

## Review (Narrative)

# Cancer: Intrinsic versus Extrinsic Factors on Its Genesis

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**SUMMARY**

Cancer as one of the leading causes of death has been a major concern for medical practitioners and researchers for many years, not just because of the diagnosis and treatment, but understanding the roles of intrinsic and extrinsic factors on its genesis. Some of the recent discoveries about cancer are the roles of xenobiotics and some internally produced biological molecules in forming tumors when brought in contact with living tissue. The discovery of the roles of intrinsic and extrinsic factors in mutagenesis has since been extensively examined with various experiments and data collected from neoplasm with the various carcinogens. The detailed studies of cancer genesis have proved that extrinsic factors, such as chemicals and radiation at different wavelengths, and some biological molecules play critical roles in mutagenesis. The main purpose of this review is to weigh the effects of the various factors (intrinsic and extrinsic) on cancer genesis. ■

**KEYWORDS** Cancer; Risk factor; Pathogenesis; Mortality

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**H**ow does cancer develop? What are the risk factors affecting cancer's genesis? It is unclear for its underlying mechanisms even great progress has made. Individual is not isolated from other surrounding environments, but intertwined with each other. Current investigations disclosed the contributing factors to the pathogenesis of cancer: intrinsic versus extrinsic aspects. The eventual balance between these two types of factors determines the direction of cancer's initiation and development (1). Whether you can stand well or want to keep away from this life-threatening disease, consider it and keep them in mind.

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## INTRINSIC FACTORS

Intrinsic carcinogenic agents may be defined as biological molecules produced within the host, which are capable of causing tumors in the living tissues. Unlike extrinsic agents that are foreign to the body, they are synthesized by the organism itself. In many cases, intrinsic and extrinsic agents may be somewhat arbitrary; however the definition must be flexible. In some cases, for example, methylcholanthrene which has been categorized as foreign compound may also be produced as a result of abnormal metabolism of the bile acid. Although it is likely that the larger amount of this molecule is not synthesized in the body, however, the fact that it can be produced within the body as a result of abnormal metabolism also classifies it endogenous (intrinsic). It is not in all cases that the organism synthesizes these intrinsic agents by itself, and this has been examined during the metabolism of some foreign molecules which are naturally not carcinogenic, however, converted to carcinogenic agents by metabolism (2).

In fact, there are many instances where some foreign compounds that are not carcinogenic are degraded in the body by the normal metabolic processes and converted into potent carcinogens. Studies have also proved that some viral molecules that induced tumors may be categorized as intrinsic because they might have acquired their carcinogenic property from earliest host. In the case that the viral particle was acquired from another host, it may then be categorized as intrinsic factor even though it was not the original part of the new host. However, carcinogenic viruses have a common feature, which differentiate them from other cancer-inducing agents. Unlike other carcinogenic agents, carcinogenic viruses have high level of specificity, which means that

they induce the same tumor even in different hosts. The simplest interpretation of this is that other carcinogenic agents are capable of causing different types of cancer in different tissues (3).

In the previous paragraphs we saw that intrinsic carcinogenic agents and extrinsic agents may be confusing to a lesser extent. These are just some demonstrations that show how complex intrinsic carcinogenic agents could be. There are a couple great classes of carcinogenic agents that are produced within the organism, and these are the agents that clearly define intrinsic factors (4). Some of these agents are sex hormones. One of the debate questions about the effects of sex hormones in cancer genesis is whether these hormones play roles in tumor formation in non-sex tissues. Obviously, the carcinogenic sex hormones are capable of inducing tumors in tissues such as the liver and subcutaneous fibroblasts. Based on studies, intrinsic carcinogenic agents are capable of inducing tumors on different tissues within the same host (5).

## Effects of Sex Hormones on Cancer Genesis

The sex hormones that regulate the normal development and functions of sex organs of animals are collectively known as estrogens in females, and androgens in males. These hormones are some of the complex chemicals in animals, and the structural and functional complexity is one of the reasons why they are able to induce some forms of tumors in non-sex tissues. All the sex hormones have one property in common, and that is the ability to stimulate the growth of immature sex tissues.

The high incidence of cancer of the sex tissues of women and the obvious changes in the breast due to ovarian function has led to the discovery of the effects of sex hormones in cancer genesis. The earliest experimental studies of the effects of sex hormones in cancer genesis involved ovariectomy in some cases of breast cancer in women. The experimental procedure to study the effects of the sex hormones in cancer genesis was first performed in 1916 by Lathrop and Loeb (4). The two authors discovered that cancer occurrence in the experimental animals decreased among the female groups that was prevented from breeding. However, the same experiment shows that cancer occurrence was prevalence in breeding animals of the same stock. The findings of the two authors were later confirmed that ovarian grafts induced mammary cancer in castrated male mice.



