Predictability in Science: Accuracy and Limitations
Pontifical Academy of Sciences, Acta 19, Vatican City 2008
www.pas.va/content/dam/accademia/pdf/acta19/acta19-veronesi.pdf

THE NEW POSSIBILITIES OF PREDICTION AND PREVENTION OF CANCER

UMBERTO VERONESI

Cancer is an environmental disease. Carcinogenic agents are extensively spread throughout the environment, inclusive of all the elements in which we live. Therefore all agents, of any type, which come in contact with the human body, are defined environmental agents. They include carcinogens in the air, in the water and in food.

In addition there are all those agents which form part of our daily behaviour, cigarette smoke, cosmetics of any type, pharmaceutical drugs, children's toys coated with substances which may contain chemical carcinogens, pesticides, asbestos, benzene in gasoline and in addition radiation of different kinds, such as ionizing radiation from the earth, from cosmic rays, and from radon gas present in our homes. There are viruses in the environment, such as HPV for cancer of the uterus, bacteria, helicobacter pylorus for gastric cancer and parasites such as schistosoma haematobium for cancer of the bladder.

All those agents, although innumerable and varied, have a common mechanism to induce cancer. They damage the DNA of a somatic cell creating a lesion, which we call a 'mutation', of one or more genes. This lies at the root of the carcinogenic process, as the specific gene mutation gives the cell the ability to proliferate without the usual limitations imposed by the harmony of all our organs and tissues. In other words the mutated cell is a cell which escapes from the normal 'program' of the organism and becomes a deviated cell.

Therefore this minimal error in the complex 'software' which regulates all our functions may lead to serious and tragic consequences.

Fortunately, our body has a good 'repair system', rich in enzymes which are able to repair the damage of the DNA and eliminate the dangerous mutation.

If the DNA repair enzymes work properly there will be no cancer; if the enzymes are not active enough the mutated cell will progressively develop into a true carcinoma (Fig. 1). The carcinogenic process generally takes a certain number of years, from 3 to 20.

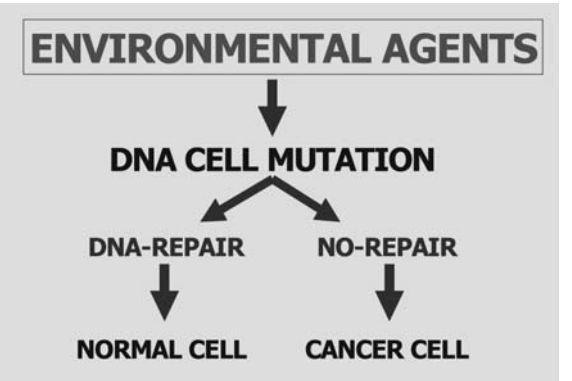


Figure 1.

The natural defence mechanism via DNA repair enzymes is genetically regulated and this accounts for the personal or familial predisposition to develop cancer lesions.

Constitutional, genetic	3%
Constitutional acquired (reproductive endocrine factors)	12%
Environmental (chemical, physical viral)	85%

Figure 2. Factors which lie at the origin of cancer.

The causes of cancer are therefore mainly environmental. True hereditary cancers are uncommon, while a number of tumours, in particular breast carcinoma, are linked to reproductive endocrine conditions.

How did we discover that most cancers have an environmental origin? The answer came from epidemiological research in three different areas. The first was the different incidence of the various tumours in different countries (geographic pathology). Figure 3 (see page 274) shows the inci-

dence of the most common types of tumour in the various parts of the world. The fact that there is a great difference among various countries is a reflection of the different lifestyles of the world populations. Therefore lung cancer is common among populations where cigarette smoking is common, cancer of the uterus in countries where HPV infection is endemic, cancer of the liver in areas where hepatitis B virus is diffuse and so on (Figs. 4-12, see pages 274-275).

The second area of epidemiological research refers to migrant population studies. In fact, if cancer really is genetically determined, when a population living in a country where there is a high incidence of a certain cancer decides to emigrate to a country where the incidence of that particular cancer is low, then the migrant's risk should remain at the same level. The opposite will hold if the cancer is due to environmental factors. All the studies are in favour of the latter hypothesis.

