CANCER OF THE BREAST **MEDICAL APPENDIX**

(Carcinoma of the breast)

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 breast is a malignant tumour of the breast. Most of these tumours are carcinomas. Several distinct forms of carcinoma-in-situ have been recognised. These may remain static, regress or proceed to invasive malignant disease.

4. Carcinoma of the breast is not a single disease and there appear to be two major subgroups. In one of these the disease remains localised to the breast and rarely, if ever, metastasises. The other subgroup already has micrometastases at the time of its earliest clinical manifestation.

5. There are also several different histological types of breast carcinoma. Invasive breast carcinoma is usually referred to as carcinoma of breast – not otherwise specified (NOS). This constitutes about 70% of breast carcinomas. It is also known as scirrhous carcinoma. Medullary carcinoma constitutes about 5% of cases. Colloid and tubular carcinoma together also constitute about 5% of cases. Inflammatory carcinoma (mastitis carcinomatosa) usually, but not exclusively, occurs during pregnancy or lactation.

CLINICAL MANIFESTATIONS

6. There are few early symptoms of cancer of the breast. 80% present as painless breast lumps. The local tumour growth rate is very variable, as is the rate of metastatic spread. Local breast pain, skin oedema and tethering, satellite skin lesions, ulceration, secondary infection and haemorrhage may occur.

7. Lymph node spread to axillary or internal mammary lymph nodes is common. Arm oedema may be evident and spread by blood, particularly to bone, lung and liver, are well recognised. Metastatic spread may be associated with secondary anaemia, cachexia and anorexia.

8. Scirrhous carcinoma is a hard irregular swelling. Skin tethering, nipple retraction and infiltration of the chest wall may occur. Medullary carcinoma usually affects younger age groups. Colloid and tubular carcinomas occur in the elderly.

Characteristics of neoplasia

9. Tumours arise when tissue growth becomes insensitive to normal control mechanisms. Usually, cells multiply in response to a reduction in tissue cell density, the process ceasing when normal tissue architecture is restored. Tumours arise from a common ancestral cell which, years before clinical disease becomes apparent, begins to reproduce inappropriately. Malignant transformation results from mutation in the cell's genetic material.

10. These genetic mutations change the amount or the activity of the protein product. Two particular gene classes play major roles in triggering cancer. Normally **proto-oncogenes** encourage cell growth and reproduction: **tumour suppressor genes** oppose it. Mutated proto-oncogenes become **carcinogenic oncogenes**, driving excess cell multiplication. Inactivated tumour suppressor genes contribute to cancer by depriving the cell of its braking system. For cancer to develop, mutations need to occur in several of the original cell's growth control genes.

11. Cells insensitive to growth control generate, within tissues, subpopulations of cells whose subsequent progress depends on selection pressure, favouring the emergence of cells with the greatest growth potential. It is this process which determines the histology of a tumour and its clinical course. Tumour cells usually retain the characteristics of their tissue of origin. However, tissue differentiation involves the synthesis of molecules not essential to cell survival, and so loss of the parent tissue markers may confer growth advantage. Dedifferentiation in a tumour implies high growth rate and high malignancy. Tumours can also metastasise (migrate via the lymph or blood stream) to other parts of the body, producing **metastatic** deposits.

AETIOLOGY

General risk factors for all cancers

12. Much is now understood about the origins and mechanisms of cancer in general, but the precise cause of individual tumours often remain unknown.

Age

13. Some risk of cancer occurs at every age, but the risk for particular types varies at different ages. Most commonly there is a progressive increase in incidence from childhood to old age, (cancers of the skin, lung, gastrointestinal and genitourinary tracts, multiple myeloma and chronic lymphatic leukaemia). The rate of increase is typically proportional to the 4th or 5th power of age. Less commonly there may be a peak in early life, with decline thereafter to zero, eg retinoblastoma or nephroblastoma.

