



Research Article

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# A Systemic Knowledge-Based Approach to Understanding and Treatment of Cancer Diseases

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## Abstract

Plausible knowledge is, no doubt, the only reliable ground of any treatment method and any strategy of treatment. An attempt has been made by the author to bring plausible knowledge of the sources of occurrence of HPV genotypes, which provoke cancer diseases, and knowledge of their epidemiological character - into a system. Not the methods of treatment themselves, but a systemic knowledge-based (and, so, methodologically organized) approach, which presumes systemic organization and systemic application of definite treatment methods, is recommended in the capacity of the way of proper organization of any treatment process in cancer cases. Moreover, a scheme implementing such an approach to prevention of HPV-induced cancer cases is described. The pattern of sequential development of understanding of the depth of HPV impact upon people (from the viewpoints of (i) provoking various forms of cancer and (ii) causing extensive morbidity and mortality) is described.

The types of viral sources, which reflect the human organism's potential from the viewpoint of its capabilities to protect itself against HPV-conditioned cancer cases, have been identified and are described. Infecting people with highly oncogenic HPVs is gradually acquiring epidemiological character of its progression. In this connection, human health risks may grow. High-risk HPV genotypes, which cause definite cancer cases, have been analyzed. Knowledge-based treatment strategies have been brought into a system. A systemic knowledge-based approach bound up with constructing treatment plans is discussed.

**Keywords:** Carcinogenic impact of HPVs, Knowledge-based approach, Epidemic character of HPV impact progression, Cancer acquisition risk, Morbidity, Mortality

**Abbreviations:** ELISA: Enzyme-Linked Immunosorbent Assay; HR: High Risk; IR: Incidence Rate; PCR: Polymerase Chain Reaction; VA: Viral Agent; VLP: Virus Like Particle; VP: Viral Particle

## Introduction

### The Aspects of Problem Consideration: A Knowledge-Based Approach to Understanding and Treatment of Cancer Diseases and the Epidemiological Character of the HPV Impact

The issue of plausible knowledge is gradually becoming all the more principal issue in finding an efficient approach to treatment of any disease. Plausible knowledge and reliable biomedical grounds may form the basis of the treatment method. And it is ever more important that plausible knowledge would become the ground for any treatment strategy, which would ensure the remission.

In the present paper, carcinogenic impact of Human Papillomaviruses (HPVs) upon people and its epidemiological character are discussed from the viewpoint of a systemic knowledge-based approach to deep understanding and efficient treatment of cancer diseases. This approach formulated by the author presumes not simply application of treatment methods in each definite case, but application of a systemic knowledge-based (and, so, methodologically organized) approach, which presumes systemic organization and systemic application of an integrated system constructed of a sequential set of definite treatment methods organized into a se-



quence of treatment stages. This systemic knowledge-based approach is recommended below in the capacity of the key approach to the proper organization of any cancer treatment process.

The approach to be proposed implies not only application of biological methodological grounds in solving medical treatment problems, but also application of the systems science (systemological) approaches.

In turn, epidemiology is a developed branch of medicine. The issues bound up with modeling epidemics in medicine are known to be discussed from the 1970s [1]. Various stochastic models were proposed in the 1990s [2]. Furthermore, in the 1990s [3] and later, in the 2010s, ideas of prevention of epidemics in communities were discussed [4], and even immunity potentials of human organisms (preventing diseases and even epidemics) were analyzed with the aid of mathematical bioscience techniques [3]. Traditions of mathematical biology in the aspect of constructing epidemic mathematical models were retained and continued in the beginning of the XXI century [5-7] (epidemic models with varying infectivity). For example, multi-patch and multi-group epidemic models were constructed [5].

During a long time period since the 1990s, investigations of cancer etiology, cancer therapy (pharmacology, immunotherapy, etc.) and surgery were conducted in the aspect of epidemiology. The issues of prevention, survivorship and, in this connection, surveillance were widely discussed. Furthermore, in 2003-2023, various issues of HPV infecting of people were discussed also in connection with development of such infecting in the aspects of virology [8-11] and evolution of the papillomaviridae family [12].

With time, the specialists, who considered themselves involved in problems of medical epidemiology, started to speak about epidemics bound up with HPVs rather freely [13]. It was logical that epidemiology bound up with HPVs developed mainly in the medical aspect: vaccines, treatment of anogenital warts [14], safety measures for surgeons conducting ablation procedures [13,15,16], etc.