In fact, when Japanese people leave Japan, where gastric cancer incidence is the highest in the world, to migrate to the United States, where gastric cancer incidence is very low, in a couple of generations the incidence of gastric cancer diminishes to reach the levels of the American populations. The third type of study is time-trend analysis of cancer over a period of decades. For example in 1950s Italy women were affected by cancer of the uterus and men by cancer of the stomach. At the end of the century both uterus and gastric cancer were no longer the leading types of cancer while women were affected mainly by cancer of the breast and men by cancer of the lung. The latter is undoubtedly largely due to the habit of smoking and the former to the fact that women have very few pregnancies, or little or no breast feeding and above all have their first child much later in life than they would have had 50 years ago.

How then, can mortality rates be reduced?

Mortality may be reduced by (a) reduction of carcinogens in the environment, (b) use of drugs or active principles which will block the carcinogenic process and (c) an early detection of cancer and adequate, timely treatment.

1. Reduction of Carcinogens in the Environment

In 1985 two renowned British epidemiologists Doll and Peto, conducted a review of a large number of papers addressing cancer incidence, and prepared a list of categories of carcinogenic agents from which it could

be concluded that it is in the food that we should look if we want to find the key carcinogens. Tobacco smoking is the second cause, according to Doll and Peto, followed by infectious agents and reproductive factors. Air pollution only accounts for a mere 2% (Table 1). Food by itself may stimulate uncontrolled cell proliferation but, above all, it is a carrier of many carcinogenic agents present in the environment. Meat for example comes from animals which graze in the open air and their very act of eating the grass introduces all the carcinogenic agents polluting the ground into their bodies.

TABLE 1. CANCER CAUSES

Kind of exposition	Risk distribution
Food	35
Tobacco	30
Viral	10
Reproductive Factors	7
Occupational Activities	4
Geographic Factors	3
Air Pollution	2
Medical Drugs	1
Unknown Factors	?

From Doll and Peto 1985.

Ingesting a lot of meat, in fact, increases the risk of intestinal cancer. Cancers are therefore closely related to nutrition and diet, with an increased risk arising from the eating highly caloric food rich in animal fat and a reduced risk arising from the consumption of fruit and vegetables. Figure 13 (page 276) shows the strict correlation between meat consumption and colorectal cancer incidence in the five continents and Figure 14 (page 276) shows how the increased consumption of fruit and vegetables leads to a notable reduction of cancer risk in various organs.

Furthermore, food may be contaminated by residual pesticides and particularly one known as aflatoxin which is one of nature's most active carcinogenic agents. Aflatoxins are a group of secondary metabolites which are cancer causing by-products of a mould that grows on grains and nuts, particularly peanuts.

Although aflatoxin is most commonly produced when the potentially affected foods are incorrectly stored, recent studies have documented that it arises in fields, particularly as a consequence of severe climatic changes or if the plants undergo attacks by insects. Most industrialized nations impose strict regulations on aflatoxin levels in food for human consumption. However, many of these products are employed in animal feed, and if an animal consumes infected food, the aflatoxin is transmitted to humans via contaminated milk and meat products. Aflatoxin is a carcinogen for certain animals, particularly cattle.

Among humans, it is associated with liver cancer, particularly in Third World nations where malnutrition and other health problems are also prevalent.

Animals grazing on bracken may exhibit various signs of toxicity, including tumours in the upper gastrointestinal tract and bladder, which are attributable to the carcinogen ptaquiloside. The corresponding glucoside may be present in bracken at a concentration of 13,000 ppm. Metabolism of this compound gives rise to alkylation adducts in DNA.

Milk from bracken fern-fed cows induces cancer in experimental animals. Bracken may pose a carcinogenic hazard for humans in populations identified as exposed in Japan, Costa Rica and the United Kingdom.

There are some organochlorines, such as DDT and other pesticides, which are resistant to degradation, and are highly lipid-soluble. They thus persist in the environment and are bioconcentrated in the human food chain. Related industrial chemicals such as polychlorinated biphenyls behave in the same manner. DDT and a number of other organochlorine pesticides cause liver cancer in rats. DDT has been especially linked with an increased risk of pancreatic cancer, breast cancer, lymphoma and leukaemia in humans.

Some organochlorines exhibit sex steroid activity in relevant assay systems, and these pesticides are considered to potentially subvert endocrine-regulated homeostasis.

When meat and fish are cooked at high temperatures, certain heterocyclic amines are formed as a result of the pyrolysis of two amino acids, namely creatine and creatinine. Heterocyclic amines are carcinogenic in various organs of mice, rats and non-human primates, although their carcinogenic potential in humans is yet to be established.

Various genetic polymorphisms mean that heterocyclic amine metabolism can vary from individual to individual.

