

Cancer is rust...

When metal is exposed to water and oxygen, it slowly starts to change. The iron is corroded and transformed from metallic iron to iron oxide. The rust replaces the "healthy" metallic iron and eats away at the metal, weakening its structure. Paint, oil and protective coatings are all effective ways to guard metal against corrosion, but rusting occurs if the paint is damaged, if the oil dissipates or if the finish is scratched - exposing the metal to oxidants. Corrosives can also encourage rust formation, salt being a good example.

Just like rusting metal, which needs to be exposed to water and oxygen, cancer has several developmental stages:

- **Initiation** - the exposure of a cell to a carcinogen
- **Promotion** - the uncontrolled cellular proliferation of cancer cells
- **Progression** - the continuing growth and spread of cancer throughout the body

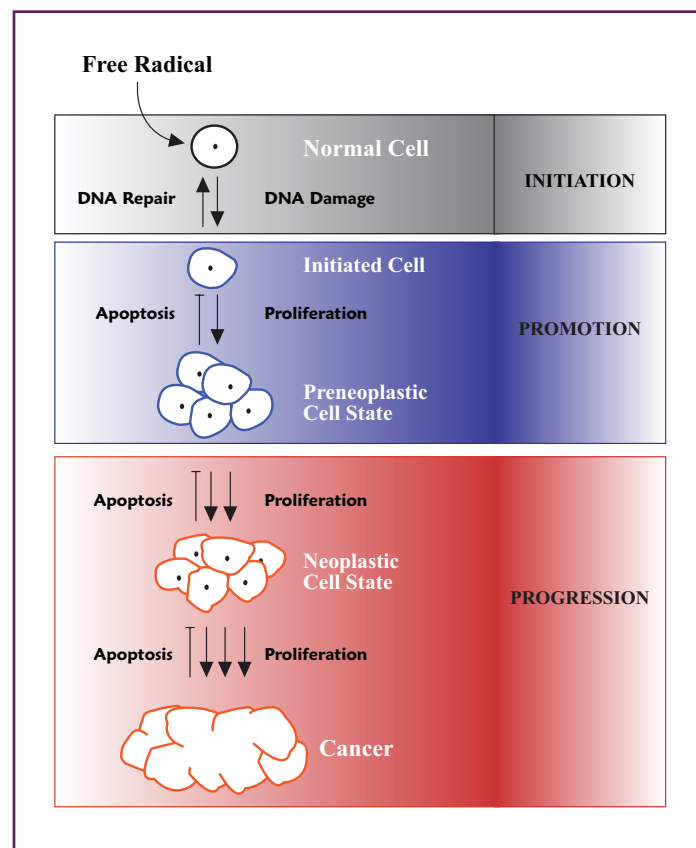




Figure 1: Initiation, promotion and progression of cancer.

Rust is "metallic" cancer. Like rust, cancer is a space-occupying lesion - cancerous cells occupy the space that was previously inhabited by healthy cells. Cancer slowly eats away at healthy tissues, monopolizes resources and eventually weakens organ function.

As corrosive agents promote the rusting of metal, specific chemicals cause damage to DNA and increase the risk of developing cancer - such chemicals are known as carcinogens.

Cancer arises from DNA damage to a specific cell. In a cancer cell, several consecutive cellular mutations have inactivated the tumor suppressor genes responsible for inducing the cellular death of old or abnormal cells - a process known as apoptosis. Abnormal cells typically die to preserve the rest of the organism. However, once the tumor suppressor genes have been inactivated, the cell becomes immortal and DNA damage accumulates. This inevitably leads to genetic instability and DNA mutations, which in time results in the creation of a cell that replicates uncontrollably, leading to cancer. The cancerous cells invade normal tissues either through direct contact or spread to distant sites via metastasis. The growing tumor draws resources away from important physiologic functions, replaces normal tissues and restricts the function of vital tissues. Cancer eventually becomes a life-threatening situation.¹

