6. MODELLING THE RELATIONSHIP BETWEEN RISK, DOSE AND TIME

CHAPTER 6

MODELLING THE RELATIONSHIP BETWEEN RISK, DOSE AND TIME

6.1 Introduction and rationale

The previous two chapters developed the statistical methods now available for fitting models to data from cohort studies. It was emphasized that the association between excess risk for disease and the temporal record of exposure may depend on many features of the exposure history, and that a misleading picture may emerge from the analysis if a relevant variable is omitted. An example is given in Figure 5.6, where much of the apparently powerful effect of time since first exposure is shown to result from a major change in exposure at the Montana smelter in 1925. The purpose of this chapter is to describe the types of variable that one might expect to be important, either from the behaviour of excess risk observed in previous studies, or from models of carcinogenesis derived theoretically but supported by both experimental and epidemiological results. Attention will also be given to the forms of dose-response curve that past experience or theoretical considerations would suggest might be appropriate. It is important, furthermore, that, however excess risk is modelled, the results of the analysis respond to the basic aims of the study. The underlying purposes of the investigation need to be kept firmly in view. These aims are essentially of two types – first, to provide a scientific basis for public health and, second, to contribute to the understanding of the biology of human disease. The former requires accurate assessment and prediction of risk, the latter requires an understanding of the role in the disease process played by different exposures over time.

In the area of public health, epidemiology is expected to assist in resolving such questions as:

(i) In early detection programmes for breast cancer, the breasts of women aged over 40 years might be exposed every year, or every two years, to a low dose of radiation, perhaps 0.2 rads per examination. Does this dose, cumulated over time, represent an appreciable hazard for inducing breast cancer? Is the hazard comparable in magnitude to the reduction in breast cancer mortality attributable to screening?

(ii) Do the materials used to replace asbestos represent a carcinogenic hazard? Are the data currently available sufficient to assess whether the risk is appreciably less than that associated with asbestos?

(iii) The carrier state for hepatitis B virus is a major risk factor for primary liver

cancer. Given the dynamics of infection with this virus in a population, what long-term effect on liver cancer rates would be predicted by a mass vaccination programme?

To answer questions of this type, models are required relating risk to exposure, both in terms of the degree of exposure and the time during which exposure occurred. These models should provide a reasonable basis for extrapolation from the observed range of exposure to the levels of interest. Examination of the currently available data on a range of exposures should indicate what type of behaviour is observed epidemiologically, thus suggesting which models have empirical support (see §6.2).

To assist in understanding the biology of human disease, biological models of disease causation and development are helpful. These models come mainly from experimental or in-vitro work, in which the process of carcinogenesis is observed at the cellular level. To translate models constructed to describe cellular events into models that can describe events at the population level, i.e., incidence rates, requires a degree of abstraction that is best handled by mathematics. For this reason, mathematical models of the carcinogenic process have received considerable attention, since they have the potential for describing in a unified way a wide variety of phenomena. Use of these models for interpretation of epidemiological data may assist in understanding the mode of action of agents carcinogenic to man. Section 6.3 outlines some of the models of carcinogenesis that have been proposed, with the implication of these models for the behaviour of incidence rates. In §6.4, we attempt to describe the data of §6.2 in terms of these models.

The material of §§6.2 to 6.4 highlights the variables that appear to be the most concise predictors of future risk. These variables would therefore appear to be those of greatest value to incorporate in analyses of epidemiological studies.

In §6.5, we consider further the data from the South Wales cohort of nickel refiners to illustrate how multistage concepts may be used to aid in the interpretation of epidemiological results.

6.2 Dose-time relationships observed in epidemiological studies

In this section we examine the metameters of dose or exposure that have been used in a number of situations, the relationship of these metameters to excess risk and the influence of different time variables. The latter include duration of exposure, time since first exposure, time since exposure stopped and age at first exposure. The effect of these factors on incidence rates differs for different exposures, presumably in a manner determined by the mode of action of the exposure. This topic is considered in §§6.3 and 6.4.

As observed in Chapter 1, most of the data that provide quantitative information on the relationships of both time and dose with excess risk come from cohort studies, and we limit our discussion mainly to data of this type. The main factor thus excluded, for which quantitative data relating dose and risk are available, is alcohol. Quantitative data relating alcohol consumption to cancer come predominantly from case-control studies, some of which were described extensively in Volume 1.

(a) *Lung cancer and cigarette smoking*

The cohort study for which the most extensive follow-up results have been reported is that of the British doctors. In the publication (Doll & Peto, 1978) that considered specifically the quantitative association of amount smoked and duration of smoking with lung cancer risk, attention was confined to lifelong nonsmokers or men who reported a regular smoking pattern in response to the three questionnaires (i.e., men who started smoking between ages 16 and 25 years, and who never reported stopping, changing by more than five cigarettes/day, or smoking any form of tobacco other than cigarettes). The purpose of these restrictions was to obtain the most accurate estimate of the dose-response curve by limiting the analysis to individuals with the most stable and most accurately recorded smoking histories. A summary of the basic data has been given in Table 4.21, where person-years and numbers of observed lung cancer deaths are tabulated by current age and amount smoked. The analysis investigating the relationship between dose and risk used as a measure of dose the average number of cigarettes smoked per day. A two-factor multiplicative model was fitted (expression 4.2), with one set of parameters giving age effects and the second set of parameters giving dose effects. The ratio of these latter parameters can be interpreted as relative risks. The results of a similar analysis by the original authors are displayed in Figure 6.1. The exclusion from the formal analysis of those men smoking more than 40 cigarettes a day has aroused some discussion, but is defended at length by them. The functional form used by the authors to fit the curve of Figure 6.1 is

$$\text{Relative risk} = 0.0278(\text{Dose} + 6)^2, \tag{6.1}$$

the baseline being taken as nonsmokers. As described in Tables 4.22 and 4.23, other functional forms could be used to fit the observed curve, such as:

$$\text{Relative risk} = (1 + \text{dose})^k$$

or

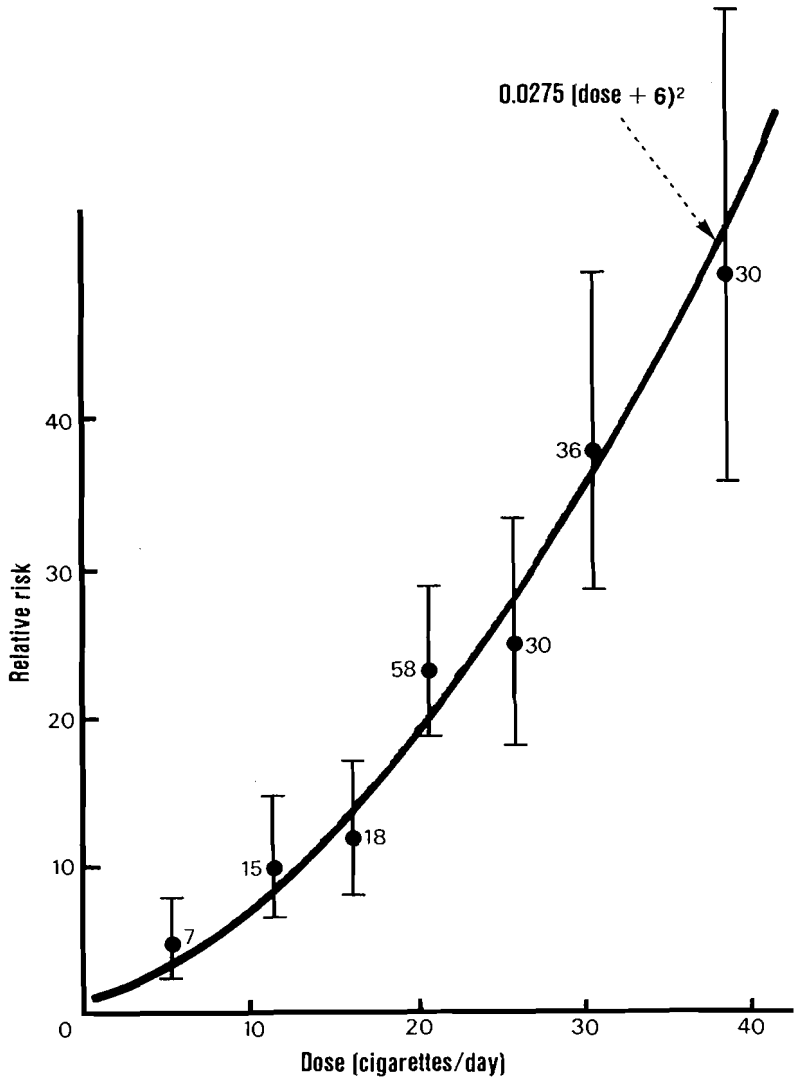
$$\text{Relative risk} = 1 + b\ \text{dose} + c\ (\text{dose})^2,$$

which may yield a sightly better fit than the curve given in Figure 6.1. All three, however, indicate significant upward curvature.

This analysis has used data in which within-individual variation in smoking habits has been reduced to a minimum. In other studies, in which individuals with varying smoking habits were not excluded from the published analyses, the dose-response relationship appears almost linear. The main point at issue here, however, is not the existence of some upward curvature, but the metameter of exposure that was used – average number of cigarettes smoked per day.

The age parameters obtained from the preceding analysis were normalized to be interpretable as age-specific rates, standardized for dose. The logarithm of the rate was plotted against the logarithm of the age and against the logarithm of the duration of smoking before onset of disease (taken as age – 22.5). Both gave a reasonably straight line, although with a different slope, reflecting the high correlation between the

Fig. 6.1 Relative risk of lung cancer in terms of number of cigarettes smoked per day. The numbers of onsets in each group are given, and 90% confidence intervals are plotted. The point for those smoking more than 40 cigarettes/day is omitted. From Doll and Peto (1978)



resulting estimates of k and w when fitting models of the form

$$\text{Mortality rate} \propto (\text{Age} - w)^k, \tag{6.2}$$

where $\propto$ denotes proportionality.

The choice between age or duration of smoking as the time variable to use to describe the mortality rates among smokers cannot be made on statistical grounds from these data. However, the exponent of 4.5 for duration of smoking is similar to the exponent for the power curve describing age-specific lung cancer rates among nonsmokers. Testing for interaction with dose gave no indication that the relationship of mortality with duration of smoking varied with amount smoked. Mortality rates for lung cancer among continuing smokers in the British doctors study could therefore be

Table 6.1 Evolution of mortality from lung cancer among ex-cigarette smokers[a]

	Time since smoking stopped (years)				
	0	<5	5–9	11–14	>15
No. of deaths among ex-smokers[b]		10	12	8	7
No. of deaths as percentage of no. expected among continuing smokers	100	68	35	25	11
No. of deaths divided by no. expected among lifelong non-smokers (i.e., relative risk)	15.8	10.7	5.9	4.7	2.0

[a] From Doll and Peto (1976)
[b] Excluding those who stopped smoking after developing lung cancer

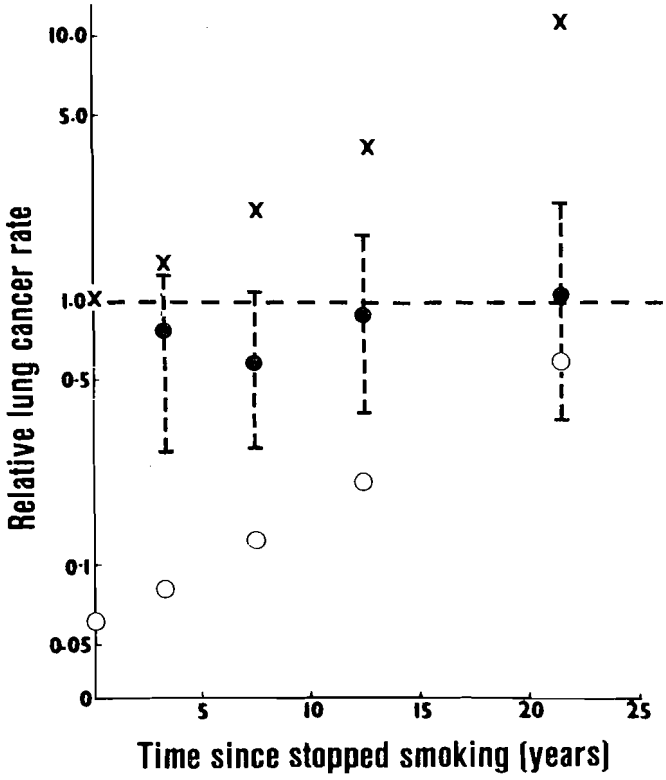
succinctly summarized by a single expression incorporating both amount smoked and duration of smoking, as follows:

$$\text{Mortality rate} \propto (\text{cigarettes/day} + 6)^2(\text{Age} - 22.5)^{4.5}. \tag{6.3}$$

In an earlier paper reporting on the same study, data were also given for ex-smokers (Doll & Peto, 1976). Within a few years of quitting smoking, lung cancer rates fell away from the rates seen in continuing smokers and after 15 years or more approached levels seen in nonsmokers of the same age. Table 6.1 gives the falling relative risks. The evolving risks after quitting smoking are displayed in Figure 6.2, from which it appears that the absolute rate for lung cancer freezes at the level reached when smoking stopped. Thus, for an ex-smoker, lung cancer rates can also be expressed in terms of duration of smoking and average amount smoked per day, as in expression (6.3). Duration of smoking could clearly be replaced by time since smoking started minus time since smoking stopped; the choice of which two of these three variables to use in expressing the effect of time is somewhat arbitrary. In the present situation, duration of smoking and time since stopped appear the most appealing. In a later example, time since first exposure is of particular importance.

In the British doctors study, the age at which cohort members started to smoke showed insufficient variation for it to be adequately studied. The preceding description of risk applies to individuals who started to smoke around the age of 20 years. The effect of age at which smoking started can be examined from other studies. Some results are given in Table 6.2, taken from the Dorn study of US military veterans (Kahn, 1966). Although the range of ages at starting to smoke is not large, it is broad enough to see that the mortality rates, given the duration of smoking, are independent of the age at starting. Thus, equation (6.3) above, expressing mortality as a function of dose and time, holds irrespective of the age at starting, provided that (age − 22.5) is replaced by duration of smoking. Thus, lung cancer rates among current smokers or ex-smokers can be expressed accurately just in terms of duration of smoking and of average number of cigarettes smoked per day.

