Congresso IATMO
Trieste 19-21 Ottobre 2007

Antioxidants in cancer prevention and therapy

relatore: dott. Antonio Maria Pasciuto


EUROPEAN
ACADEMY
FOR ENVIRONMENTAL
MEDICINE

The particular purpose is:

- developing,
- promoting,
- qualifying approaches in theoretical and clinical - practical environmental medicine.

EUROPEAN ACADEMY FOR ENVIRONMENTAL MEDICINE

Objective is the promotion of

- preventive environmental protection in health services,
- science and research,
- education and training of medical professionals

EUROPEAN ACADEMY FOR ENVIRONMENTAL MEDICINE

Cancer: definition

Cancer is a disease characterized by a population of cells that grow and divide without respect to normal limits, invade and destroy adjacent tissues, and may spread to distant anatomic sites through a process called *metastasis*.

Cancer may affect people at all ages, but risk for the more common varieties tends to increase with age.

Cancer causes about 13% of all deaths.

Cancer: causes

Nearly all cancers are caused by abnormalities in the genetic material of the transformed cells. These abnormalities may be due to the effects of carcinogens, such as tobacco smoke, radiation, chemicals, or infectious agents. Other cancer-promoting genetic abnormalities may be randomly acquired through errors in DNA replication, or are inherited, and thus present in all cells from birth. Complex interactions between carcinogens and the host genome may explain why only some develop cancer after exposure to a known carcinogen. New aspects of the genetics of cancer pathogenesis, such as DNA methylation, and microRNAs are increasingly being recognized as important.

Cancer and genetic

Genetic abnormalities found in cancer typically affect two general classes of genes. Cancer-promoting *oncogenes* are often activated in cancer cells, giving those cells new properties, such as hyperactive growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments. *Tumor suppressor genes* are often inactivated in cancer cells, resulting in the loss of normal functions in those cells, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system.

Importance of environment

We could define health as a balance between man and environment.

Therefore the whole existence fluctuates across a dynamic balance between man and environment that, if broken, carries inevitably from the well-being to the illness.

Illness derives from imbalances interacting in a unique and unrepeatable manner in a social and environmental contexts. Man’s existence is a delicate and precarious balance between micro and macro-environment, individuality and environmental contexts.

Epigenetics

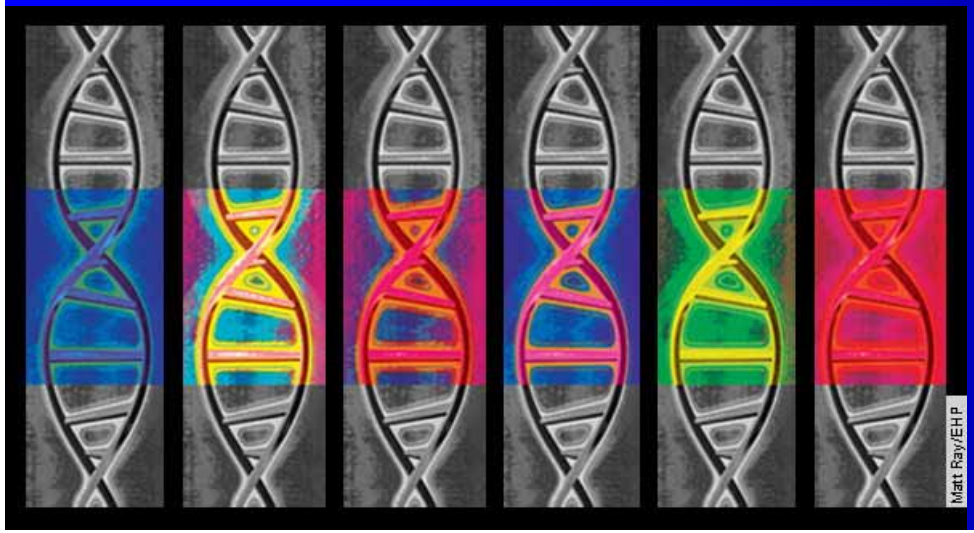
Epigenetics is a term in biology used today to refer to features such as chromatin and DNA modifications that are stable over rounds of cell division but do not involve changes in the underlying DNA sequence of the organism.These epigenetic changes play a role in the process of cellular differentiation, allowing cells to stably maintain different characteristics despite containing the same genomic material. Epigenetic features are inherited when cells divide despite a lack of change in the DNA sequence itself and, although most of these features are considered dynamic over the course of development in multicellular organisms, some epigenetic features show transgenerational inheritance and are inherited from one generation to the next.