Estimated New Cases*

		Males		Females			
Prostate	232,090	33%			Breast	211,240	32%
Lung and Bronchus	93,010	13%			Lung and Bronchus	79,560	12%
Colon and Rectum	71,820	10%			Colon and Rectum	73,470	11%
Urinary Bladder	47,010	7%			Uterine Corpus	40,880	6%
Melanoma of the Skin	33,580	5%			Non-Hodgkin Lymphoma	27,320	4%
Non-Hodgkin Lymphoma	29,070	4%			Melanoma of the Skin	26,000	4%
Kidney and Renal Pelvis	22,490	3%			Ovary	22,220	3%
Leukemia	19,640	3%			Thyroid	19,190	3%
Oral Cavity and Pharynx	19,100	3%			Urinary Bladder	16,200	2%
Pancreas	16,100	2%			Pancreas	16,080	2%
All Sites	710,040	100%	All Sites	662,870	100%		

Estimated Deaths



		Males		Females			
Lung and Bronchus	90,490	31%			Lung and Bronchus	73,020	27%
Prostate	30,350	10%			Breast	40,410	15%
Colon and Rectum	28,540	10%			Colon and Rectum	25,750	10%
Pancreas	15,820	5%			Ovary	16,210	6%
Leukemia	12,540	4%			Pancreas	15,980	6%
Esophagus	10,530	4%			Leukemia	10,030	4%
Liver and Intrahepatic Bile Duct	10,330	3%			Non-Hodgkin Lymphoma	9,050	3%
Non-Hodgkin Lymphoma	10,150	3%			Uterine Corpus	7,310	3%
Urinary Bladder	8,970	3%			Multiple Myeloma	5,640	2%
Kidney and Renal Pelvis	8,020	3%			Brain and Other Nervous System	5,480	2%
All Sites	295,280	100%	All Sites	275,000	100%		

Figure 2: Leading Cancers in the US.

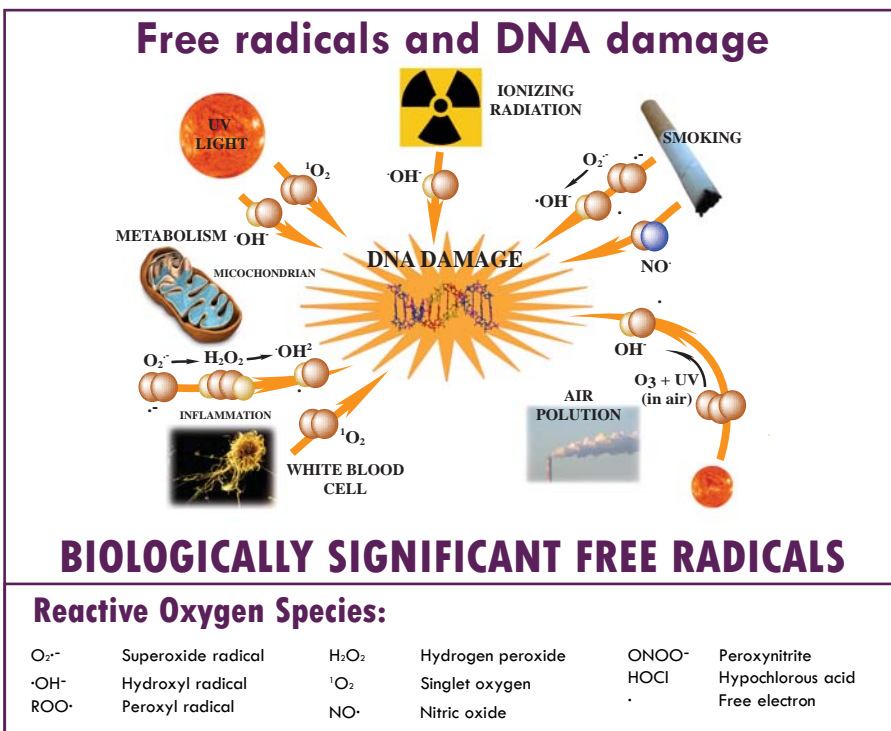
Source: Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. CA Cancer J Clin. 2005 Jan-Feb;55(1):10-30.