Fig. 6.2 Mortality rates (logarithmic scale) of lung cancer in ex-smokers (●), expressed as a proportion of the rates expected in regular cigarette smokers at the ages at which smoking was stopped; by time since smoking was stopped. For comparison, similar proportions are shown for regular cigarette smokers of the same age (×) and for lifelong nonsmokers of the same age (○). From Doll (1978)



(*b*) *Asbestos and mesothelioma*

The high risk of cancer, mainly lung cancer and mesothelioma, following asbestos exposure has been extensively studied. A recent review (Peto, J. *et al.*, 1982) has examined in detail the risk of mesothelioma as a function of time, using the results of the five studies for which mesothelioma rates were available by time since first

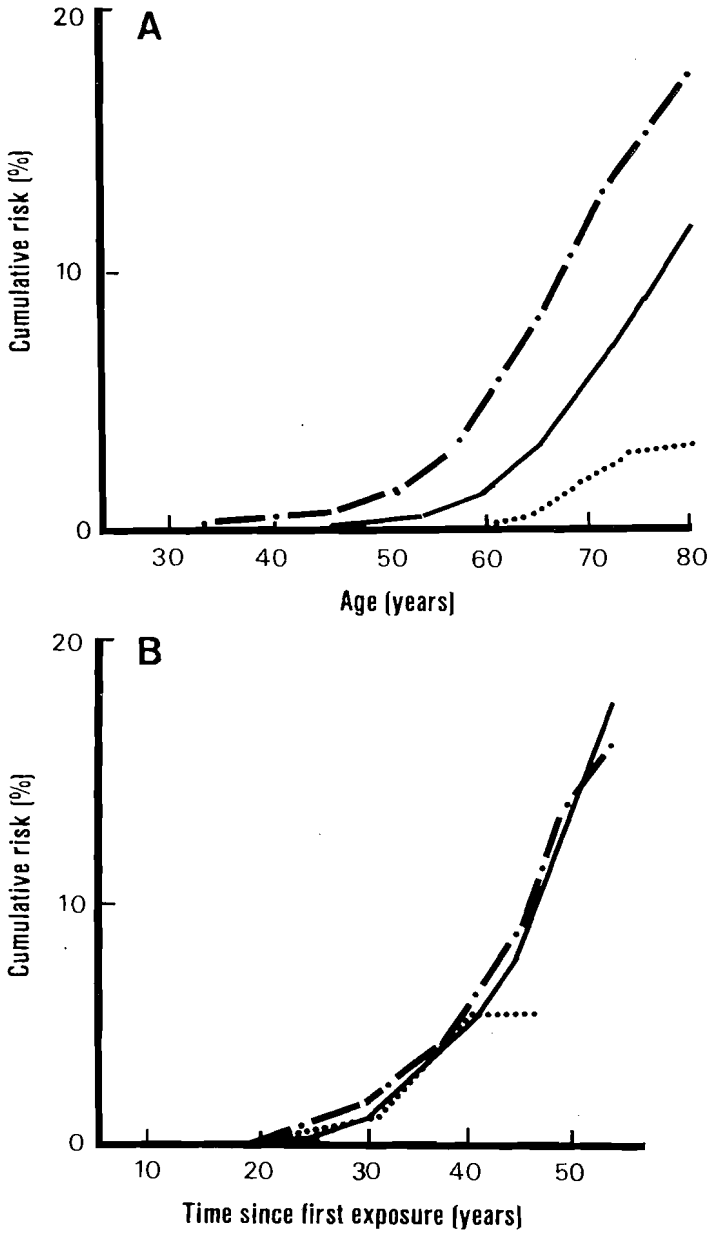
Table 6.2 The effect of age at starting to smoke on mortality from lung cancer[a]

Age at starting to smoke (years)	Annual mortality rate per 100 000 population (age in years)	
	55–64	65–74
<15	251	
15–19	168	
20–24		241
25+		162

[a] From Appendix Table D of Kahn (1966)

exposure. The effect of age at first exposure was investigated in the cohort of North American insulation workers, which contributed two-thirds of the mesothelioma cases recorded in the five studies. Mesothelioma is rare among the general population, so that cases unrelated to asbestos in the study population would be unlikely. Thus, as in the analysis of the nasal sinus cancers in §5.6, mortality rates from mesothelioma among the exposed can be examined without the need for reference to a background rate. Mortality rates are shown in Figures 6.3A and 6.3B by age at death and by age at

Fig. 6.3 Cumulative risk of dying of mesothelioma in the absence of other causes of death among North American insulation workers first exposed to asbestos at age 15–25 (·–·–), 25–34 (——) or over 35 (· · ·), against age (A) and against years since first exposure (B). From Peto, J. *et al.* (1982)



first exposure. As for lung cancer and cigarette smoking, age at first exposure does not affect the rates. The superposition of the curves in Figure 6.3B is striking.

Since age at first exposure can be ignored, curves of similar form can be used to relate time since first exposure to mesothelioma rates for each cohort without need for a stratification by age. Figure 6.4, displaying data for US insulation workers, indicates that mesothelioma rates increase with a power of age since first exposure:

$$\text{Mesothelioma mortality rate} = b(\text{time since first exposure})^k. \tag{6.4}$$

One might interpret the parameter b to represent in some way the intensity of the exposure, and the parameter k to represent an inherent characteristic of the process of mesothelioma development. k might be similar in different cohorts, whereas b would be expected to vary between cohorts. The results of fitting the above expression simultaneously to the data from all five cohorts, with the same value of k for each cohort but allowing b to vary, are given in Table 6.3. The fit is excellent, and holds equally well for either pleural or peritoneal tumours (with a value for k of 3.2). As in the preceding example with cigarette smoking, other models of the form:

$$\text{Rate} \propto (\text{time of exposure} - w)^k$$

fit the data equally well, and in fact the expression

$$\text{Mesothelioma rate} = b(\text{time since first exposure} - 10)^2$$

fits better than (6.4) in the first 15 years, and equally well thereafter. Subtracting ten years may reflect the length of time taken for a transformed cell to progress into a fatal tumour.

The preceding discussion has ignored both length of exposure and any effect of stopping exposure. Once asbestos exposure has taken place, however, fibres remain in the body, and the relationship between external exposure and the more relevant tissue exposure is unclear. The latter may well continue long after the former has been removed. For this reason, both duration of exposure and time since last exposure are ill-defined for asbestos. Furthermore, it is clear from Table 6.3 that an adequate description of mesothelioma rates can be given without taking account explicitly of exposure cessation.

The parameter b, which varies considerably between the cohorts given in Table 6.3, would represent effective dose, incorporating average length of exposure, intensity of exposure and the potency for mesothelioma induction of the specific type of fibre. No data currently available suggest that the parameter k differs between cohorts with long-term continuous exposure and those with short-term exposure.

Thus, rates for mesothelioma induced by asbestos can be well summarized in terms of time since first exposure, together with some measure of cumulative exposure, which combines duration with dose level. The contrast with the cigarette smoking–lung cancer relationship is marked, and will be discussed in §6.3 in terms of models of carcinogenesis.

Fig. 6.4 Mesothelioma mortality among North American insulation workers first exposed 1922–1946, by time since first exposure. Bars indicate 95% confidence intervals. From Peto, J. *et al.* (1982)

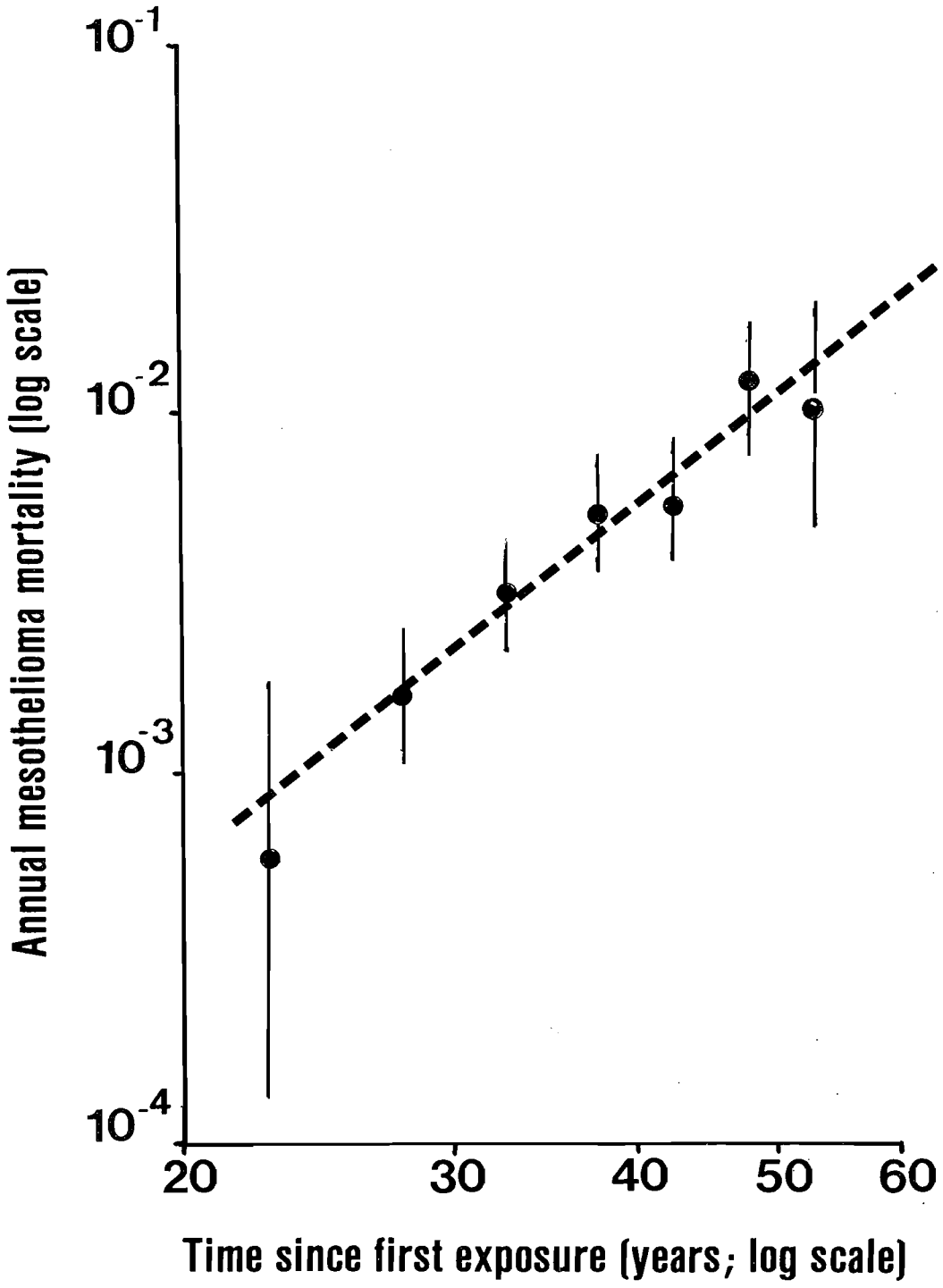


Table 6.3 Numbers of mesotheliomas (N), and man–years (M–Y) of observation in studies of asbestos workers. Expected numbers (E) are obtained by fitting death rate = b (time since first exposure)$^{3.20}$, where b is constant[a]

Study		Years since first exposure									
		10–	15–	20–	25–	30–	35–	40–	45–	50+	Total
Selikoff *et al.* (1979)	N			3	22	47	46	25	28	9	180
North American insulation	E			4.58	22.59	44.26	41.64	31.17	23.59	12.17	180.00
workers (mixed exposure;	M–Y			4939	12815	14711	8756	4391	2328	872	48812
$b = 4.37 \times 10^{-8}$)											
Newhouse & Berry (1976)	N	1	6	15	11	12					45
Factory workers (mixed	E	2.59	6.32	10.37	12.84	12.87[b]					45.00
exposure; $b = 4.95 \times 10^{-8}$)	M–Y	16167	13438	9862	6423	3772					49662
Peto, J. (1980)	N	0	0	1	2	2	2	0			7
Chrysotile textile	E	0.16	0.52	1.10	1.77	1.69	1.32	0.44			7.00
workers ($b = 2.94 \times 10^{-8}$)	M–Y	1633	1800	1761	1496	837	414	92			8093
Hobbs *et al.* (1980)	N	1	12	13							26
Australian crocidolite	E	4.53	8.32	13.15[c]							26.00
miners ($b = 2.94 \times 10^{-8}$)	M–Y	27172	17012	12028							56212
Seidman *et al.* (1979)	N	0	0	2	5	7	0				14
US amosite factory workers	E	0.58	1.48	2.73	4.01	4.68	0.52				14.00
($b = 4.91 \times 10^{-8}$)	M–Y	3628	3274	2618	2026	1383	98				12927

[a] From Peto, J. *et al.* (1982)
[b] 30 or more years; 32.5 assumed in calculating expected number
[c] 20 or more years; 22.5 assumed in calculating expected number

(c) *Asbestos and lung cancer*

Among cohorts exposed to asbestos, in which excesses of both mesothelioma and lung cancer are observed, the ratio of the excess number of lung cancers to the number of mesotheliomas decreases sharply with increasing time since first exposure. It increases, however, with increasing age at first exposure. It is clear, therefore, that the excess of lung cancer evolves with time in a different manner to the excess of mesothelioma.

A number of cohorts have been extensively studied, and a review of the major studies has been made by Acheson and Gardner (1980) to establish dose-response patterns. A linear relationship between cumulative dose and excess relative risk has been observed in several studies – for example, the study of Quebec asbestos miners (Fig. 6.5). Workers at an amosite asbestos factory in New Jersey during the Second World War were heavily exposed for short periods, and study of this cohort has provided a clear picture of a linear relationship between duration of exposure and excess relative risk (Fig. 6.6) (Seidman *et al.* 1979). In one study, little extra effect of reported asbestos exposure levels was seen after adjusting for duration of exposure (Peto, J., 1980). That is to say, duration of exposure may give a measure of cumulative dose which cannot be appreciably improved by measurement of dose level, given the relative imprecision of these latter measurements, at least in previous decades.