Tobacco

The smoking of tobacco is known to be the main cause of human cancer-related deaths worldwide. Smoking most commonly causes lung cancer. For a smoker, lung cancer risk is related to tobacco smoking parameters in accordance with the basic principles of chemical carcinogenesis: carcinogen dose, the duration of administration and exposure intensity are known to be risk determinants. Here, women are at least as susceptible as men. It is consistently clear that there is an increased risk of lung cancer (relative to a non-smoker) at the lowest level of daily consumption, and this bears at least a linear relation to increasing consumption. The risk is also proportional to the duration of smoking. Hence, the annual death rate from lung cancer among 55-64 year-olds who smoke 21-39 cigarettes per day is about three times that of those who commenced smoking at the age of 15 than it is for those who started smoking at 25. Smoking of black tobacco cigarettes represents a greater risk for most tobacco-related cancers than does smoking of blond cigarettes. Similarly, filtered and low-tar cigarettes entail a lower risk for most tobacco-related cancers than do unfiltered and high-tar cigarettes. Looking at communities worldwide, incidence of lung cancer varies dramatically. High rates are observed in parts of North America, while developing countries have the lowest rates. In the USA, Europe and Japan, 83-92% of lung cancers in men and 57-80% of lung cancers in women are tobacco – related. In addition to lung cancer, smoking causes cancers of the larynx, oral cavity, pharynx, oesophagus, pancreas, kidney and bladder. Dose-response relationships between number of cigarettes smoked and risks for developing these cancers have been consistently found. A pattern of decreased risk of lung and other smoking dependent cancers is commonly observed to follows smoking cessation ('quitting') relative to those who continue to smoking.

The relative risk of cancer at most sites is markedly lower than that of current smokers after five years' cessation, although risks for bladder cancer and adenocarcinoma of the kidney appear to persist longer before falling off. Despite the clearly established benefits of cessation, the risk for ex-smokers does not decrease to that enjoyed by so-called 'never smokers'. Exposure to environmental tobacco smoke causes lung cancer and possibly laryngeal cancer. Although the burden of disease is much less than in active smokers; the relative risk has been estimated at about 1.15-1.2 (Fig. 15).

Substances	Tobacco smoke (per cigarette)
Volatile aldehydes	
Formaldehyde	20-105 µg
Acetaldehyde	18-1,400 µg
Crotonaldehyde	10-20 µg
***N*-Nitrosamines**	
N-Nitrosodimethylamine	0.1-180 ng
N-Nitrosodiethylamine	0-36 ng
N-Nitropyrolidine	1.5-110 ng
Tobacco-specific nitrosamines	
N'-Nitrosonornicotine (NNN)	3-3,700 ng
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	0-770 ng
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	+
N'-Nitrosoanabasine (NAB)	14-46 ng
Metals	
Nickel	0-600 ng
Cadmium	41-62 ng
Polonium 210	1-10 mBq
Uranium 235 and 238	-
Arsenic	40-120 ng
Polycyclic aromatic hydrocarbons	
Benzo[a]pyrene	20-40 ng
Benzo[a]anthracene	20-70 ng
Benzo[b]fluoranthene	4-22 ng
Chrysene	40-60 ng
Dibenzo[a,l]pyrene	1.7-3.2 ng
Dibenzo[a,h]anthracene	+

Figure 15.

Infectious Agents

For more than 100 years it has been known that infectious agents can cause cancer. In 1911 Peyton Rous demonstrated that sarcomas in chickens were caused by an infectious agent, later identified to be a virus. Today, there is a raft of evidence, experimental and epidemiological, to indicate that a variety of infectious agents constitutes one of the main causes of cancer worldwide. Viruses are the main agents, at least eight different viruses being associated with particular tumour types, with

varying degrees of certainty. Some 2,000 million people worldwide have serological evidence of current or past hepatitis B virus (HBV) infections and about 350 million of these people are chronic carriers of the virus. It has been estimated that 60% of primary liver cancer cases worldwide and 67% of cases in developing countries are attributable to chronic persistent infection with HBV.

Approximately 25% of liver cancer cases worldwide can be attributed to HCV.

HPV DNA is found in virtually all invasive cervical cancers, indicating that HPV is an essential cause.

Epstein-Barr virus (EBV) infection is ubiquitous. In developing countries, infection is acquired in childhood, while in developed countries infection is delayed until adolescence.

Individuals with high titres of antibodies to various early and late EB antigens are at a higher risk of developing Burkitt's lymphoma and Hodgkin's disease.

