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Not peer-reviewed version

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Posted Date: 5 February 2025

doi: 10.20944/preprints202502.0321.v1

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Article

An Innovative Model for Cancer: Interdisciplinary Research Involving Biology and Psychology

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Abstract: Background: Malignant tumors are diseases that seriously threaten the human health. However, the etiologies of most human tumors, including many solid malignant tumors and hematological malignancies, are currently unclear. Methods: In this study, a conceptual model of the physiological human body, based on the view of life and the environment, was established using physical modeling. Results: This model was used to provide reasonable explanations for tumor-related questions, predict framework for cancer treatment, and suggest intervention techniques for before and after the diagnosis. The inferences made using this model were also consistent with the biopsychosocial model used in modern medicine and with the requirement of holism in traditional medicine. Conclusions: The model proposed in this study will provide novel ideas for the treatment of cancer.

Keywords: cancer; theoretical model; interdisciplinary research; integrative medicine

1. Introduction

Malignant tumors are currently one of the major global public health problems. According to the International Agency for Research on Cancer (IARC), one in five people worldwide will develop cancer during their lifetime, and approximately one in nine men, and one in 12 women, will die from cancer [1]. The prevention and treatment of cancer has become an important issue that is highly concerning to the medical community worldwide.

Although the development of allopathy contributed greatly to early advances in biomedicine, this method has shown certain limitations. Many chemotherapy drugs have hematological toxicity, and numerous biomedical approaches are inherently carcinogenic [2,3]. Additionally, precision-based approaches in biomedicine contradict not only the biopsychosocial model (BPSM) proposed by Engel, but also the holistic concept of traditional medicine [4,5]. Indeed, interest in integrative medicine has been steadily increasing [6–8].

The biomedical system itself faces numerous challenges. First, humans are conscious beings possessing both natural and social attributes. Biomedicine is focused on the investigation of molecular pathways in order to uncover the mechanisms of cancer; however, the origins of life and consciousness are also important unsolved mysteries. Lives are unimaginably complex networks. If the human civilization does not yet fully understand the normal phenomena of life, how can we fully explain pathology through biomedicine? Additionally, although clinical diagnostics repeatedly emphasize the importance of etiological diagnoses, many internal diseases, including mental disorders, are currently diagnosed according to clinical symptoms, syndromes, and test results, rather than etiologies. To illustrate this notion, gastrointestinal hemorrhage can be diagnosed using symptoms, while nephrotic and Cushing's diseases are diagnosed as syndromes. Hypertension, diabetes, and arrhythmia are diagnosed using laboratory results, while some diseases, such as Hodgkin's lymphoma, are named after the physicians who first described them. Currently, the etiologies of the vast majority of chronic diseases are considered unknown. If we do not understand the etiologies, how can we cure chronic diseases?

Furthermore, pathophysiologists indicate that, during the process of disease occurrence and development, evidence-based medicine cannot distinguish between causes and outcomes. The traditional theory of polygenic diseases states that complex diseases are determined by a combination of genetic and environmental factors, emphasizing the important connection between genetic factors and diseases. Therefore, in biomedicine, much effort is devoted to genetic testing. However, statistical analysis only indicates correlation, and correlation does not prove causation [9]. From the perspective of etiological diagnoses, conclusions may change. For example, genetic factors are highly correlated with skin color, and the incidence of skin cancer in individuals with medium to dark skin is much lower than in those with light skin. However, ultraviolet radiation can be a fundamental cause of skin cancer [10,11]. Genetic factors increase tumor liability, but they are not the etiologies. Geneticists have also found that earlier studies estimated the heritability of schizophrenia to be as high as 80%, but studies using DNA data showed that the heritability is less than 3%, raising the question of “missing heritability” [12,13].

Natural selection has eliminated groups with low environmental fitness. Typical genetic diseases having a reproductive origin are actually uncommon. Moreover, heritability in statistical models may include genetic and cultural transmission inheritance; however, psychological behavior is greatly influenced by the environment. It is difficult to fully distinguish between genetic and environmental influences. As a result, genes are sometimes falsely credited for the effects of the environment [12].