Progression of the most part of HPV-induced cancer cases could not be rigorously defined by specialists as epidemic in its character. Meanwhile, already in the 2000s, some of the specialists spoke about emerging (NB!) epidemics of human papillomavirus-induced cancers [13]. Such conclusions necessitated reliable scientifically assessed grounds [17,18].

In the 2000s, there appeared epidemiological classifications of HPV types, which caused cervical cancer. Already in 2003, an epidemiological classification of HPV genotypes bound up with cervical cancer was discussed in *N Muñoz, et al.*, [19]. In 2006, a description of the epidemiology of genital HPV infection was given by *H Trotter, et al.*, [20]. In 2007, *EM Sturgis, et al.*, discussed an emerging epidemic of HPV-induced cancers [13].

Despite the absence of real HPV-conditioned cancer pandemics during the recent two decades, HPVs were discussed as the factors provoking the diseases capable of extensive human infecting

and characterized by “a definite epidemiological potential” (2006-2017) [4,13,20-24]. A review of the current knowledge of epidemiology, pathogenesis, and prevention of HPV infecting may be found in [23]. Noteworthy, over many years, HPV-conditioned cancer forms represented the main cause of cancer-related deaths in the world [25].

Furthermore, the epidemiological character of human papillomavirus infection was considered in several aspects, including the aspect of HPV pathogenesis [23]. It was shown that target cell cyclophilins facilitated HPV16 infecting [26], and vesicular trafficking of incoming HPV16 into the Golgi apparatus and into the endoplasmic reticulum required elevation of  $\gamma$ -secretase activity [27]. No wonder that *L. Bruni, et al.*, (see the summary report of 2019) indicated the epidemiological character of HPV-infecting as to the proved fact [28]. Some results of an epidemiological investigation of the process of high-risk HPV infecting of the people characterized by cytological abnormalities (revealed in the processes of screening of cervical cancer cases) were published by *W. You, et al.*, (2018) [29].

So, it was logical that during the time period from 2003 to 2023, the fundamental biomedical approaches were dominant in laboratory diagnostics of HPV-induced cancer cases in principle, and in ascertainment of the epidemiological character of HPV-infecting, which caused various cancer forms [4,8,9,13,21-24,29].

In the review publications of 2012-2022, two teams of talented researchers logically considered the impact of HPVs upon people as a kind of “global heavy burden of human papillomaviruses and the related diseases” [21,24,30-32]. Epidemiology of HPV-induced cancer diseases was discussed in *A. Kombe, et al.*, (2021) [32].

Furthermore, the issues of HPV-induced morbidity and mortality were discussed [33,34]. The teams headed by *T.R. Buchman, et al.*, (2016) and *J.Y. Lei, et al.*, (2020) analyzed these issues in connection with vulvar, vaginal and cervical cancer cases provoked by HPVs, while emphasizing the improper impact of 2-, 4-, and 9-valent prophylactic HPV vaccines [35,36]. Moreover, in 2017, *C. de Martel, et al.*, spoke about “the worldwide burden of the forms of cancer attributable to HPVs” [24]. This consideration included the details important from the viewpoint of understanding of substantial details, e.g., with respect to (a) HPV genotype, (b) country and even (c) site in the scrutinized country, where the corresponding cancer forms were spread [24].

A specific phenomenon, which implied co-circulation of several HPV genotypes in one site and was in 2007 interpreted as “integration”, was attributed to epidemiology [37]. Furthermore, the probability and even the estimated lifetime of acquiring HPVs were discussed already in 2014-15 [38,39].

In the present publication, the author wanted to encourage comprehensive and professional discussion of virally induced cancer problems in the world on the whole. The author is sure that validation of the novel treatment objectives, targets, and the corresponding novel surgical or therapeutic approaches are urgently needed.

The hypothesis: Deep understanding of possible approaches to diagnostics and treatment of HPV-induced cancer diseases (these approaches being based on the plausible and deep knowledge of the biomedical grounds of HPV-induced cancer cases) is the key issue in provision of adequate and efficient treatment of cancer diseases.