Human T-cell lymphotropic virus (HTLV-1) infection occurs in clusters in Japan, Africa, the Caribbean, Colombia and Melanesia. There may be as many as 20 million people worldwide infected with this virus. A strong geographical correlation suggests that HTLV-1 is the main etiological factor in adult Tcell leukaemia/lymphoma. Human herpesvirus 8

Infectious agent	Cancer site/cancer	Number of cancer cases
H. pylori	Stomach	490,000
HPV	Cervix and other sites	550,000
HBV, HCV	Liver	390,000
EBV	Lymphomas and nasopharyngeal carcinoma	99,000
HHV-8	Kaposi sarcoma	54,000
Schistosoma haematobium	Bladder	9,000
HTLV-1	Leukaemia	2,700
	Total infection-related cancers	1,600,000

Figure 16.

(HHV-8) infection appears to be common in Africa and in some Mediterranean countries but rare elsewhere. HHV-9 DNA has been detected in over 90% of Kaposi sarcomas and rarely in control patients. Helicobacter pylori infection is one of the world's most common bacterial infections. H. pylori undoubtedly plays a role in gastric cancer, but there are other contributory cofactors, such as diet (Fig. 16).

Environmental Pollution

Air, water and soil pollution is estimated to account for 1-4% of all cancers. A small proportion of lung cancers (>5%) can be ascribed to industrial effluent, engine exhaust output and other outdoor toxins. Carcinogenic indoor air pollutants include tobacco smoke, and cooking fumes in particular regions, including parts of Asia.

The carcinogenic pollutants for which most information is available include toxic asbestos in urban air, indoor air pollutants, chlorination by products and other contaminants of drinking water. The carcinogenic hazard of asbestos dust has been recognized since the 1950s (Fig. 17).

Study	Population, follow-up	Number of subjects	Exposure range	Contrast / Controls	Relative risk of lung cancer (95% CI)
Pope et al. 1995	151 Areas, USA, 1982-89	552,138	FP 9-33 μg/m³ Sulfur dioxide: 3.6-23 μg/m³	Highest vs. lowest areas	FP: 1.03 (0.80 - 1.33) Sulfur dioxide: 1.36 (1.11 - 1.66)

Figure 17.

Medicinal Drugs

Certain cancer treatment drugs may, on rare occasions, lead to second primary tumours.

Modern medicine has hundreds of drugs at its disposal, many of which are an essential part of the doctor's armamentarium in effectively treating a vast panoply of diseases. A small fraction of such drugs have been found, however, to have the side-effect of carcinogenicity. This occurs mostly in certain drugs that have to be administered at high doses or for prolonged periods of time (Fig. 18).

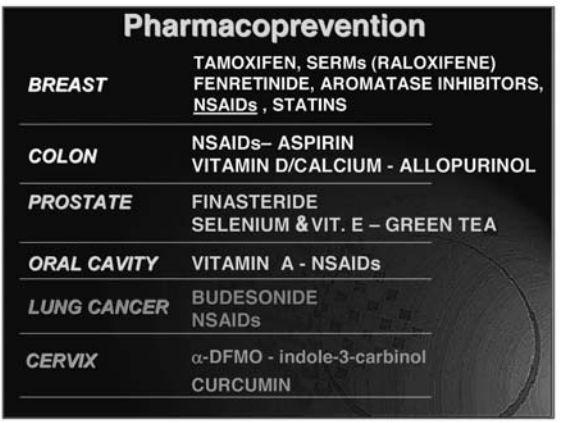
Drug or drug combination	Cancer Type
IARC Group 1	
Analgesic mixtures containing phenacetin	Kidney, bladder
Azathioprine	Lymphoma, skin, liver and bile ducts, soft connective tissues
N,N-bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	Bladder
1,4-Butanediol dimethane-sulfonate (Myleran; Busulfan)	Leukaemia
Chlorambucil	Leukaemia
Methyl-CCNU	Leukaemia
Ciclosporin	Lymphoma, Kaposi sarcoma
Cyclophosphamide	Leukaemia, bladder
Diethylsilbestrol	Cervix, vagina
Etoposide in combination with cisplatin and bleomycin	Leukaemia
Melphalan	Leukaemia
MOPP and other combined (anticancer) chemotherapy including alkylating agents	Leukaemia

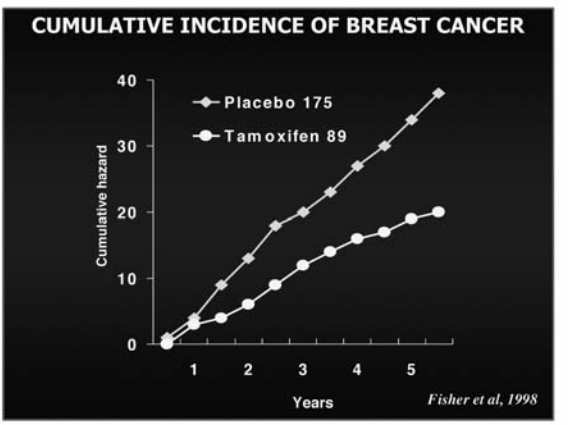
Figure 18.

