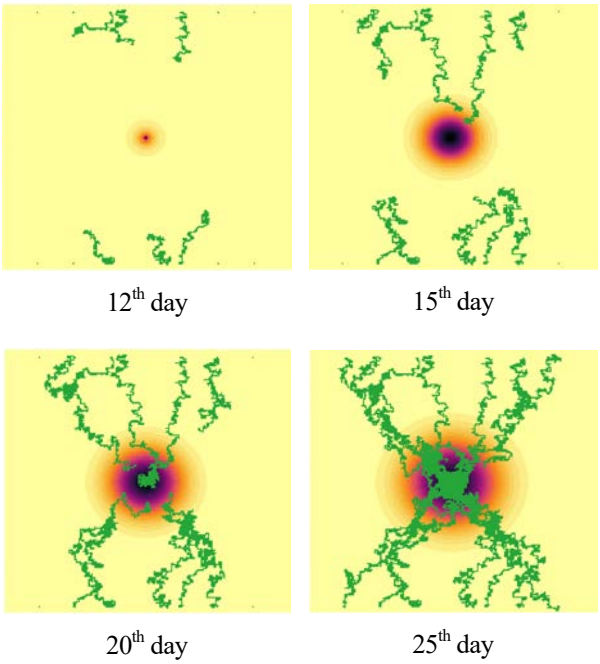
The model allows considering peculiarities of angiogenesis if a tumor grows fast. In this case, vascular endothelial growth factor is released in substantial quantities due to considerable nutrient deficiency. This leads to chaotic vascular growth. The modeling results obtained for a ‘solid’ fast-growing tumor are given in Figure 3.



35th day 46th day

59th day 91st day

Figure 2. Growth of a 'solid' tumor with a low cell division rate in dynamics



12th day 15th day

20th day 25th day

Figure 3. Growth of a 'solid' tumor with a high cell division rate in dynamics

The model also makes it possible to examine peculiarities of tumor growth in dynamics considering different functional abilities of the immune system. Figures 4 and 5 provide the results obtained by computing growth of a fast and slow tumor considering different functionality levels of the immune system. Functionality within a scenario computation was identified by solving the evolution equation (Formula 9); we considered some levels of functionality in a person aged 40 years under different lifetime exposures to aluminum. Functionality of the immune system was $F = 0.93$ under a daily intake of 0.4 mg/kg per day. Functionality was $F = 0.67$ and $F = 0.46$ under daily intakes of 4 mg/kg and 40 mg/kg per day accordingly.

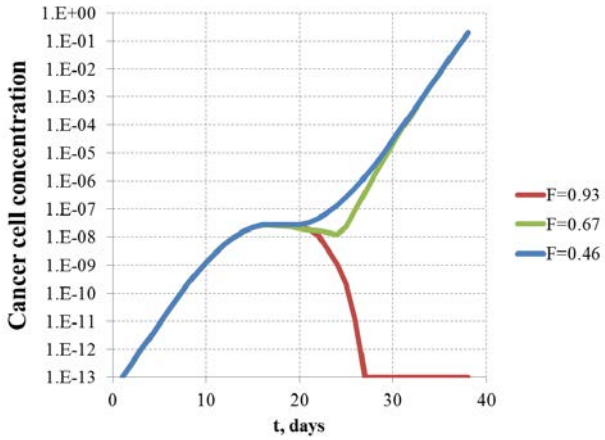



Figure 4. Growth dynamics for a tumor with high division rate considering the immune system functionality

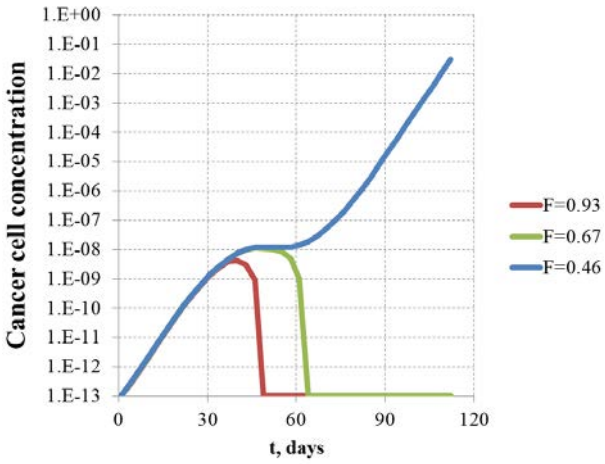



Figure 5. Growth dynamics for a tumor with low division rate considering the immune system functionality