In the works of the author's research team, it has been proved that highly oncogenic capsid proteins HPV6 L1, HPV11 L1, HPV16 L1 and HPV18 L1, which co-circulate in the social (sexual) sphere and in the environmental sphere (air-borne and water-borne spread of Viral Particles (VPs)), represent inductors of definite forms of cancer in people [40]. Despite all doubts, these HPV genotypes incur real risks bound up with cancer acquisition by the people and, in the perspective, may cause epidemics [13].

**Problem statement:** The requirement of multi-aspect biomedical safety of the people from various HPVs (on account of the degree of hazards represented by these Viral Agents (VAs)), necessitates development of a systemic knowledge-based approach to deeper understanding and more efficient treatment of such diseases. This approach implies: (a) obtaining plausible and deep knowledge about the causes and sources of occurrence of HPV DNA in the organisms; (b) elaboration and application of a complex of methods and techniques intended (i) for reliable detection of HPVs and (ii) efficient treatment of the organism.

## Approaches and Methods

### A Systemic Knowledge-Based Approach to Understanding and Treatment of Cancer Diseases

Obtaining plausible solutions of the problems, which are bound up with prevention of diverse cancer cases induced by highly oncogenic HPVs, implies application of the factor of knowledge. In other words, it presumes deeper understanding of (i) channels via which fresh and active HPVs get into the human organism (despite high potentials of its immune system [41,42]); (ii) genotypes, in which HPVs may be represented on the subcellular level and, so, can persist in the human organism; (iii) epidemiological problems, which get more aggravated with every next decade; (iv) facts of multi-drug-resistance of HPVs; (v) resistance of HPV16 to alcohol-based disinfection (with ethanol and isopropanol), but sensitivity to hypochlorite and high concentrations of peracetic acid-silver-based disinfectant; etc. This knowledge indicates the necessity of new disinfection protocols for healthcare equipment. So, acquisition of plausible knowledge not only about a definite disease and about methods of its treatment, but also regarding possible sources (/causes) of this disease and the aids of protection, represents a very important issue.

### On the Way to a Universal and Transparent Knowledge-Based Treatment Approach

In the present investigation, which the author considers as research (not a review) one, methods of identification, analysis and comparison of a sequence of data obtained by the author (and inte-

grated with the data obtained by the predecessors) have been applied to construct a systemic knowledge-based approach as a methodology of investigations, analyses and treatment. In this context, the approach itself (bound up with application of known medical treatment methods in each case) implies reconsideration. The approach proposed by the author allows one to reconstruct a set of methods good for treatment of a definite disease into a transparent knowledge-based universal treatment approach applicable to any disease of a given class (in our case, HPV-induced oncogenic diseases are implied).

HPV-induced oncogenic diseases represent a challenging direction of biomedical research. Diagnostics and treatment of such diseases are of interest in each definite case. Meanwhile, it so happened that, with time, the specialists acquired knowledge about (data and facts indicating to) the epidemiological status of such diseases. The total set of such data determined a definite contemporary level of biomedical knowledge related to the epidemiological status bound up with such diseases.

Techniques of clinical analyses of HPVs, which for a long time were applied in clinical practice, presumed either the Polymerase Chain Reaction (PCR-) analysis or the technique of Enzyme-Linked Immunosorbent Assay (ELISA). For a long time, the PCR analysis was a universal tool for detecting HPV agents (and, so, revealing the cancer cases, which might be attributed to HPVs). Obviously, the mechanisms of these two detecting techniques are different. ELISA has become an efficient additional technique in cases of doubt in the analytical results obtained with the use of PCR and the need for their verification.

In many cases, the above two techniques demonstrated incompatible results. Noteworthy, results of application of these two techniques were unequal from the viewpoint of revealing the epidemic character of the scrutinized disease. So, in the long run, it was found expedient to apply ELISA as a more advanced technology for detecting HPVs. The time optimality and the quality of diagnostics of cancer cases on preclinical and clinical stages were conditioned by the goal of their immediate and efficient treatment. It is absolutely logical that it is important to reveal and study a cancer case (i.e., to detect the total set of its symptoms) at an early (i.e., curable) stage.

## Results

### Understanding of the Epidemiological Status of Cancer Disease Progression

The global Incidence Rate (IR) of HPV-induced carcinogenic diseases was rather high during the recent 20 years. This was partially due to the fact that both the individuals with various prevalent forms of HPV-induced cancer and the sources of HPVs could not be timely and efficiently identified. On the first stage, this was understood in the aspect of necessity in advanced technologies bound up with detection of viruses.