Cancer is a serious health concern and a leading cause of death in developed countries. In both the United States and Canada, one-in-four deaths are attributable to cancer - more than 1500 deaths per day.² In Canada, 38% of women and 44% of men will eventually develop cancer. Twenty-four percent of Canadian women and 29% of Canadian men will die of cancer. Cancer is the leading cause of premature death in North America.^{3,4} (See Figure 2)

Causes

Oxidative stress and free radicals

Oxidative stress is an important factor in the development of cancer. Oxygen free radicals are produced 1) in the mitochondria during normal metabolism 2) in the atmosphere due to pollution 3) by white blood cells in inflamed tissues and 4) by UV light.⁵



Oxidation damages DNA and leads to genetic mutations which can initiate cancer. Experiments have shown that oxidative damage is an etiological factor in several cancers.⁶ Damage induced by oxidation leads to DNA breaches and modifications. This causes genetic instability and leads to DNA transcription or replication errors - which can cause cancer.⁷

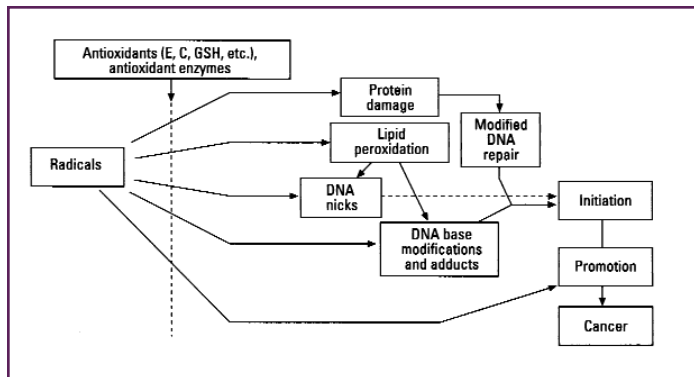


Figure 3: Representation showing how free radicals can damage cellular structures and lead to cancer. Antioxidants quench free radicals preventing this harmful interaction. Redrawn from (9).

The presence of oxidants in high concentrations is lethal to cells and causes apoptosis even in healthy cells. Lower (but still high) concentrations of oxidants interfere with cellular genetic expression. This can induce the cellular proliferation necessary for the development of cancer.¹⁰ (See Figure 3)

Antioxidants oppose and prevent the formation of free radicals. Diet-derived antioxidants are essential to counteract the body's burden of oxidants and free radicals because endogenously produced antioxidants are not sufficient to offset the metabolic burden of free radicals.^{11,12} (See Figure 4)

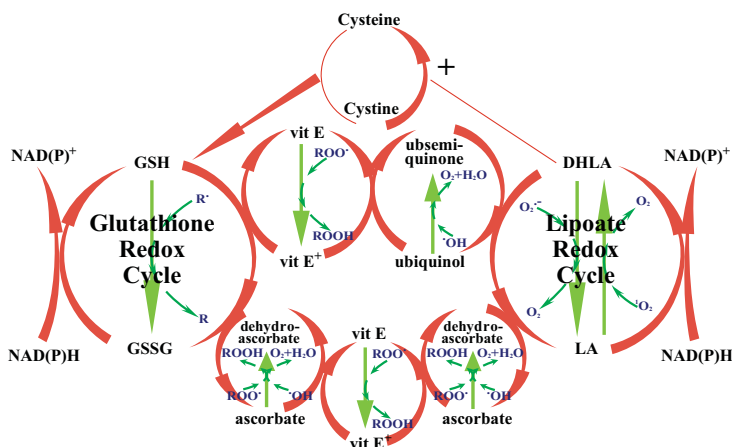


Figure 4: Removal of free radicals by the Networking Antioxidants. (R•, radicals; R, non-radicals)

Toxins and carcinogens

Several chemicals are known carcinogens and promote the development of cancer. Carcinogens damage DNA and interfere with normal cellular function. Individual exposure to carcinogens varies greatly and is related to diet, lifestyle and environmental factors. Carcinogens bind to DNA, hence their name: DNA adducts. DNA adducts impede the replication and repair of DNA, which promotes genetic mutations and cancer.

