

How does cancer begin?

A brief description of the multistage model of cancer

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When an organism is exposed to a toxic chemical, the nature and extent of the damage depends on the nature of the chemical and extent of the exposure (at what concentration, for how long). Usually, the effect of a chemical on an individual is progressive: increased exposures cause increased damage. In the case of cancer however, either the subject has a tumor or does not; there are no half measures. What changes with the dose of a carcinogenic chemical is not the severity of the response, but the chance that it will occur. Thus, for carcinogens the dose-response relationship is described in terms of risk associated with exposure to a certain level of a chemical for a certain amount of time.

The most widely accepted mathematical model for cancer is the "multistage model of carcinogenesis." Its basic hypothesis is that cancer results from alterations in growth-regulatory genes, so that affected cells are no longer subject to the strict control of growth and differentiation of normal tissue cells. The observed process has three phases:

- **Initiation**, in which some genetic alteration occurs in a target cell,
- **Promotion**, in which the altered cell grows and develops a clone group of altered cells appearing as a tumor,
- **Progression**, in which the tumor cells grow, become more aberrant and invade surrounding tissues; this requires a series of secondary genetic changes.

The multistage model of human cancer is based on the idea that several successive mutational events are necessary to result in the disease. Current research on human tumor development suggests that five or more different mutations may be required to generate malignant tumor cells. This helps explain why cancer is associated with age.

Genetic changes, which can be produced by reactive chemicals damaging the DNA, are the essential feature of the initiation phase, and are also thought to be involved in the later stages. To model what is known about the carcinogenic process, researchers assume there is no threshold dose. Any exposure to a toxicant that can damage DNA involves some risk of contributing to the carcinogenic process. Because cancer develops over time, and through multiple stages, the risk posed by single carcinogenic exposures is likely to be very small. However, continued exposures to carcinogens over time is statistically associated with disease. More recent research suggests that the multi-stage progression is actually a series of cycles of genetic damage followed by cell growth. In this case, certain exposures that interfere with this cycle at later stages could be just as damaging as those causing initiation.

Based on what is known about the relationship between DNA damage and cancer induction, researchers also assume that the relationship between dose and carcinogenic response is linear at low doses. At higher doses (such as those in animal cancer bioassays) the response curve may become steeper. Theory suggests that added exposures over time actually may have a multiplicative, rather than a simply additive, effect on probability of disease. Repeated low-dose exposures over a lifetime can, therefore, significantly increase probability of disease. This is in contrast to threshold models commonly used to assess noncarcinogenic risks in which the damage process only begins when some protective factor or process has been exceeded.

Most of the documented examples of human cancer induced by chemical exposures involved repeated exposures over time and across disease pro-

gression stages. Similarly, most animal studies involve prolonged exposures, usually for most of the expected lifetime of the test animals. One important point of the multistage model, which is supported by experimental findings in human and animal studies, is that while high-dose, short-term exposures to carcinogens are an appropriate public health concern, so too are lower-dose exposures that can contribute to cumulative genetic damage over long periods of time. Particularly given a consistent background of carcinogenic exposure, the issues of multistage development and the multiplicative effect of repeated exposures make examination of and prevention of exposure to any carcinogens a public health concern.

Extended mathematical models have been developed to help analyze these situations. The "two-stage clonal expansion model" proposed by Moolgavkar and co-workers of the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center in Seattle, may do a better job of predicting promoter effects by taking into account the processes of cell death and cell division. The long-term effects of these processes may be particularly important in infants and children, whose tissues are undergoing high rates of cell division as a natural part of maturation. Also, the long period of expected lifespan following an exposure during infancy may increase the chances of seeing adverse effects with a very long latency (the time between the initial exposure and the observation of the final result, such as a tumor).

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