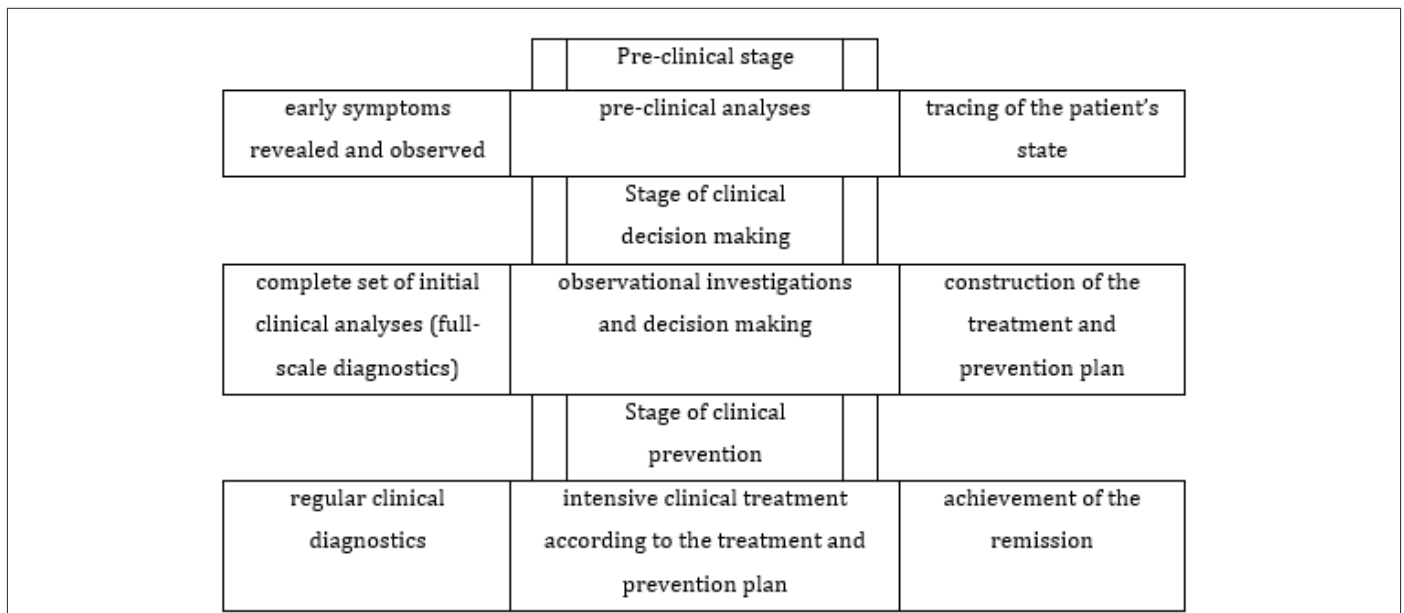
Besides developing the technologies, it was quite important to trace the way of the patient from the stage of preclinical cancer

case diagnostics to the stage of his clinical remission. Meanwhile, despite obvious symptoms easily revealed, many patients stayed out of clinics (because this was their will). The issue of preliminary identification and analysis of prevalent cancers in patients was not something unusual in clinical practice (say, on the stage of observational investigations).

Application of the author’s systemic knowledge-based approach to understanding and treatment of the corresponding diseases in clinical practice (in trials of cancer screening and later in

prevention) has given the author an opportunity to practically construct a pattern of possible treatment and prevention.

The scheme conceptually demonstrating a systemic knowledge-based approach to understanding the case and a treatment approach to the disease, which presumes (i) tracing of the patient’s state by symptoms, (ii) clinical decision making, (iii) construction of the treatment and prevention plan, (iv) undertakings bound up with prevention of HPV-induced cancer cases, -is shown in Figure 1.



**Figure 1:** A scheme conceptually demonstrating a systemic knowledge-based approach to understanding the case and to the disease treatment, which presumes prevention of HPV-induced cancer cases.

All the stages of this treatment scheme surely presume avoidance of transition of the cancer disease into the metastatic phase, i.e., are oriented to reduction of the mortality percentage. Various early-observation approaches aid the available methods of handling screening-revealed cancers [43]. For example, in many earlier discussed case investigations, endoscopic analyses allowed the specialists to obtain current diagnoses needed.