Fig. 6.5 Dose–response relationships for lung cancer following asbestos exposure in Quebec miners and millers. From Acheson and Gardner (1980)

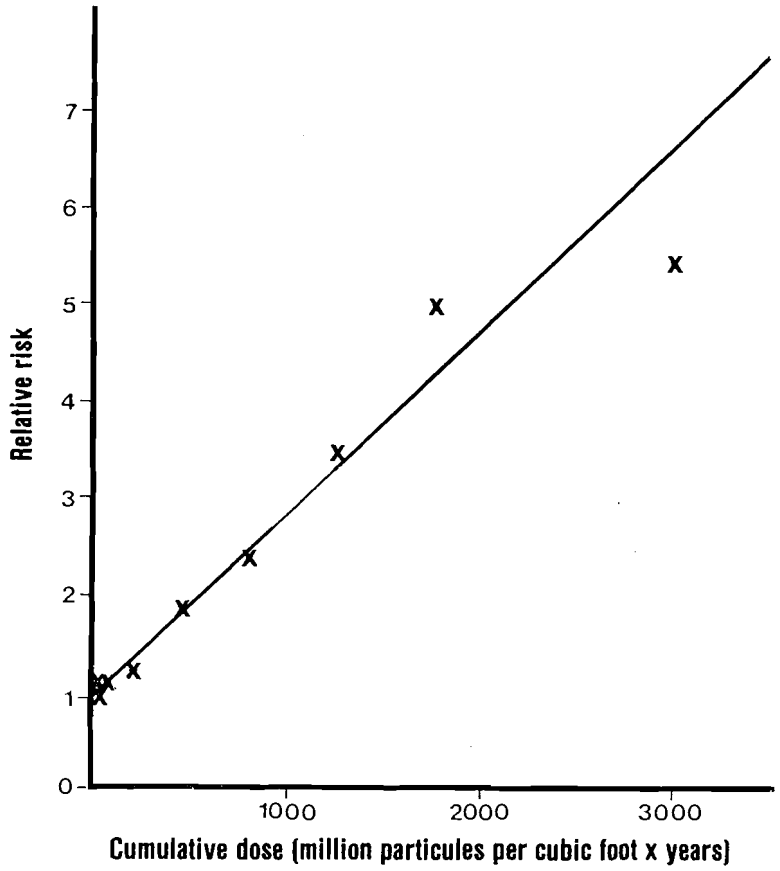
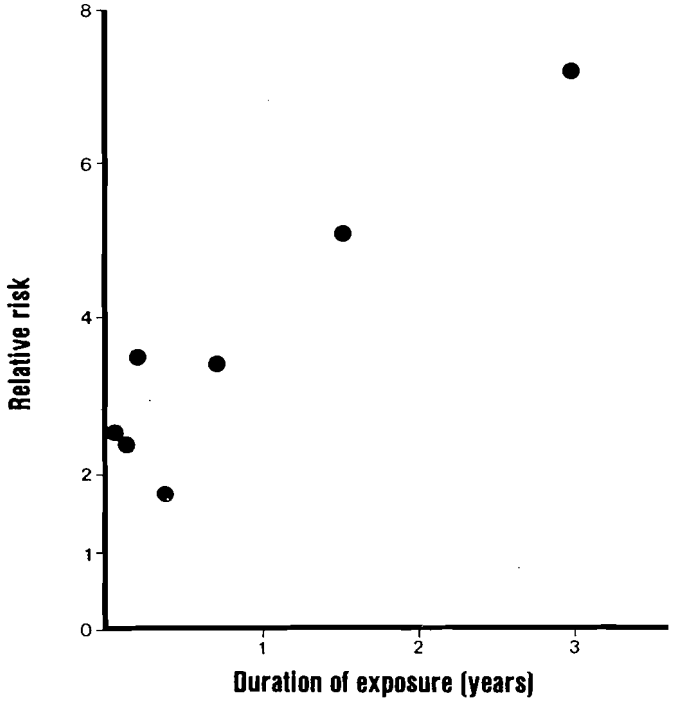


Fig. 6.6 Relative risk of death from lung cancer in a group of amosite insulation workers, by duration of exposure (after Seidman *et al.*, 1979). From Acheson and Gardner (1980)



In the study of US insulators, follow-up has continued for 50 years since first exposure; the excess relative risk for lung cancer by year since first exposure is given in Table 3.10, and by age at first exposure in Table 6.4.

From Table 3.10 one can see that the relative risk reaches a plateau some 15 years after start of exposure, where it remains indefinitely. There is some indication that 40 years or more after exposure starts the relative risk begins to decrease. The significance of this fall is doubtful, however, since one might expect the attrition of smokers,

Table 6.4 Expected and observed numbers of deaths from lung cancer among 17 800 asbestos insulation workers, 1 January 1967–31 December 1971; distribution by age at onset of exposure[a]

Age at onset of exposure (years)	Deaths from lung cancer		
	Expected[b]	Observed	Ratio
<25	18.19	102	5.61
25–34	15.20	66	4.34
35–44	8.78	38	4.33
45+	2.25	7	3.11

[a] From Selikoff *et al.* (1973)

[b] Expected deaths are based upon age-specific death rate data of the US National Office of Vital Statistics. Rates for 1968–1971 were extrapolated from rates for 1961–1967.

particularly heavy smokers, to be even more rapid in this cohort than in the general population (see Chapter 3). This differential attrition would lead to an apparent fall of the excess relative risk of lung cancer with time, and contribute to the observed decrease. As mentioned earlier, the effect of stopping exposure is difficult to assess for asbestos. As seen in Table 6.4, the relative risk is roughly independent of age at first exposure, although a slight fall with increasing age is seen. Since lung cancer rates increase rapidly with age, the absolute excess risk rises rapidly with age at first exposure.

This overall behaviour has been summarized by saying that the excess relative risk of lung cancer increases linearly with duration of exposure and, for given duration of exposure, is independent of age at first exposure or time since first exposure. This behaviour should be contrasted with that seen for cigarette smoking, where the absolute rather than the relative excess risk was related to duration of exposure.

(*d*) *Radiation and leukaemia*

The association of leukaemia with radiation exposure was the original focus of several of the large cohort studies initiated in the 1950s, notably the study of patients with ankylosing spondylitis (Court Brown & Doll, 1965) and of women with cervical cancer (Hutchison, 1968). The study of atomic bomb survivors was, of course, much more broadly based, the Life-Span Study representing a systematic search for all mortality differentials associated with radiation, but the excess of leukaemia excited interest first.

In both the atomic bomb and the ankylosing spondylitis studies, the excess mortality from leukaemia was greater and occurred earlier than the excess mortality due to other malignancies. A joint analysis has been made of these two studies investigating the effects of age at exposure and time since exposure (Darby, 1984; Darby *et al.*, 1985). The excess of leukaemia reaches a peak in the first five years after exposure, and then declines steadily. Little excess is seen among the ankylosing spondylitis patients more than ten years after exposure, whereas among the atomic bomb survivors, with a higher initial risk, an excess is still seen more than 20 years after exposure.

Little variation in relative risk is seen with age at exposure among the ankylosing spondylitis patients, nor among the atomic bomb survivors 15 years of age or more at exposure. Atomic bomb survivors less than 15 years of age at exposure, however, suffered a markedly higher risk. Among this latter group, the risk rose more rapidly, attained a higher peak, and then fell off more sharply (Beebe *et al.*, 1977; Ishimaru *et al.*, 1979; Committee on the Biological Effects of Ionizing Radiation, 1980).

The excess of leukaemia is confined to acute and nonlymphocytic leukaemia, none of the studies showing an excess of chronic lymphocytic leukaemia. In the study of ankylosing spondylitis patients, in which analyses have been based on death certificates and comparison with general population mortality rates, no formal analyses have been made by leukaemia subtype, since no population mortality rate is available. In the original analyses, however, none of the leukaemia deaths was attributed to the chronic lymphocytic type. Among the atomic bomb survivors, mortality rates for the subtypes

of leukaemia can be studied since the comparison is with the lightly exposed (less than 10 rads) members of the cohort.

The follow-up of women irradiated for cancer of the cervix (Day & Boice, 1983) used cancer occurrence as an endpoint, and incidence rates from cancer registries as the basis for comparison. These data could therefore also be examined by subtype of leukaemia, illustrating the advantage of incidence rather than mortality as an endpoint, i.e., the ability of cancer registries to produce accurate population rates by finer disease categories. The results are shown in Figure 6.7. The excess risk reaches a peak in the first five years – although it is more modest than the peak seen in the ankylosing spondylitis series – then falls away to inappreciable levels ten years or more after exposure. The risk for chronic lymphocytic leukaemia is, if anything, below that of the general population.

Comparison of the excess risk seen in these three studies presents an apparent paradox. Both the cervical cancer patients and the ankylosing spondylitis patients received very high doses of radiation to part of the active bone marrow (several thousand rads). In contrast, the larger excess risk among the atomic bomb survivors was induced by a few hundred rads of whole-body irradiation, all the active bone marrow receiving similar exposure. The dose-response curve appeared approximately linear, as shown in Figure 6.8. [We shall leave aside in this discussion the different effects seen in Hiroshima and in Nagasaki, between sexes and between the neutron and gamma-ray components of the exposure. Resolution of these differences awaits new dose estimates (see, for example, Fujita, 1984) and may also depend on differential

Fig. 6.7 Observed to expected ratios of nonlymphocytic and acute leukaemia among patients with invasive cervical cancer treated with radiotherapy by time since diagnosis of cervical cancer; 80% confidence intervals presented. From Day and Boice (1983)

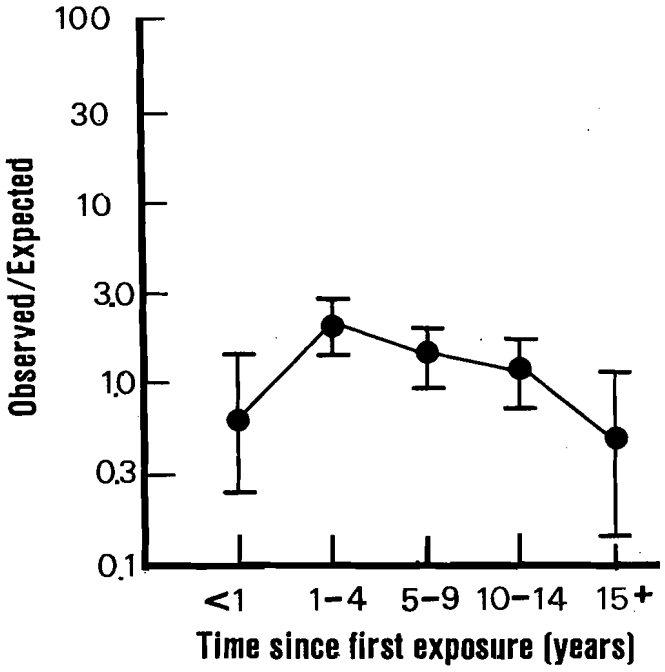
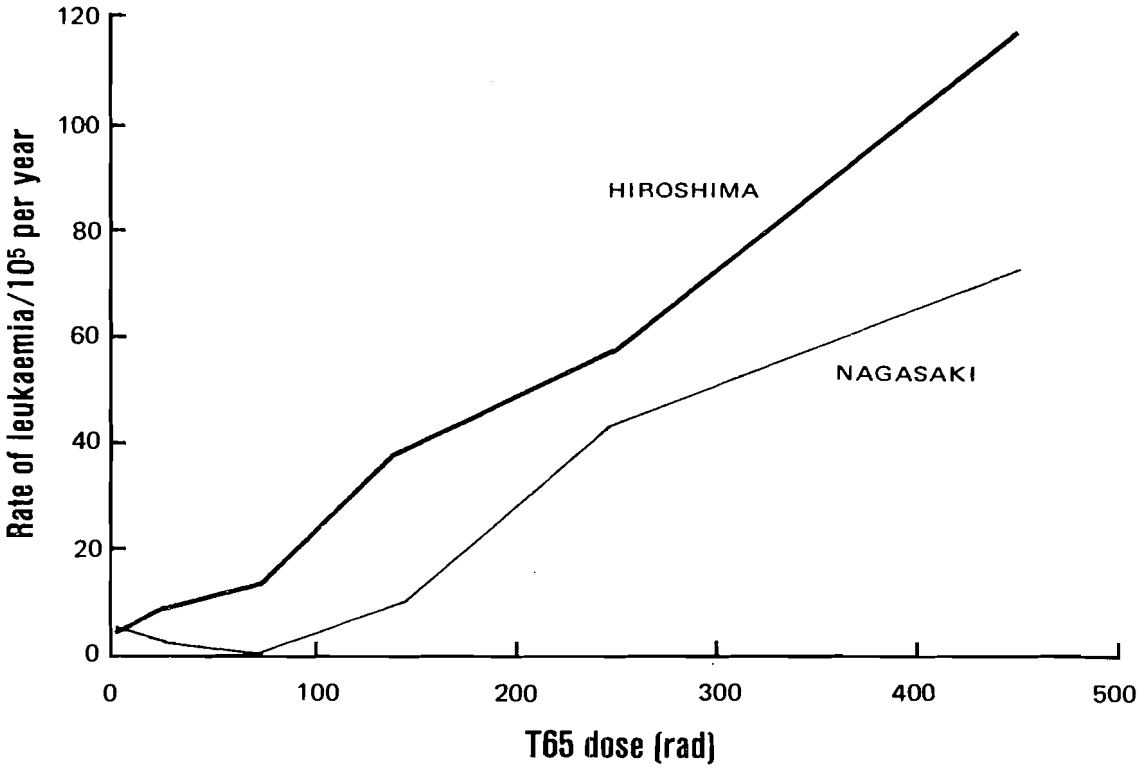


Fig. 6.8 Leukaemia deaths among Japanese survivors of the atomic bomb explosion, per 100 000 persons per year by (T65) dose and city. From Beebe *et al.* (1977)