Gender

14. The incidence of cancer in relation to gender is not straightforward and it is changing – probably due to lifestyle and occupational changes. At the beginning of the last century, overall cancer was more common in women due to the frequency of cancer of the cervix and the rarity, in both men and women, of cancer of the lung. Now, in developed countries, cancer is more common in men.

Latent period

15. There is a delay between initial exposure to carcinogen and clinical disease. With short intense exposures, eg to ionising radiation at Hiroshima, solid tumours increase in incidence for 15-20 years. Incidence may then continue to rise, level off or decline, depending on the tumour type. For acute leukaemia there is a peak incidence at about 5 years and very few cases appear after 30 years. Short intense exposure to carcinogens is exceptional and, where exposure is chronic and prolonged, eg due to occupation, smoking or sunlight, cancer incidence increases with exposure duration. Precisely how this operates and how subsequent risk is affected by removal from the exposure is unknown.

16. Clinical cancer is the end result of a multistage process involving initiating and promoting agents. If the carcinogen is an initiating agent, eg asbestos, rather than a substance influencing a later stage nearer clinical manifestation, eg cigarette smoking, cancer incidence in the population may continue to rise, albeit more slowly, for a considerable time after exposure to the carcinogen has ceased.

Risk factors in the individual case of all cancers

17. The main factors that determine whether a particular individual develops cancer relate to constitution and exposure to environmental factors.

Genetics

18. The close connection between certain chromosomal abnormalities associated with recognised clinical syndromes and subsequent tumour development, eg polyposis coli and cancer of the large bowel, and xeroderma pigmentosum and skin tumours, confirms that an individual's genetic make-up has an effect on his susceptibility to cancer.

19. Many studies have looked at cancer rate in the families of individuals with the disease. There appears to be no material tendency for cancer in general to cluster in families and no genes have been identified that increase the risk of cancer in all tissues. However, all common cancers do cluster in families to some extent – the risk of a sibling of a patient developing a tumour at the same site is twice normal. This might be due to genetic susceptibility but could equally well reflect lifestyle, eg diet, hygiene or a common legacy of infections in early life.

Environmental factors

20. Our knowledge of the environmental causes of cancer relies on animal laboratory investigation and human epidemiology, with the two approaches complementing each other. Since there are features common to most cancers, there are factors which can cause cancer at all or many sites. Present evidence confirms the importance of life-style factors in cancer causation.

Tobacco smoke

21. Cigarette smoking is thought to cause 30% of all cancer deaths, and has been conclusively linked to cancer of the lung, upper respiratory tract, oesophagus, bladder, stomach, liver, kidney and chronic myeloid leukaemia. It may also cause cancer of the colon and the rectum. Relevant factors include number of cigarettes smoked, tar content, age at smoking onset and duration of habit.

Diet

22. There is good evidence that some common cancers would be less common if diet were modified. Animal fat consumption, particularly red meat, high salt intake and ingestion of very hot beverages and food have all been linked to specific cancers. Similarly what is **not** in the diet may be important. Low consumption of vegetables and fruit, in the presence of high calorie intake, is associated with several different tumour types, eg childhood obesity and cancer of the breast and prostate, adult obesity and endometrial cancer. Consumption of alcohol (particularly along with cigarettes) increases the risk of cancer of the upper respiratory and digestive tracts. There is evidence that as little as two drinks a day may contribute to breast, colon and rectal cancer. In total, diet is considered to account for 30% of all cancer mortality in developed countries, alcohol for a further 3%, and salt for 1%.

Radiation

23. Radiation is difficult to avoid and, in total, radiation of all types causes 2% of all cancer deaths. Most of these deaths result from natural sources, particularly sunlight, UVB.

    - **UVB radiation** causes 90% of all skin cancers, including basal cell cancers, malignant melanoma and squamous cell carcinoma.

    - **Electromagnetic radiation** as a cause of cancer has been the subject of several recent studies. The results are confusing and inconsistent and reported associations may not be causal. It is of two main types:

        I. **Extremely low frequency fields**, e.g. power lines and household appliances. Basic science confirms that these radiations are of too low frequency to initiate cancer causing genetic mutation as they are of insufficient energy to ionise molecules.

