DEFINITION

1 Thyroid nodules are common with a spectrum ranging from benign to malignant. Some nodules are true benign adenomas and others are definite carcinomas but between these many nodules are potentially malignant and the precise relationship between benign and malignant nodules is speculative. Although relatively rare, accounting for less than 1% of new malignancies annually in Britain, thyroid cancer is the most common type of endocrine malignancy. Cancers of the thyroid are usually classified into the following histological groups:

- Papillary carcinoma
- Follicular carcinoma
- Medullary carcinoma
- Anaplastic carcinoma

2 Malignancies of other tissues may also occur in the thyroid gland:

2.1. **Miscellaneous tumours**. The thyroid may be the site of non-Hodgkin's lymphoma, which accounts for up to 50% of thyroid cancers, mostly in elderly women. More rarely, Hodgkin's lymphoma, sarcoma, teratoma, squamous cell carcinoma, mucoepidermoid carcinoma or haemangioepithelioma may occur.

2.2. **Secondary tumours**. Due to its rich vascularity, the thyroid is a common site of metastatic cancers, notably from malignant melanoma and cancers of the lung, breast and oesophagus.

CLINICAL MANIFESTATIONS

3 The most frequent presenting symptom is a swelling in the thyroid gland. If the tumour secretes thyroxine, the condition may present with the symptoms and signs of hyperthyroidism.

4 **Papillary carcinomas**. These account for about 70% of thyroid cancers. There is a bimodal peak incidence, the first and greater peak occurring in the second to third decade and the second in later life, with a female preponderance in a ratio of about 3.1. They are slow growing and may be present for decades without causing symptoms. They infiltrate locally to involve lymph nodes, the strap muscles of the neck and the trachea. Cervical lymph node enlargement may be the presenting feature. Blood-borne spread is to the lungs and bone.

5 **Follicular carcinomas**. This group accounts for 15-20% of thyroid cancers. They tend to occur in later life and affect females more commonly than males. They may take up iodine and respond to thyroid stimulating hormone. Rarely, frank hyperthyroidism may result. These tumours classically spread by blood rather than local infiltration. Metastases are common in lungs and bone. A rare sub-type of follicular cell carcinoma is the Hurthle cell tumour.

6 **Medullary carcinomas**. These arise in the parafollicular or C cells and account for about 5% of thyroid cancers. They may be familial and secretion of calcitonin is pathognomonic. The usual presentation is with an asymptomatic thyroid nodule. They may be part of the multiple endocrine syndrome. In such an event they are present along with phaeochromocytoma, parathyroid adenomas or mucosal and cutaneous neurofibromata, and the biochemical presentation can be dramatic. They infiltrate locally and metastasise to the lungs.

7 **Anaplastic carcinoma**. This type comprises about 5% of thyroid cancers, usually occurring in the sixth to seventh decades of life and with a female preponderance. It is locally invasive, highly malignant and very resistant to treatment. Characteristically, it presents with rapid, painful thyroid enlargement, often with dyspnoea or dysphagia.

AETIOLOGY

General risk factors for all cancers

8 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 individual cancers

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

Genetics

10 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.

11 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 or hygiene or a common legacy of infections in early life.

Environmental factors

12 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

13 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

14 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

15 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 the UVB element in sunlight. 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**, eg 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**, eg 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 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 increase 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 ~~id~~ 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

16 The effects of ionising radiation depend on the exposure size of the accumulated dose.

Therapeutic drugs

17 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

18 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

19 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.

20 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 thyroid cancer

21 There are two types of **familial** thyroid cancer, both of which are rare.

21.1. Medullary carcinoma can be either sporadic or familial when it is transmitted as an autosomal dominant trait and is frequently bilateral. It may be associated with the syndrome of multiple endocrine neoplasia.

21.2. Both papillary and follicular carcinomas may occur as part of the familial hamartoma syndrome.

22 Thyroid cancer, particularly the papillary type, is strongly linked to both external and internal **ionising radiation**. The risk is greater for females and is inversely related to the age at which exposure occurs. People of Jewish decent are at higher risk than other ethnic groups who have been studied.

22.1. The Radiation Effect Research Foundation follow-up studies of atomic bomb survivors showed a much increased incidence of thyroid malignancies. A similar effect resulted from atomic bomb tests in the Marshall Islands. More recently, the Chernobyl reactor accident caused an increased incidence of thyroid cancer, especially in children. In all these incidents, the effect was attributable to the inhalation or ingestion of the released radioactive isotopes.

22.2. Treatment with ionising radiation to the head, neck and upper thorax was popular for many conditions, some of them minor, in the past.

22.3. The development of benign or malignant thyroid tumours may occur as little as four years after exposure but the increased risk of cancer persists for more than thirty years.

23 There is no evidence of an increased risk of malignancy in adults treated with radioactive iodine (I^{131}) for thyrotoxicosis.

24 There is wide variation in the geographical incidence of thyroid cancer which does not correlate with low dietary iodine intake or with endemic goitres, although thyroid tumours in animals can be produced by iodine deprivation.

CONCLUSION

25 Carcinoma of the thyroid gland is a malignant tumour of the thyroid gland, the causes of which are discussed above and include exposure to ionising radiation. The course of the condition is unaffected by environmental factors other than those involved in its treatment.

26 There is no evidence that carcinoma of the thyroid is caused by climatic extremes, trauma, dietary deficiency, physical or mental stress or lowered resistance arising from hardship or other diseases.

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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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