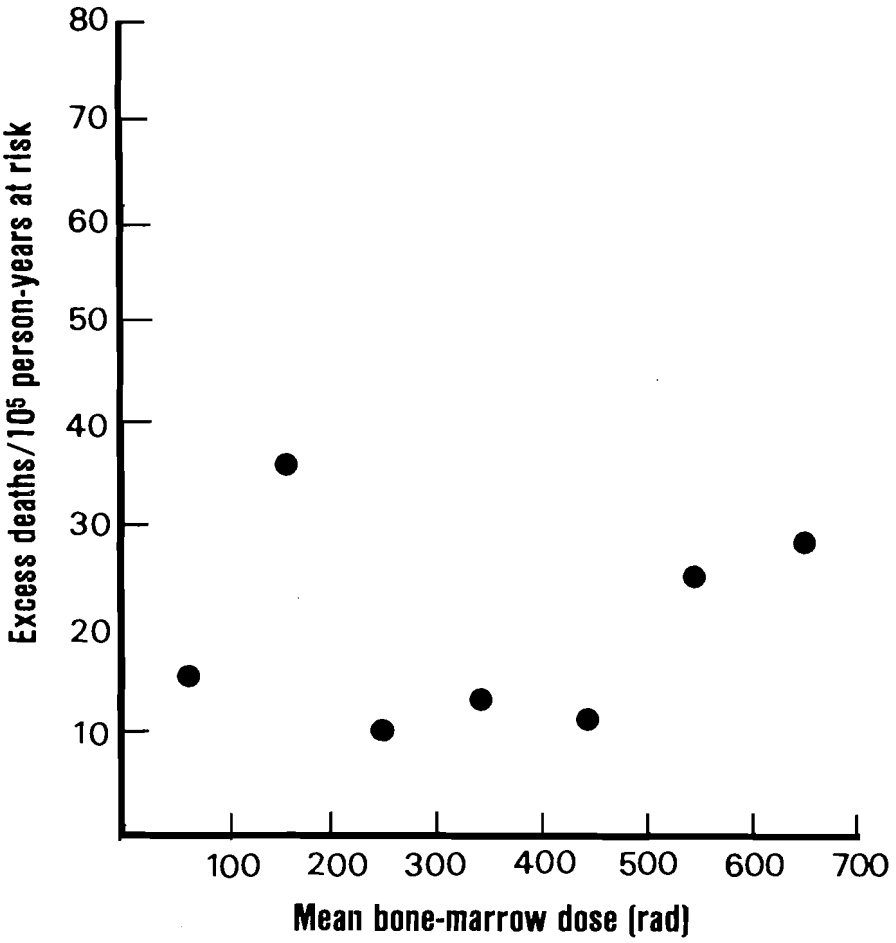
accuracy of the dose estimation (Gilbert, 1984)]. If this linear dose-response derived from the atomic bomb survivors could be extrapolated to higher dose levels, one might expect considerably larger risks in the two studies of irradiated patients. In the cervical cancer study, for example, one would have expected several hundred excess leukaemias rather than the 20 or so actually observed.

In the ankylosing spondylitis study, using as a measure of dose the mean exposure to the active bone marrow, no increase in risk with increasing dose is seen (Smith & Doll, 1982) (Fig. 6.9). The proposed explanation for the observed lack of linear increase in the dose-response curve is that radiation can sterilize cells as well as transform them, the sterilized cells having no potential for malignant growth. Sterilization is the major effect at high doses, transformation at lower doses. Incorporating cell sterilization into a dose-response model (see Brown, 1977) has led to expressions such as

$$\text{Excess relative risk} \propto \text{Dose} \cdot \exp(\alpha\text{Dose} - \beta\text{dose}^2). \qquad (6.5)$$

Using this model with average dose to the active bone marrow gave a reasonable fit to the data of Figure 6.9. On occasion, however, it might be preferable to integrate expression (6.5) over the distribution of dose to the active bone marrow rather than to use simply the average dose. Such a calculation would, of course, require accurate determination of the dose distribution. One can see that this approach might be more suitable for the cervical cancer patients, among whom most of the active bone marrow received either a dose of which the major effect is cell sterilization, or a dose too low to

Fig. 6.9 Radiation–leukaemia dose–response curve seen among ankylosing spondylitis patients given one course of radiotherapy. From Smith and Doll (1982)



affect risk appreciably. Integrating expression (6.5) over a dose distribution of this type would clearly lead to a low predicted excess risk, as observed, whereas use of the average dose would predict considerably higher risk levels. [In fact, the results of a case-control study of leukaemia within the cervical cancer cohort indicate the importance of a cell-killing term in the dose-response relationship (M. Blettner, personal communication, 1986).]

These results demonstrate the importance of using available biological information to guide the choice of model that one uses. Uncritical use of models chosen for their statistical simplicity can lead to misleading or paradoxical results. To quote Pike (1985), 'At times, we may need to be more subtle in our approach.'

(*e*) *Radiation and breast cancer*

Several studies have examined the excess risk for breast cancer seen in groups of women exposed to radiation either for medical purposes or as a consequence of the atomic bomb explosion. The two largest studies are of the atomic bomb survivors and of Canadian women with tuberculosis examined by fluoroscopy (Howe, 1982). Two other widely quoted studies are of fluoroscopy-treated patients in Massachusetts (Boice

& Monson, 1977) and of radiation-treated mastitis patients in New York (Shore *et al.*, 1977). As described in Appendix IB, there has been an extensive effort to determine the dose received by each atomic bomb survivor, and for the cohorts of women irradiated for medical purposes considerable documentation of individual dose levels has been available. Although the duration of radiation treatment was relatively short when compared to the duration of some occupational exposures, being almost always less than five years, there were considerable differences in the degree of dose fractionation. In the atomic bomb survivors, the total dose was received from one explosion, whereas in the fluoroscopy series, a woman may have received several hundred fluoroscopies over a number of years, and in the mastitis series women may have received five to ten exposures over a period of weeks. No major difference has been seen in breast cancer risk attributable to the degree of fractionation, and analyses have been based on the total dose received. The three determinants of risk that have been studied in some detail are the total dose, the time since the dose was received, and the age at which the dose was received. Since the underlying breast cancer rates in the populations studied vary widely – for example, between Japan and the USA or between age groups – attention has also been given to the problem of which effect measure is more appropriate, relative excess risk or absolute excess risk. The two measures give estimates of lifetime risk which differ considerably, as discussed in Chapter 4.

The Massachusetts fluoroscopy study, the New York study of mastitis patients and the study of atomic bomb survivors have been analysed jointly (Land *et al.*, 1980). A number of models have been fitted, expressing the mortality rate of breast cancer, I, as a function of radiation dose, D, in particular

$$I(D) = \alpha_0 + \alpha_1 D \qquad \text{A.}$$

$$I(D) = \alpha_0 + \alpha_1 D + \alpha_2 D^2 \qquad \text{B.}$$

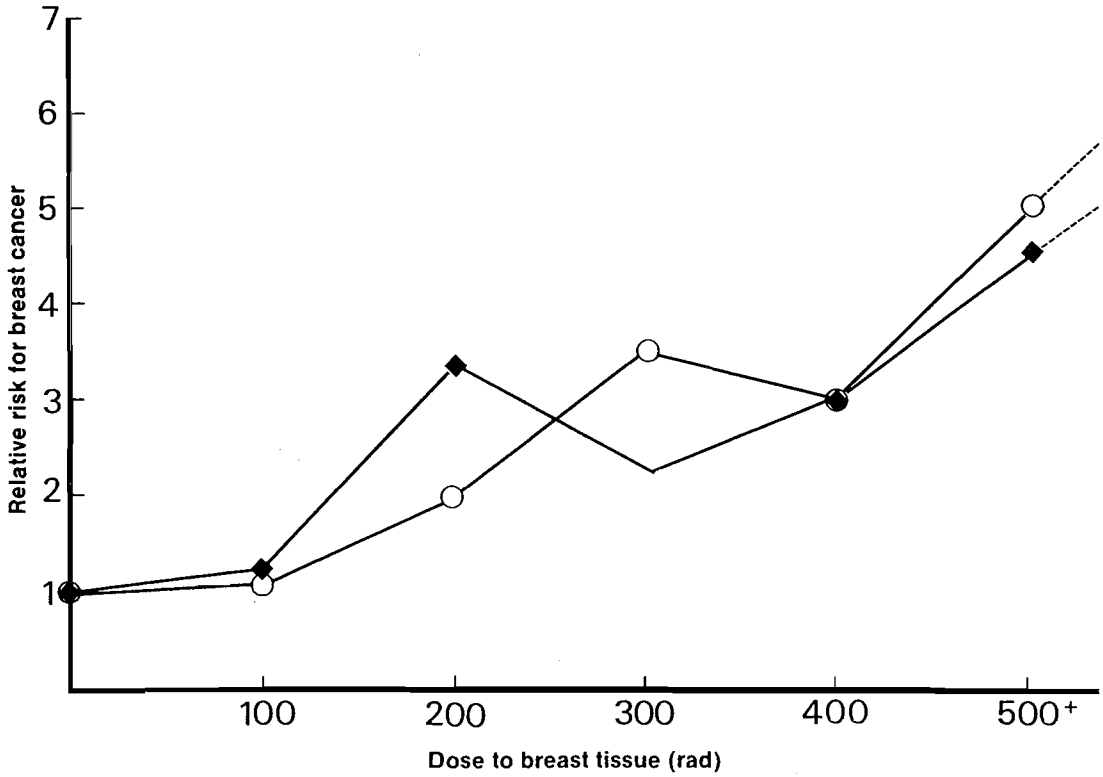
$$I(D) = (\alpha_0 + \alpha_1 D)\exp(-\beta_2 D^2) \qquad \text{C.}$$

$$I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2)\exp(-\beta_2 D^2) \qquad \text{D.}$$

The last two models introduce a possible effect of cell killing, as discussed in the previous section. In the mastitis study, model C was an improvement over model A (Land *et al.*, 1980), whereas in a separate analysis of the Canadian fluoroscopy study model A fitted well in the high-dose range (Miller *et al.*, 1987). The difference in the shape of the dose-response curve between these two studies in the high dose range (400–1000 rads) might be attributed to the higher dose rate, i.e., lower degree of fractionation, in the mastitis study. Apart from high doses in the mastitis series, model A gave an adequate fit to the different series of data, and the main findings of the different analyses can be summarized as follows:

(i) The dose-response appears linear throughout the range of dose observed (see Figure 6.10). A suggestion of a downturn at high dose levels, which might be predicted on the basis of models incorporating cell killing, is seen in the mastitis series, but not in the atomic bomb survivors nor in the Canadian fluoroscopy series.

Fig. 6.10 Increase in relative risk for breast cancer as radiation dose increases in the Canadian fluoroscopy (○) and atomic bomb (◆) studies



(ii) The excess relative risk appears some ten years after exposure, and continues thereafter at a roughly constant level. Even after 40 years, there is no indication of a diminution (see Figure 6.11). The absolute excess risk increases with time since exposure.

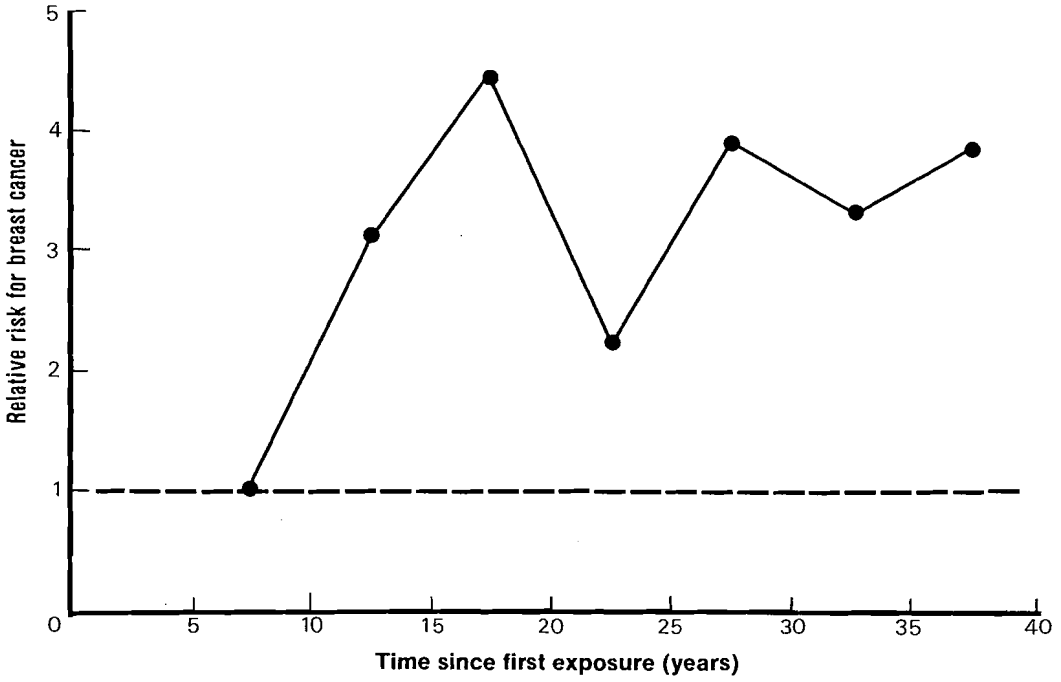
(iii) The excess relative risk is greater at younger ages at exposure, with little excess seen among women over 40 years of age when irradiated (Howe, 1982). Recent results from the atomic bomb survivors and from children irradiated for an enlarged thymus suggest that the excess relative risk is even higher among those exposed when aged 0–9 than among those aged 10–19 at exposure.

(iv) The absolute excess per unit dose in young Japanese women was similar to that seen in white American women, the excess relative risk being correspondingly larger. This finding is in contrast to the constancy of relative risk throughout the period of follow-up noted in point (ii) above, indicating that hypotheses of constant relative or constant absolute excess risks are both simplistic, and neither forms a sound basis for extrapolating results from one population to another.