Examples of carcinogens include aflatoxins, chemicals from tobacco and heterocyclic amines. (See Figure 5) Aflatoxins are produced by fungus of the *Aspergillus* family and can grow on foods such as grains and nuts. The ingestion of aflatoxins increases the likelihood of developing liver cancer. Similarly, PAH and NNK found in tobacco smoke cause lung cancer. Epidemiological evidence also suggests that heterocyclic amines produced when meat is heated above 180°C promote colon, breast and stomach cancers.

The International Agency for Research on Cancer (IARC) is responsible for the assessment, identification and classification of carcinogens. So far, its Program on the Evaluation of Carcinogenic Risks to Humans has published 88 monographs on substances classified as "carcinogens to humans".¹³ Monographed carcinogens include drugs, chemicals and infectious agents. Causal relationships between specific compounds and cancer are carefully assessed and are often confirmed through epidemiological studies. For example, the dangers associated with aflatoxins were discovered in the 1960's in animal studies and were confirmed through epidemiological evidence.¹⁴ The problems associated with the ingestion of aflatoxins are compounded by the fact that exposure to aflatoxins during a hepatitis B infection further increases the risk of hepatocellular cancer. Hepatitis B infection is a major cause of liver cancer worldwide.

To this day, aflatoxins remain one of the most researched and well-documented carcinogens. The toxin is metabolized in the liver and binds to DNA to form an aflatoxin-N7-guanine adduct. The concentrations of such adducts in the liver are directly related to the formation of tumors (see figure 5).¹⁵ The link between aflatoxins and liver cancer has led to regulations aimed at reducing human exposure to the toxin.¹⁶

From Aflatoxin to Liver Cancer

- | | |
|----------------------------------------------------------------|------------------------------------------------------------------------------------|
| 1 Aspergillus mold grows on food | 5 DNA adducts lead to abnormal DNA replication |
| 2 Mold produces Aflatoxin | 6 DNA mutation: Aflatoxin leads to the substitution of guanine (G) for thymine (T) |
| 3 Toxins are ingested and reach the liver | 7 Mutation of p53 gene: Cellular apoptosis is compromised |
| 4 DNA adduction: Aflatoxin binds to DNA at guanine (G) residue | 8 Hepatocellular carcinoma |

Carcinogens from food, tobacco, drugs and other environmental toxins have similar effects on DNA and cause cancer through genetic mutations. Individual susceptibility to carcinogens varies greatly. How rapidly a carcinogen can be metabolized and eliminated depends on both genetic and environmental factors. The activity of specific enzymes involved in metabolism can be predetermined by genetic factors but lifestyle and dietary factors also influence how quickly toxins can be eliminated.¹⁷

Immune dysfunction

The body has several defense mechanisms against cancer. Cellular systems such as base and nucleotide excision repair mechanisms are important for the reversal of DNA damage. Cells where DNA damage accumulates are destroyed through programmed cellular death (apoptosis). In cells where genetic mutations have inactivated apoptosis, the immune system is responsible for the destruction of the abnormal cells. Cancer can only develop if it can evade all of those extensive cancer surveillance systems.

The immune system is essential for the elimination of tumor cells. Patients born with immune disorders are more likely to develop cancer.¹⁸ AIDS, which ravages the immune system, also predisposes one to Kaposi's Sarcoma, a malignant neoplasm that affects the skin, and spreads to the viscera and lymph nodes.

