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New Genetic Approach in Early Detection of Cancer

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Abstract

Cancer is a major health problem all over the world, the main obstacle facing cancer prevention is a lack of precise approach for early detection and prevention strategies of the disease. All previous works on cancer dealt with only infected patients. New technique under accurate statistical experimental design must be developed in order to early diagnose of the disease. This will be done through molecular characterization of genomic DNA of thousands of cancer infected as well as healthy people living in high and low risk environmental conditions. Genetic variations (differences) for resistant/tolerant versus susceptible individuals to cancer incidence exist within communities and various regions. The result of such molecular genetic variations will play role in answering the questions of why do the majority of people living in high environmental risk area never get cancer? And why do some people living in low environmental risk area get cancer? Previous studies reported that the current theory dealing with cancer cause is that long periods of exposure to environmental risk factors (carcinogenic, pollutants, smoke, chemical and others) have had a major effect in modifying the constitution of the genome (gene) through mitosis mutation. Contrary to that, the current article hypothesizes that cancer occur as a result of presence of sensitive gene(s) that inherited by infected individuals coupled and interacted with environmental causes. So it is a vital issue to investigate the relation between resistant versus susceptible individuals to cancer incidence and their molecular characterizations (genetic make-up) to identify the molecular genetic differences (genes or alleles, that are associated with resistance or susceptibility to cancer), as molecular genetic markers to be used as early detection of individuals susceptible to cancer.

Keywords: Malignant; Genetic markers; Cancer, High risk environment

Introduction

Background

According to the World Health Organization (WHO), the worldwide incidence of cancer was 10.5 million in 2000 and it will be 30 million by 2020. Currently, more than 25 million people are living with cancer. It was reported that cancers figure among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 [1]. WHO defined cancer as a generic term for a large group of diseases that can affect any parts of the body. Other terms used are malignant tumors and neoplasm. The main feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and can then invade adjoining parts of the body and spread to other organs which is the major cause of death from cancer [1]. The great majority of cancer cases are due to environmental (risk) factors (exposure to smoke, radiation, diet, chemicals and pollutants). These factors act, by changing the gene of a cell (mutation). Genes are found in the DNA in each cell. They control the cell functions, including how quickly it grows, how often it divides, and how long it lives. Researchers estimate that there are 35,000 different genes in each cell. Genes control the cells function by making specific proteins via correct instructions or "code", (transcription and translation) where the protein can perform the correct function for the cell. All cancers begin when one or more genes in a cell are mutated, or changed in the code. This creates an abnormal protein, which provides different information than a normal protein, which can cause cells to multiply uncontrollably and become cancerous [2]. As long as these cells remain in their original location, they are considered benign; if they become invasive, they are considered malignant. Cancer cells in malignant tumors can often metastasize, sending cancer cells to distant sites in the body where new tumors may form [3]. There are two basic types of genetic mutations:

• Acquired mutations are the most common cause of cancer. These occur from damage to genes during a person's life. They are not passed from parent to child. Factors such as tobacco, ultraviolet (UV) radiation, viruses, and age cause these mutations. Cancer that occurs because of acquired mutations is called sporadic cancer.

• Germline mutations, which are less common, are passed directly from a parent to a child. Because the mutation affects reproductive cells, it passes from generation to generation. Cancer caused by germline mutations is called inherited cancer [2]. Furthermore, the malfunctioning genes can be classified into three groups.

- The first group, called proto-oncogenes, produces protein products that normally enhance cell division or inhibit normal cell death. The mutated forms of these genes are called oncogenes.

- The second group, called tumor suppressors, makes proteins that prevent cell division or cause cell death.

- The third group contains DNA repair genes, which help prevent mutations that lead to cancer [3].

Nevertheless, cancer is a process with three steps: initiation, promotion and progression. Each step plays a vital role in stopping the cancer process. Since a period of many years usually exists between the initiation of the cancer process and the onset of the symptoms, cancer prevention methods like risk control and early detection are most effective in the first two steps. The first step involves changes to the genetic code (DNA) of a cell called *initiation*. Initiation is simply a mutation. Usually, initiation by itself is not enough to produce cancer;

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the body's repair systems can replace damaged sections of DNA, which allow the cell to recover under normal circumstances. If the cell reproduces while the DNA is damaged, more abnormal cells can be made that may develop into cancer. The altered cells undergo more changes that may require an additional substance called a *promoter*. A promoter is something that speeds up the pace of cell division, which can create more genetic mutations. A promoter may be a hormone such as estrogen or a toxic substance such as a chemical in tobacco smoke. Some chemicals in the environment are toxic substances that can produce cancer. Most chemicals act by causing the initiation step in the cancer process (altering the DNA), but they also can act as promoters. The last step is *progression*, which means that the cells have begun to grow out of control and is the basis for all cancers. The out of control cells form a tumor. A tumor is simply a mass of abnormal cells that keep growing and can extend into nearby tissues or spread to other parts of the body. No one completely understands this process [4-6]. These changes are the result of the interaction between a person's genetic factors and 3 categories of external agents, including:

• Physical carcinogens, such as ultraviolet and ionizing radiation;

• Chemical carcinogens, such as components of tobacco smoke, aflatoxin and arsenic ; and

• Biological carcinogens, such as infections from certaruses, bacteria or parasites [1].