(*f*) *Radiation and bone tumours*

This example contrasts the effect seen in two different studies of the different isotopes of radium, which after ingestion have been incorporated into the bone tissue. The first study is of radium dial painters (Rowland & Lucas, 1984), who by habitually

Fig. 6.11 Relative risk for breast cancer as a function of time since first exposure to radiation in the Canadian fluoroscopy study (Howe, 1982)



licking their paint brushes absorbed quantities of ^{226}Ra. The half life of ^{226}Ra is long (1600 years), so that exposure to the decay products continued virtually at constant levels after absorption of the radium. The effect on subsequent risk is shown in Figure 6.12A, with little indication of a decline in the number of cases even after 40 years. It is thought that most of the intake of ^{226}Ra occurred in the first ten years after entry, since brush-licking apparently stopped in 1926. The dose-response has also received close attention in this study, a function of the form

$$(\alpha + \beta \text{ dose}^2) \exp(-\lambda \text{ dose})$$

giving the best fit. As for the leukaemia dose-response, a cell sterilization term improves the fit.

The second study investigated ankylosing spondylitis patients in the Federal Republic of Germany who were given ^{224}Ra as treatment (Mays & Spiess, 1984). ^{224}Ra has a half-life of several days, so that exposure to the decay products effectively ceases a few days after treatment stops. The subsequent risk of bone tumours is shown in Figure 6.12B, in which a wave pattern to the excess risk is discernible, similar to that seen for leukaemia. The comparative behaviour of bone tumours and leukaemias in this study is given in Figure 6.13. Indications of a similar wavelike pattern to the excess risk of bone tumours are seen after short-term exposure to external gamma rays (Day & Boice, 1983; Kaldor *et al.*, 1987).

These two examples illustrate the care that is required in defining time since exposure; the relationship between tissue dose and external exposure requires close attention.

Fig. 6.12 (A) Bone sarcoma appearance times after exposure to ^{226}Ra (half-life, 1600 years). (B) Bone sarcoma appearance times after exposure to ^{224}Ra (half-life, 3.6 days). From Mays and Spiess (1984)

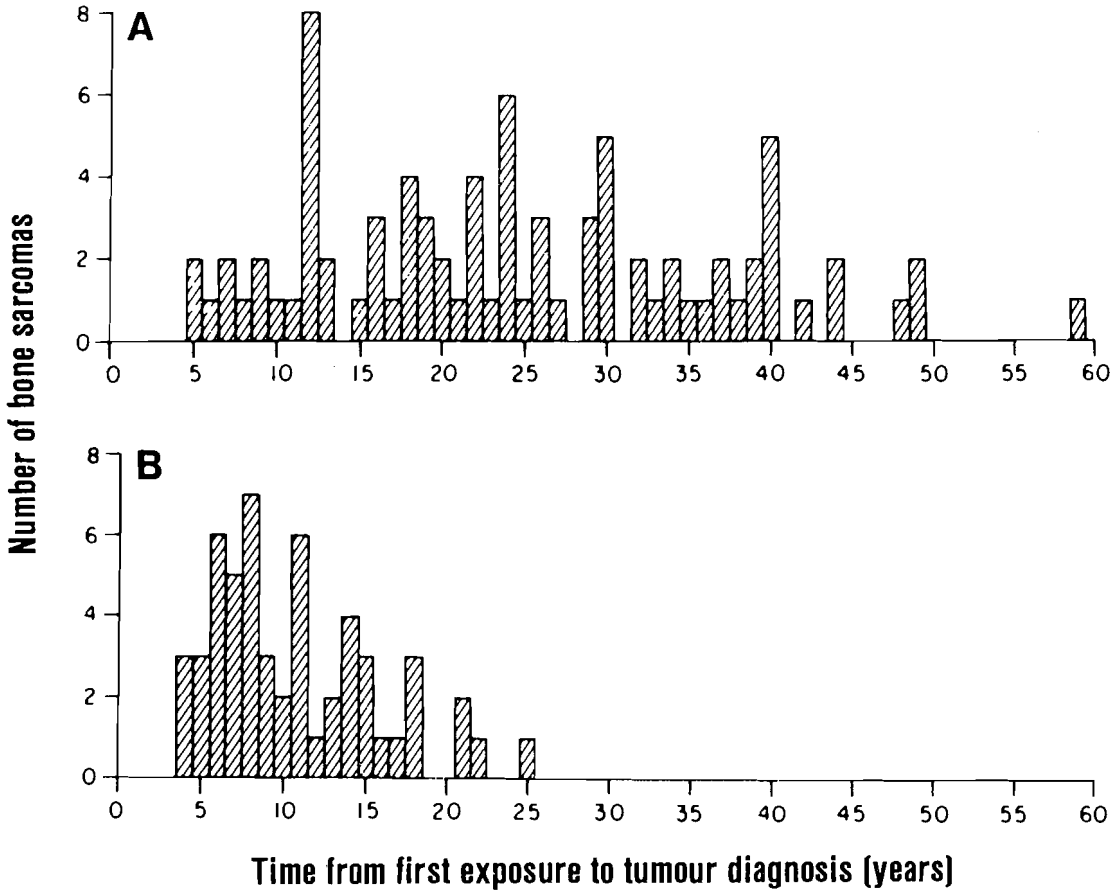
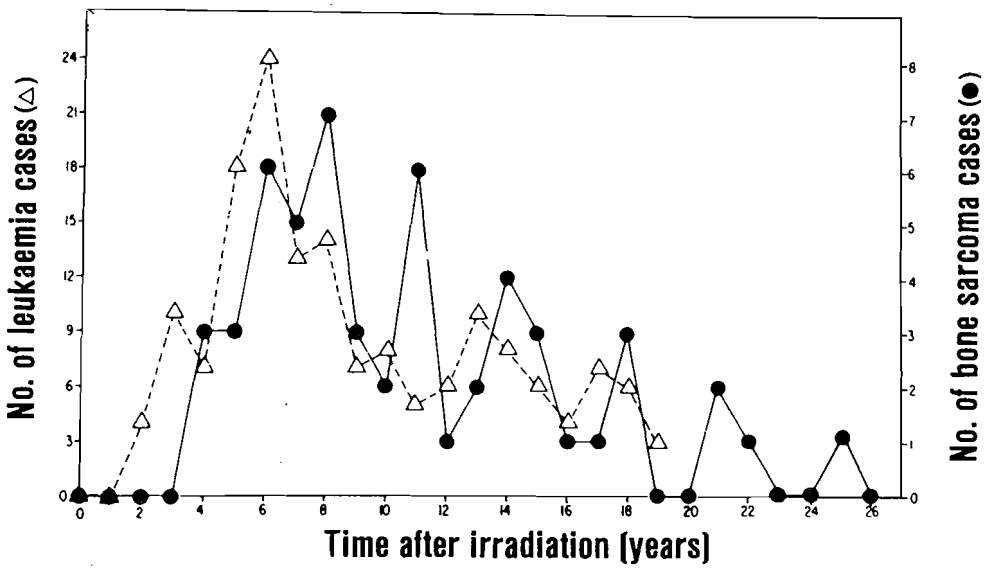


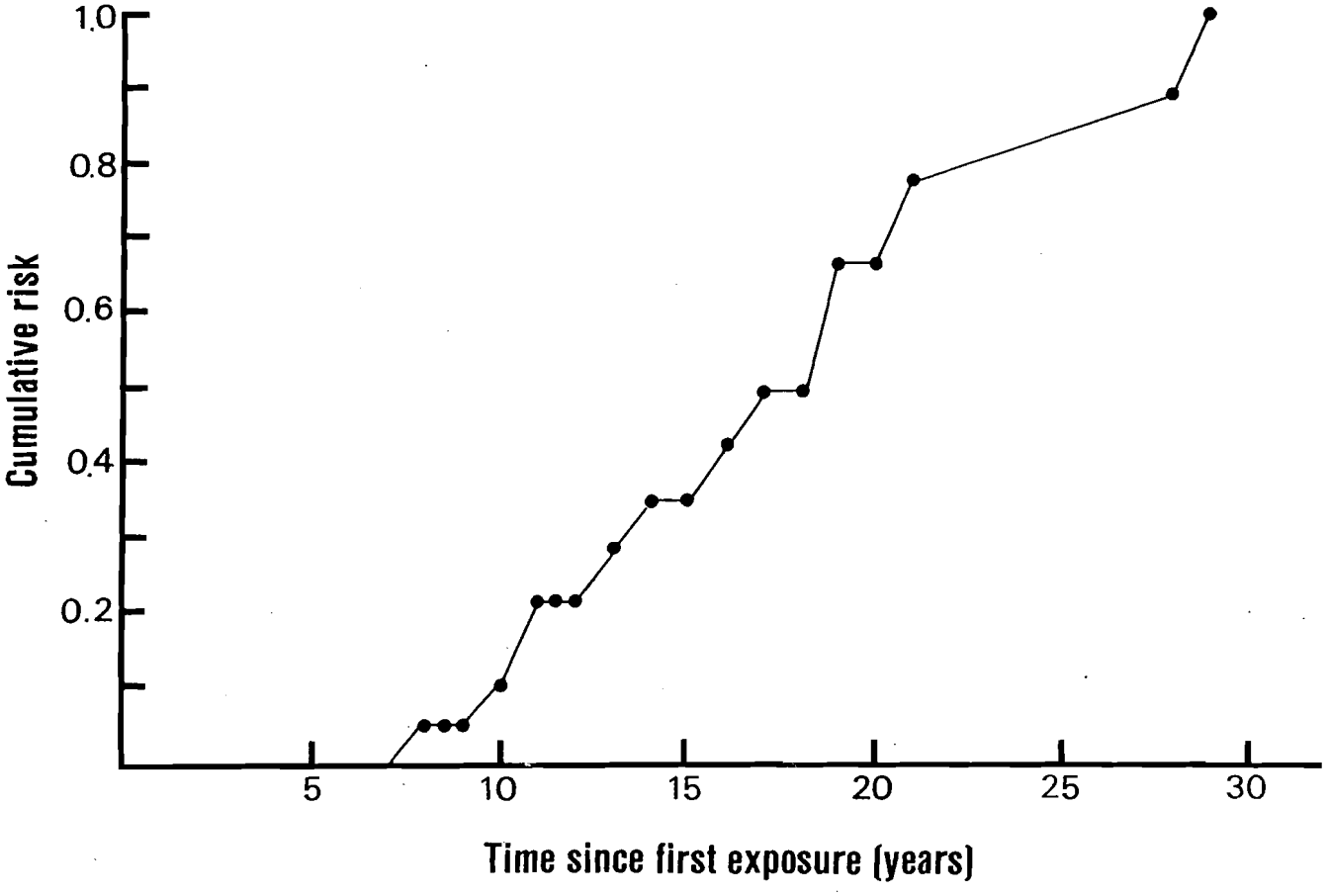
Fig. 6.13 Appearance times of bone sarcomas in patients exposed to a short half-life radium isotope (●) and of leukaemias in the atomic bomb survivors (△). From Mays and Spiess (1984)



(*g*) *Bladder cancer and exposure to benzidine*

The purpose of this example (Zavon *et al.*, 1973) is to illustrate the point that, even with a very small cohort and no clear measure of exposure (environmental measures of exposures related to different job categories varied by a factor of 10^4 in this study), an illuminating description of the excess risk can be given. The study relates to a small group of men employed in the manufacture of benzidine. Other exposures were recorded, but none represented a hazard for bladder cancer comparable to that of benzidine. Of the 28 men employed, 15 developed bladder cancer – a remarkable excess. Of even greater interest is to plot the cumulative increase in risk with years of employment for those who remained continuously employed, deriving Nelson plots (see Figure 6.14 and equation 5.16) such as are commonly used in the analysis of skin-painting experiments of carcinogenicity (IARC, 1982b). The cumulative risk of bladder cancer is 50% at 15 years, rising to 100% after 25 years. In this situation, such a presentation of the data essentially contains all the information in the results pertaining to bladder carcinogenesis. It is certainly much more informative than a statement that 15 bladder cancers were observed in a cohort of 28 workers, with an expected number (not given in the paper) of the order of 0.1.

Fig. 6.14 Cumulative absolute risk of developing a bladder tumour as a function of duration of continuous exposure to benzidine (from data of Zavon *et al.*, 1973). From IARC (1982b)



(h) Lung cancer among US uranium miners

The excess lung cancer risk seen among US uranium miners has been the subject of a number of reports (Waxweiler *et al.*, 1981), the most recent of which takes the follow-up to the end of 1977. Whittemore and McMillan (1983) focused their analysis on the joint effects of radiation (mainly alpha particles emitted during the radioactive decay of radon and its daughter products) and cigarette smoking. A case-control approach was adopted in which, for each lung cancer death, four control subjects were randomly selected from among those born within eight months of the case and known to survive him. The joint effects of radiation and smoking were modelled in a number of ways. First, radiation exposure was expressed as cumulative exposure in terms of working level months (WLM), based on extensive environmental measures of radon daughter levels, and cigarette smoke exposure was expressed in terms of total packs of cigarettes ever smoked (PKS). Both cumulative exposures were truncated ten years before the death of the lung cancer cases, and, for controls, ten years before the death of the matched case, as an approximate way of incorporating latency.

Since a case-control design was used, the relative risk was taken as the effect measure. A number of models were fitted, to investigate the following questions:

(1) Is the combined effect of radiation and smoking better described in additive or multiplicative terms?
(2) What is the shape of the dose-response curve?
(3) Does total amount smoked or average amount smoked per day provide a simpler description of tobacco-associated excess risk?

To investigate the first two issues, cumulative exposure to both factors was categorized. Writing the excess relative risk in the ith radiation category as $\beta_{i,\mathrm{R}}$ and in the jth smoking category as $\beta_{j,S}$, alternative models representing multiplicative and additive joint action were fitted

$$\mathrm{RR}_{ij} = (1 + \beta_{i,R})(1 + \beta_{j,S}) \quad \text{Multiplicative}$$
$$\mathrm{RR}_{ij} = 1 + \beta_{i,R} + \beta_{j,S} \quad \text{Additive}$$

and the two models compared with one describing general joint action

$$\mathrm{RR}_{ij} = 1 + \beta_{ij},$$

where RR_{ij} is the risk for individuals in category i for radiation and category j for smoking, relative to those in the baseline category for both exposures.

The multiplicative model was not significantly worse than the general model, whereas the additive model fared badly. Thus, although the additive and multiplicative models were not compared directly, the latter certainly appeared to be preferable. This finding is in contrast to the interactive effect on lung cancer of smoking and radiation seen in the atomic bomb survivors study, which appeared to be additive or even subadditive (Prentice *et al.*, 1983). In the one case, there was continuous exposure to alpha particles, and in the other there was instantaneous exposure to gamma rays; whether this difference reflects different measurement errors or more basic differences in mode of joint action is unclear.

