Oncological Terrain-Dependent, Inherited Real Risk of Cervical Cancer: pathophysiology, diagnosis and primary prevention

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ABSTRACT

High-risk human papilloma viruses (type 16 and 18) are generally considered to be the causative agent of cervical carcinogenesis, but a number of other unknown factors, both genetic and environmental, are associated to the development of such a cancer, as the alterations in mitochondrial DNA. We explore the role played by mtDNA alterations in cervical cancer oncogenesis and its Oncological Terrain-Dependent, Inherited Real Risk, at the light of Quantum Biophysical Semeiotics biological evaluation. Quantum Biophysical Semeiotics theory is an extension of medical semeiotics. It is grounded on a multidisciplinary approach that involves chemistry and biology, genetics and neuroscience, chaos theory and quantum physics. It is based on the method of Auscultatory Percussion, through which by means of the common stethoscope, it is possible to listen to the signs that the body gives us when appropriately stimulated. The stimuli are used to induce consistent behaviour in precise and well defined biological systems of the human body, thus giving local qualitative and quantitative information on the state of health or disease, whether potential, being developed but not yet evident by usual clinical trial, effective or even in chronic phase. The Quantum Biophysical Semeiotics theory provides very detailed case studies based on the latency time, duration, and intensity of the reflexes, which play a central role in such a clinical diagnostic method, that can be used for therapeutic monitoring allowing an original primary and pre-primary prevention of cervical cancer.

Key-words: cervical cancer, Oncological Terrain, clinical diagnosis, microcirculation, mtDNA, HPV, mitochondrial DNA, Inherited Real Risk, primary prevention, quantum therapy

Introduction

According to the majority of Authors, human papilloma virus (HPV, type 16 and 18) infection is the main causal factor for cervical cancer (CC), but there are data suggesting that genetic factors could modulate the risk for CC. onset. Sibling studies suggest that maternally inherited factors could be involved in CC. High risk human papilloma viruses (hr-HPV) are known to be the etiological and causative agents of cervical cancer disease. On the other hand, other cofactors are considered to be important in cervix carcinogenesis. Mutations in mitochondrial DNA (mtDNA) as well as alterations in mtDNA content [1] have been reported in numerous cancers examined to date [2].

A recent Indian study reveals that mtDNA is highly altered in cervical cancer [3]. A Mexican study evidences that *the association of mtDNA with CC and HPV infection is clear* [4]. Other studies shows that the majority of high-risk HPV infections go away on their own and do not cause cancer [5], in accordance with the American National Cancer Institute (NCI): "Still, of the women who do develop abnormal cell changes with high-risk types of HPV, only a small percentage would develop cervical cancer if the abnormal cells were not removed." This is confirmed by a recent South African research showing that a large number of young sexually active women get infected by HPV, but only a small fraction of them have persistent infection and develop cervical cancer, pointing to co-factors including host genetics that might play a key role in outcome of the HPV infection [6]. For instance, there is CCR2-64I variant polymorphism that is associated with the risk of cervical cancer but does not affect the susceptibility to HPV infection or HSIL in South African women of black and mixed-ancestry origin. This result implies that the role of CCR2 is important in invasive cancer of the cervix but not in HPV infection or in the development of pre-cancers. On the other side, mtDNA C150T polymorphism was positively associated with HPV infection and subsequent CC risk among Chinese women [7].

HPV test is a primary screening test for cervical cancer prevention, because there is clear scientific evidence that a screening based on validated tests for the DNA of oncogenic HPV as primary test and applying an appropriate protocol is more effective than screening based on cytology in preventing invasive cancers of the uterine cervix [8], but maternally inherited factors, such as mtDNA genetic tests are not yet widely taken in consideration and available on a large scale.

Which is the prime cause of cervical cancer? What is the difference between causes and co-causes, factors and co-factors? All these are important, unresolved issues, even at the light of the most recent studies. Novel researches agree that mtDNA mutations may play a role in cervical precursor lesions and cancer but do not clarify the border line between causes and risk factors: *the role of mtDNA in cervical carcinogenesis* is not yet fully understood and remains to be solved [9].