        II. **Radiofrequency electromagnetic radiation**, e.g. cellular telephones, microwaves and living creatures. Although more energetic than I. (above), they are still unable to cause molecular ionisation.

    In conclusion at this date there is no good scientific evidence that electromagnetic radiation causes cancer. Any possible association remains hypothesis.

- **Ionising radiation**

Ionising radiation can penetrate animal tissues and damage DNA and theoretically has the power to produce cancer in most tissues. The actual risk due to exposure to ionising radiation may, however, be different. It is often overestimated and not evidence based. Amongst Japanese residents of Hiroshima and Nagasaki who survived more than a year after detonation, only 1% have died of tumours.

Studies of humans exposed to high dosage of ionising radiation, eg the Japanese atomic bomb survivors, or individuals medically irradiated for tumours, have shown an increased incidence of cancer due to that exposure. There is, however, no firm evidence from human low-dose epidemiological studies which unequivocally demonstrates an increase in cancer incidence. This may be due to the very large size of study population, which would be needed to demonstrate an increased incidence.

For radiation protection purposes it is, therefore, accepted that there is no threshold level below which no carcinogenic effect is produced, and the risk of a cancer developing is extrapolated on a dose-proportional basis from high to low doses and dose rates.

All humans are constantly exposed to ionising radiation, from both the natural environment and man-made products. The natural sources include cosmic radiation from space, radiation from the ground and from inhaled and ingested materials. Air travel and mining both increase exposure to background radiation. Radiation originating in the body comes mainly from potassium, while lungs are exposed through radon in inhaled air. Man-made radiation comes from medical uses, past atomic tests, man-made products and radioactive waste.

Natural radiation differs depending on location. In the UK the average annual dose is less than 2,000 microsieverts. There is, however, a considerable range; it may rise to 8,000 microsieverts in some areas and to 100,000 in some homes. The UK average annual dose from man-made sources in total is less than 300 microsieverts and, again, there may be variation.

From 1952 to 1958 the UK carried out 21 atmospheric nuclear tests in the Pacific Ocean. The locations were chosen because of their isolation and low natural radiation level. On average the Christmas Island annual background radiation is less than 700 microsieverts.

Radiation dose

24. The effects of ionising radiation depend on the exposure size of the accumulated dose. A discussion of radiation dose is at Annex A.

Therapeutic drugs

25. About 20 agents, not all of which are in current use, are known to cause cancer. Potential carcinogens may still be used if the hazard is judged to be less than the chance of saving a life, eg certain cancer drugs. Close scrutiny is kept on drug hazards and the position of oestrogens in hormone replacement therapy (HRT), known to cause endometrial cancer, and of the oral contraceptive pills, which have been associated with carcinoma of the cervix, breast and hepatoma, is closely monitored. Together, prescribed drugs are held responsible for less than 1% of all fatal cancers.

Occupation

26. Historically, study of occupational exposures has identified many important carcinogens. Material or process modification and, latterly, health and safety statute have removed many potential hazards in the developed world. However, the long latent period of cancer means that a considerable time will be required for the effects of industrial carcinogens to be eliminated and, equally, that new hazards may remain unsuspected for a long time. At present overall, occupation is considered responsible for 2-3% of all fatal cancers in developed countries. Particularly important occupational carcinogens are asbestos dust exposure, exposure to combustion products of fossil fuels and ionising radiation.

Pollution

27. Investigation of the relation between environmental pollution – air, soil and water – and cancer is difficult because of the widespread nature of pollution and similar risk to people over a wide geographical area. It is generally accepted that, in the UK at the beginning of the last century, air pollution via combustion may have contributed to a few percent of lung cancers. Over the last 30 years with increasing statute on pollution reduction, this has become much less common. Advances in chemical analysis have allowed recent interest in pollution of soil and water as possible cancer risks.