To investigate the shape of the dose-response curve, cumulative radiation exposure and cigarette smoking were introduced as quantitative variables. A number of models were considered, including

$$\begin{aligned} RR &= (1 + \beta_1 WLM)(1 + \beta_2 PKS) \\ RR &= 1 + \beta_1 WLM + \beta_2 PKS \\ RR &= \exp(\beta_1 WLM + \beta_2 PKS) \\ RR &= (WLM + BGR)^{\beta_1}(PKS + BGS)^{\beta_2}, \end{aligned} \tag{6.6}$$

where BGR and BGS are background rates for radiation and smoking exposures, respectively.

The first of these four models fit as well as the previous multiplicative model using categorized exposure variables, whereas the maximum achieved by the likelihood function under the other models was markedly less. Adding quadratic terms to give models such as

$$RR = \{1 + \beta_1 WLM + \beta_2 (WLM)^2\}(1 + \beta_3 PKS)$$

did not improve the fit appreciably.

The relative risk can thus be taken from these data to rise linearly with increasing cumulative exposure to each variable, the effect of the two variables combining multiplicatively.

Models using average number of cigarettes smoked per day were also investigated, but performed less well than the models given above using cumulative pack-years of cigarettes.

No effect on the relative risk of lung cancer was seen for age at start of underground mining after controlling for age at lung cancer death, year of birth and cumulative exposure to radiation and smoking.

It is interesting to note that total number of packs of cigarettes smoked is the most useful single measure of smoking, in contrast to the British doctors study where risk was modelled in terms of the number of cigarettes smoked per day. In that study, however, absolute rates were modelled, whereas relative rates were modelled in the miners study. If, among continuing smokers, absolute risk is proportional to:

$$(\text{Cigarettes per day})(\text{Duration of smoking})^4$$

and the baseline rates are proportional to the fourth power of age, then simple calculations show that the relative risks in different age groups are approximately equal among people who have smoked the same total number of cigarettes (up to ten years before death). Assuming that smoking started at 20 years of age gives Table 6.5, in which column 3 gives rates at different ages for smokers who smoke the same number of cigarettes per day, and column 5 gives rates at different ages for smokers who have smoked the same total number of cigarettes, excluding the last ten years.

The relative risks in the last column, which relates to total amount smoked truncated ten years before death, are almost constant, whereas in column 4 the risks vary fourfold (see Table 2.6 of Volume 1). The range of ages covers the great majority of deaths seen in the miners study so that a one-parameter model using total dose

Table 6.5 Comparison of the relative risk of lung cancer at different ages for continuing smokers classified either by number of cigarettes smoked per day (columns 3 and 4) or by total number of cigarettes smoked (columns 5 and 6)

Age at death (years) (1)	Rate among non-smokers (2)	Rate among smokers (constant no. of cigs/day) (3)	Relative risk (col. 3/col. 2) (4)	Rate among smokers (constant total no. of cigs) (5)	Relative risk (col. 5/col. 2) (6)
40	$\alpha_1 4^4$	$\alpha_2 2^4$	$\frac{k}{16}$	$4\alpha_2 \cdot 2^4$	$\frac{k}{4}$
50	$\alpha_1 5^4$	$\alpha_2 3^4$	$\frac{k}{7.7}$	$2\alpha_2 \cdot 3^4$	$\frac{k}{3.9}$
60	$\alpha_1 6^4$	$\alpha_2 4^4$	$\frac{k}{5.1}$	$\frac{4}{3}\alpha_2 \cdot 4^4$	$\frac{k}{3.8}$
70	$\alpha_1 7^4$	$\alpha_2 5^4$	$\frac{k}{3.8}$	$\alpha_2 5^4$	$\frac{k}{3.8}$
80	$\alpha_1 8^4$	$\alpha_2 6^4$	$\frac{k}{3.2}$	$\frac{4}{5}\alpha_2 \cdot 6^4$	$\frac{k}{3.9}$

Where $k = \alpha_2/\alpha_1$

is sufficient to describe smoking-associated variation in relative risk for the entire cohort.

This example indicates that the metameter of dose to use to achieve the simplest explanation may differ depending on whether absolute or relative risks are being investigated.

The preceding examples have demonstrated the important role in determining risk that may be played by time since first exposure, age at first exposure, and duration of exposure. In terms of defining metameters of dose, both dose rate and cumulative dose can offer advantages, depending in part on whether absolute or relative risks are being described. The use of duration of exposure can be considered a surrogate measure of cumulative dose in studies in which dose levels are inadequately measured.

In these examples we have not emphasized time since exposure stopped as an independent time variable, and it can obviously be derived from time since first exposure and duration of exposure. There may, however, be occasions on which it is the variable of major interest as an indicator of the effect to be expected from intervention measures. At times, also, risk may be more appropriately modelled in terms of duration of exposure and time since stopping exposure, so that time since first exposure would enter into the model only as their sum. Thus, for example, if relative risks are being modelled, then the lung cancer–cigarette smoking relationship for ex-smokers might be more simply modelled in terms of time since quitting and cumulative amount smoked (see Table 6.1), rather than in terms of a model incorporating time since smoking started.

6.3 Multistage models of carcinogenesis

A conceptual framework that facilitates understanding of the relationship between the different variables discussed in the previous section is provided by multistage models of carcinogenesis. A number of different models have been proposed at one time or another; we concentrate mainly on one of the simplest – the Armitage-Doll model (Armitage & Doll, 1961). Some of the details of the model may be uninterpretable biologically, but the broad features have gained increasing biological and experimental support in the past decade. It is these features that have value as an interpretive tool in epidemiology. It is not our purpose here to review in detail the role of multistage models, or the experimental evidence supporting the nature of the different stages (see, for example, Börzsönyi *et al.*, 1984). The aim of this section is simply to indicate the aid to interpretation that these models can bring.

The Armitage–Doll model supposes that a cancer arises from a single, originally normal cell, which undergoes a series of transitions, after the last of which it is capable of uncontrolled malignant replication. The number of cells at risk at the start is assumed to be large and the probability of a transition assumed to be small for any individual cell. Cells are assumed to be in the initial, i.e., normal, stage at time zero, and k transitions are assumed to be required for malignancy.

Suppose the probability of a transition from stage i to stage $i+1$ in time interval t, $t+\delta t$ is given by $\lambda_{i+1}(t)\delta t$, and that all transitions are independent of each other. Then, denoting by $N_i(t)$ the number of cells in stage i at time t, we can write down an expression for the rate of change of $N_i(t)$ with time, namely

$$\frac{dN_i(t)}{dt} = \lambda_i(t)N_{i-1}(t) - \lambda_{i+1}(t)N_i(t)$$

for $i = t, \ldots, k$.

We assume that transitions are rare, and that at time $t = 0$

$$N_i(0) = 0 \qquad i \geq 1$$
$$N_0(0) = N.$$

Putting $N_i(0)$ greater than zero for $i > 0$ would be a way of modelling genetic predisposition to cancer, as proposed by Knudson (1971). Since transitions are assumed to be rare, good approximate solutions to this set of differential equations are given by the simpler set of equations

$$\frac{dN_i(t)}{dt} = \lambda_i(t)N_{i-1}(t) \tag{6.7}$$

for $i = t, \ldots, k$.

The degree of approximation involved in (6.7) has been discussed by Moolgavkar (1978). For many tissues, when exposure consists largely of the background common to most individuals in a particular society, the transition rates may vary little with time. We then have $\lambda_i(t) = \lambda_i$ and

$$N_i(t) \propto t^i$$

for $i = 1, \ldots, k$.

The probability that a cancer occurs is the probability of a transition from stage $k-1$ to stage k. If the transition rates are constant, this probability is simply proportional to the number of cells in stage $k-1$, so that the incidence rate at time t, $I(t)$ say, is proportional to $N_{k-1}(t)$, given by

$$I(t) \propto t^{k-1}. \tag{6.8}$$

As is well known, plotting the logarithm of incidence against the logarithm of age results for many tumours in a straight line with a slope of between 4 and 5 (see Volume 1, Chapter 2, page 61; and Cook *et al.*, 1969), indicating that (6.8) is a good description of the background age-specific rates for many tumours in a variety of different populations, with k equal to 5 or 6.

This simple multistage model gives a reasonable description of the epidemiology of many nonhormonally-dependent cancers of epithelial origin, and can be modified straightforwardly to incorporate age-dependent hormonal changes. More general models have been developed which take account of time-varying cell kinetics and which fit the epidemiological behaviour of a wider range of malignancies, described, for example, by Moolgavkar and his coworkers (e.g., Moolgavkar *et al.*, 1980), to which the reader is referred for further details. A review by Knudson (1985) gives a good description of the biological background.

We now turn our attention to the effect on cancer incidence of exposure additional to the background, to examine how the types of behaviour described in the previous section can be predicted by multistage considerations.

(*a*) *Implication for the effect on tumour incidence of exposures of limited duration*

The effect of changing exposures is to change the transition rates given in expression (6.7). Thus, suppose that, during an interval extending from time t_0 to time t_1, the transition rates increase from λ_i to $\lambda_i + \mu_i$, for $i = 1, \ldots, k$. The extent to which the transition rates are modified, given by the μ_i, can be taken to represent the mode of action of the exposure in augmenting risk for a cancer. For example, when studying the induction of tumours on mouse skin by initiation-promotion experiments, initiating agents would be associated with large values of μ_1, whereas promoting agents would be associated with relatively large values of μ_{k-1} or μ_k.

The cancer incidence rates in times after t_0 would then be proportional to $N_{k-1}(t)$, given by:

$$N_{k-1}(t) = N \int_0^t \lambda^*_{k-1}(u_{k-1}) \int_0^{u_{k-1}} \lambda^*_{k-2}(u_{k-2}) \cdots \int_0^{u_1} \lambda^*_1(u_1)\, \mathrm{d}u_1\, \mathrm{d}u_2, \ldots, \mathrm{d}u_{k-1}, \tag{6.9}$$

where

$$\begin{aligned} \lambda^*_i(t) &= \lambda_i + \mu_i \quad \text{for} \quad t_0 < t < t_1 \\ &= \lambda_i \text{ otherwise.} \end{aligned}$$

This expression is a polynomial of degree $k-1$ in t. Attempts have been made to fit explicitly these expressions both to experimental (Lee, unpublished data, as quoted by Whittemore & Keller, 1978) and to epidemiological data (Thomas, D.C., 1982). Since

no specific meaning can be given to the individual parameters, and epidemiological data will hardly ever be extensive or detailed enough to permit much precision in joint inferences for the full set of μ_i, this approach has not been widely adopted. It has been more common to use expression (6.9) in a heuristic way, to examine the behaviour predicted by the Armitage–Doll model in a few simple situations with plausible biological interpretation and to assess qualitatively the concordance between the observed epidemiological behaviour and the various paradigms (Day & Brown, 1980). Examination of these simple situations also provides insight into which variables to use to describe the effect of time on risk.

In the experimental situation, the separate effects of initiation and promotion have been demonstrated in the development of tumours at many sites (Börzsönyi *et al.*, 1984). Although these terms have specific meanings, which it would be hazardous to apply outside a well-defined experimental situation, one might interpret them as indicating in a more general sense the possibility of action at early or at late stages in the carcinogenic process. We therefore examine the effect on incidence rates that this multistage model would predict for agents which act predominantly at early stages and for agents which act predominantly at late stages. An interesting discussion of the relationship between the terms 'early-stage' and 'late-stage', as used by epidemiologists, and 'initiation' and 'promotion', as used by experimentalists, is given by J. Peto (1984).

We consider an early-stage agent to be one that affects only the first transition rate, i.e., only μ_1 is nonzero, and a late-stage agent as one for which only μ_{k-1} is nonzero. It should be noted that a late-stage agent is taken to affect not the last but the penultimate transition. An agent that alters the rate of transition into the cancerous state would have an immediate effect on cancer rates, which is rarely observed. An effect on the penultimate transition appears to correspond to more frequently observed behaviour. We take k equal to 5, as suggested by Cook *et al.* (1969), to examine arithmetically the predicted behaviour.

For an early-stage carcinogen, acting between times t_0 and t_1, we have, from expression (6.9),

(i) before exposure ($t < t_0$),

$I(t) \propto t^4$. There is clearly no excess risk and the expression is the same as (6.8).

(ii) during exposure ($t_0 < t < t_1$),

$I(t) \propto t^4 + \beta(t - t_0)^4$. The excess absolute risk is proportional to a power of *duration of exposure* (or, equivalently, time since first exposure); the excess relative risk is given by $\beta(1 - t_0/t)^4$, which rises slowly to its asymptotic value of β. (The quantity β represents the potency of the extra agent, relative to the background, and is given by the ratio μ_1/λ_1.)

(iii) after exposure ($t > t_1$),

$I(t) \propto t^4 + \beta\{(t - t_0)^4 - (t - t_1)^4\}$. The excess absolute risk is dominated by the term $(t - t_0)^4$, proportional to a *power of time since first exposure.* The excess relative risk is dominated by the term $\beta(1 - t_0/t)^4$, as if exposure had continued. The effect of the term $(t - t_1)^4$ in reducing the excess relative risk comes into play only slowly.

For a late-stage carcinogen acting between times t_0 and t_1, we have

(i) before exposure ($t > t_0$),

$I(t) \propto t^4$ when $t > t_0$, as before.

(ii) during exposure ($t_0 < t < t_1$),

$I(t) \propto t^4 + \gamma(t^4 - t_0^4)$, where $\gamma = \mu_4/\lambda_4$ is the potency of the extra late-stage agent, relative to the background. The excess relative risk is given by $\gamma\{1 - (t_0/t)^4\}$, which rises rapidly to a plateau at the value γ.

(iii) after exposure ($t > t_1$),

$I(t) \propto t^4 + \gamma(t_1^4 - t_0^4)$. The excess absolute risk remains indefinitely at a *constant value.* The excess relative risk falls proportionately to a power of t, after exposure stops at t_1. The greater the age at which exposure stops, the more gradual is this fall.