Animal studies have confirmed that immune deficiencies lead to tumor formation. Mice having a poorly functioning immune system are more likely to develop spontaneous tumors.¹⁹ Studies also show that tumors that develop in immunodeficient mice are rejected if transplanted into mice with a normal immune system. Conversely, normal mice injected with cells from tumors of other mice with normal immune systems will develop cancer.²⁰ In humans, the importance of immune surveillance can be portrayed in stem cell or organ transplant patients who are immunosuppressed and more likely to develop cancer.²¹⁻²³

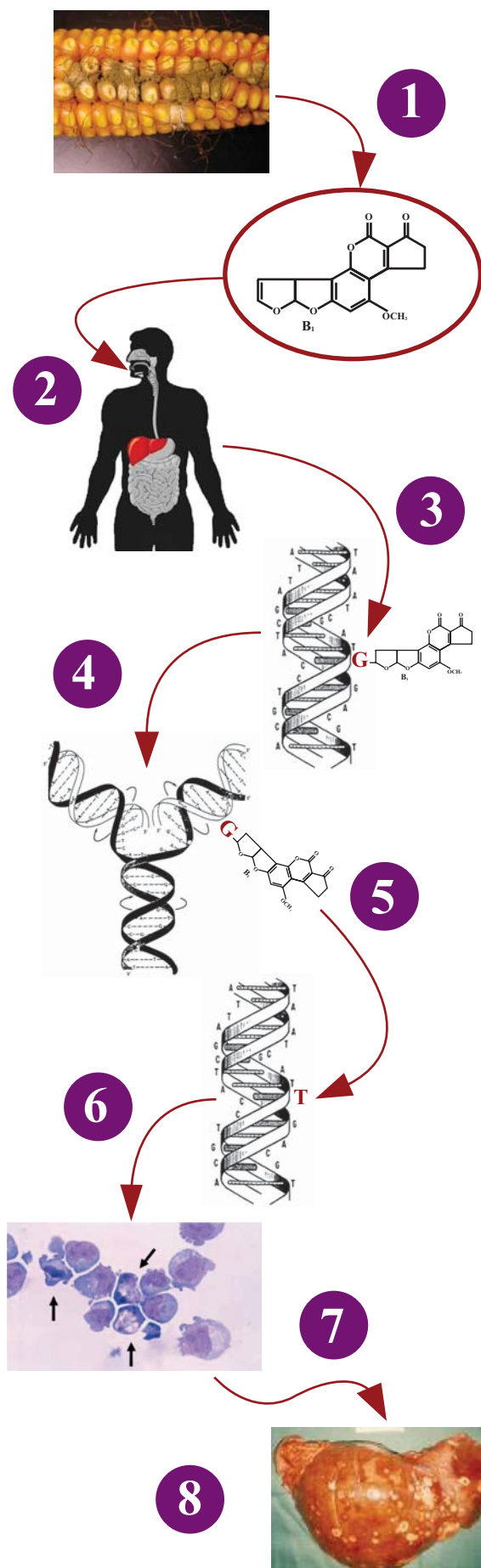


Figure 5: From mold to carcinoma: exposure to aflatoxin and the development of hepatocellular carcinoma.

Tumors release proinflammatory messengers, which attracts immune cells to the area. This promotes the elimination of cancer cells that had previously escaped the immune system - a process known as the adaptive immune response. The adaptive immune system specializes in the elimination of pathogenic challenges and is activated by non-specific immune messengers.