Majority of the earliest research on the effects of sex hormones in cancer genesis was centered on the sex tissues. However, there are several other findings that explain the carcinogenic effects of sex hormones in non-sex tissues. While experimental studies support the effects of sex hormones in non-sex tissues in mice kept under standard condition, such results may not hold true in humans because of the exposures to other hazardous substances in the environment and workplace. Furthermore, the comparison of carcinogenic effects of sex hormones in man and in woman might be subjected to objections (6). Such comparison to a greater extent would be valid if the results were obtained from animals that are kept under the same conditions.

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## EXTRINSIC FACTORS ON CANCER GENESIS

In the first few paragraphs of this review article we talked about intrinsic factors and the effects on cancer genesis. We focused on sex hormones as the major intrinsic factor and discussed the roles in tumor formation. In this section we will discuss about extrinsic factors, what they are, and how they contribute to the formation of cancer cells.

Extrinsic agents are substances that are foreign to the body. They are generally referred to as xenobiotics because the body recognizes them as foreign. These substances are not produced in the body, but when introduced into the system undergo metabolism. There are thousands of such chemical substances, and human beings are exposed to hundreds of them each day. Several experiments have been performed to study the effects of these foreign molecules in cancer formation. In the next

couple paragraphs we discuss the major extrinsic agents and their roles in cancer genesis.

### Categories of the Extrinsic Carcinogenic Agents

Extrinsic carcinogenic agents may be categorized based on the nature of the agent, the chemical composition, and the mechanisms of carcinogenicity (7). There are hundreds of chemical compounds that are capable of inducing cancer on living tissues; however, it may be too cumbersome to discuss each and every one of them. These chemical compounds may be hydrocarbons in nature, metals, halogens, or even non-metals.

The most common extrinsic carcinogenic agents are radiation, polycyclic hydrocarbons, and aliphatic hydrocarbons. Hydrocarbons, being the major contaminants in the environment, home, and workplace, have been studied extensively to fully understand their roles in cancer genesis.

### Carcinogenic Effects of Polycyclic Hydrocarbons

The large percentages of chemical agents that induce cancers are polycyclic in nature. In the last several years, studies have been devoted to unravel the mechanisms of action of these rigid chemicals in cancer genesis. Some of the earliest methods to determine the carcinogenic properties of polycyclic hydrocarbons are skin painting and subcutaneous injection. When stock mice were skin painted with active agents, epitheliomas was induced. However, when inbred A strain mice was injected with active agents, sarcomas was induced at the site of injection.



tion. In general, when the carcinogenic properties of hundreds of polycyclic hydrocarbons were reviewed, it was discovered that such tumors can be induced in mice under arbitrary experimental conditions. Research conducted by Andervont using 1,2,5,6-dibenzanthracene also induced sarcomas in all the inbred strains of mice tested (5).

Several experiments conducted to determine the carcinogenic properties of polycyclic hydrocarbons revealed that certain cancers can be induced in mice. Epitheliomas, sarcomas, hemangioendotheliomas, pulmonary tumors, and adenocarcinomas of the stomach are some of the cancers that can be induced by polycyclic hydrocarbons. It was also discovered that some of the induced cancers occur at the same time in the same animal. Research conducted also proved that leukemia can be induced in mice by polycyclic hydrocarbon (8).

### **The Metabolic Fate of Hydrocarbons in the Body**

Researchers have carried out extensive studies in order to determine the fate of injected hydrocarbons in different species of animals. These studies were conducted in two forms, namely (i) observation of the agents, the distribution, and persistence in the tissues, and (ii) the isolation of the agent or its product from the feces and urine of the treated animals. The distribution of the agents in tissues can be examined by their fluorescence properties in the UV rays. Using this method, researchers have been able to determine the fate of the major carcinogenic hydrocarbons in the tissues of experimented animals (9, 10).

### **Ultraviolet Light as an Extrinsic Carcinogenic Agent**

Not everyone talks about the effects of UV light in cancer genesis. However, those who are really exposed to radiations are more likely to develop tumor cells (11). Apart from the effects of radiation in the mutation, chemicals such as lead are also potent carcinogen.

### **Studies of the Dosage of Intrinsic and Extrinsic Carcinogenic Agents**

One of the core areas of interest in the study of extrinsic carcinogenic agents is the determination of the dosage that is sufficient to induce cancer in the experimented animals. In most cases, the dosage of the carcinogenic

agents is arbitrarily selected to at least enable the animal respond to the more active agents. In real life scenario, exposure to extrinsic carcinogenic agents may be very low compared to the dose administered to the experimented animals. However, there are evidences that some extrinsic carcinogenic agents may induce cancer even at the lowest concentration (12).