The different effects on subsequent incidence rates thus described are shown schematically in Figures 6.15A and 6.15B. In Figure 6.15A, the effect of starting a continuous exposure at age 30 years is shown for an early-stage and a late-stage agent. In Figure 6.15B, the effect is shown of stopping at age 40 an exposure that has been operating throughout life, contrasting the effects of early- and late-stage agents. Risk rises more slowly after exposure starts, and falls more slowly after exposure ceases. As might be expected, the effect of changing exposure to early-stage agents is greatly delayed compared to the effect of changing exposure to late-stage agents. Thus, intervening to reduce exposure to late-stage agents will have a relatively rapid effect, whereas permitting even short-term exposure to early-stage agents will have long-term consequences.

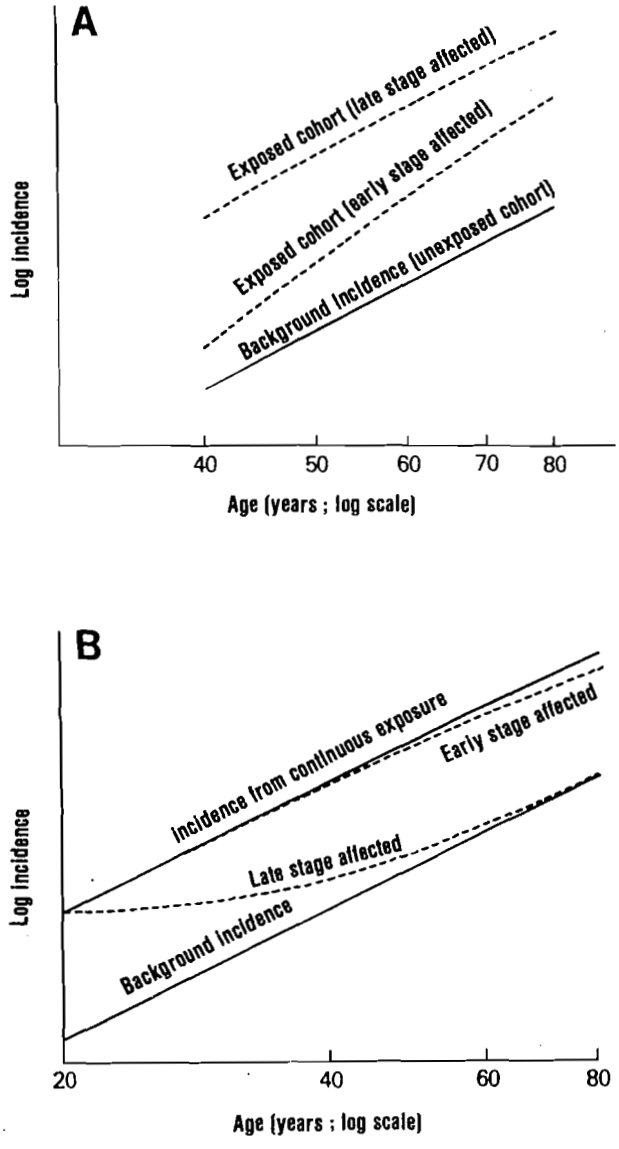
There are also differences between early- and late-stage agents in the effect of the age at which exposure starts, as can be seen by the expressions given above. For an early-stage agent, the absolute excess risk depends only on time since first exposure (for continuing exposures) and is unaffected by age at first exposure. Since the background rates are rising with age, relative risks decrease with age at first exposure. By contrast, for continuous exposure to late-stage agents, the absolute excess risk increases with a power of age, and the excess relative risk, proportional to $1 - (t_0/t)^4$ is roughly independent of age at first exposure once t is appreciably greater than t_0.

For an agent that affects both early- and late-stage transitions, acting between times t_0 and t_1, the behaviour is a mixture of the two simpler models, given as follows:

$$\begin{aligned}
&\text{before exposure } I(t) \propto t^4, \quad t < t_0,\\
&\text{during exposure } I(t) \propto t^4 + \beta(t - t_0)^4 + \gamma(t^4 - t_0^4)\\
&\qquad\qquad + \beta\gamma(t - t_0)^4 \quad \text{for} \quad t_0 < t < t_1\\
&\text{and after exposure } I(t) \propto t^4 + \beta\{(t - t_0)^4 - (t - t_1)^4\} + \gamma(t_1^4 - t_0^4)\\
&\qquad\qquad + \beta\gamma(t_1 - t_0)^4 \quad \text{for} \quad t_1 < t.
\end{aligned}$$

The last two expressions have terms for the early-stage effect, the late-stage effect and both effects acting together. Which term predominates depends on the relative magnitudes of the early-stage effect, β, and the late-stage effect, γ; but if both effects

Fig. 6.15 (A) Age-specific cancer incidence for a cohort continuously exposed to a carcinogen from 20 years of age. (B) Effect of stopping exposure at 20 years of age when carcinogenic exposure started at birth: age-specific incidence. From Day and Brown (1980)



are appreciable then the combined effect, the term with $\beta\gamma$, would tend to dominate. In this case, while exposure lasts, the behaviour of the excess risk is dominated by the term $\beta\gamma(t-t_0)^4$, so that it resembles an early-stage agent. After exposure stops, the excess risk is dominated by the term $\beta\gamma(t_1-t_0)^4$, and so resembles a late-stage agent.

The distinguishing features of early- and late-stage agents, and those that affect both stages, are summarized in Table 6.6.

Table 6.6 Summary of the qualitative features of evolving risk following exposure to early-stage and late-stage carcinogens

	Early-stage	Late-stage	Both stages affected (about equally)
Evolution of risk during exposure	Time since first exposure of prime importance. Relative risk rises slowly to reach a plateau. Age at first exposure does not modify absolute excess risk. Relative risks decline with increasing age at first exposure, for given duration of exposure.	Age of primary importance. Relative risk rises rapidly to reach a plateau. Absolute excess risk increases with increasing age at first exposure. Relative risks nearly independent of age at first exposure, for given duration of exposure.	Behaviour may be more like an early-stage agent with main effect related to time since start of exposure (i.e., duration of exposure); absolute excess risk not related to age at start of exposure.
Evolution of risk after exposure stops	Absolute excess risk increases for many years as if exposure were continuous. Relative risk increases after exposure stops, then remains at a plateau.	Absolute excess risk remains constant at level attained when exposure stops. Relative risk declines rapidly.	Behaviour may be more like a late-stage agent with absolute excess risk remaining at level attained when exposure stopped, i.e., related to duration of exposure. Relative risk declines rapidly.

6.4 Interpretation of epidemiological data in terms of multistage models

One can now review some of the epidemiological behaviour described earlier in the chapter in the light of the multistage models of the preceding section. One should stress that the aim is not to classify the agent itself, but, more modestly, to indicate how the agent acts on a particular organ, in conjunction with whatever other carcinogenic factors may be present. Classification of carcinogens by their mode of action is still considered to be premature (IARC, 1983).

(*a*) *Mesothelioma and asbestos*

The induction of mesothelioma by asbestos corresponds closely to that expected from early-stage effects. The absolute excess risk is independent of the age at which exposure starts, and can be adequately described solely in terms of a power of time since first exposure (Peto, J. *et al.*, 1982).

(*b*) *Lung cancer and smoking*

The rates of lung cancer among smokers and ex-smokers are those to be expected if cigarette smoke affects both early and late stages. The absolute excess risk is well described in terms of a power of duration of exposure, both for those continuing to smoke and for those who have stopped smoking (Doll, 1971, 1978). A large

case-control study has also shown that the greater the age at which smoking stopped, the smaller the fall in relative risk after quitting smoking (Lubin *et al.*, 1984).

(*c*) *Lung cancer and asbestos*

Asbestos behaves as a late-stage agent in the induction of lung cancer, the absolute excess risk rising rapidly with increasing age at first exposure and the relative risk remaining roughly constant. The risk increases much sooner after the start of exposure than does the risk for mesothelioma. The fact that the excess relative risk remains at roughly constant levels for several decades after external exposure stops is not consistent with a late-stage effect, but, as mentioned earlier, cessation of external exposure is not synonymous with stopping tissue exposure, since the asbestos fibres remain in the body.

(*d*) *Radiation and breast cancer*

The multistage models considered so far in this chapter have assumed homogeneity of the transition rates over age, implying that there is no age-related change in the susceptibility of the target tissue. This assumption must be relaxed for hormonally-dependent organs such as the breast. Modification of the assumption to incorporate the hormonal dependence of breast tissue leads to a model for breast cancer, which fits the epidemiological behaviour well (Moolgavkar *et al.*, 1980; Pike *et al.*, 1983). These modifications include decreasing susceptibility to early-stage effects with increasing parity, and hence in general with increasing age, and the existence of endogenous late-stage agents that are related to ovarian activity and so decrease at the menopause. The effect of short-term exposure to ionizing radiation is mainly that of an early stage agent, since susceptibility to early-stage events decreases with age. Thus the excess relative risk decreases with increasing age at exposure and, after exposure of short duration, rises to a plateau where it remains for at least 40 years. The excess risk induced by radiation increases more slowly with time the lower the age at exposure, and radiation-induced breast cancers occur only at ages when breast cancer arises spontaneously. Thus, for girls exposed when under ten years of age, the increase in incidence may take 30 years to become apparent, whereas for women over 30 years of age at exposure, an excess risk becomes appreciable within ten to 15 years. This effect of age may reflect the age-related changes in the strong endogenous late-stage factors.

6.5 Implications for the effect of dose on cancer incidence

(*a*) *Form of the dose-response relationship*

In the straightforward formulation of a multistage model given earlier, the incidence rate at age t is proportional to the product of the transition rates:

$$t^{k-1} \prod_{i=1}^{k} \lambda_i.$$

If the transition rates are increased by an additional exposure operating throughout life (λ_i increasing to $\lambda_i + \mu_i$), then the incidence rates will be proportional to

$$t^{k-1} \prod_{i=1}^{k} (\lambda_i + \mu_i). \tag{6.10}$$

It is often assumed that the transition rates are linearly related to dose rate, d, say, expressed, for example, in units of mg per kg per day; that is, one can express each μ_i as $\mu_i = \beta_i d$. This assumption has been the basis of much work on low dose extrapolation in the USA (Crump & Howe, 1984). The excess relative risk can then be expressed as a polynomial in dose rate of degree k or less with positive coefficients, at all ages. The excess absolute risk will, of course, increase steadily with a power of age.

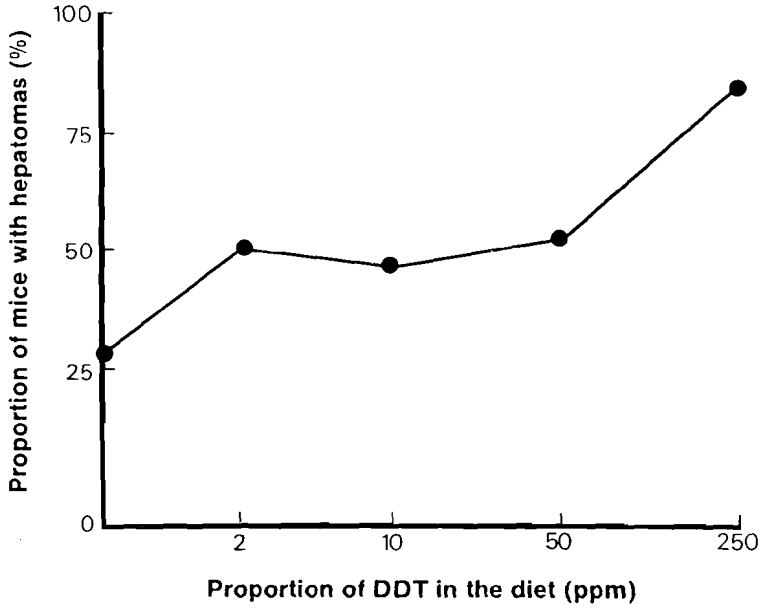
Although fitting of low-order polynomials of dose rate is common practice, their uncritical use without prior examination of the general shape of the dose-response curve requires caution, for several reasons. First, most of the exposures in which we are interested are not continuous throughout life. They are often of limited duration, starting perhaps in early adult life, and, as seen in previous sections, the effect on excess risk may be more complex. Although for a given period of exposure the form of (6.9) indicates that the effect of dose is still through a low-order polynomial, the excess risk is dominated by the duration of the period of exposure and the age at which it occurred. Second, dose is seldom measured with great accuracy, and errors of measurement modify the observed dose-response relationship. More importantly perhaps, the observed exposure rates may be related only indirectly to tissue exposure rates. Thus, the dose-response of oesophageal cancer (see Volume 1, Chapter 6), and perhaps also bladder cancer, with cigarette smoking expressed in terms of cigarettes per day, appears to be sublinear, represented better by a square root transformation than by a low-order polynomial.

Third, the mechanism of action of the agent may be different from that assumed in this derivation of expression (6.10), and a dose-response curve of quite different shape may be appropriate. Two examples suffice to illustrate the point. The relative risk for oesophageal cancer rises exponentially with daily alcohol consumption (see Volume 1, Chapter 6). The mechanism of action of alcohol is at present unclear – apparently, it is not mutagenic and the oesophagus would probably not be exposed to its mutagenic metabolites, but it is difficult to see how an exponential dose-response would be generated by the mechanism described above. In the experimental field, the dose-response in CF1 mice (Tomatis *et al.*, 1972) relating hepatoma induction to DDT intake cannot be described in terms of a low-order polynomial with positive coefficients (see Fig. 6.16). Again, the mechanism of action of DDT as a carcinogen is not known; it may operate through modulations of enzyme systems. In order to determine whether unexpected behaviour of this type is occurring, plots of the risk against categorized levels of the exposure should be performed, to visualize the general shape of the dose-response curve, as stressed in Chapter 4.