28. Another complicating factor in accurately attributing risk of cancer to individual external agents is **interaction**. Some carcinogenic agents act together to produce effects much greater than the sum of the separate individual effects, eg smoking and asbestos in relation to cancer of the lung, smoking and alcohol in relation to carcinoma of the oesophagus, and aflatoxin and hepatitis B infection in cancer of the liver.

Specific risk factors for breast cancer

29. Cancer of the breast is the most common cancer in women in the developed world. In England and Wales recent cancer registry statistics show it to represent 11% of all cancers, and in the 1991 national mortality statistics it accounted for 10% of all cancer deaths. It is less common in Asia and Africa, but the incidence in these populations is rising. Ultimately, it is thought that the incidence will become uniform throughout the world.

30. The global imbalance in incidence, together with the occurrence of strains of mice which are obese and develop mammary cancer spontaneously, has led to the view that diet, in particular overnutrition, (especially high animal/saturated fat content) is an important factor in the aetiology. The mechanism is unknown.

31. Epidemiological studies have identified many common features in women presenting with breast cancer but, to date, the significance of the majority of these is unknown.

32. In the last few decades studies have shown that there is an increased risk of the disease in first degree relatives of patients with cancer of the breast, particularly if the patient had bilateral disease or onset prior to the menopause. (Veranesi et al 1995). At present, it is not possible to define how much of this increased risk is due to shared life-style and how much is true genetic predisposition.

33. Reproductive history is important in the disease. The evidence shows there to be a greater prevalence of breast cancer in single, divorced or widowed women compared with married women. A few particular types of benign breast disease (diffuse papillomatosis and atypical hyperplasia) increase the risk of breast cancer. It is, however, accepted that the most common types of benign breast disease (fibroadenomas and cystic disease) do not represent a risk factor.

34. Nulliparous women have an increased risk of breast cancer, whereas multiparity and a full-term pregnancy before the age of 20 protect women from the disease. Similarly, women who have their ovaries removed before age 40 are protected. These observations suggest that hormones play a role. It has not yet been clarified which hormones are critical and how they act.

35. Laboratory animal experiments support a central causal role for oestrogen. That is, however, counter to the human evidence, eg repeated full-term pregnancies from an early age are protective, and the highest incidence is found in old women, ie those with low oestrogen levels.

36. Progesterone has been suggested as protective but, again, supporting evidence is weak.

37. The fact that the incidence is high in post-menopausal women, that some studies have shown high androgen levels and low progesterone in premenopausal women with the disease (Secreto et al 1984), and that Japanese women, who have a lower incidence of breast cancer than British women, have lower plasma androgen levels, has led to proposals that androgens may be causally involved.

38. Studies of the association of breast cancer with the use of oral contraception have produced conflicting results. Some studies suggest any risk is lessened if a low-oestrogen dose pill is taken. The effect in positive studies is seen only during, and for a short period after, use but there appear to be no effects in later life.

39. The effect of HRT in later life has been extensively studied, with recording of ambiguous results. There is some suggestion that HRT may become relevant if prolonged – producing slightly increased risk of the condition.

40. That breast cancer may arise from exposure to ionising radiation has been confirmed by the atomic bomb survivor data of the Radiation Effects Research Foundation, in-patients receiving radiotherapy for post-partum mastitis or who had multiple fluoroscopies during treatment of pulmonary tuberculosis. The breasts of young women are especially vulnerable to injury by ionising radiation. Breast cancer risk following exposure to ionising radiation declines with age at exposure, and women older than 30 years at exposure have a very low risk of radiation-induced breast cancer (Tokmaga et al 1984: Miller et al 1989). These data are important in relation to decisions on screening by repeat mammograms.

41. Cancer of the breast has not been shown to be caused by climatic extremes, trauma, physical or mental stress, or lowered resistance arising from hardship or other diseases. There is no evidence that its progress is dependent on external factors other than medical treatment.

42. Cancer of the breast in men accounts for about 1 per cent of the total cases. In men the mean age is greater than for women. In contrast to female breast cancer, cancer of the male breast may be associated with benign breast disease. It may also be associated with orchitis or orchidectomy. The condition is commoner in men with Klinefelter's syndrome and in those treated with exogenous oestrogen for genital tumours.