In order to overcome the limitations of biology and statistics in medicine, physical modeling was used in this study to establish a conceptual model. This model will regard the human body as a whole, and will ignore the complex intercellular signaling pathways by acknowledging the high orderliness of living organisms. The purpose of this study was to explain cancer from a novel perspective.

2. Results

2.1. Model Assumptions and Related Concepts

- (i) There are no verifiable genetic-material abnormalities of reproductive origin.
- (ii) Cells can replicate and differentiate correctly in a suitable environment, and the human body can also correctly develop in a suitable external environment.
- (iii) Aging and mutated cells, which appear spontaneously, can be effectively eliminated by normal immune system.
- (iv) The whole body is highly ordered (healthy) before the effects of adverse exogenous factors.
- (v) Model-related concepts are described in Table 1.

Table 1. Model-related concepts.

Concept	Definition
Protective barrier	Abbreviated as Category 1 barrier, refers to all the barriers located mainly at the surface of the body, isolating the human body from the outside world or the zygote/gamete; these include skin, blood-air, mucous-HCO ₃ ⁻ , filtration, placental, and blood-testis barriers.
Internal barrier	Abbreviated as Category 2 barrier, refers to all the barriers located within the human body, protecting important organs from changes in the internal environment. These include a total of three layers of the blood-brain and blood-thymus barriers.
Collection of peripheral cells	A collection of living cells existing between Category 1 and Category 2 barriers, and containing cells that form the Category 2 barriers.

Peripheral environment		Commonly known as the internal environment. It is composed of all the intercellular substances between Category 1 and Category 2 barriers including fluid (such as plasma, tissue fluid, and lymphatic fluid) and solid (such as fibrous tissues and extracellular matrix) components.
Collection of central cells	of	A collection of living cells within the blood-cerebrospinal fluid barrier, excluding the cells that form the wall of the blood-cerebrospinal fluid barrier.
Central environment		The central environment is composed of all the intercellular substances within the blood-cerebrospinal fluid barrier.
Collection of immune cells	of	Vague concept. A collection of living cells in the corresponding environment, the main functions of which are immune defense, surveillance, and self-stabilization. These cell types include but are not limited to blood cells such as granulocytes, lymphocytes, and monocytes/macrophages.
Collection of immune molecules	of	Vague concept. A collection of all the immune molecules present in a corresponding environment including immunoglobulins, complement, and cytokines.
Collection of receptor cells	of	Vague concept. A collection of living cells existing in a corresponding environment. The main functions of these cell types are receiving external or internal stimuli.

2.2. Model Establishment

In ecology, the environment refers to everything surrounding a particular biological subject, and the biological subject can be an individual or a collection of individuals. If each somatic cell is considered an independent individual, the human body is actually a complex and highly ordered multicellular society. Additionally, there are many physiological barriers inside and outside the human body. These barriers isolate the internal environment from the external one, and protect vital organs from the impact of changes in the internal environment. Based on this notion of a collection of living organisms (cells), barriers, and the environment, the human body can be divided into several relatively independent regions and simplified to a conceptual model (Figure 1, A and B).

