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SUSCEPTIBILITY TO CARCINOGENIC EFFECT OF IRRADIATION

Relationship to age at time of exposure

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Abstract

Age at time of exposure is an important host factor influencing the subsequent cancer risk. Before completion of organogenesis, the fetus may be rather resistant, but thereafter the growing tissues of children are more susceptible than those of young adults. At greater age of adults at the time of exposure there is an increase in the subsequent absolute number of 'excess' cancer cases, but the relative risk (excess in relation to expectation) is rather constant for a given kind of radiation exposure as judged from the presently rather small number of investigations.

Irradiation accounts for about 10 per cent of all human malignancies in the Scandinavian area (7). The majority is due to ultraviolet irradiation (UV) and less than 3 per cent of the total cancer morbidity burden can be attributed to the effects of ionizing irradiation (20). Lifestyle is a major determinant of UV exposure, and modern technology accounts for about half the ionizing irradiation.

Ionizing irradiation has long been recognized as a health hazard. However, there has been renewed interest in the study of parameters besides UV exposure that are important for tumour development because of the recent realization that UV irradiation not only causes skin carcinomas but most likely also contributes to the development of human melanomas (12, 34, 49) and may cause murine leukaemia (11). Presently, we shall confine ourselves to discussing the importance of age at the time of exposure for subsequent tumour development.

Cancer intensity (risk of developing cancer in a coming year provided one is alive at the start of that period) roughly doubles every decade after the age of 30. The following factors explain this statistical correlation between cancer and age: (a) The mean latent period from exposure to clinically detectable tumour is about 7 years for radiation-induced leukaemia and 20 years for solid tumours (22, 50); (b) with increasing age the risk of exposure increases; (c) the changes of normal ageing alter the immediate response to carcinogens and probably also alter whatever defensive host responses there may be to malignant cells. The present article will deal specifically with these latter points.

Data from the literature

A retrospective study on the relationship between leukaemia and *prenatal exposure of humans* to irradiation indicates that the exposure rate of leukaemic children exceeds that of healthy controls by 25 to 75 per cent (28). Prospective studies of children exposed in utero to irradiation from atomic explosions (21) or to diagnostc irradiation (9) have not supported such a connection, and the question of an association between in utero irradiation and human cancer therefore remains unresolved (29).

When *mice* and *embryos* have been irradiated before or during the period of major organogenesis (days 6–12 in mouse and rat), the offspring kept for

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life very seldom has developed tumours. However, after the completion of organogenesis, the risk of tumour induction rapidly increases (3, 41, 42, 51).

Furthermore, all available evidence indicated that growing tissue of *children and adolescents* is more susceptible to cancer induction by some agents than the tissue of adults. Examples are leukaemia after irradiation of children (43) and breast cancer appearing after irradiation, the adolescent girl being most at risk (19, 32).

It is less clear whether normal ageing influences the susceptibility of adults to the tumour-inducing effect of a carcinogen to which the person has not previously been exposed. The human environment is so complex that non-exposure to a certain chemical can hardly ever be ascertained, yet several epidemiologic studies have dealt with this question.

The incidence of 'excess' cases of uterine cancer increases with age at the time of radiation treatment for metropathia hemorrhagica (44). For patients treated with radiation for cancer of the cervix uteri, the relative risk of secondary primary cancer in the organs having received irradiation in one study was about 1.4, but the ratio of observed to expected cancers for these sites did not vary appreciably with respect to age at irradiation (24). Patients irradiated for ankylosing spondylitis also had more excess cases of cancer the older they were at the time of irradiation (6). The ratio of observed to expected cancer incidence, however, did not increase with age at the time of treatment due to the age-dependent rise in spontaneous incidence (45).

A recent study of A-bomb survivors by BEEBE et coll. (1) clearly demonstrated that for persons aged 20 or above this age, there was an enlarged absolute excess risk with increasing age at the time of irradiation. Very important, they also found evidence that most radiation-induced cancers do not develop until the irradiated persons have reached the age when the type of tumour in question shows up spontaneously, which implies that age-dependent factors influence the expression of the disease. These findings were corroborated by KATO & SCHULL (23) who also observed that while there is a higher absolute risk of radiation-induced cancer with advancing age at bomb detonation, the *relative* risk of cancer observed in irradiated persons of a given age at detonation/observed in controls of the same age at detonation is highest in the young age cohorts.