CONCLUSION

43. **Cancer of the breast** is a malignant condition affecting the breast tissue in both males and females. Despite considerable investigation, and excepting the associations listed above, no external cause has been identified. There is no evidence that the course of the condition is affected by environmental factors, other than those involved in its treatment.

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Annex A

Radiation dose

1. The first definition of a unit of radiation dose was made in 1928 by the International Congress of Radiology. The roentgen (R) was defined as that quantity of radiation which produces in 1 cm of air one unit of charge of either sign, thus defining a unit of exposure. Units of **absorbed dose**, the actual energy absorbed in the tissue being irradiated are now used. The radiation absorbed dose or **rad** is now cited in SI (Systeme Internationale) units – joules per kg – of absorbing material. The fundamental unit, 1 joule/kg, is 1 gray (1 Gy), equivalent to 100 rads (R).

2. Different radiation types have greater or lesser effect per unit dose, so they are all expressed relative to the effects of X-rays, ie. a unit equivalent dose is used. To calculate the roentgen equivalent in man (**rem**), the absorbed radiation dose is multiplied by a radiation weighting factor, dependent on type and energy of the radiation. The current SI unit of equivalent dose is the **Sievert**. For X-rays and gamma rays the equivalent dose in sieverts and the absorbed radiation dose in grays are the same. The relationship between the different dose units is:-

   1 gray (Gy) = 1 joule/kg = 100 rads (R) = 100 rems (r) = 1 sievert (Sv) = 1,000 millisieverts (mSv) = 1,000,000 microsieverts (microSv). Typical doses of radiation include:

   Chest X-ray – 0.02 mSv
   Brain scan – 7 mSv
   Bone scan – 4 mSv
   Average annual UK dose from cosmic rays – 0.26 mSv
   Average annual UK dose from gamma rays – 0.35 mSv
   Average annual UK dose from natural background radiation – 2.2 mSv

3. **Effects of total body irradiation**

Equivalent dose (Sv)	**Effect**
Sub lethal to man 0.0001 (0.1 mSv)	Around 2 weeks' natural background radiation, no detectable effect
0.001 (1 mSv)	Around 6 months' natural background radiation, no detectable effect
0.01 (10 mSv)	No detectable effect
0.1 (100 mSv)	Minimal decrease in peripheral lymphocyte count, no clinical effect
1 (1000 mSv)	Mild acute radiation sickness in some individuals (nausea, possible vomiting), no acute deaths, early decrease in peripheral lymphocyte count, decrease in all WBC and platelets at 2-3 weeks, increase in late risk of leukaemia, solid tumours

Equivalent dose (Sv)	Effect
Lethal to man 10 (10,000 mSv)	Severe acute radiation sickness, severe vomiting, diarrhoea, death within 30 days of all exposed individuals. Severe depression of blood cell and platelet production, damage to gastrointestinal mucosa.
100 (100,000 mSv)	Immediate severe vomiting, disorientation, coma, death within hours
1000 (1,000,000 mSv)	Death of some micro-organisms, some insects within hours
10,000 (10,000,000 mSv)	Death of most bacteria, some viruses
100,000 (100,000,000 mSv)	Death of all living organisms, denaturation of proteins

Radiation dose limits

4. Since the days of Marie Curie it has been appreciated that ionising radiation exposure may be hazardous to health. Radiation dose limits were first recommended for ionising radiation exposure in 1928. The statutory limit on the amount of radiation to which the general public may be exposed in excess of natural background radiation and excluding medical exposure is set, from 1 January 2000, at 1 mSv per annum.

5. The most important source of man-made exposure is medical investigation which accounts for 90% of man-made exposure. Average natural background radiation is raised to 2.6 mSv by all man-made exposure. UK estimated exposure, excluding medical investigation, is 0.04 mSv. Other statutory limits include occupational dose limits. From 1 January 2000, these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers.

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