Specific epigenetic processes of interest include paramutation, imprinting, gene silencing, X chromosome inactivation, maternal effects, the progress of carcinogenesis, many effects of teratogens and technical limitations affecting parthenogenesis and cloning.

Environment, genetics and cancer

A variety of compounds are considered as epigenetic carcinogens. They result in an increased incidence of tumors, but they do not show mutagen activity (toxic compounds or pathogens that cause tumors incident to increased regeneration should also be excluded). Examples include diethylstilbestrol, arsenite, hexachlorobenzene, and nickel compounds.

+



= CANCER

Homeostasis: definition

Homeostasis is that property of either an open system or a closed system, especially a living organism, which regulates its internal environment so as to maintain a stable, constant condition (autoregulation). Multiple dynamic equilibrium adjustments, controlled by interrelated regulation mechanisms, make homeostasis possible.

Homeostasis and cancer

Every organism that finds itself in a certain environment is exposed to innumerable physical influences (physical, chemical and biological). Therefore their structures and functions change themselves incessantly all life long producing a functional adaptation to the external influences. This balance is kept by complex systems of “self-control” and of “homeostasis”.

Inside our organism operate many autonomous mechanisms that allow the function of the system. The organism keeps staying healthy until self-regulation is possible.

Cancer and chemicals

The main factor that changed our life in the last 50 years certainly is the discover of antibiotics, and the consequent considerable reduction of mortality caused by micro-organisms.

Furthermore very important is the production of a very big amount of chemical substances, that we now find in the environment in thousands of tons.

Not everybody smokes

Man, environment and adaptation

It is well known that stressful rhythms of modern life and environmental pollution produce early ageing and also chronic illnesses. Few people realize that in the last hundred years we changed completely our environment contaminating air, ground and water with chemical substances, and electromagnetic sources. The “System Earth” does not succeed anymore to dispose of these substances and all living organisms come continually in contact with them, taking them in their structures. It is calculated that everyone come in contact with at least 500 synthetic substances every day. The human body did not succeed, in only 100 years, to evolve itself in order to live well in this new environment and produces illnesses.

Environment and cancer

The XENOESTROGENS (or environmental estrogens) are various substances present in the environment. They imitate endogenous estrogens or modify their activity. The most dangerous ones are the synthetic molecules produced after the second world war in form of pesticides, drugs, fuels and plastics. They are strongly suspected to promote breast cancer.

In the North Pole, 7% of all bears is born with features of hermaphroditism because of the high concentration of DDT in the polar ice coming from countries which used it.

Electrosmog and cancer

According to many scientists, the exposition to electromagnetic fields normally presents at home and at work may cause the onset of symptoms like weakness, loss of vitality, loss of sleep, immune deficiencies, stress, disorder of heart rhythm, depression and many more, included the higher incidence of brain tumors.

Electrosmog: the cry of Munch

Cancer (illness):“Mathematic” definition

$$\text{Illness} = \frac{\text{Pathogenetics factors}}{\text{Defense capacity}}$$

Free radicals

Atomic or molecular species with unpaired electrons on an otherwise open shell configuration. These unpaired electrons are usually highly reactive, so radicals are likely to take part in chemical reactions. Free radicals play an important role in a number of biological processes, some of which are necessary for life, such as the intracellular killing of bacteria by neutrophil granulocytes. Free radicals have also been implicated in certain cell signalling processes. The two most important oxygen-centered free radicals are superoxide and hydroxyl radical. They are derived from molecular oxygen under reducing conditions. However, because of their reactivity, these same free radicals can participate in unwanted side reactions resulting in cell damage

Free radicals and cancer

Many forms of cancer are thought to be the result of reactions between free radicals and DNA, resulting in mutations that can adversely affect the cell cycle and potentially lead to malignancy. Some of the symptoms of aging such as atherosclerosis are also attributed to free-radical induced oxidation of many of the chemicals making up the body.

Reactive oxygen species (ROS)

Reactive oxygen species (ROS) include oxygen ions, free radicals and peroxides both inorganic and organic. They are generally very small molecules and are highly reactive due to the presence of unpaired valence shell electrons. ROSs form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress ROS levels can increase dramatically, which can result in significant damage to cell structures. This cumulates into a situation known as oxidative stress. Cells are normally able to defend themselves against ROS damage through the use of enzymes such as superoxide dismutases and catalases. Small molecule antioxidants such as ascorbic acid (vitamin C), uric acid, and glutathione also play important roles as cellular antioxidants. Similarly, polyphenol antioxidants assist in preventing ROS damage by scavenging free radicals.