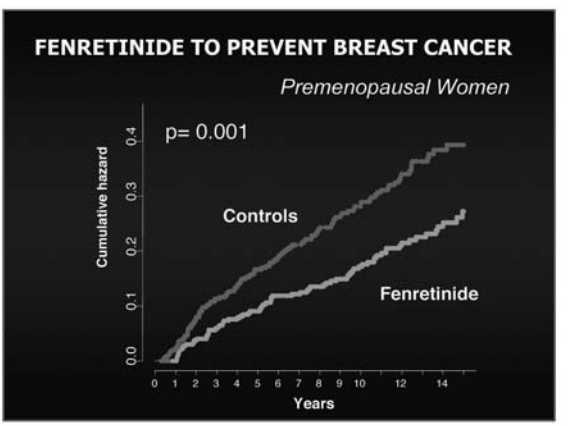
2. Pharmacoprevention

The pharmacological prevention of cancer represents a comparatively novel field in clinical oncology, but it offers a very promising approach to reducing the burden of cancer and its incidence. Other medical disciplines, such as cardiology have taken this route, whereby it is common practice to treat subjects at higher risk for cardiovascular disease long before clinical evidence. This has made a definite contribution to a lower mortality. A similar strategy can be adopted for cancer prevention in 'at higher risk' subjects.

The peculiarity of carcinogenesis is that it is a multistep, multipath and multifocal process, involving a series of genetic and epigenetic alterations which develop from genomic instability all the way to the final development of cancer. This is the key notion lying behind the rationale for intervention in the initial steps of the process, by employing natural or synthetic agents potentially able to delay, arrest or even reverse the pathogenesis of cancer.


Pharmacoprevention
BREAST
TAMOXIFEN, SERMs (RALOXIFENE)
FENRETINIDE, AROMATASE INHIBITORS,
NSAIDs , STATINS
COLON
NSAIDs– ASPIRIN
VITAMIN D/CALCIUM - ALLOPURINOL
PROSTATE
FINASTERIDE
SELENIUM & VIT. E – GREEN TEA
ORAL CAVITY
VITAMIN A - NSAIDs
LUNG CANCER
BUDESONIDE
NSAIDs
CERVIX
α-DFMO - indole-3-carbinol
CURCUMIN


CUMULATIVE INCIDENCE OF BREAST CANCER
Placebo 175
Tamoxifen 89
Cumulative hazard
40
30
20
10
0
1
2
3
4
5
Years
Fisher et al, 1998


FENRETINIDE TO PREVENT BREAST CANCER
Premenopausal Women
p= 0.001
Controls
Fenretinide
Cumulative hazard
0.0
0.1
0.2
0.3
0.4
0 1 2 3 4 5 6 7 8 9 10 12 14
Years

Since the process is mostly very long (10-20 years, sometimes more), there is potentially a great deal of time to assess the true risk and intervene with nutrients and/or pharmacological agents which will interrupt the chain of molecular events long before the onset of clinical symptoms. This may prove of particular use where solid tumours are concerned, which are often characterised by multifocality and metachronous growth of lesions resulting from the plausible concept of field carcinogenesis and intraepithelial clonal spread.

Recently, a number of compounds have shown to be clinically effective at various organ levels, covering all the three settings in which prevention may be typically divided into, namely: primary, where the goal is to prevent the onset of the disease, selecting healthy cohorts at high risk because of their environmental or lifestyle or familial/genetic factors; secondary, aimed at treating a population possessing a premalignant condition or an in situ neoplasia thereby blocking its evolution to cancer; and tertiary, which is aimed at protecting against second primary tumours in subjects previously cured for a cancer.