Based on the modeling results, it is obvious that cancer cells are destroyed in both scenarios without any manifestation of disease if damage to the immune system is minimal and its functionality is $F = 0.93$. If damage to the immune system is medium and its functional-

ity is $F = 0.67$ and the initial conditions are the same, changes in the cancer cell concentration lead to a tumor invitation in the first scenario; in the second scenario, slow evolution of a tumor allows the immune system to produce the necessary quantity of immune elements in due time. If damage to the immune system is high and its functionality is $F = 0.46$, abnormal cells divide without any limitations and this results in a tumor reaching its critical size; that is, a neoplasm goes beyond an organ and we can assume metastasis has begun.

Five hundred numeric experiments were accomplished using imitation modeling based on the Monte Carlo simulation. As a result, statistical data were collected that allow estimating a risk of tumor evolution. The modeling results are provided in Figure 6; the graph analysis clearly shows that a risk of tumor initiation equals 0.495 if the immune system functionality is below $F = 0.4$ and this may lead to death in case no medical intervention is provided. Therefore, even if the immune system is fully functional and $F = 1$, a risk of a tumor initiation with this set of parameters is above zero and a negative outcome is probable.

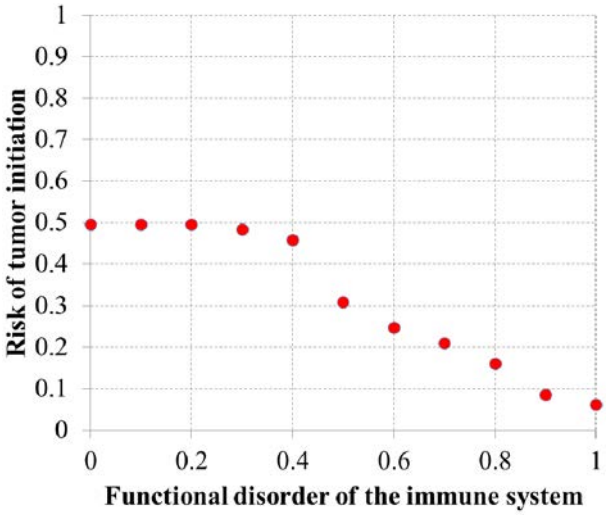



Figure 6. Results of modeling probable outcomes of tumor growth considering effects of the immune system functionality

**Conclusions.** The suggested predictive model provides qualitative description of abnormal cells occurrence in the body and how their quantity changes considering angiogenesis, fast and slow tumor initiation and growth. An approach is suggested to estimate influence of chemical environmental factors on a cancer dynamics. The study also covers estimation of impacts exerted on cancer clinical course and outcome by parameters that determine the body state (the immune system in particular) and properties of abnormal cells. Use of this approach makes it possible to identify those elements functionality of which is the key factor that determines cancer development. The suggested model is a simplified description of complex interactions between multiple regulatory systems ongoing in the body during tumor initiation and evolution. However, it still gives an opportunity to analyze interactions between many regulatory systems involved in these processes. Laboratory tests of samples only allow seeing tumor structures existing at the moment of tissue sampling. In contrast to that, mathematical modeling identifies principles of dynamic tumor evolution and conditions necessary for initiation of each culture of abnormal cells.

Study of effects produced by adverse environmental factors on tumor initiation has great socioeconomic significance. This allows predicting cancer prevalence as well as developing effective measures for prevention of such diseases and improving quality of life for people who live in areas with unfavorable environmental conditions.

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**Competing interests.** The authors declare no competing interests.

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