**On the Epidemiological Character of Development of HPV Influence Upon People**

Detailed analysis of the problem in the aspect of the author’s systemic knowledge-based approach to understanding the case and to treatment of the disease has given the author an opportunity to understand the sequences in (a) growth of the medical knowledge (about the circumstances and/or known facts/factors indicating to the disease epidemic status, and, so, giving evidence of the contemporary level of the scientific knowledge) and, therefore, in (b) development of the forms of representing the data bound up with the influence of the circumstances and/or known facts/factors upon the conclusion on the epidemic status of the disease.

The influence of HPVs upon people has been sequentially

(within the short, 24-year history) developing according to a logical scheme systematically shown in Table 1 below. Detailed consideration of these data may allow one to trace the character of such influence containing epidemiological elements. Indeed, growth of the numbers of morbidity and mortality in connection with HPVs may be noticed (Table 1).

Column 1 in Table 1 represents sequentially acquired knowledge of the circumstances, facts/factors indicating to the disease epidemic status. The sequence (up-down) of information in this column reflects the steps passed by medical specialists and scientists in understanding the problem, and, in this sense, reflects the contemporary level of world medical knowledge.

Column 2 in Table 1 represents sequentially formulated knowledge of the form of representing the data bound up with the influence of circumstances and/or known facts/factors upon the conclusion on the epidemic status of the disease. This may be, e.g., description of (i) the influence of HPVs, (ii) cancer cases. This form of representation reflects the level of understanding (by the specialists) of the influence of circumstances and facts/factors upon the situation.

**Table 1:** Sequential (historical) development of understanding of the depth of HPV impacts upon people from the viewpoints of (i) provoking various forms of cancer and (ii) causing extensive morbidity and mortality.

Data (knowledge) about the circumstances and/or known facts/factors giving evidence of the contemporary level of the world medical scientific knowledge	The form of representing the data bound up with the influence of the circumstances and/or known facts/factors upon the conclusion on the epidemic status of the disease	Evidence in the literature
Elucidation of the knowledge (facts) of hazardous impact of HPVs upon people	Generalized descriptions of papillomaviruses	[Narvskaya, 2011; La Rosa, 2016; Kombe, et al., 2021; Bruni, et al., 2023]
Knowledge of carcinogenic aspects of HPV infecting and virological aspects of its progression	Description of various cancer cases induced by HPVs, which provoke diseases characterized by a definite epidemiological potential	[Muñoz, et al., 2003; Kreimer, et al., 2005; Sturgis & Cinciripini 2007; Asiaf, et al., 2014; You, et al., 2018]
Knowledge of the facts bound up with diversification of the forms of cancer provoked by HPVs	Data bound up with growth of the number of morbidity cases in connection with diverse forms of cancer provoked by HPVs	[Buchman, et al., 2016, Bruni, et al., 2019]
Knowledge of the global burden of HPV-related viral diseases	Data bound up with growth of the number of HPV-related viral diseases (detailed descriptions of the cases)	[Arbyn, et al., 2011; Forman, et al., 2012; Oeffinger, et al., 2015; Kombe, et al., 2021]
Knowledge of the global heavy burden of specific cancer diseases induced by HPVs	Data bound up with growth of the number of various cancer cases and diseases in connection with HPVs (detailed descriptions of the cases)	[Forman, et al., 2012; de Martel 2012; Siegel, et al., 2014; deSantis, et al., 2015; Teras, et al., 2016; de Martel 2017; Torre, et al., 2018; deSantis & Jemal, 2018; deSantis, et al., 2019]
Knowledge about the growth of the number of mortality cases provoked by HPV-induced cancer cases	Data bound up with growth of the number of mortality cases in connection with HPVs (detailed descriptions of the cases)	[Buchanan, et al., 2016, deSantis, et al., 2017; Bray, et al., 2018; Sung, et al., 2021; Juul, et al., 2022]
Understanding of obvious necessity of immediate protection of the patients against HPV-induced cancer cases	Conclusion on the urgent need of immediate prevention of HPV infection and HPV-induced cancer cases	[Narvskaya 2011; Asiaf, et al., 2014, Wong, et al., 2019; Wang, 2022; Song & Bretthauer, 2023]
Understanding of possible approaches to prevention and protection of patients against HPVs inducing hazardous cancer cases and their treatment	Conclusion on the urgent need of immediate protection of patients against hazardous HPV-induced cancer cases	[Narvskaya 2011; Asiaf, et al., 2014; Wang, 2022; Song & Bretthauer, 2023]
Knowledge of possible approaches to protection of patients against HPVs inducing hazardous cancer cases and their treatment	Conclusion on definite measures (undertakings) bound up with protection of the patients against HPV-induced cancer cases and their survival	[DeSantis, et al., 2014; Asiaf, et al., 2014; FZ Zhang, et al., 2022; Juul, et al., 2022]