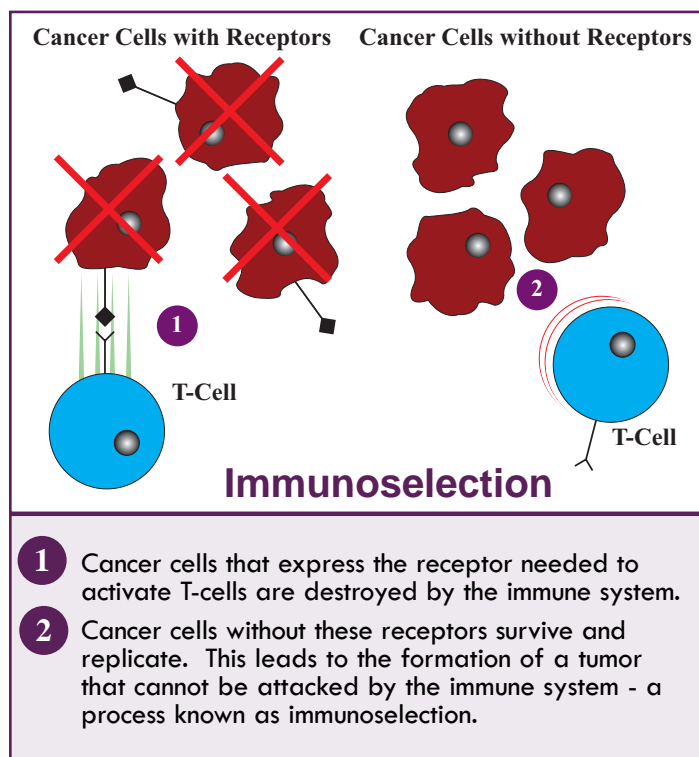


Figure 6: Failure of tumor elimination.

The appearance of tumors that evade the immune system is partly a consequence of immunoselection. Cancer cells are genetically unstable which means that their characteristics are changing rapidly. The immune system will selectively target and destroy cells that can easily be recognized. This implies that cancer cells, which cannot be identified, will survive and proliferate to form immune resistant tumors.

Genetic predisposition

We all have genetic polymorphisms. Polymorphisms are natural genetic variations with a high enough prevalence at the population level that they cannot be referred to as genetic mutations. Polymorphisms may reduce the activity of specific enzymes and some polymorphisms reduce the activity of cancer prevention mechanisms. Some individuals are born with genetic variations that make them more prone to developing cancer.²⁴⁻²⁷ The inactivation of tumor protein 53 (also known as p53) is a good example of a genetic polymorphism that predisposes to cancer. Individuals with genetic variations affecting the p53 gene are more susceptible to cancer because fewer mutations are required to shutdown apoptosis (several successive mutations are

needed to inactivate apoptosis). Studies have shown that individuals with polymorphisms affecting codon 72 (a section of DNA that codes for a specific amino acid) are 3.9 times more likely to develop stomach cancer.²⁸ Similarly, genetic variations affecting the immune system can weaken the immunity, impede immunosurveillance and increase the incidence of cancer.

Chronic Inflammation

Chronic inflammation can lead to the development of cancer. Inflammation results from the activation of immune cells, mainly neutrophils and macrophages. When immune cells are activated, they release inflammatory mediators; and toxins, which include reactive oxygen species. The purpose of inflammation is the destruction of the offending agent. Unfortunately, chronic inflammation leads to oxidative stress in surrounding cells. Oxidation promotes cellular and DNA damage which predisposes one to genetic mutations and cancer.²⁹ Examples of chronic inflammatory conditions potentially leading to cancer include asbestosis, inflammatory bowel disease, Barrett's dysplasia and gastritis (see figure 7 on next page). This is why treatments aimed at the reduction of inflammation have been shown to prevent cancer.³⁰