3. Early Detection

It is an oft-quoted truth in cancer care that if the tumour is discovered at an early stage – the chances of cure are much higher compared with cases where diagnosis is late. A case in point is the near-epidemic increase in breast cancer incidence being due to the introduction of population-based mammography screening. The analysis of large randomized trials has shown that in women aged 50 to 69 years, mammography screening can reduce mortality from breast cancer by 25-30%. For women in the 40-49 year age group the screening efficacy is significantly less. Considering other cancers, early detection programs are thriving for cancers of the uterine cervix, intestine, prostate and lung (Fig. 19).

With a more widespread use of screening programs and educational initiatives, future cancer mortality for the more common tumours is expected to see a notable reduction.

One of the greatest hopes lies in the technological development of diagnostic tools. So-called diagnostic imaging equipment is becoming more and more sophisticated and will form the basis for new progress in early cancer detection (Figs. 20-24, see page 277).

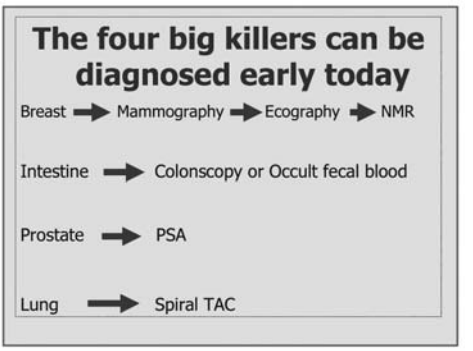


Figure 19.

4. Molecular Oncology

The discovery of the sequences of human DNA has led to the '*decodification*' of the role of the 30.000 genes present in every human cell and given rise to biomolecular oncology, the main medical revolution of recent decades. The fields of interest are many and are of great value (Fig. 25) and will in a decade lead to a number of discoveries which may herald the victory of our fight against cancer.

In conclusion, although the individual assessment of the risk of developing cancer may be an arduous task, prevention of cancer is possible, provided that the population is correctly informed and that the public health authorities are aware of, and sensitive to, the issues involved (Figs. 26-27).

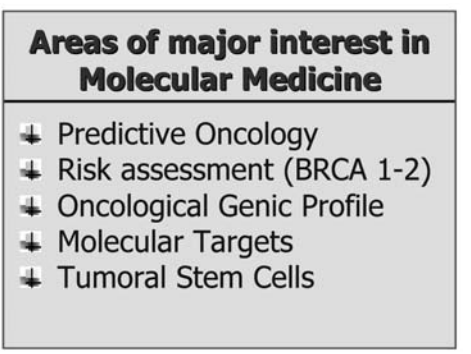


Figure 25.

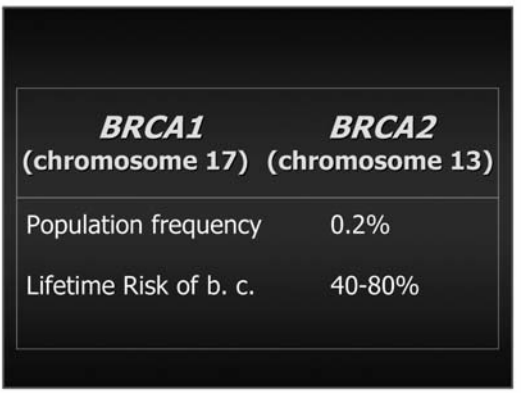


Figure 26. The mutations in chromosome 17 (BRCA1) AND 13 (BRCA2) create a condition of notably increased risk for breast cancer and, to a more limited extent, for ovarian carcinoma.

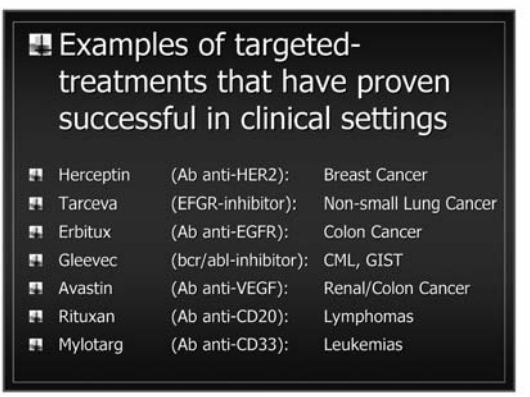


Figure 27. Molecular oncology studies have led to the discovery of many molecules and monoclonal antibodies which direct themselves towards a specific molecular target due to a specific DNA mutation.