For a better comprehension of the mechanism of cervical cancer oncogenesis new approaches and insights should be explored as those offered by Quantum Biophysical Semeiotics **(**QBS) theory and method.

Oncological Terrain-Dependent, Inherited Real Risk of Cervical Cancer: Pathogenesis

QBS theory provides a clinical, reliable method for bed-side diagnosing cervical cancer, even in its pre-clinical stages [10]. QBS is a new discipline in medical field and an extension of the classical medical semeiotics. It is a scientific trans-disciplinary approach that is based on the "Congenital Acidosic Enzyme-Metabolic Histangiopathy" (CAEMH) [11], a unique mitochondrial cytopathy that is present at birth and subject to medical therapy. The presence of intense CAEMH in a well-defined area (e.g., myocardium) is due to gene mutations in both nDNA and mtDNA.

At the base of all these alterations there are both parenchymal and microvascular inherited alterations (nDNA and mtDNA), which parallel the former, according to the theory of Angiobiopathy, which completes Tischendorf's Angiobiotopy theory [12]. In fact, all complex gene mutations parallel biological system dysfunctions, because, to be significant, whatever gene mutation has to bring about well-defined biological system functional modification, we can now study by means of a stethoscope. This is the basis for one or more QBS constitutions [13], in our case, Oncological Terrain [14], which could bring about their respective Inherited Real Risks (IRR) [15-17], e. g., IRR of breast cancer [18]. The QBS method allows the clinical and pre-clinical diagnosis of the most severe diseases, such as the IRR of cervical cancer [19, 20], which is achieved in the easier way through the auscultatory percussion of the stomach [21, 22].

The patho-physiology of QBS reflexes is based upon local microvascular conditions. In case of genetic alteration of both DNAs, intense CAEMH, and IRR of cervical cancer there is a typical, inherited microcirculatory remodeling, worsened by well-known environmental risk factors, due to vasomotility and vasomotion impairment (e.g., functional imperfection) and structural obstructions, due to the newborn, pathological, type I, sub-type a) oncological, Endoarteriolar Blocking Devices (EBDs), discovered by one of the authors, and Arteriovenous Anastomosis (AVA) [10, 11, 15].

With the aid of QBS method, physicians can bedside recognize, in an easy, quick, and reliable manner, the possible presence of maternally-inherited Oncological Terrain, and Oncological Terrain-dependent, IRR, based on the presence of above-mentioned typical microcirculatory remodeling of cervical microvessels, characterized by the newborn-pathological, type I, subtype (a) Oncological, EBDs [10, 11], *conditio sine qua non* of cervical cancer [19].

In spite of genetic testing, bedside ascertaining particularly cervical cancer IRR in well-defined trigger points allows physicians to perform an efficient malignancy primary prevention in a few minutes. In addition, testing for mutations cervical cancer susceptibility genes or for their diminished expression adds to the ability to assess cervical cancer IRR at an individual level, because local biological activity, examined with the aid of QBS, results significantly abnormal.

Oncological Terrain-Dependent, Inherited Real Risk of Cervical Cancer: Clinical Diagnosis

The objective QBS examination allows physician to bedside recognize and quantify, in a few minutes, first of all, the presence, or not, of Oncological Terrain (OT) in any subject, and secondly, in case of a positive OT aspecific QBS sign, if it is specifically related to an Inherited Real Risk (IRR) of cervical cancer , overt cancer,

even initial, through the evaluation of several semeiotics signs, i.e., assessing vasomotility, vasomotion and typical pathological EBDs.

In following, we briefly resume the easier way for the diagnosis of this pathology or of its Oncological Inherited Real Risk: unavoidable is the knowledge of the Gastric Aspecific Reflex (G.A.R.) realized by means of the Auscultatory Percussion of the Stomach [10, 21].

Through QBS method, physicians can evaluate, at the bed-side, with a stethoscope and the auscultation of any viscera (i.e., stomach, ureter), mitochondria functions, as well as the behavior of any biological system.

From their birth, almost all individuals show the presence of CAEMH [10, 11], subsequently evolved first into pre-metabolic syndrome [23] and later on into metabolic one, under the negative influence of well-known environmental factors. Common human disorders may occur exclusively in individuals with related QBS constitutions and related Inherited Real Risk [10-18]. In fact, not "all" the individuals, even though obese and/or hypertensive, are at risk of diabetes mellitus, with the same probabilities [16].