Defense capacity

1) Immune system

Immune system: collection of mechanisms within an organism that protects against infection by identifying and killing pathogens and tumor cells

2) Detoxification

Removal of toxic substances from the body. It is one of the major functions of the liver, lower gastrointestinal tract and kidneys thanks to enzymatic systems and antioxidants.

Defense mechanisms and cancer

It is necessary to know, that every time that a person enters in
contact with chemical substances, (by breathing, ingestion or
through the skin) even though in very little amount (not capable to produce obvious pathological reactions), it is submitted to a biological "work".
The body utilizes a series of enzymes and the immune system
to dispose of such substances, consuming energies and nutrients (salts, amino acids, vitamins ecc…).

Antioxidants

An **Antioxidant** is a molecule capable of slowing or preventing the oxidation of other molecules.
Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent.
Oxidation reactions can produce free radicals, which start chain reactions that damage cells.
Antioxidants terminate these chain reactions by removing radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. As a result, antioxidants are often reducing agents such as thiols or polyphenols.

Antioxidants: classification

Non-Enzymatic antioxidant

- Alpha tocopherol (vitamin E)
- Beta Carotene
- Ascorbic acid (vitamin C)

Antioxidant enzymes

- Superoxide dismutase (SOD)
- Glutathione peroxidase enzyme
- The catalase enzyme
- Other Antioxidants

Alpha tocopherol (vitamin E)

Is the major lipid soluble antioxidant found in cells. The name originated in the early 1920s when vegetable oil was discovered to restore fertility in rats. This unknown substance was designated vitamin E by Sure in 1924. The term *tocopherol* was first used by Evans. Because this compound permitted an animal to have offspring, he named it *tocopherol* from the Greek word *tokos*, meaning childbirth, and added the verb *phero*, meaning to bring forth. To indicate the alcohol nature of the molecule, *ol* was added to the ending.

Beta Carotene

Carotenoids are pigmented micronutrients present in fruits and vegetables.

Carotenoids are precursors of vitamin A and have antioxidant effects. While over 600 carotenoids have been found in the food supply, the most common forms are alpha-carotene, beta-carotene, lycopene, crocetin, canthaxanthin, and fucoxanthin. Beta-carotene is the most widely studied. It is composed of two molecules of vitamin A (retinol) joined together. Dietary beta-carotene is converted to retinol at the level of the intestinal mucosa.

Ascorbic acid (vitamin C)

Ascorbic acid (vitamin C) is a water-soluble, antioxidant present in citrus fruits, potatoes, tomatoes and green leafy vegetables.

Humans are unable to synthesize l-ascorbic acid from d-glucose due to absence of the enzyme L-glucolactone Oxidase (*Ensimnger et al.1995*). Hence, humans must therefore obtain ascorbic acid from dietary sources.

Natural antioxidants are present in fruit and vegetables

WHO reccomandation:

Eat **5 fruit** or **vegetables** a day

Superoxide dismutase (SOD)

SOD is an endogenously produced intracellular enzyme present in essentially every cell in the body.

Cellular SOD is actually represented by a group of metalloenzymes with various prosthetic groups. The prevalent enzyme is cupro-zinc (CuZn) SOD, which is a stable dimeric protein (32,000 D).

SOD appears in three forms:

1) Cu-Zn SOD in the cytoplasm with two subunits, and

2) Mn-SOD in the mitochondrion

(*Mayes, 1993; Warner, 1994*).

A third extracellular SOD recently has been described contains Copper (CuSOD).

Glutathione peroxidase enzyme

Glutathione peroxidase enzyme

The glutathione redox cycle is a central mechanism for reduction of intracellularhydroperoxides. (Fig.5).

Source and Nature:

It is a tetrameric protein 85,000-D. it has 4 atoms of selenium (Se) bound as seleno-cysteine moieties that confers the catalytic activity. One of the essential requirements is glutathione as a cosubstrate.

Glutathione peroxidase reduces H_2O_2 to H_2O by oxidizing glutathione (GSH)

These enzyme also require trace metal cofactors for maximal efficiency, including selenium for glutathione peroxidase; copper, zinc, or manganese for SOD; and iron for catalase (*Halliwell,1995*).

The catalase enzyme

The catalase enzyme:

This enzyme is a protein enzyme present in most aerobic cells in animal tissues.