REFERENCES

1. *World Cancer Report*. WHO – OMS – IARC. Edited by Stewart BW and Kleihues P. IARC Press, Lyon 2003.
2. Doll R, Peto J. *Asbestos: effects on health of exposure to asbestos. A report to the Health and Safety Commission*, London: HMSO, 1985.
3. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998; 90(18):1371-88.
4. Veronesi U, Mariani L, Decensi A, Formelli F, Camerini T, Miceli R, Di Mauro MG, Costa A, Marubini E, Sporn MB, De Palo G. Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer. *Ann Oncol*. 2006 Jul;17(7):1065-71.
5. Veronesi U, Bonanni B. Chemoprevention: from research to clinical oncology. *Eur J Cancer*. 2005;41(13):1833-41.

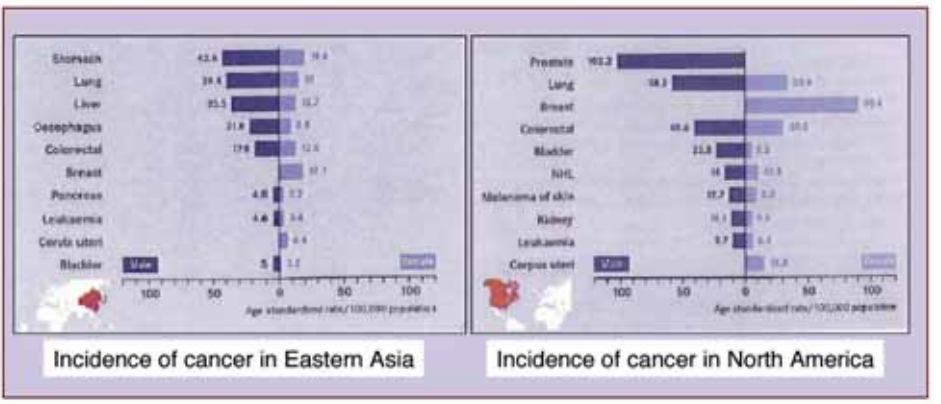


Figure 3.

Figure 4.

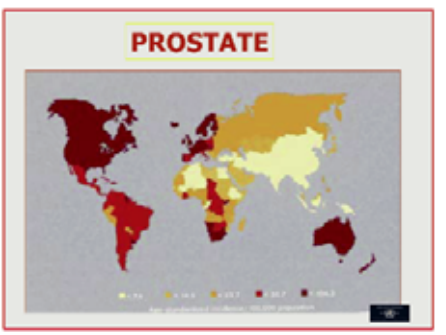


Figure 5.

Figure 6.

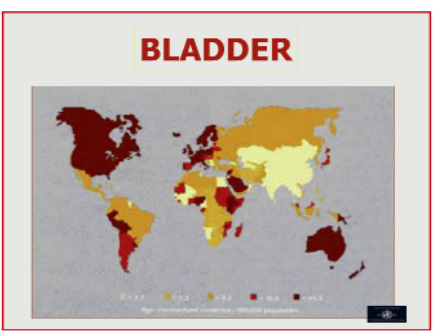


Figure 7.

Figure 8.

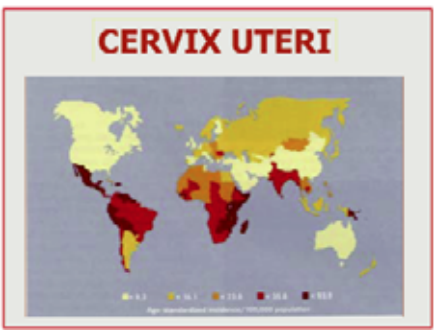


Figure 9.

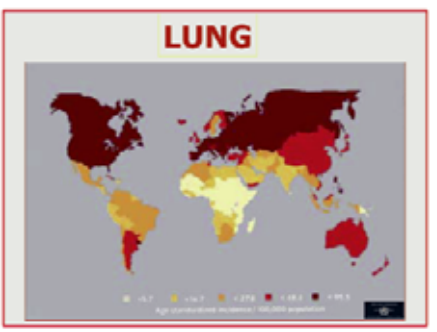


Figure 10.

Figure 11.

Figure 12.