In health, in supine position, psycho-physically relaxed, with open eyes, aiming to lower significantly melatonin secretion, an "intense" digital pressure applied upon OT trigger points (skin projection's area of SST-RH, GH-RH or epiphysis) does not bring about a simultaneous G.A.R. (the reflex appears physiologically after 16 seconds) in case of negative Oncological Constitution (absence of OT) [10, 24].

On the contrary, under the same above-mentioned conditions, a positive OT is revealed by a simultaneous G.A.R. The diagnosis of positive Oncological Terrain should be refined through other QBS signs to assess in deep the possible local presence of any IRR of cancer, i.e., the IRR of cervical cancer.

According with QBS theory, the reaction to HPV infection is related to QBS Constitutions of the patient and in particular to the presence, or not, of Oncological Terrain [10, 19, 24]. Positive OT and positive IRR of cervical cancer are the *conditio sine qua non* for the onset of cervical cancer. As a matter of facts, without OT and OT-dependent, Inherited Real Risk of cervical cancer, such a malignancy cannot occur.

As a consequence, i.e., type 16 and type 18 HPV should be considered as risk factors, rather than causes of cervical cancer, but in presence of OT-Dependent, IRR of cervical cancer. The prime condition of cervical cancer onset is the genetic alteration of mtDNA, biologically expressed by an intense CAEMH and a positive OT. However, the mere presence of Oncological Terrain is not sufficient to justify the risk of cervical cancer. The initiation and evolution of cervical cancer depends on the presence of its Inherited Real Risk. In case of negative OT, or in case of positive OT, but without IRR of cervical cancer, there is not any risk for the onset of this tumor, independently from all environmental risk factors, who play a key role as co-causes of malignancy if and only if the prime cause is present.

A digital pressure of "mean" intensity, applied upon cervix (or its skin projection's area), brings about G.A.R., whose latency time (Lt), duration (D), intensity and Microcirculatory Functional Reserve (MFR), which parallels the G.A.R. duration, informing on tissue oxygenation at rest, as well under stress situations [10]. In health, in supine position, digital pressure of "mean" intensity, applied upon cervix trigger points – or directly on the uterine cervix - brings about cervical G.A.R. after a latency time (Lt) of 8 seconds. Cervical G.A.R. lasts less than 4 s, soon thereafter disappearing for 3-4 s. Afterwards, a second reflex occurs. The duration of cervical G.A.R. unfolds the MFR activity of related microvessels, technically speaking, the Tissue Microvascular Unit (T.M.U.), thus correlated with the function and anatomy of the microcirculatory bed.

At this point of examination, the physician quickly interrupts the digital pressure for exactly 5 s. Then, Lt of G.A.R. is evaluated again: reflex Lt physiologically raises to 16 s, cervical G.A.R. lasts less than 4 s, disappearing after roughly 4 s: these values evidence a *physiological preconditioning* [10, 11, 24].

In summary, when digital pressure is of mean intensity, physiological Lt of cervical G.A.R. is 8 s at the first evaluation (*basal-line value*), but increases, clearly doubling, in the second as well as in the third one, due to the physiological activation of MFR.

In individuals at IRR of cervical cancer, *base-line* Lt is still physiological in the first evaluation (8 s). However, cervical G.A.R. lasts 4 s or more and disappears for less than 3 s. Moreover, preconditioning results pathological, as Lt is less than 16 s: these values give evidence of a *pathological preconditioning*.

Interestingly, in patients with cervical cancer, even clinically silent, the *basal value* of latency time of cervical G.A.R. appears to be less than 7 s at first evaluation and becomes lower in the second one, in relation to the seriousness of underlying disorder (Table 1).

In healthy subjects the *preconditioning* brings about, as natural consequence, an optimal tissue supply of material-information-energy, by increasing the local *flow-motion as well as flux-motion*.

On the contrary, if the 'Inherited Real Risk' of cervical cancer is present, *preconditioning* data are almost the same as the basal ones, but Lt is a little shorter than physiological one. Finally, in overt disease, *preconditioning* shows an altered and shorter Lt of reflex in relation to the seriousness of the underlying disorders.