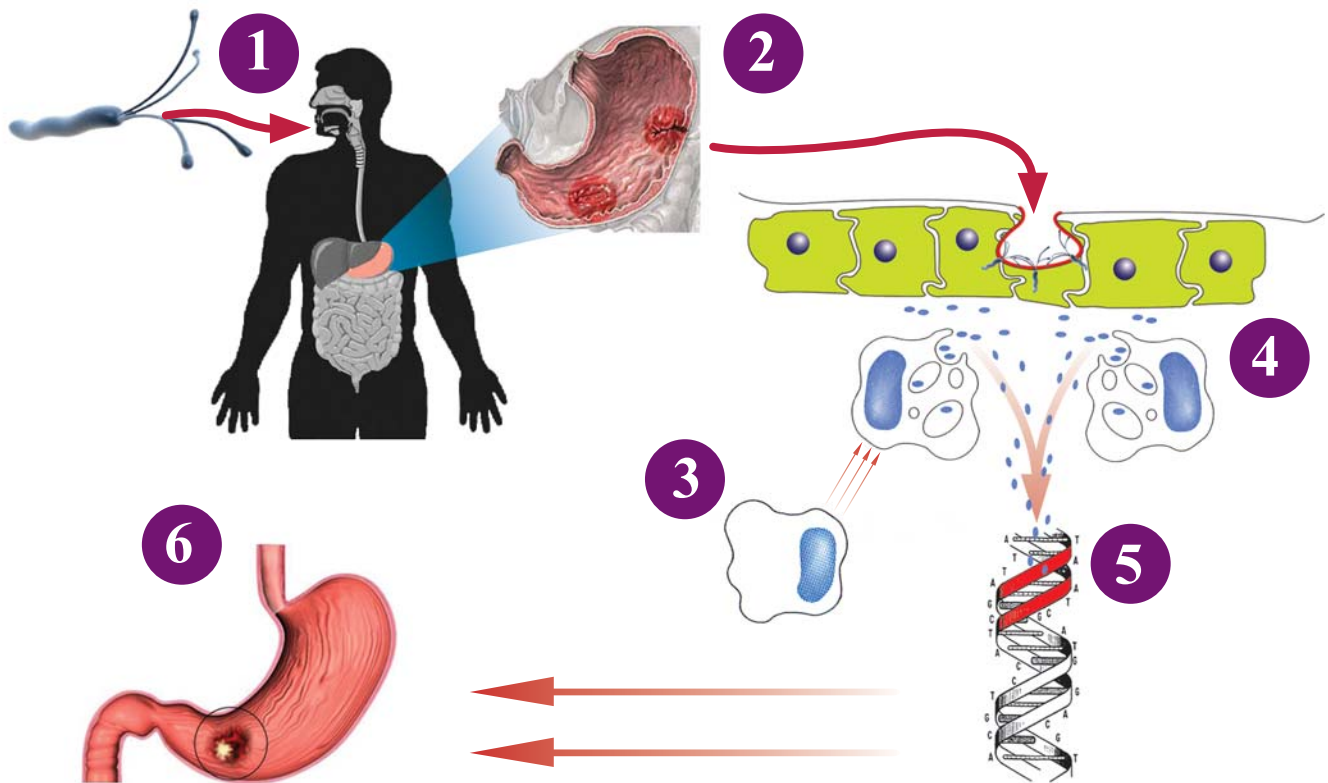
We regard cancer as fundamentally abhorrent, yet the process which leads to the faulty mutations behind cancer is also responsible for the adaptive mutations which drive evolution. Although most mutations are detrimental, every so often a new DNA mutation confers an advantage, enabling its carrier to produce more offspring to propagate the new DNA sequence. Cancer may therefore never disappear and it may not be in our interest to irradiate genetic mutations. Genetic mutations that occur during conception are, after all, nature's attempt to find a better way...

References

- 1 Fenton RG, Longo DL. Cell Biology of Cancer. Harrison's Principles of Internal Medicine 15th Edition. McGraw-Hill. 2001
- 2 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. CA Cancer J Clin. 2005 Jan-Feb;55(1):10-30.
- 3 Canadian Cancer Society/National Cancer Institute of Canada: Canadian Cancer Statistics 2006, Toronto, Canada, 2006
- 4 Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. CA Cancer J Clin. 2005 Jan-Feb;55(1):10-30.
- 5 Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007 Apr;39(1):44-84. Epub 2006 Aug 4.
- 6 Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006 Mar 10;160(1):1-40.
- 7 Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007 Apr;39(1):44-84. Epub 2006 Aug 4.
- 8 Pryor WA. Cigarette smoke radicals and the role of free radicals in chemical carcinogenicity. Environ Health Perspect. 1997 Jun;105 Suppl 4:875-82.
- 9 Pryor WA. Cigarette smoke radicals and the role of free radicals in chemical carcinogenicity. Environ Health Perspect. 1997 Jun;105 Suppl 4:875-82.