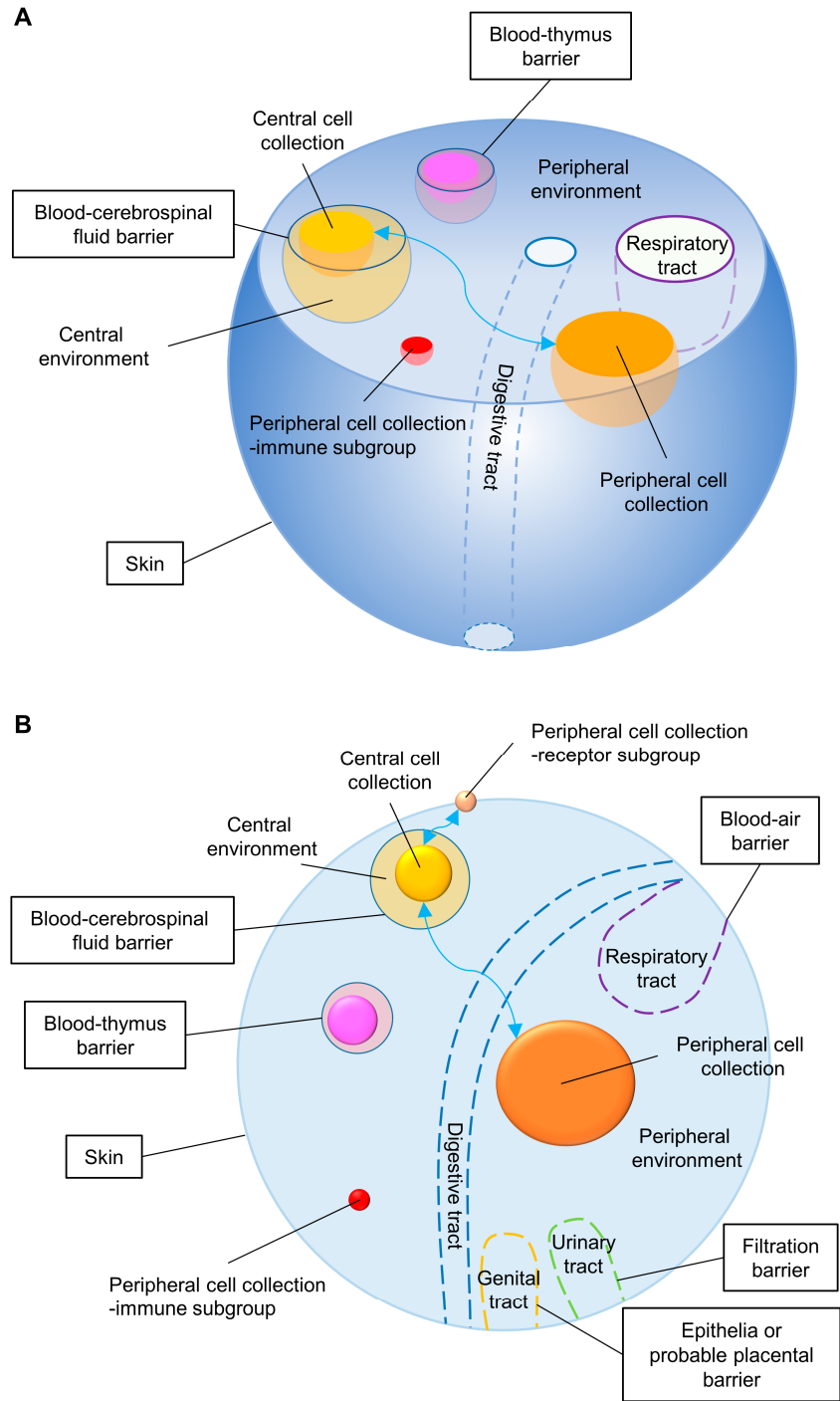


Figure 1. A conceptual model of the human body based on the view of life and the environment. If the human body is considered as a container filled with cells and intercellular substances, then the model of the human body appears similar to a cell model. Consequently, the peripheral cells, central nervous system, and thymus are similar to inhabitants living together in the internal environment. The digestive tract is a tube that runs through the human body, while the respiratory and urogenital tracts are blind tubes. Additionally, due to the existence of the blood-thymus and blood-brain barriers, cells of the thymus and the central nervous system also possess their own microenvironments. The thymus can also be represented in a similar way as the central nervous system, but relevant annotations were omitted here. **(A)** A three-dimensional schematic diagram. **(B)** A planar schematic diagram (female). The blue arrows indicate possible neural connections, and the blocks indicate barriers.