It is noteworthy that although a rise in susceptibility with age is seen in some tissues, there is no evidence that mammary tissue ever becomes susceptible again after its susceptible period in adolescence (33). Thus, different tissues have their maximum susceptibility at a different age. Furthermore, the increase in relative risk after irradiation varies considerably, e.g. it is high with the relatively rare thyroid cancer and low with the common colon tumours.

In experiments with *adult animals*, the conditions are more well defined with regard to the type of irradiation and the dose involved. However, the dose necessary to induce a few tumours in adult mammals far exceeds the exposure humans encounter. The size of the irradiation doses used in the animal experiments may easily conceal the differences in susceptibility that may appear when the doses do not exceed repair capacities (37).

When senescent BALB/c mouse skin was exposed to carcinogens, the susceptibility increased as compared with younger adult skin. This was the case both when tumours are induced with β-irradiation (10) and UV light (11). Skin grafted from middle-aged to young recipients developed the same increased susceptibility to carcinogens with further ageing as non-grafted skin. The high susceptibility to carcinogens of senescent skin must thus derive from local, autonomously developing alterations in the skin itself.

Discussion

The high susceptibility of *children* and of *animal fetus* after the first embryo period as caused by the numerous mitoses (growth) is supported by the peak susceptibility of mammary tissue to the tumour-inducing effect of irradiation at the age of puberty. If for comparison we look at the effect of chemical carcinogens, we find that female rats develop the largest number of mammary tumours when given the carcinogen as adolescents. As this is the case with both a directly acting carcinogen and one that requires metabolic activation, the age-related changes probably occur within the mammary glands which are characterized by rapid proliferation of duct cells at this age (15). However, although proliferating tissue generally appears more susceptible to tumour induction on irradiation than cytokinetically more quiescent tissue, induction of malignancy in the developmentally most active tissue of early embryos seems difficult. The need for a certain, but not too advanced cellular differentiation for easy cancer induction is also known for chemical (39) and viral

(8) carcinogenesis. All normal cells contain oncogens (30) and with the realization that oncogens are activated during normal differentiation (14), it becomes likely that the state of the oncogens or their suppressors is responsible for this connection between age and susceptibility of proliferating tissue to tumour induction.

An enhanced susceptibility in *senescence* cannot be accounted for by presence of many mitoses. There may be a message in the rather constant ratio between enhancement in tumour incidence by a certain dose/mode of irradiation and the spontaneous tumour incidence at each age. If the so-called spontaneous and irradiation-induced tumours share a common rate-limiting step this could give the constant ratio observed. Normal ageing is accompanied by loss of repetitive sequences, at least for some cell types (48), and accompanied by demethylation of DNA (40). The importance of these DNA alterations is presently unknown. It is more certain that the state of some DNA repair systems plays a role. Excision repair capacities of cells from different species correlate well with the age at which cancer occurs (16). The relative capacity for DNA repair in different tissues influences the site of tumour development in an organism (38). Finally, there is a decrease in DNA repair capacity in ageing individuals (2, 27, 35). It is improbable, at least for skin, that local immunologic factors should play a role. Syngrafting which does not perceptibly influence the age-dependent susceptibility of skin to irradiation induction of cancer does change the number of Langerhans' cells in the skin as its response to sensitization (52). The general immune status, however, may be of some importance in connection with UV-induced tumours which are strongly antigenic as opposed to tumours induced with ionizing irradiation (25). Evidence of an immune response to the tumour cells, which is important for the development of the tumour, has been provided by the observation of an increased risk of developing carcinoma on partial abrogation of the cellular immune reactivity before UV irradiation (36). UV irradiation of skin furthermore causes a generalized suppression of some cellular immune responses in the bodies of mice (13) and man (17). This together with the known decline in cellular immune reactivity (T-cell functions) in older persons (18) makes it likely that the decline in general immune reactivity contributes to the enhanced susceptibility to the carcinogenic effect of UV light in older persons.

An *additive effect* of certain chemical carcinogens and irradiation is well known (26, 46, 47). A biochemical explanation may turn out to be shared pathways for repair of DNA damage by the chemical and actinic effects (4). It therefore becomes a pressing task for the future to study the interrelationship between the effects of irradiation and various chemicals in different age groups. The human environment invariably involves exposure to both types of carcinogens, and normal ageing is known also to increase the susceptibility to certain chemical carcinogens (5). With the continuing increase in mean remaining lifetime of e.g. the 50-year-olds (31), it becomes increasingly important to avoid carcinogenic exposure even in the elderly, especially since their susceptibility to tumour induction may be higher than that of younger adults.

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