Table 1 contains the knowledge about the impact (upon people) of HPVs inducing hazardous cancer cases (diseases) characterized by a definite epidemiological potential [4,11,32,44].

The issues given in Table 1 were discussed with an explicit emphasis upon the epidemiological character of the cases (squamous cell carcinomas [8], other cancer cases [23] emerging epidemics of HPV-associated head and neck cancers [13] etc. Moreover, epidemiological classifications of human papillomavirus types provoking cervical cancer cases were proposed [19].

Regarding the data related to the growth of the number of HPV-bound diseases the reader may be addressed to [22,32,45,46]. As far as data bound up with growth of the number of various cancer cases and diseases in connection with HPVs are concerned, we address the reader to [21,22,24,47-52]. The data bound up with growth of the number of mortality cases in connection with HPVs were discussed in [34,35, 53-55].

Urgent need of immediate prevention of HPV infecting and protection of the organism against HPV-induced cancer cases was discussed in [4,23,56-58] colorectal cancer. Moreover, some of these

works considered cancer cases in the epidemiological aspect [58]. Conclusions were made on definite measures bound up with protection of the patients against HPV-induced cancer cases and their survival [23,55,59, 60].

#### **About the Revealed Causes (Sources) of Carcinogenic Diseases Conditioned by Various HPV Genotypes**

Note, abnormalities revealed in the investigation conducted by the World Health Organization were also bound up with cervical cancer, a typical form of the disease conditioned by various genotypes of HPV infection [61].

Analysis conducted by the author (the exposure characterization and assessment) has given an opportunity to identify 4 types of carcinogenic disease sources, which characterize the human organism's potential in the aspect of its capabilities to protect itself against HPV-caused cancer cases (see Table 2). These are: (1) diseases conditioned by various HPV genotypes, (2) organism's cytological abnormalities, (3) abnormalities bound up with molecular pathogenesis and (4) diseases conditioned by HPV genome variants or by various genetic mutations. It is important to understand

that carcinogenic diseases or organism’s abnormalities are also conditioned by definite genotypes of HPVs.

Cellular (cytological) organism’s abnormalities (in comparison to the norm) were discussed in [29,62-68]. Such abnormalities have been revealed, e.g., in the processes of screening of many cervical cancer cases, which cause carcinogenic diseases due to weakness of the organism’s intracellular preventive mechanisms. Meanwhile, in many cases, the organism’s cytology and cellular (cytological) organism’s functions remain normal despite the impact of HPV16, HPV18 and HPV45 [63,64,67,69].

*EM Venceslau, et al.*, discussed “detection of HPVs” (with the aid

of primers MY09/MY11 and GP5+/GP6+) in patients with cytologic and/or colposcopic changes [65]. *D Wolday, et al.*, discussed distribution of HPV genotypes in women having normal and abnormal cervical cytology [67]. *W You, et al.*, discussed abnormal cytological findings revealed in the process of cervical cancer screening [29]. Two teams of researchers [66-67] considered the case of vaginal dysbiosis in connection with the risk of HPV-induced cervical cancer. *J Norenhag, et al.*, described the case of cervical dysplasia [68].

The abnormalities bound up with molecular pathogenesis were discussed in [32,70,71]. The diseases conditioned by HPV genome variants or various genetic mutations were discussed in [72-85] (Table 2).

**Table 2:** The types of viral sources, which reflect the human organism’s potential from the viewpoint of its capabilities to protect itself against HPV-conditioned cancer cases.