Using this model for analysis, it is important to note the following aspects. (i) Areas that communicate with the external environment, such as the lungs and intestine, or areas having barriers due to differences in cellular genotype, such as the testes and placenta, will be considered independent from the internal environment. (ii) Psychological research has shown that psychological phenomena originate from the objective reality. Without the stimulation of the objective reality, the human brain cannot produce psychological activity independently. Social reality has a decisive constraining effect on human psychology. Therefore, this study classified psychological and behavioral factors as exogenous, similar to the approach employed in pathophysiology.

3. Discussion

3.1. Pathogenic Pathways of Exogenous Factors

In fact, many modifiable risk factors have already been proven to be cancer causing [14]. Based on known etiologies, the following pathways are used by adverse exogenous factors to affect the human body (Figure 2A).

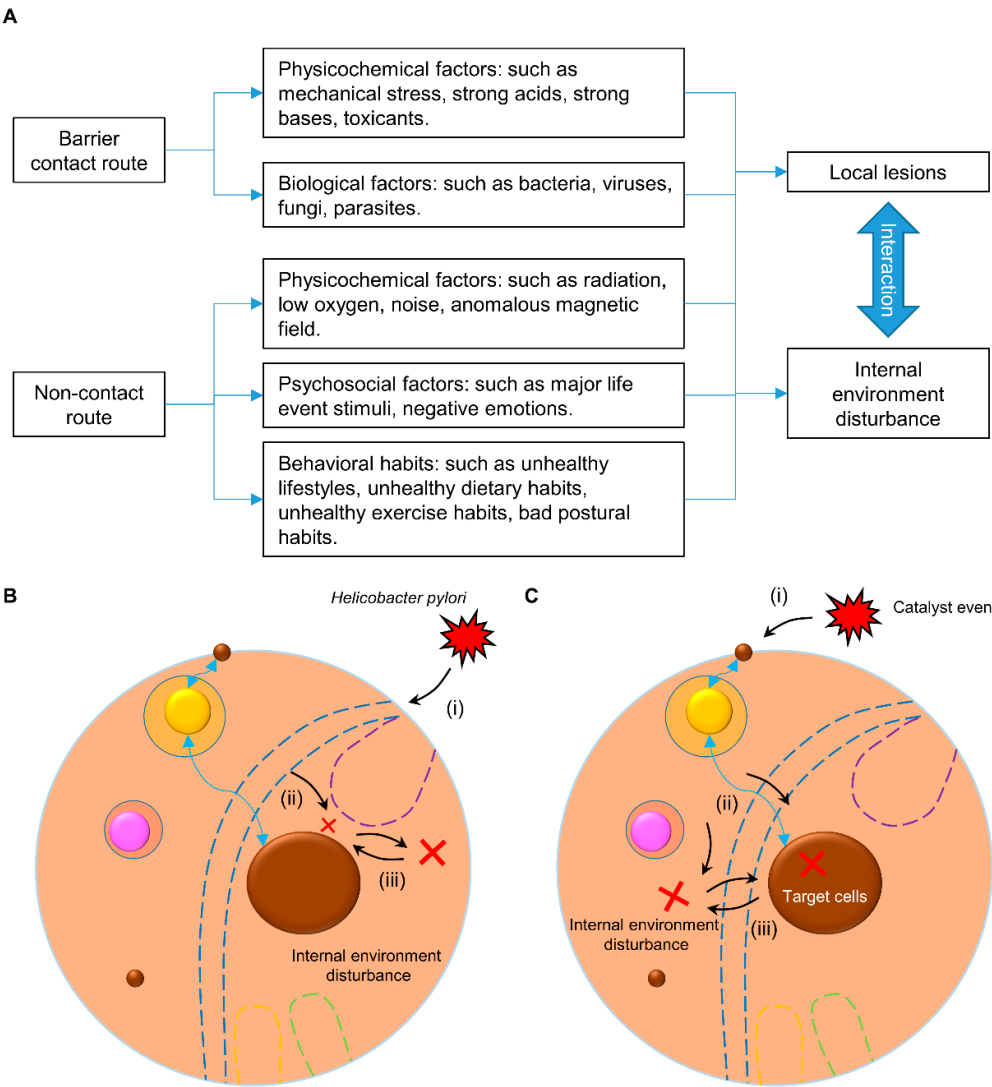


Figure 2. Adverse exogenous factors affecting the human body. (A) Pathways (postnatal stage): Adverse exogenous factors may affect local environment or the whole internal environment through the neurohumoral pathway. Local lesions can affect the whole body, and the status of the whole body can also affect the occurrence