Taking the dosage of intrinsic factor, such as sex hormones into consideration, one may expect increase in cancer occurrence in the sex tissues of sexuality active animals. However, this may not hold true in most cases because certain factors, such as radiation, influence the possibility of cancer formation.

### **Roles of Proto-Oncogene in Cancer Formation**

Proto-oncogene is a sequence of the DNA and a positive growth regulator, which promotes normal cell differentiation and proliferation. Several proto-oncogenes play different roles in cell growth, and a slight change in the sequence of a proto-oncogene can lead to a serious alteration in the products. Oncogene is formed as a result of mutation in the parent DNA (proto-oncogene) and has the ability to induce uncontrolled cell growth, which can further lead cancerous tumor (13).

Oncogenes were first discovered in some RNA viruses that contain reverse transcriptase. In the 1970s, two American microbiologists verified the theory that healthy somatic cells contain viral oncogenes that can cause cancer when triggered.

Proto-oncogenes can be transformed in three different ways in humans, all of which lead to the loss of regulatory ability. There are evidences that extrinsic factors, such as radiation and chemical agents play major roles in the transformation of proto-oncogenes. One of the ways by which proto-oncogenes are transformed is by point mutation. The little alteration in the normal sequence of the genetic material is also responsible for converting some RAS proto-oncogenes to oncogenes.

The second process of transformation of proto-oncogenes is by translocation of fragments of the chromosome. This process is quite uncommon, however, if translocation happens, it can lead to uncontrolled cell growth, which eventually turns to cancer. There are evidences that chemical agents as well as radiation play roles in this process. The common forms of cancer that occur as a result of translocation are leukemia and lymphomas.

The third process of oncogenesis is amplification of proto-oncogenes. Like the two previous methods, amplification can result in overproduction of growth protein thereby leading to uncontrolled cell growth.

## FACTORS THAT INFLUENCE CARCINOGENICITY

It would be improper to give reports of the carcinogenic properties of certain substances without considering the factors that influence it. Researchers have studied the effects of concomitant materials on the carcinogenic properties of both intrinsic and extrinsic agents (14). The four major factors are discussed in the subsequent paragraphs.

### First, the Nature of the Solvent

Obviously, carcinogenic hydrocarbons are insoluble in water. However, if homogenous solutions must be applied to the experimental animals, fat solvents must be used. Researchers have applied various fat solvents in their studies of carcinogenic properties of hydrocarbons. Among the solvents commonly used are chloroform, benzene, acetone, lanolin, ether, sesame oil, tricapyrylin and lard. It has become evident that the solvent used played major role in the outcome of the experiment. Chloroform, for instance, has some reproducible properties; however, when applied to the skin it produces some unfavorable pathological effects. Besides the untoward effects of the solvents, it has been discovered that the carcinogenic effects of some hydrocarbons might be greater in certain solvents than in another. This effect was justified that methycholanthrene produce rapid epidermal carcinogenesis with acetone than with benzene (8).

### Second, Effect of Dietary Fat

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It has been discovered that unhealthy fat can increase the growth of tumor cells in experimental animals. Studies have shown that animals fed with different kinds of fat develop oily skin, which promotes the absorption of extrinsic carcinogens through the skin. However, if such animals are fed with a specific fat, and the skin condition is normal, the growth of tumor cells will be lesser in the animals compared to those that were fed with different kinds of fat.

### Third, Effect of Added Materials

There are certain non-carcinogenic substances which when administered together with carcinogenic hydrocarbons resulted in either suppression or augmentation of tumor cells. According to Berenblum, croton oil when applied together with 3,4-benzopyrene in acetone increases skin carcinogenesis. Sall and Shear also discovered that creosote oil augment skin tumors when administered with various hydrocarbons.

### Fourth, Inhibition of active agents by weak agents

One of the interesting findings about carcinogenesis is how weakly carcinogenic hydrocarbons reduced the carcinogenic effect of more active agent when applied together on the skin of mice. This effect was demonstrated by applying the mixtures of 1,2,5,6-dibenzanthrene and 1,2,5,6-dibenzacridine on mice skin. The weaker agent competitively reduced the effect of the active carcinogen by blocking the physiological sites within the experimented animal.

In sum, both intrinsic and extrinsic factors play serious roles in cancer genesis. It is very unlikely for someone to discuss in isolation the role of intrinsic agents without talking about extrinsic agents. Formation of tumor cells usually has more than one cause hence, both intrinsic and extrinsic factors play critical roles in cancer formation. ■

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