Catalase is present in all body organs being especially concentrated in the liver & erythrocytes. The brain, heart, skeletal muscle contains only low amounts.

Catalase and glutathione peroxidase seek out hydrogen peroxide and convert it to water and diatomic oxygen. An increase in the production of SOD without a subsequent elevation of catalase or glutathione peroxidase leads to the accumulation of hydrogen peroxide, which gets converted into the hydroxyl radical. Indeed research in the pathogenesis of Down's syndrome has revealed that the existence of trisomy 21 leads to the overproduction of SOD, the gene for which is located also on chromosome 21. This finding is intriguing in that it reveals the possibility of a genetic link to the increased activity of free radicals.

Other Antioxidants

Other antioxidants

Retinoids:

Retinol, retinoic acid but not retinyl palmitate or retinyl acetate all have antioxidant properties (*Prasad, 1989*). However, retinoids in general are not classified as antioxidants as they mainly function as antiproliferatives.

Glutathione (GSH):

GSH is synthesized intracellularly from cysteine, glycine, and glutamate.

In addition to its role as a substrate in GSH redox cycle, GSH is also a scavenger of hydroxyl radicals and singlet oxygen. It is capable of either directly scavenging ROI or enzymatically via glutathione peroxidase, as described previously. In addition, GSH is crucial to the maintenance of enzymes and other cellular components in a reduced state. GSH also has an important role in xenobiotic metabolism and leukotriene synthesis. It is found in millimolar concentration in all human cells (*Halliwell, 1994*).

The majority of GSH is synthesized in the liver, and approximately 40% is secreted in the bile. The biologic role of GSH in bile is believed to be defence against dietary xenobiotics and lipid peroxidation in the lumen of the gut and protection of the intestinal epithelium from oxygen radical attack (*Aw, 1994*).

Fruit and vegetables can help us

Fruit and vegetable extract supplementation significantly enhanced multiple measures of immune function in elderly subjects, and improved IL-2 levels in smokers.

Fruit and vegetable extract supplementation offers a novel way to improve compliance with current nutritional reccomendations and may potentially lower risk disease.

Inserra et al. Integrative Medicine

Fruit and vegetable supplementation reduce DNA damage

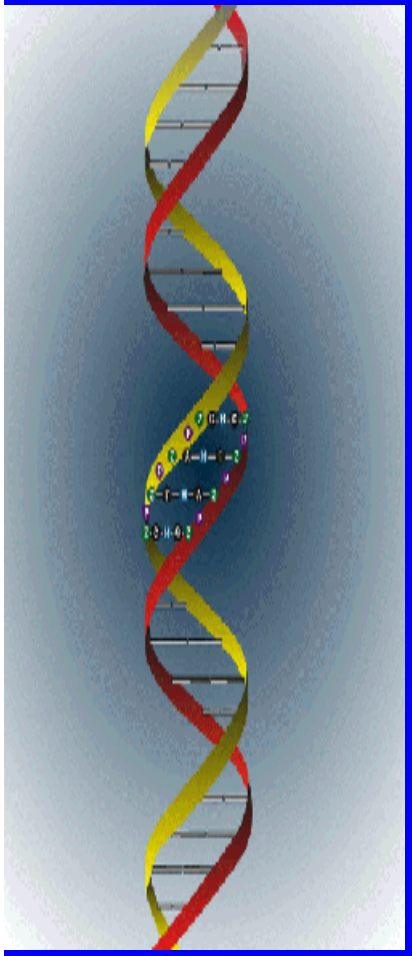
Fruit and vegetables consumption has been heralded for its ability to decrease the overall risk of developing cancer and other disease. Mounting evidence supports the beneficial nature of antioxidants, carotenoids, and other phytonutrients found in fruit and vegetables. One proposed mechanism of antioxidant protection is the shielding of cellular DNA from oxidative damage and therefore mutations. A daily course of fruit and vegetable extract supplementation may reduce the level of DNA damage in the peripheral lymphocytes of seniors.

Smith, Inserra et al. Nutrition Research

Antioxidants and cancer

Antioxidants provide a source of protection against cancer-causing free radicals. As we age, free radical levels in the body rise so that a continuous intake of antioxidants is important to assure our protection. Taken together, antioxidants are helpful but are not a magic bullet against cancer. Along with exercise, a positive attitude and an overall healthful, whole food diet, antioxidants are invaluable tools to defend against cancer-causing cell damage and prolong a healthy life.

Antioxidants and cancer



+

+

We can help our patients in many ways

Environment care and use of antioxidants

Thank you for your attention