and development of local lesions. **(B) Adverse biological factors:** (i) *Helicobacter pylori* enters the digestive tract through the mouth. (ii) *H. pylori* colonizes the surface of gastric mucosal epithelial cells, altering the local microenvironment and establishing a chronic infection. (iii) Interaction occurs between the local and overall environment. **(C) Adverse psychosocial factors:** (i) A catalyst event causes emotions. (ii) By stimulating the autonomic, sympathetic, and parasympathetic nervous systems, as well as the hypothalamic-pituitary-adrenal axis and hypothalamic-sympathetic medullary system, emotions can affect target cells, such as endocrine and immune cells, and the internal environment, through neurohumoral pathways. (iii) An interaction occurs between abnormal cells and the internal environment.

Barrier contact route: (i) Physicochemical factors: coal tar, for instance, could directly cause cancer, while tobacco is the principal cause of lung cancer [1,15]. (ii) Biological factors: an example of this is an infection with *Helicobacter pylori* (Figure 2B). Chronic *H. pylori* infection is considered the principal cause of noncardia gastric cancer [1]. Chronic inflammation may induce genomic damage, which is closely related to the occurrence and development of tumors [16].

Non-contact route: (i) Physicochemical factors: many environmental physical factors exert significant adverse effects on the immune system. For example, the DNA and nuclear membrane of cells are the prime targets of ionizing radiation, especially in the thymus. Low dose ionizing radiation may permanently alter immune fitness and therefore accelerate immune senescence [17]. (ii) Psychosocial factors: adverse stimulation of the nervous system can cause changes in various systems throughout the whole body by affecting the thalamus, hypothalamus, and brainstem, leading to functional disorders of the body (Figure 2C). Acute and chronic stress can significantly alter the immune response [18,19]. (iii) Behavioral habits: sedentary behavior, for instance, was associated with increased body fat and has paralleled the increase in the prevalence of multiple chronic diseases [20,21]. Malnutrition is the primary cause of human immune suppression, while overnutrition, such as obesity and high cholesterol, also exerts adverse effects on the immune system [22–24]. Although the consequences of adverse behavioral habits may partially overlap with adverse barrier contact (such as tobacco smoking leading to increased exposure to chemical carcinogens), this route mainly emphasizes individual subjectivity.

3.2. Uncovering the Mysteries of the Tumor

Because correlation does not prove causation, only the diseases proven to have a causal relationship with abnormalities stemming from a reproductive origin were defined as typical genetic diseases in this study. Examples of such conditions include the trisomy 21 syndrome and Huntington's disease, which are caused by abnormalities in fertilized eggs. Besides, research shows that immune responses decrease with aging, contributing to the increased incidence of chronic diseases [25]. However, aging does not necessarily mean disease, and tumors can occur at any age. Thus, the immune senescence caused by aging, and the immaturity of immune system during child development, were not considered in this study. According to the genetic theory, cancers are approximately divided into two types: inherited cancer-predisposing syndromes only involve several rare cancers, while non-syndromic tumors include most common tumors. The former will be simplified as hereditary tumors, while the latter, which are complex diseases in the traditional sense, will be designated as non-hereditary tumors and will be discussed later.