Justification

Cancer detected by the conventional histopathology, hematology and immunohistochemistry technique that the pathologist may perform on the tissue or blood specimen. As there is no precise approach for better early detection of cancer, a new technique under accurate statistical experimental design must be developed in order to early diagnose the disease. This can be a useful tool in the future for early speculate the susceptibility and consequently the occurrence of cancer, where therapy and cure can be more effective.

Objective

The objective of this article is to investigate the prevalence and relation between resistant/tolerant and susceptible (infected) individuals to cancer incidence using molecular characterizations (genetic make-up) of individuals living in high and low risk areas to identify molecular genetic markers to be used as early detection of individuals susceptible to cancer at early stage of life (Genetic Markers Assisted in Early Detection of Cancer).

Resistant *versus* susceptible individuals to cancer

According to the information available to pathologists, many q**uestions are still unsolved and that should be studied and investigated through the field of molecular pathology. These are:**

- Why do the majority of people living in high environmental risk area never get cancer?

- Why healthy parents got a child with congenital birth defects? Did Child get mutation through meiosis? But why parents did not get mitosis mutation?

- Is there any specific age at which specific gene starts and/or shows mitosis then cancer symptoms? or is there any specific age at which gene (allele) in somatic cells under specific environmental risk factor to show its expression?

- How long does it take for a gene subjected to risk factors to show mitosis then cancer or how long does it take for a gene in somatic cells subjected to risk factors to show its expression?

- How much carcinogenic or what would be the amount of risk factor to initiate mitosis in the gene or how much carcinogenic or what would be the amount (sufficiency or available) of risk factor to initiate it's expression and to manifest cancer?

- How long or how fast can allele destroy targeted cells?

- What are the percentages of genetic and environmental variations contributed to cancer incidence?

- How many resistance/sensitive genes influence cancer incidence? Are the contributions of these genes equal?

- How do alleles at different loci express and interact? additive? dominance and epistasis?

All these questions should be addressed to WHO, regional, national and international related scientific institutions as well as funding agents to solve and secure the answers of the above questions through this article (Hope to be a long term international project).

Context and scope

Mutations are mostly meiotic in origin. Germinal mutations are those that occur in the egg or sperm cells and therefore can be passed on to the organism's offspring. Mutation is the ultimate source of genetic variation [5,6]. Studies showed that there are two different genetic mechanisms for disease resistance/susceptibility:

Monogenic resistance/susceptibility, which is based on single genes (qualitative character or Mendelian disorder), and is not influenced by environment factors. Most diseases are controlled by a single gene. Monogenic diseases result from modifications in a single gene occurring in cells of the body (such as sickle cell anemia).

Quantitative resistance/susceptibility which depends on two or more genes (multi-loci genes). Quantitative characters (such as development of several diseases) not only depend on few genes but also on environmental factors as well as their interaction. Quantitative characters occur as the result of gene(s) expression, frequently coupled with environmental causes. Gene resistance/sensitivity refers to the different gene expression of a genotype in response to different environments.

Reports indicated that the genetics of cancer resistance has been largely unexplored. Differences in DNA make individuals unique and offer the opportunity for resistance or sensitivity to cancer. This article hypothesizes that cancer occur as the result of already existing sensitive mutant gene(s) in cells of specific organ in the body coupled with environmental causes (risk factors). The nature of caner depends on the functions performed by the existing sensitive genes (genes expression) in the specific cells which initiated by specific risk environmental factors. These genes will allow us to test the hypothesis that polymorphic alleles of these genes are related to the ability of individual to combat with cancer, through the approach mentioned below. As modern genetic analysis techniques allow rapid screening of individual for structural variation in distinct genes. Recently, it is well documented that most loci were highly polymorphic, showing an average of at least 5 alleles per gene (locus), consequently, these give thousands of genotypes in the population. These already existing alleles in the body will allow us to test the hypothesis that polymorphic alleles of these genes are related to the ability of individual to combat with cancer, through the approach mentioned below. If molecular genetic variation can be identified genes

that segregate with disease resistance/sensitive, it will be possible to use these modern methodologies to detect individuals carrying bad gene (allele). Identifying genes significant in the expression of genetic resistance/tolerance towards environmental factors will be vital issue, as carriers of these sensitive gene(s) at early stage of life may then undergo enhanced surveillance, chemoprevention, or preventative surgery to reduce their subsequent risk. Therefore, the approach listed below one can investigate the above questions and test the hypothesis proposed by this article for the manifestation of cancer. This will be intended to strengthen the guidance for health policy, implementation of cancer prevention strategies in the world (as preliminary global plan of action for control of cancer).