BACTERIA TO CARCINOMA

How Chronic Inflammation can lead to Cancer



- 1** Helicobacter Pylori enters the body through the ingestion of waste tainted food or water
- 2** H. Pylori infects the stomach lining and ulcers develop
- 3** Infection and ulceration leads to the mobilization of immune cells

- 4** Immune cells release inflammatory mediators and reactive oxygen species (ROS)
- 5** Chronic inflammation leads to prolonged exposure to ROS, damaging DNA
- 6** Stomach cancer develops

10 Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol.* 2007 Apr;39(1):44-84. Epub 2006 Aug 4.

11 Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact.* 2006 Mar 10;160(1):1-40.

12 Fang YZ, Yang S, Wu G. Free radicals, antioxidants, and nutrition. *Nutrition.* 2002 Oct;18(10):872-9.

13 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. International Agency for Research on Cancer. <http://monographs.iarc.fr/>

14 Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Environmental and chemical carcinogenesis. *Semin Cancer Biol.* 2004 Dec;14(6):473-86.

15 Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Environmental and chemical carcinogenesis. *Semin Cancer Biol.* 2004 Dec;14(6):473-86.

16 Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Environmental and chemical carcinogenesis. *Semin Cancer Biol.* 2004 Dec;14(6):473-86.

17 Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Environmental and chemical carcinogenesis. *Semin Cancer Biol.* 2004 Dec;14(6):473-86.

18 Hosokawa M. Combination of AHCC and Chemotherapy. *Anti-Cancer Drugs.* 9,343-350,1998.

19 Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFN γ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature.* 2001 Apr 26;410(6832):1107-11.

20 Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFN γ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature.* 2001 Apr 26;410(6832):1107-11.

21 Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation.* 2005 Oct 15;80(2 Suppl):S254-64.

22 Trofe J, Beebe TM, Buell JF, Hanaway MJ, First MR, Alloway RR, Gross TG, Woodle ES. Posttransplant malignancy. *Prog Transplant.* 2004 Sep;14(3):193-200.

23 Penn I. Malignant melanoma in organ allograft recipients. *Transplantation.* 1996 Jan 27;61(2):274-8.

24 Nevanlinna H, Bartek J. The CHEK2 gene and inherited breast cancer susceptibility. *Oncogene.* 2006 Sep 25;25(43):5912-9.

25 Mathew CG. Fanconi anaemia genes and susceptibility to cancer. *Oncogene.* 2006 Sep 25;25(43):5875-84.

26 Rogowski W. Genetic screening by DNA technology: a systematic review of health economic evidence. *Int J Technol Assess Health Care.* 2006 Summer;22(3):327-37.

27 Liu WZ, Jin F, Zhang ZH, Wang SB. Role of detection of microsatellite instability in Chinese with hereditary nonpolyposis colorectal cancer or ordinary hereditary colorectal cancer. *World J Gastroenterol.* 2006 Aug 7;12(29):4745-9.

28 Yi SY, Lee WJ. A p53 genetic polymorphism of gastric cancer: difference between early gastric cancer and advanced gastric cancer. *World J Gastroenterol.* 2006 Oct 28;12(40):6536-9.

29 Ernst P. Review article: the role of inflammation in the pathogenesis of gastric cancer. *Aliment Pharmacol Ther.* 1999 Mar;13 Suppl 1:13-8.

30 Grosch S, Maier TJ, Schiffmann S, Geisslinger G. Cyclooxygenase-2 (COX-2)-independent anticarcinogenic effects of selective COX-2 inhibitors. *J Natl Cancer Inst.* 2006 Jun 7;98(11):736-47.

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