Tumors are diseases characterized by abnormal cellular proliferation and are usually clonal (commonly studied by oncology). Because normal immune surveillance can effectively eliminate abnormal cells, the survival of abnormal cells indicates that the body also has an abnormal immune surveillance (commonly studied by tumor immunology, Figure 3A). Because the model eliminates the concepts of tissues and organs, the immune system will include only the collection of immune cells and molecules. The abnormality of immune surveillance indicates the abnormalities of immune cells and/or molecules. Because immune molecules are constituents of the internal environment, abnormalities of the immune molecules indicate abnormalities in the internal environment. Abnormalities in immune cells may be caused by sporadic mutations, radiation damage, and

abnormalities in the immune microenvironment. Considering that: (i) The frequency of nuclear DNA mutations is generally low, and sporadic mutations are eliminated by the monitoring system; (ii) the origin and differentiation sites (including the bone marrow, thymus, spleen, and lymph nodes) of the principal immune cells do not directly contact the external environment and can only be accessed through bodily fluids. Then, with the exception of direct DNA damage, the appearance of numerous abnormal immune cells indicates an abnormality in the internal environment, regardless of whether or not it meets the testing standards. Hematological malignancies, which are constituents of abnormal immunity to some extent, differ slightly from solid malignant tumors; however, the essence of abnormal cellular proliferation remains the same. Moreover, due to the interactions between living organisms and the environment, abnormal cells or immune cells generated by radiation will exert greater or lesser effects on the internal environment, after which abnormalities in the internal environment will again affect the immune cells. The carcinogenic effect of radiation usually has a latent period of several years, likely because the internal environment of the normal human body is relatively stable, and the expansion of abnormal cells and modification of the environment require time. This process is illustrated in Figure 3B, and intracranial tumors can be analyzed in a similar manner.

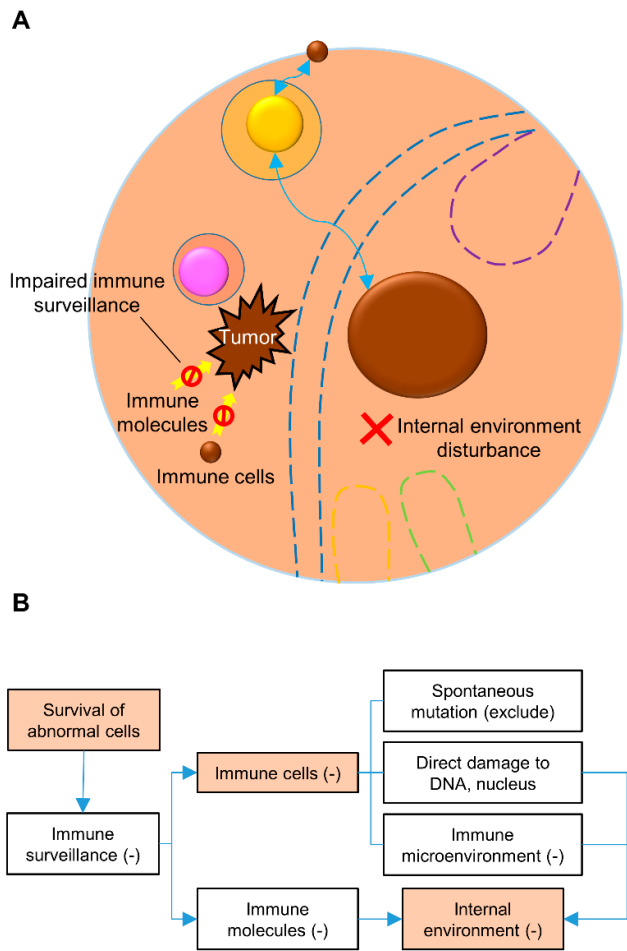


Figure 3. Outcomes and derivation of non-hereditary tumors. (A) The outcomes of non-hereditary tumors, with a mass of abnormal cells, impaired immune surveillance, and disturbance in the internal environment. (B) Initial state of non-hereditary tumor (indicated in orange). Negative signs represent abnormal states.