Types of viral sources, which condition definite virally induced carcinogenic diseases	Carcinogenic diseases or organism’s abnormalities conditioned by definite genotypes of HPVs	Evidence in the literature
The types of sources, which are external with respect to a definite human organism	Diseases conditioned by various genotypes of HPVs	[World Health Organization, 2020]
The types of sources, which depend on the states of a definite organism (defined by its specific internal protective potential realized on the intracellular level) that may become (or not) the ground for the sources of abnormalities (or violations) in functioning of this organism at the cellular level	Cellular (cytological) organism’s abnormalities or violations	[Bruni, et al., 2010; Venceslau, et al., 2014; van de Wijgert, et al., 2017; Wolday, et al., 2018; You, et al., 2018; Brusselaers, et al., 2019; Gilham, et al., 2019; Norenhag, et al., 2020]
The types of sources, which depend on the functions of the capsid protein L1 bound up with molecular pathogenesis caused, for example, by a definite form of carcinogenic disease	Abnormalities bound up with molecular pathogenesis1	[Longworth & Laimins, 2004; Malhone, et al., 2018; Kombe, et al., 2021]
The types of sources, which depend on HPV genome variants and on genetic variations (mutations) of definite HPVs	Diseases (cases) conditioned by HPV genome variants or various genetic mutations	[Ho, et al., 1993; Burk, et al., 2013; Cornet, et al., 2013; Chen, et al., 2014a; Chen, et al., 2014b; Chen et al., 2015; King, et al., 2016; Graham, 2017; LeConte, et al., 2018; Tan, et al., 2019]

Remarks to Table 2: 1-L1 was a subject matter of several therapeutic investigations bound up with HPVs because of the presence of high-affinity domains with the host responsible for stimulating the immune response [32,42,70] and, specifically, its ability to self-assemble into highly immunogenic, non-infectious Virus-Like Particles (VLPs) [32,71-73].

**Discussion**

Analysis of the results of this investigation has given the author an opportunity to state the following. The factor of knowledge has become the decisive one in all scientific spheres and in medicine [62]. This factor defines the state and the level of contemporary medicine. Absence of due high-level knowledge very often incurs deficit of positive results of any medical treatment. This, first of all, relates to immune-compromised patients, patients undergoing surgical operations, serious treatment errors.

Knowledge and understanding of all the principal issues are important in the stages of (a) pre-clinical investigation of the patient, (b) clinical observational investigations before the decision mak-

ing, and (c) clinical treatment.

Understanding of the issues of cancer epidemiology may not be ignored. Knowledge of the epidemiological status of an HPV-induced disease is always a result of investigations oriented to various aspects bound up with progression of this disease. Promotion of deeper knowledge of (i) epidemiology of cancer diseases, as well as (ii) benefits of vaccination, might, in our opinion, form positive attitude of people (potential patients) to medicine in principle, to treatment methods, to cancer vaccines, etc. Furthermore, deeper understanding of virological and epidemiological aspects of diseases could scatter myths of spurious side effects of diseases and side effects of their treatment.

As noted above, already in 2007, specialists in HPV-related cancers started to speak about epidemics bound up with HPVs more freely [13]. It was logical that epidemiology bound up with HPVs even in recent years (2019-2023) developed mainly in the traditional medical aspect: Viral Agents (VAs), carcinogenic cases, application of vaccines, treatment of anogenital warts [14], safety measures for surgeons conducting ablation procedures [15,16], etc.

Mortality worldwide owing to 36 cancers in 185 countries was discussed [34].

As it has been ascertained in our investigation, there are carcinogenic diseases or organism's abnormalities conditioned by definite genotypes of HPVs and bound up with the cases conditioned by HPV genome variants and various genetic mutations. It is known that HPVs use the recombination-dependent replication mechanism for the vegetative amplification of their genomes in the differentiated cells [73]. HPV genome variants were discussed in [77]. Differences in the viral genome between the HPV-induced positive cervical cancer and the HPV-induced oropharyngeal cancer were studied (2018) [85]. Furthermore, distribution of HPV 16 E6 gene variants considered in screening of women was analyzed (2019), and its relationships with progression of cervical cancer and, hence, cervical lesions were understood (2019) [86]. Mutations may lead to elevation of cervical cancer risk worldwide [82]. Furthermore, in order to estimate the HPV prevalence in patients' cancer diseases, meta-analysis was conducted in [87] (the case of gastric cancer), and the potential role of such meta-analysis from the etiological viewpoint was assessed.