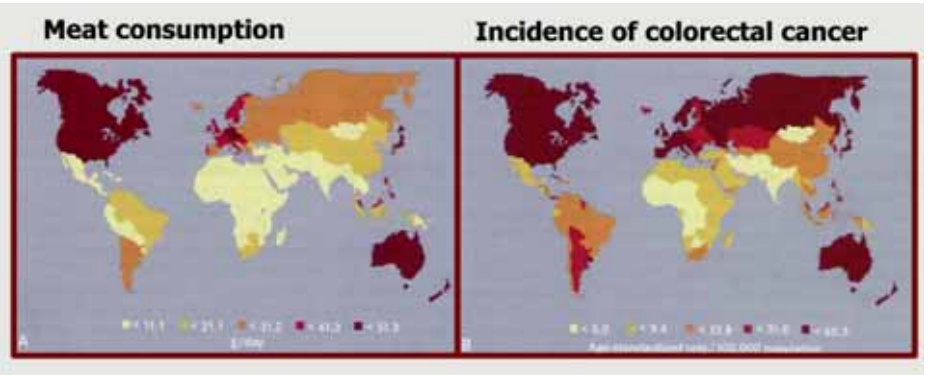


Figure 13.

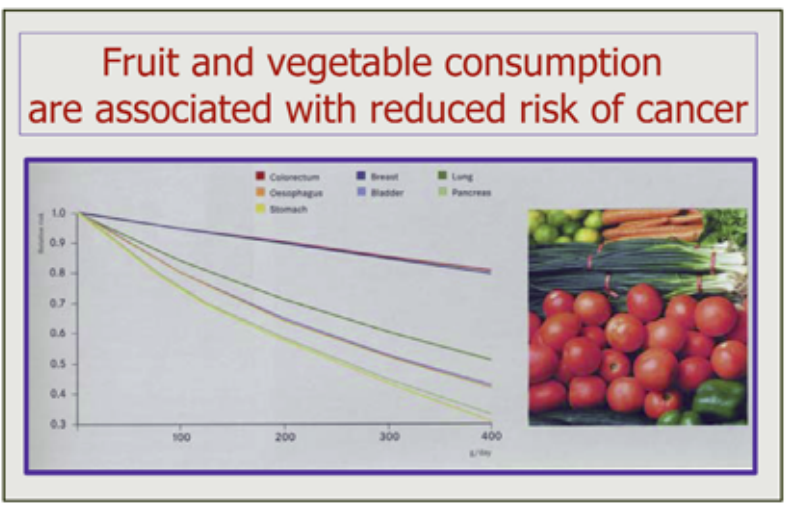


Figure 14.

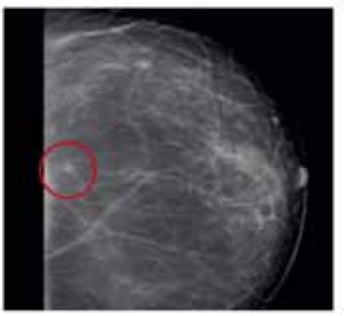


Figure 20.

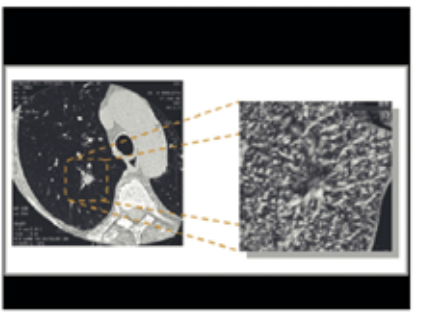


Figure 21.

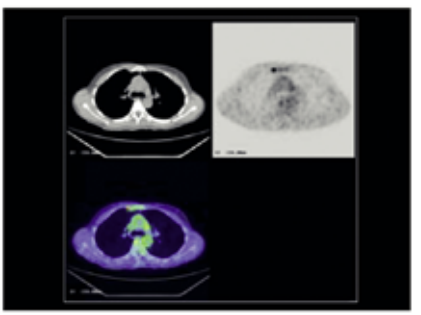


Figure 22.

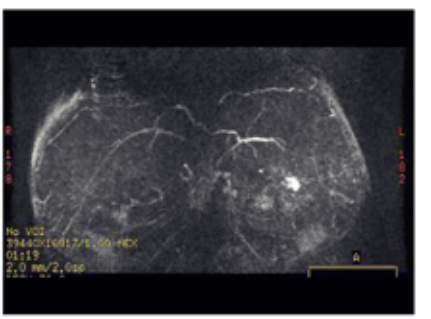


Figure 23.

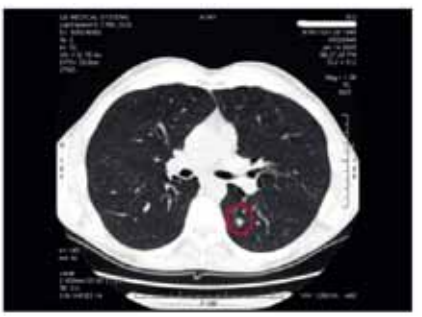


Figure 24.