Normal living organisms are highly ordered. They adapt to their environment, possess multiple internal mediating and reparative mechanisms, and feed on negative entropy [26]. This means that if we exclude the sporadic survival of abnormal cell during immunocompromised periods of elderly and children, then normal living organisms (including cells) likely do not actively cause disease until they can no longer resist the entropy increase in the universe or encounter cellular replicative senescence [27]. If it can be proven that living organisms inevitably cause diseases without the reasons above, then those diseases would be the typical genetic diseases. The self-repairing ability of living organisms also explains some rare self-healing phenomena observed in complex diseases. These rare self-healing phenomena, which modern medicine is unwilling to acknowledge, are similar to when reversible cell damage is reversed after the cause of the damage is removed.

Using the above analysis, the following deduction could be inferred: adverse exogenous factors use different pathways and mechanisms (Figure 2, A to C) to cause disorders of the internal environment within a local or overall milieu, or cellular damage with a secondary disturbance of the internal environment, leading to immune abnormalities. The appearance and survival of tumor cell may be caused by sporadic mutation or carcinogenic factors, accompanied by immune abnormalities. To sum up, in the case without considering aging or immaturity, non-hereditary tumors are possibly the result of toxic effects by adverse exogenous factors. They may be states of mutual adaptation among abnormal cloned and immune cells, and the abnormal internal environment. This is similar to biological evolution and adaptation occurring at the cellular level. This deduction coincides with the evolutionary theory of cancer [16].

3.3. Difference Between Benign and Malignant Tumors

A tumor is similar to an abnormally added organ or system in the body (Figure 3A). The essential difference between benign and malignant tumors may depend on the ability of abnormal masses to interfere with the internal environment. Thus, the risk factors of cancer development may include the number of abnormal cells, speed of proliferation, strength of secretory ability, and presence or absence of a capsule. Additionally, the differentiation degree of a tumor may indicate a disorder of the internal environment, and may, therefore, be highly correlated with patient prognosis.

3.4. Limitations in Biomedicine

The survival of somatic mutations in non-hereditary malignant tumors are outcomes of immune deficiency. Because of the excessive specialization that exists in biomedicine, many physicians lack the knowledge of psychology and focus too narrowly on making an accurate diagnosis based on outcomes rather than on evaluating etiologies. Additionally, biomedicine does not usually factor in etiologies such as cognition, behavior, or habits, while the diagnosis of cancer may be traumatic and may accelerate a patient's death. Therefore, although cancer research in biomedicine is fruitful, its clinical effects are limited.

3.5. Convergence with Traditional Medicine

Because abnormal cells and immune cells are adapted to the abnormal internal environment, it is possible to stop abnormal cloning from proliferating or even causing death by adjusting the state of the internal environment. Concurrently, the recovery of the internal environment may also slowly restore the patient's immune function. This inference provides the scientific basis for the tumor treatment philosophy that includes the concepts of "equilibrium", "harmonizing yin and yang", and "surviving with cancer", employed in traditional Chinese medicine [28,29].

3.6. Cancer Treatment Framework

In the following section, pathogenic pathways (Figure 2A) were combined with outcomes (Figure 3A) to discuss a treatment framework for non-hereditary malignant tumors (excluding intracranial tumors). Mainly, interventions for physiological disorders (outcomes), identification and

interventions for pathogenic factors (etiologies), and psychosocial interventions before and after diagnosis (prevention) will be discussed.

3.6.1. Intervention for Physiological Disorders

The human medicine has mastered the following relevant concepts: (i) Elimination of abnormal cloning, such as removing solid masses using surgery and inducing remission of hematological malignancies. (ii) Restoration of homeostasis. Studies have shown that a major obstacle in the immunotherapy used against solid tumors is the immunosuppressive environment [30]. Therefore, intervention strategies for the internal environment must become an important part of treatment. These should include, but not be limited to, the regulation of whole-body balance using traditional medicine [5,28,31], plasma exchange [32,33], and hemodialysis [34]. (iii) Immune recovery: Patients can expect natural recovery after homeostasis has been restored. Additionally, hematopoietic stem cell transplantation (HSCT) is considered as an approach to rebuild immunity and is generally used to treat hematological malignancies. HSCT is generally not recommended for most therapies against solid tumors; however, we must note that without interfering with homeostasis (even make it worse sometimes) and etiologies, numerous studies show that HSCT in breast cancer improves progression-free-survival (PFS) and may still represent a clinical option for select patients with specific biological characteristics [35,36]. (iv) Other symptomatic support and nutritional support treatment.