## Conclusions

Plausible knowledge is the only reliable ground of any efficient treatment method, any strategy of treatment. The issues of carcinogenic impact of HPVs upon people have been discussed above. An attempt to bring plausible knowledge of the sources of occurrence of HPVs, which provoke cancer diseases, as well as knowledge of their epidemic character, into a system has been undertaken. This approach presumes not simply application of treatment methods in each definite case, but involvement of a knowledge-based (and, so, methodologically organized) approach, which presumes systemic organization of the treatment process and systemic application of known treatment strategies and methods within the frames of an integrated methodological strategy. This knowledge-based approach is recommended by the author in the capacity of the key approach to the proper organization of any cancer treatment process. A scheme representing a systemic approach to prevention of HPV-induced cancer cases has been proposed (Table 1).

Furthermore, in the case of application of a systemic treatment strategy, the hazards possible for the people are seen in a more explicit form. Human health risks, which form the potential of progression of HPV-infecting, and which may cause epidemics, are seen as more concrete.

It is possible to draw the following additional conclusions.

1. On the whole, the author's findings represent issues which seem to be well-known ones, in the aspect of systems science. These findings, which are based on a systemic knowledge-based approach, have uncovered the knowledge about the following types of sources of carcinogenic diseases bound up with HPVs: (1) globally conditioned sources, which are external with respect to a definite human organism, and which condition the diseases at the expense of (a) various HPV gen-

otypes or (b) genetic variations (mutations) of HPVs; and (2) abnormalities in a definite organism, which are determined by its internal conditions: (i) cytological (intracellular level) abnormalities, (ii) molecular and (ii) genetic abnormalities (Table 2).

2. Many researchers have come to the conclusion on the epidemiological character of the carcinogenic impact of HPVs upon people. Indeed, infecting people with highly oncogenic HPVs is gradually acquiring epidemic character. The epidemic character of cancer diseases has been discussed above from the viewpoint of this systemic knowledge-based approach to understanding and treatment of diseases in principle. In this situation, a systemic knowledge-based approach (to deeper understanding and treatment of definite diseases) discussed in the manuscript is considered as a support for medical professionals in planning and application of definite treatment strategies. In this case, methods are considered within the frames of a systemic treatment strategy based on the plausible and systemic knowledge about a definite class of cancer diseases, and about the sources and causes of these diseases.

The author's findings have contributed to the knowledge about the following types of epidemics, which may potentially be provoked by HPVs: (i) epidemics possible in connection with circulation of HPV genotypes in a definite site; (ii) epidemics possible in connection with co-circulation of various HPV genotypes in the same site; (iii) epidemics bound up with external factors (specific epidemics possible in society or else in the natural environment).

3. It is known that immunity potentials of many human organisms prevent various diseases and, in this connection, probably also epidemics [3,41].

Already in 2003, an epidemiological classification of HPV genotypes bound up with cervical cancer was constructed [19]. In 2006, a description of the epidemiology of genital HPV infection was given by H *Trottier, et al.*, [20]. In 2007, *EM Sturgis, et al.*, discussed an emerging epidemic of HPV-induced cancers [13]. Reviews of the current knowledge of epidemiology, pathogenesis, and, in this connection, prevention of human papillomavirus infection can be found in [14,23].

In 2018, multi-patch and multi-group epidemic models were constructed [5], and results of epidemiological investigations of the process of high-risk HPV infecting of the people characterized by abnormal cytology were published by *W You, et al.*, [29].

HPV epidemiology of cancer diseases was discussed in [32]. Epidemic models with varying infectivity were proposed in [6,7]. *M Song, et al.*, (2023) published their results of epidemiological investigations of HPV-induced cancers [60]. So, there is no doubt that HPV-induced cancer diseases and the character of carcinogenic impact of HPVs upon people have a definite epidemiological character.

4. It is very important to orient further investigations directed to prevention of infecting people with HPVs causing cancer cases to deeper understanding of the mechanisms of cancer acquisi-

tion and, in this connection, to (i) application of the systemic knowledge-based approach, (ii) constructing not only social barriers against infecting, but also, possibly, development of some natural environmental barriers against papillomaviruses. It is expedient to reveal an extended spectrum of important environmental factors (to be taken into account and assessed), consider these factors as biomarkers, and already now (iii) search for the keys to deeper understanding of possible epidemics.

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## Author Contributions

Formulation and conceptualization of the basic ideas, data analysis, interpretation and systematization, preparation of the figure and the tables, and writing the paper - Michael Yu. Chernyshov.

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