At this point, we come back to the former example: in the initial phase of cancer, which evolves very slowly toward successive phases, QBS "basal" data can seem apparently normal. However, under careful observation, the duration of cervical G.A.R. is equal or more than 4 s (the normal value is less than 4 s), indicating a local microcirculatory disorder.

In these cases, *preconditioning* allows in a simple and reliable manner to recognize the pathological modifications, mentioned above, which indicate the altered physiological adaptability, even initial or slight, of the biological system to changed conditions as well as to increased tissue demands. The various QBS parameters, related to a defined biological system, parallel and are consistent with the data of *preconditioning*.

Cervical Gastric Aspecific Reflex - mean intensity digital pressure on cervical trigger points (cervix skin's projection)

Latency time (Lt) in seconds	Latency time after preconditioning (pause of 5 sec.)	Reflex Duration (D) in seconds	Diagnosis
Lt = 8	Lt = 16	3 < D < 4	Health
Lt = 8	Lt < 16	D ≥ 4	Inherited Real Risk of cervical cancer
7 < Lt < 8	Lt < 16	D > 4	Inherited Real Risk of cervical cancer in evolution
Lt ≤ 7	Lt < 14	D >> 4	Cervical cancer

Table 1. Diagnosis of IRR of Cervical Cancer. Legend: Lt =Latency time of cervical G.A.R.; D = Duration of G.A.R.

Oncological Terrain-Dependent, Inherited Real Risk of Cervical Cancer: Primary and Pre-primary prevention

QBS tools are not only useful for diagnostic purposes, but also for therapeutic advices, because they can measure the microcirculatory activity, related to the local tissue function and structure, according to Angiobiopathy theory, before and after each preventive therapy, in order to understand the effectiveness of remedies.

Some years ago, one of the authors [10, 13] let us an open question: are QBS Constitutions and IRR of degenerative pathologies reversible? Through proper prevention treatments termed “type A” or “green” therapy including, i.e., modified Mediterranean diet, CoQ10 and conjugated-melatonin, a genetic reversibility for future generations (pre-primary prevention) is possible [25, 26], but this could not be enough for the current generations, especially under negative environmental conditions. The “green” therapy stimulates the activity of mitochondria by acting on metabolism, peptides' net, but also improving, normalizing mitochondrial and tissue oxygenation, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy above mentioned, CAEMH, is the *conditio sine qua non* of more frequent and severe human disease. By this way tissue oxygenation and mitochondrial activity improve, mitochondria run well, but the genetic alterations of mtDNA still remain: CAEMH, QBS Constitutions and IRR of diseases are yet positive, but the IRR becomes “residual”. This means that a continuative “type A” therapy removes the heritable risk, avoiding disease’s onset, despite the genetic problem is not yet healed. Since 2011, QBS method allows an efficient pre-primary prevention with recursive effects [27] able to reverse the genetic alteration of both nDNA and mtDNA, namely the mitochondrial cytopathy at the base also of degenerative pathologies such as cervical cancer, according with the Principle of Recursive Genome Function [28-30]. This is possible under a “type B” or “blue” therapy. In particular, we have successfully tested a Quantum Therapy based on millimeter waves with ‘Extremely High Frequencies’ (EHF) for the pre-primary prevention of cancer [25, 27], Type 2 Diabetes Mellitus [31], osteoporosis [32] and Coronary Artery Disease [17, 33].

Conclusions

QBS theory gives new insights in the understanding of cervical cancer oncogenesis. QBS method allows to distinguish between the causes and risk factors of this tumor, thus favoring a more efficient approach in terms of pre-primary and primary prevention, due to the diagnosis both of Oncological constitution (or Oncological Terrain) and Inherited Real Risk of cervical cancer.

With the help of the QBS diagnosis a pre-primary and primary prevention of cervical cancer on finely selected subjects is possible on very large scale, not anymore on all the women in some populations, such as is currently being done. This approach, at no cost for the national health services, requiring only the use of the stethoscope, promotes psychological, economic and health benefits for the individual and for the whole community, if and when adopted after a proper training and experimentation.

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