

(including hepatoma, hepatocellular carcinoma)

DEFINITION

1. Cancer is a term which embraces a large number of different diseases, the common feature of which is a malignant tumour. This is a growth (neoplasm) which is not circumscribed but which infiltrates the surrounding tissues and metastasises (spreads to other sites in the body, thereby producing secondary deposits). Any tissue in the body may be affected.
2. Cancers are classified according to the tissue of origin. **Carcinoma** arises from epithelial tissue and **sarcoma** from connective tissue. The suffix **-blastoma** implies a tumour of embryonic origin.
3. Cancer of the liver is a malignant tumour of the liver. It may arise from the liver cells (hepatocytes), from the bile duct epithelium or from the supporting mesenchymal tissue. Hepatocellular carcinoma (or hepatoma), which arises from the hepatocytes, is the most common primary cancer of the liver.
4. Other primary malignant tumours of the liver include cholangiocarcinoma, sarcoma, angiosarcoma, mesothelioma, reticuloendothelioma and squamous cell carcinoma. All these tumours are exceedingly rare.
5. Hepatocellular carcinoma may occur as a single mass or as scattered nodules. It invades the portal and hepatic veins and spreads to the abdominal lymph nodes and bones. In 80% of cases there is pre-existing cirrhosis. However in young adults it usually occurs in a non-cirrhotic liver.

CLINICAL MANIFESTATIONS

6. Cancer of the liver may present with abdominal pain, an abdominal mass, fever or weight loss. The tumour may rupture causing a haemo-peritoneum or it may present as obstructive jaundice.
7. Non-metastatic effects of malignancy such as hypoglycaemia, hypercalcaemia and porphyria cutanea tarda may occur.

AETIOLOGY

8. Cancer is not one disease but a group of widely different diseases. While some aetiological factors may be common to a number of different types of cancer, each type should be recognised to be an individual disease with its own specific aetiology.
9. The common feature of all cancers is the loss of control over normal cell division and differentiation. Cell division proceeds by a complex sequence of events. For this to be maintained in a normal way it must be strictly controlled. It has been found that certain regions of the chromosomes are vital to this control. These regions are called oncogenes. While the oncogenes perform normally, cell division and differentiation remain under control.

10. The process whereby oncogenes lose control of cell division and differentiation is known as activation. When this occurs cell division and differentiation become chaotic and neoplasia (carcinogenesis) ensues. The factors which activate oncogenes are numerous and varied, some being endogenous, others environmental. There is evidence that in most types of cancer a number of different factors play a part at different stages of the neoplastic process.
11. Some types of cancer are strongly genetically determined with a family history, for example retinoblastoma. In other types of cancer an external agent is the dominant factor, for example aniline dyes, which will cause carcinoma of the bladder in 100% of cases following sufficient exposure.
12. Some individuals are **genetically determined** to be more likely to develop cancer and there is a strong history of certain type of cancer in their family of origin. Some cancers are more common in one sex than the other.
13. During life many **constitutional factors** are present which may activate oncogenes. These include humoral factors, immunological factors and the normal ageing process during which spontaneous changes affect the genes (somatic mutations).
14. For the most part, cancer is commoner at the extremes of life. This may be because the immune system is relatively less efficient in the young and the elderly. In addition, with increasing age, the summation of naturally occurring somatic mutations and any exposure to carcinogens may become sufficient to activate oncogenes.
15. **Environmental factors** play a part in the aetiology of some types of cancer. The following groups of factors have been identified:
 - 15.1. **Chemical**, for example aniline dyes and carcinoma of the bladder.
 - 15.2. **Physical** agents, for example asbestos and mesothelioma.
 - 15.3. **Ionising radiation** which when a certain dose is exceeded will cause cancer in some, but not all, tissues.
 - 15.4. **Ultraviolet radiation** which may cause cancer of the skin. Its tissue penetration is limited and so it does not cause cancer in the deeper tissues.
 - 15.5. Some specific **viruses** have been identified which play a part in the causation of particular types of cancer, for example hepatitis B and primary carcinoma of the liver.
 - 15.6. It has been suggested that a wide variety of other environmental factors may cause certain types of cancer. Many of these suggestions have been based on animal studies, in vitro experiments or on epidemiological studies with small samples of inadequate controls. These contentions are still at the stage of speculation.

16. There is marked geographical variation in the incidence of this tumour. In Western Europe and North America it is uncommon, although there is evidence that the incidence may be rising. In Africa and South East Asia the incidence is 20-30 times higher than in the Western World.
17. In most cases of primary liver cancer the precise cause remains obscure. There are however several well recognised associations.
18. In the Western world the development of hepatocellular cancer is seen in individuals with previous cirrhosis, particularly macronodular cirrhosis caused by alcohol ingestion or chronic active hepatitis. The individuals most at risk are the elderly or late middle-aged males.
19. In high incidence areas, the average age of affected persons is lower and fewer individuals have pre-existent cirrhosis.
20. It might be expected that alcoholics are at greater risk of liver cancer because of their development of macronodular cirrhosis. However some alcoholics develop primary liver cancer in the absence of macronodular cirrhosis. This suggests that some other factor, perhaps malnutrition, may also be involved.
21. Much circumstantial evidence links hepatitis B infection with primary liver cancer. The high incidence areas of both the tumour and hepatitis B infection correspond closely. Hepatitis B infection may be associated with macronodular cirrhosis. This is not invariable and in cases of hepatitis B infection with subsequent primary liver tumour, macronodular cirrhosis is not universal. There is a close relation between hepatitis B infection and dysplasia. Viral antigens may be found in the blood and hepatocytes of primary liver cancer patients. One possible mechanism is that hepatitis B infection initiates neoplastic transformation and this becomes clinically manifest in the presence of other promoting agents.
22. Hepatitis C infection is also causally associated but there is no evidence to link hepatitis A, D or E with primary cancer of the liver.
23. The tumour may occur in relation to certain types of oral contraceptive pill.
24. In the hot humid conditions of Africa and the Far East, food, particularly groundnuts and grain, is often contaminated by aflatoxin from the mould *Aspergillus flavus*. Aflatoxins can induce acute liver injury and tumours in animals. There is therefore a possibility, which is as yet unproven, that this mechanism operates also in man.
25. The incidence of primary liver cancer is increased in patients with certain inherited metabolic disorders including tyrosinosis, type 1 glycogen storage disease and α -1-antitrypsin deficiency.
26. The incidence is also high in advanced idiopathic haemochromatosis and in Bantu siderosis.
27. In South Africa and Japan an association has been noted between the tumour and Budd Chiari syndrome due to chronic obstruction of the inferior vena cava by membranous bands of fibrosis.

28. Primary hepatocellular cancer of the liver is not associated with exposure to excess ionising radiation.
29. Of the other varieties of primary liver tumour, cholangiocarcinomas occur in an older age group and in China they arise as a complication of chronic liver fluke infection.
30. Reticuloendotheliomas or angiosarcomas are extremely rare. This has allowed for the easier recognition of causal agents and the following have been recognised; inorganic arsenic, thorostrast (a radiocontrast medium used in neuroradiology and whose metabolites were retained in the liver, spleen and marrow) and vinyl chloride.
31. Cancer of the liver is not caused by climatic extremes, trauma, physical or mental stress or lowered resistance arising from hardship or other diseases. Its progress is independent of external factors other than medical treatment.

CONCLUSION

32. Primary cancer of the liver is a malignant tumour of the liver. Constitutional and environmental factors play apart in the aetiology. The course of the condition is unaffected by environmental factors other than those involved in its treatment.

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