

# Commentary: Fifty years of the multistage model: remarks on a landmark paper

Suresh H Moolgavkar

Fifty years after its publication, the multistage model proposed by Armitage and Doll<sup>1</sup> continues to influence biological and epidemiological thinking on the processes underlying carcinogenesis. I am pleased that the *International Journal of Epidemiology* has chosen to republish Armitage and Doll's landmark paper, and I am honoured to write a commentary on it.

With the rapid advances in molecular biology over the last 50 years, we know a lot more about the process of carcinogenesis than we did when Armitage and Doll wrote their paper. Yet, the fundamental predicate on which their model is based, that malignant transformation of a normal cell results from the accumulation of a few critical mutations, remains unchallenged. To be sure, the Armitage-Doll model needs to be embellished in various ways to accommodate our current thinking on carcinogenesis. Perhaps the most important of these embellishments is the allowance for clonal expansion of partially altered cells on the pathway to cancer. Even this development was anticipated by Armitage and Doll in their follow-up paper in 1957.<sup>2</sup>

Building on ideas of Fisher and Holloman<sup>3</sup> and Nordling,<sup>4</sup> Armitage and Doll proposed that the remarkable regularity observed in the age-specific mortality rates for many adult carcinomas could be explained by a multistage model for carcinogenesis. But they went a lot further. They recognized that some carcinomas, particularly the hormone-dependent carcinomas, showed departures from this behaviour and considered reasons for such departures. In particular, they investigated the implications of carcinogens acting on various stages of the process on the temporal evolution of cancer risk. This work foreshadowed and set the stage for later work by Whittemore,<sup>5</sup> Day and Brown,<sup>6</sup> and Brown and Chu,<sup>7</sup> among others.

Following Fisher and Holloman and Nordling, Armitage and Doll restricted their attention to cancer mortality between the ages of 25 and 74 because the data were considered to be unreliable for older age groups. In this range of ages many of the carcinomas they examined exhibited log-log behaviour, i.e. the logarithm of age-specific mortality increased linearly with the logarithm of age with a slope of about 6, which accorded well with a model requiring seven stages for malignant conversion of a normal cell. In later analyses, however, it was noted<sup>8</sup> that at higher ages the age-specific rates showed substantial departures below the rates predicted by log-log behaviour. Doll and Peto<sup>9</sup> reported that lung cancer risk among men aged 80–84 appeared to be half that among men aged

75–79. They offered four possible explanations for this finding. These were under-diagnosis, selective survival, unreported cohort differences of smoking patterns in early life, and the possibility that the biology of extreme old age reduces the risk of carcinoma. A more general explanation is that human populations are heterogeneous with respect to their susceptibility to cancer, either for genetic or environmental reasons. As populations age, the more susceptible individuals get cancer so that at extreme old ages one observes cancer in only the least susceptible individuals. In a later paper, Stevens and Moolgavkar<sup>10</sup> reported that after adjustment for cigarette smoking and other temporal trends, lung cancer mortality rates among British males 80–84 were not lower than the rates among those 75–79. Nevertheless age-specific rates showed significant departures below the predictions of log-log behaviour. In fact, any general multistage model makes precisely this prediction as I discuss below.

In their original paper describing the multistage model, Armitage and Doll used a simple approximation to the exact hazard (incidence) function. While this approximation was perfectly adequate for their purposes, the exact hazard functions of fairly general multistage models have important properties that the approximations do not possess. First, the (exact) incidence functions predicted by the models approach a finite asymptote, i.e. they cannot increase without bound.<sup>11,12</sup> For the Armitage-Doll model it is easy to see that this asymptote is  $N\lambda_{\min}$ , where  $N$  is the total number of susceptible cells and  $\lambda_{\min}$  is the minimum of the transition (mutation) rates between stages.<sup>12</sup> For the log-log cancers this fact implies that with increasing age, the age-specific incidence will increasingly deviate below the line defined by the log-log relationship.

The second consequence following from consideration of the exact hazard functions of multistage models has to do with the behaviour of the age-specific incidence curve after exposure to an environmental carcinogen ceases. Suppose that exposure to an environmental agent increases the rate of one or more of the steps in the carcinogenic pathway, e.g. by increasing the rates of specific mutations or of clonal expansion of initiated cells. Suppose also that these rates revert to background rates after exposure stops. Then the exact (but not the approximate) hazard functions asymptotically approach the hazard function in those individuals who were never exposed.<sup>11</sup> This phenomenon has been observed among ex-smokers, for example. In many epidemiological studies incidence rates of lung cancer in ex-smokers appear to approach the incidence rates in non-smokers about 15 years after quitting smoking. One possible explanation for this phenomenon is that repair of damaged tissue has occurred after exposure stopped. This could well be true, but this

Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA. E-mail: moolgavkar@earthlink.net

explanation need not be invoked. The reversion of the incidence function to background rates is a mathematical consequence of multistage carcinogenesis.

The third consequence has to do with the incidence of second malignant tumours among individuals in whom one has already occurred. A computation using the exact solution shows that the age-specific incidence of second malignant tumours is higher than the age-specific incidence of the first malignant tumour (at the same age). While the incidence of second malignant tumours is difficult to study in human populations because of the treatment intervention after the occurrence of the first tumour, animal experiments appear to show that this is indeed true.<sup>13</sup> The explanation has been advanced that physiological and immunological changes after the first malignancy renders the animal susceptible to a second tumour. This may be true but the higher incidence of second tumours is a logical consequence of multistage carcinogenesis.<sup>14</sup>

It is a rare paper that continues to be widely cited 50 years after publication. The paper describing the Armitage-Doll model—often referred to as THE multistage model—is one such rare paper. I congratulate Professors Armitage and Doll on the occasion of the republication of this important and influential paper.

## Acknowledgements

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## References

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# Commentary: The age distribution of cancer and a multistage theory of carcinogenesis

Richard Doll

In 1948, when I began to work with Professor Bradford Hill at the Medical Research Council's Statistical Research Unit, ideas about the causes for cancer were still dominated by those of the great German pathologists of the 19th century. A favourite idea was that cancers arose from embryonic cells that had persisted unchanged in character in adult tissues. The idea that a cancer might arise from a mutation in the hereditary material of a somatic cell had been suggested at least as early as 1930 by

McCombs and McCombs<sup>1</sup> and this, I believe, had also been suggested some 15 years before, but I forget by whom. It was not, however, widely believed, which was surprising in view of the fact that Muller's demonstration,<sup>2</sup> as long ago as 1927, that X-rays could produce hereditary mutations in fruit flies was universally applied and its application to humans was not questioned. X-rays, however, were not thought to be able to cause cancer unless they had caused macroscopic damage to tissues.<sup>3</sup> Even as late as 1960 it was possible for Austin Brues, a distinguished American scientist, to write a 'Critique of mutational theories of carcinogenesis'.<sup>4</sup>