3.6.2. Identification of, and Intervention for, Etiologies

Although cancers are considered incurable diseases in modern medicine, they are also considered preventable [14]. However, some complex diseases may have multiple etiologies, and it may be difficult for physicians to predict patient behavior. Patients may conceal certain preferences, some etiologies may not be effectively identified by either doctors or patients, and some etiologies may even stem from social customs. Furthermore, sometimes patients understand the possible adverse effects of their lifestyle choices, but do not wish to implement changes. One such example is the smoking rate, which remains high despite the label “Smoking may lead to lung cancer” being clearly printed on cigarette packs. Another example includes lack of sleep and consumption of unhealthy foods. While most people know these habits are unhealthy, many remain unwilling to change their lifestyles. Curing cancer is, therefore, more complex of an undertaking than what can be accomplished by physicians alone. The challenges described above require medical workers to precisely tailor therapies based on the following exact etiologies: (i) Interventions for physicochemical and biological factors, such as treatment of chronic infectious lesions, and avoiding chemical carcinogens and radioactive sources; (ii) interventions for psychological behavioral factors in individual, including cognitive adjustment, behavioral (habit) adjustment, and maintaining a healthy lifestyle, such as maintaining a healthy weight by following a healthy diet; avoiding smoking and excessive alcohol consumption; sticking with appropriate exercises; keeping to a regular and healthy sleep schedule; preventing prolonged mental stress, and establishing harmonious interpersonal relationships [14,37,38].

3.6.3. Psychosocial Interventions Before and After Diagnosis

In the family and sociocultural models used in abnormal psychology, abnormalities are not just illnesses of individuals, but may be reactions to familial or social sickness. Therefore, in addition to patient evaluation, we also need to evaluate the patient’s family and even society as a whole using the following approaches: (i) Intervention for cancer patients and their families including dealing with cancer-related mental disorders, avoiding post-traumatic stress disorder, and mitigating financial toxicity of cancer [39–43]; (ii) improvement at a societal level including optimization of the medical system, elimination of cancer-related fear and discrimination, promotion of healthy lifestyles, prevention of infectious diseases, efforts to protect the environment, and promotion of both material and spiritual goals in society [44–46].

In the future, the precise diagnoses of, and interventions for, these etiologies in each cancer patient may become the main goal not only for medical workers such as physicians, clinical psychologists, nutritionists and specialists of health management, but also for the patients, their families, and sociologists.

4. Conclusions

In this study, interdisciplinary knowledge was utilized to construct a conceptual model suitable for the human body. This model meets the requirements of both reductionism in modern medicine and holism in traditional medicine.

This model was then used to provide reasonable explanations for tumor-related questions worldwide. Suggestions were also provided for a cancer treatment framework with value including: interventions for physiological disorders; identification of, and interventions for, pathogenic factors; and psychosocial interventions before and after diagnosis.

Notably, the inferences made in this study were not only consistent with the results of scientific research in modern medicine, but could also satisfy the concepts of traditional medicine. Additionally, the treatment modalities derived using this model were fully consistent with BPSM. The model proposed in this study can provide novel ideas for addressing the knowledge gaps in modern medicine, and will aid in the integration of the medical treatment concepts used in modern and traditional medicine to overcome cancer worldwide.

Acknowledgments: The author would like to thank LetPub (www.letpub.com.cn) for linguistic assistance and pre-submission expert review.

Conflicts of Interest: The author has no competing interests to declare.

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