A RECALCULATION OF THE AGE DEPENDENT DOSE-EFFECT-RELATIONSHIP OF THE LIFE SPAN STUDY OF HIROSHIMA AND NAGASAKI

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Abstract - The basis of the presented model is the multistage process of carcinogenesis as a biological effect. It provides simultaneously the age-dependent mortality of spontaneous and radiation induced solid tumors and dose-effect relationships at any age after exposure. The model has been used to describe the solid cancer mortality rates of the atomic bomb survivors of Hiroshima and Nagasaki. It has characteristics of both relative and absolute risk projections depending on the age of exposure.

INTRODUCTION

Major new insights into carcinogenesis have come from recent advances in cellular and molecular biology. The concept of oncogenes provides a simple explanation how agents as diverses as radiation, chemicals or retroviruses can induce tumors. Today it is known that a neoplasm usually arises from a single cell that has undergone a critical change. Despite its clonal origin, as the cells of a cancer grow and divide, progressive stages can be identified from preneoplasia to malignancy /1/.

To describe the age-dependent tumor incidence rate, we need to know the number of cells of an individual, cells which are able to divide and which are not yet damaged. M_0 is the number of these cells. In each of these cells are several DNA regions which are very sensitive to the induction of cancer. These are for example the proto-oncogenes, normal cellular genes, or tumor-suppressor genes. The mechanisms which convert proto-oncogenes into oncogenes, a process known as oncogene activation, are thought to be the critical genetic events in neoplastic transformation. An oncogene is a gene whose abnormal expression or altered gene product directly determines the production of the malignant phenotyp /2/. The generation of oncogenes from their non-transforming homologs, the proto-oncogenes, can occur in a variety of ways. Among other possibilities they can be generated by mutations within coding regions of oncogenes /3/. Much epidemiological and experimental evidence argues that malignant change is a process which results from multiple genetic alterations. Some of these steps involve oncogenes. The necessary mutations for the origin of cancer are assumed as independent from each other.

THE MODEL

The following differential equation describes the time dependent behaviour of the arising of the first step in the successive process of mutations.

$$\frac{dM_1(t,C,dD/dt)}{dt} = \left(B_0 M_0(t) - B_1 M_1(t)\right) P_u(C,dD/dt) \qquad (1)$$

M_1 (t, C, dD/dt) is the number of cells per individuum at time t which are in the first transformation step, for example: which have one point mutation on a critical, tumor relevant gene locus. The spontaneous cancer incidence rate is mainly dependent of the radicals produced by the natural cell metabolism and by chemical carcinogens. We describe these two damage probabilities with their concentration C. The spontaneous cancer incidence rate is also dependent on the dose rate dD/dt from natural background radiation. B_0 is the number of critical DNA bases (nucleotides) in critical codons of all tumor associated genes per cell. B_1 is the number of critical DNA bases (nucleotides) in critical codons of all tumor associated genes per cell after the first transformation. P_u (C, dD/dt) is the probability for mutations at usual conditions /4/. Equation (1) describes the first step necessary for a complete carcinogenesis. The number of steps necessary for the induction of cancer defines a system of coupled differential equations. Each transformation is represented by one differential equation. We assume that P_u (C, dD/dt) is constant over lifetime. The sink on the right side of equation (1) is due to the fact that cells which have reached the first step of damage are a source term for the second step. M_1 is several orders of magnitude smaller than M_0. Therefore this sink can be neglected and we can set M_0 (t) $\equiv M_0$ = const. Because of P_u = const. the differential equation (1) can be directly integrated:

$$M_1(t) = B_0 M_0 \; P_u \, t \qquad (2)$$

For M_i (t) we get:

$$M_i(t) = B_0 B_1 \ldots B_{i-1} M_0 P_u{}^i \frac{t^i}{1 \cdot 2 \cdot \ldots \cdot i} \qquad (3)$$