The New Approach

The project experimental design will be based on randomized complete block design with 4 categorical groups, where blood and/or tissue samples will be collected from at least 1000 persons of different age and gender categories according to the followings groups:

G1 - Healthy persons who lived in low risk environmental factors areas (as a negative control, Group 1),

G2 - Healthy persons who lived in high risk environmental factors areas (as a negative control, Group 2),

G3 - Infected persons of any type of cancers, who lived in low risk environmental factors areas (as a positive control, Group 3) and

G4 - Infected persons of any type of cancers (as a positive control Group 4).

Diversity of molecular markers at the DNA level within and among healthy versus cancer infected individuals will reveal a "Genetic Marker Assisted in Early Detection of Cancer". Molecular genomic markers such as microsatellite marker (simple sequence repeat-SSR and single nucleotide polymorphisms-SNP) can be used for assessment of genetic diversity of persons suffering from cancer compared to healthy one [7]. A blood samples from each individual will be collected. DNA will be extracted from each of the blood sample. The quality and quantity of DNA will be checked and quantification will be done by for spectrophotometer. Then PCR amplification using various primers or single nucleotide polymorphisms technique will be done. In this project PCR protocols will be used to check polymorphism of the persons under investigation.

Diversity of molecular markers within and among individuals and communities are revealing polymorphisms at the DNA level can be a key player in detection of cancer in preventive programs. Data generated from the detection of polymorphic fragments will be analyzed for the size range of fragments (bp), overall mean percentage of polymorphic loci and unique bands, allele counts and frequencies, mean number of alleles, genetic distance within and among groups, mean number of alleles per locus and alleles sequence. Furthermore, Biopsy specimens will be fixed in 10% buffered formalin and processed for routine paraffin section, using the conventional methods. The original histological diagnoses will be obtained on the hematoxylin and eosin slides and were categorized according to cancer type. Moreover, immunohistochemistry will be performed on samples.

Patients

During Vietnam War, from 1961 to 1971, between 2.5 and 4.8 million people were exposed to Dioxin. Dioxin has been recognized by the World Health Organization as a carcinogen. The Vietnamese who were exposed to the chemical have suffered from cancer, liver damage, pulmonary and heart diseases, defects to reproductive capacity, and skin and nervous disorders. Children and grandchildren of those exposed have severe physical deformities, mental and physical disabilities, diseases, and shortened life spans [8]. Likewise, many reports [9-14] indicated that Gulf Wars in Iraq during 1980, 1991 and 2003 (and continue till now !!!) have led to sharp spikes in the rates of congenital birth defects, premature births and cancer cases in Iraq, where many people are suffering from depleted uranium (DU) pollution in many regions and increased incidence of various cancers and birth defects. About 1200 tons of ammunition was dropped on Iraq during Gulf Wars. As a result, contamination occurred in more than 350 sites in Iraq. According to Iraqi government statistics, the rate of cancer in the country has increased from 40 per 100,000 people prior to the First Gulf War in 1991, to 800 per 100,000 in 1995, to at least 1,600 per 100,000 in 2005. The actual rate of cancer and other diseases is likely to be much higher than even these figures due to a lack of adequate documentation, research and reporting of cases. Moreover, cancer statistics are hard to come by, since only 50 percent of the health care in Iraq is public whereas, the other half is managed by private sector. According to a 2013 report by the Netherlands-based organization Pax Christi, Iraq has been subject to the largest use of DU munitions of all areas of conflict. Little is known about the pattern of cancer in Iraq. The need for comprehensive knowledge about cancer forms in Iraq is mandatory to plan and establish control programs for the common cancer which may be amenable to prevention, early detection and cure. Breast was by far the most common site of cancer, Lungs, bronchi, colorectal, skin, bone, ovarian, prostate and leukemia are other common sites of cancer.

It is suggested that if this article to be implemented as a long term international project by WHO, regional, national and international related scientific institutions as well as funding agents to secure genetic markers assisted in early detection of cancer, Iraqi pathologists (and may be others from various countries) can participate in this project to carry out the field work of collection of blood and tissue samples from healthy and patients individuals according the above experimental design. Moreover, DNA will be extracted from each of the blood sample. The quality and quantity of DNA will be checked. It is also suggested that all molecular assessments should be carried out at any international center with good molecular facilities [14].

Expected Impact

The aim of this project is to make efforts to advance and develop a vital medical research and technology necessary in early diagnose, control and prevention of cancer. The project will investigate the prevalence and relation between resistant versus susceptible individuals living in high or in low risk environment risk areas to cancer incidence through molecular characterizations (genetic make-up) to identify molecular genetic markers to be used as early detection of individuals susceptible to cancer at early stage of life (Genetic Marker Assisted in Early Detection of Cancer). This will be intended to strengthen the guidance for health policy, implementation of cancer prevention strategies in the world.

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