(*b*) *Metameters of dose suggested by multistage models when dose levels vary*

For an exposure additional to background, which varies throughout life with intensity $f(t)$, the additional contribution to the incidence rate at time T depends on

Fig. 6.16 Prevalence of liver neoplasms among male CF1 mice fed differing doses of DDT. From Day (1985)



the mode of action. In terms of the Armitage–Doll model, if it affects only the first stage, it is given by

$$\int_0^T (T-t)^{k-2} f(t)\,\mathrm{d}t; \tag{6.11}$$

and if it affects only a late (penultimate) stage, it is given by

$$\int_0^T t^{k-2} f(t)\,\mathrm{d}t. \tag{6.12}$$

These two expressions clearly have different implications if one requires a simple summary measure of the excess exposure. In the first case, early exposure receives the heaviest weight, in the second case late exposure. The first expression (6.11) is in fact similar to (5.1), with a latency function $w(t-u)$ taken as a power of degree $k-2$. Peto, J. (1978) has proposed a weight function of this type for mesothelioma induction after asbestos exposure, with $k=4$ to give a quadratic. As we noted above, the epidemiology of mesothelioma induction fits well the description of early-stage action.

Functions other than a quadratic have been suggested to relate the incremental exposure to future incidence. The log-normal is one, with the rationale that cancers may have a 'latency period' which is log-normally distributed (Armenian & Lilienfeld, 1974; Thomas, D.C., 1982). The choice of a log-normal distribution appears to be based on an analogy with latent periods for infectious disease rather than a consideration of the process of carcinogenesis.

For late-stage agents, expression (6.12) above does not correspond to (5.1). Weight is given to recent exposure, since the late-stage agent acts on transitions that have

already occurred. The concept of latency needs modification and cannot be simply expressed as a function such as (5.1).

For many agents, one might expect a mixture of early- and late-stage action (as seen for cigarette smoking). The appropriate weighting through the period of exposure would then be represented by a mixture of the two expressions above. In the absence of precise knowledge of the differential effects of the exposure on early and late stages, a rough approximation could be taken as constant weighting throughout the period, i.e., average dose rate, perhaps truncated some years before disease onset as in the analysis described earlier of the cohort of uranium miners.

(c) *Effects of measurement error*

The preceding discussion has assumed that exposure levels are measured without error. In many epidemiological situations, however, measurement error can be large. In cohort studies, one may be able to assume that the error distributions for cases and controls are the same, so that the unfortunate effects of differential misclassification are avoided. The effect of such errors on a single estimate of relative risk is to bias the estimate towards unity. The effect on dose-response curves, with categorized exposure data, is to decrease each point in the curve, so that the overall slope is lower. In addition, the curvature of the dose-response may be modified. The usual effect is to make the curve more concave downwards, or less convex upwards; for example, if a power of dose were to be fitted, the observed power would be less than the real power. Such an effect may be at the origin of the concave dose-response curves seen with regard to smoking for cancer of the bladder and of the oesophagus (see Fig. 6.17). Not only are smoking histories themselves in error, but it is also unclear how the effective dose should be measured. The correlation may not be high between the number of cigarettes smoked per day and the effective tissue exposure. Families of dose-response curves that allow for concavity of this type, such as

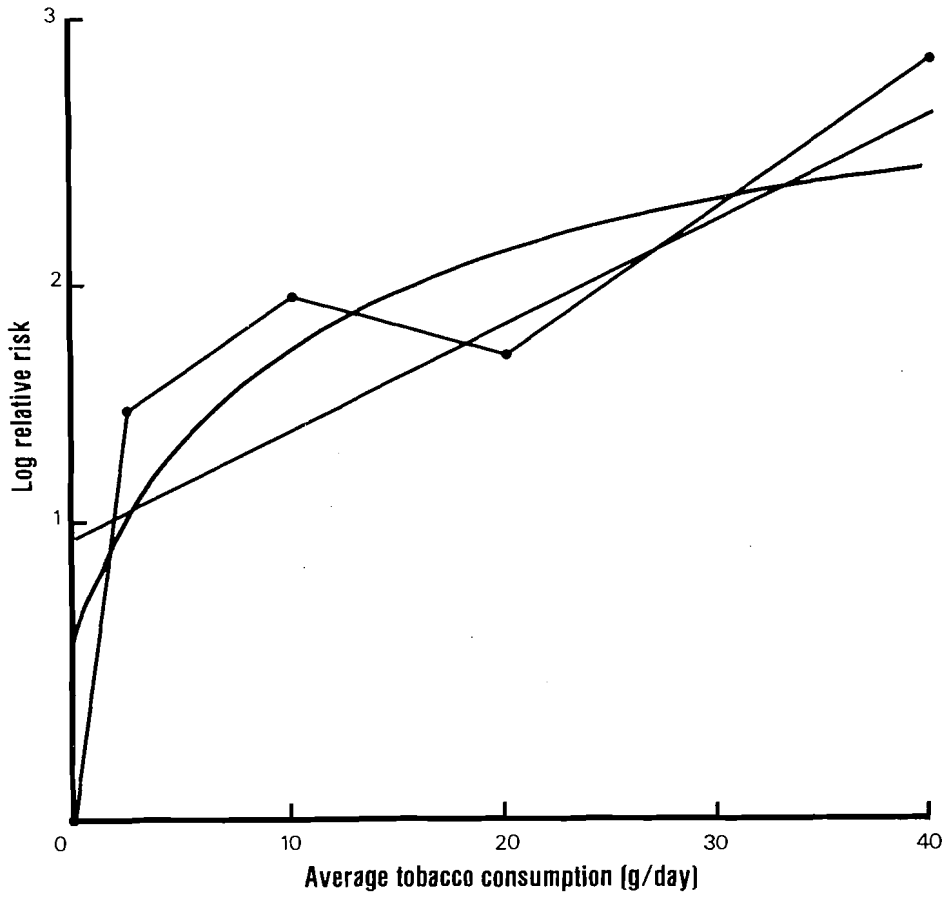
$$\text{Relative risk} = (1 + \beta \text{ dose})^k \tag{6.13}$$

may therefore be appropriate.

It should be noted that the effect of misclassification is not always to induce greater concavity in the dose-response curve; the effect depends on the distribution of the exposure variable in the population. If the distribution is positively skewed, the curvature may increase; for example, a linear dose-response curve may appear convex upwards, or the estimate of k in the expression (6.13) may be biased upwards. Some examples are given in Table 1.10.

With the uncertainties surrounding the parametric form of dose-response curve that might be used, attempts have been made to develop nonparametric approaches to the estimation of a dose-response relationship. One method has been to assume nothing except that the relationship is monotone nondecreasing, and maximum likelihood can be used to estimate the best fitting nondecreasing curve. This approach has some appeal, its drawbacks being that monotonicity may not be a valid assumption, as in the leukaemia–radiation association, and that it does not provide a concise description of the data. This latter point will be particularly apposite when dose and time variables

Fig. 6.17 Relative risk for oesophageal cancer as a function of tobacco consumption. From Volume 1, p. 221



have to be considered jointly. A further advantage of the parametric approach is that comparison between studies is facilitated.

(*d*) *Implications for the joint effect of several exposures*

With two agents, acting continuously, both of which affect some of the transition rates, one can make a simple extension of expression (6.10). If the ith transition is increased by μ_{1i} and μ_{2i} by the first and second agents respectively, then the incidence at time t will be proportional to

$$t^{k-1} \prod_{i=1}^{k} (\lambda_i + \mu_{1i} + \mu_{2i}) \tag{6.14}$$

If the effect of both agents is confined to the same single transition, and if their effects on this transition are independent, then the excess incidence at time t is simply proportional to

$$(\mu_{1i} + \mu_{2i})t^{k-1},$$

the sum of the two separate effects. The joint action is additive.

If, on the contrary, the two agents affect different transitions, so that μ_{2i} is zero if μ_{1i} is non-zero, and *vice versa,* then the excess incidence will be proportional to the product of a term involving the μ_{1i} and a term involving the μ_{2i}, of the form

$$t^{k-1} \prod_{\substack{i \text{ for which} \\ \mu_{1i} \neq 0}} (\lambda_i + \mu_{1i}) \prod_{\substack{i \text{ for which} \\ \mu_{2i} \neq 0}} (\lambda_i + \mu_{2i}).$$

The joint effect is then multiplicative.

In all situations other than these two extremes, the joint effect will lie between the additive and multiplicative, provided that the transition rates are affected independently. On many occasions, of course, the assumption of independence would be questionable: a particular genotype might respond only to a specific exposure, one exposure might modify the enzyme systems mediating the effect of the second exposure, and so on. The issues are discussed by Siemiatycki and Thomas (1981). In simple terms, however, multistage models do suggest that both additive and multiplicative joint action are plausible models to investigate, at least initially.

6.6 Application to the analysis of the South Wales nickel refinery data

A number of papers have appeared in the past few years in which an epidemiological study is analysed to provide an interpretation in terms of multistage models (Brown & Chu, 1983a; Decarli *et al.,* 1985). We present here further analyses of the South Wales nickel workers study, extending those of Chapters 4 and 5. Interpretation of the results in terms of a multistage process derives principally from the variation of risk with a number of time variables, including time since first exposure, age at first exposure, duration of exposure and time since last exposure. Lack of information on exposure levels makes it difficult to ascertain when exposure started or stopped. We shall take time of first employment as an approximation to time of first exposure. From Table 4.24, it appears that little exposure to the agent of importance took place after 1925, which we shall take as the date at which exposure stopped. (This change corresponds to some of the process changes in the factory. In 1922, arsenical impurities were removed and respirator pads introduced, and in 1924 the calciners were altered to reduce dust emission. After 1932, the amount of copper in the raw material was reduced by about 90%, and the sulphur almost completely removed.) By the definition of the cohort, no one could have retired before 1925. All individuals thus have the same date of stopping exposure, and calendar time and time since last exposure are completely confounded. For this reason, the latter variable has not been considered as a separate risk-determining factor.

As described in Chapter 4, a case-control approach within a cohort was adopted to identify high-risk areas within the factory. The results are shown in Table 6.7 (Kaldor *et al.,* 1986), and the job categories classified as high risk are indicated. An exposure index based on years of employment in these job categories was constructed, as described in Chapter 4, and used as one of the four variables chosen for closer study, the other three being age at first employment, year of first employment, and time since first employment.

Table 6.7 Regression coefficients and standard errors (in parentheses) for duration in each job category, considering all categories simultaneously[a]

Category	Lung cancer	Nasal sinus cancer	Lung and nasal sinus cancer combined
Calcining I (general and furnace)	0.17[b] (0.052)	0.063 (0.075)	0.14[b] (0.042)
Calcining II (crushing)	0.27[b] (0.11)	0.081 (0.18)	0.21[b] (0.092)
Copper sulphate	0.094[b] (0.041)	0.070 (0.051)	0.087[b] (0.032)
Reduction	0.077[b] (0.043)	−0.030 (0.061)	0.039 (0.034)
Nickel sulphate	0.094 (0.059)	0.076 (0.070)	0.088[b] (0.046)
Furnaces	0.16[b] (0.058)	0.16[b] (0.071)	0.16[b] (0.046)
Concentrates	0.12[b] (0.067)	−0.054 (0.13)	0.067 (0.060)
Gas, steam and power production	0.024 (0.047)	−0.47 (0.19)	−0.047 (0.043)
General engineering	0.043 (0.048)	−0.021 (0.065)	0.021 (0.038)
General trades	−0.057 (0.049)	−0.10 (0.075)	−0.033 (0.040)

[a] From Kaldor *et al.* (1986)
[b] Ratio of the parameter to its standard error exceeds 1.645, indicating significance at the 0.05 level (one-sided test).

Two approaches were taken to describing the excess risk. One modelled the relative excess, giving parameters equivalent to SMRs, in terms of the expression

$$\lambda_k = \mathrm{E}_k \cdot \mathrm{SMR}_0 \exp(\boldsymbol{\beta}^T \mathbf{Z}_k), \tag{6.15}$$

where λ_k is the expected number of deaths in cell k, E_k is the expected number of deaths in cell k based on population rates, SMR_0 is the risk for the baseline category relative to the population rates (in this example given by the first level for each variable in Table 6.8), $\mathbf{Z}_k$ is a vector of indicator variables giving the value of each of the four exposure-related variables, and $\boldsymbol{\beta}$ is the vector of unknown parameters to be estimated. The elements of $\boldsymbol{\beta}$ correspond to the relative risks, or SMRs, associated with different levels of the exposure variables.

The second approach modelled the excess number of cases in each cell in terms of the number of person-years in that cell (P_k), the baseline rate (R_0) for the cell chosen as the reference and terms describing the relative effect on the absolute excess of the different levels of the exposure variables. Algebraically,

$$\lambda_k = \mathrm{E}_k + P_k \cdot R_0 \exp(\boldsymbol{\beta}^T \mathbf{Z}_k). \tag{6.16}$$

In model 1, expression (6.15), the components of $\boldsymbol{\beta}$, when exponentiated, describe the relative effects of different exposure levels on the overall SMR for the cohort; in model 2, expression (6.16), the exponentiated components of $\boldsymbol{\beta}$ describe the relative effects of different exposure levels on the overall absolute excess mortality rate for the cohort, the EMR. Table 6.8 gives the results of fitting these two models for both lung and nasal sinus cancer, giving the estimated EMRs and SMRs associated with all four variables. For both cancers, there is a steady increase in risk with increasing exposure index, the increase being sharper for nasal sinus cancer. The effect of year of first employment,

Table 6.8 Estimated adjusted SMRs and EMRs for lung and nasal sinus cancer mortality[a]

Variable	Level	Lung cancer		Nasal sinus cancer	
		SMR[b]	EMR[b]	SMR[b]	EMR[b]
Age at first employment (years)	<20	1.0	1.0	1.0	1.0
	20–27.5	1.4	2.8[b]	3.3	5.1[c]
	27.5–35	1.3	2.9[b]	5.0[c]	10.9[d]
	35+	0.93	2.6	10.6[d]	36.6[d]
Year of first employment	<1910	1.0	1.0	1.0	1.0
	1910–1914	1.1	1.5	2.4[c]	2.4[c]
	1915–1919	0.57	0.95	2.9[c]	2.9[c]
	1920–1924	0.65	1.4	0.91	0.87
Exposure index	0	1.0	1.0	1.0	1.0
	1–4	1.9[d]	2.7[d]	4.7[d]	4.5[d]
	5–9	3.1[d]	4.4[d]	4.0[c]	3.9[d]
	10–14	2.6[d]	3.7[d]	12.7[d]	13.3[d]
	15+	4.2[d]	6.5[d]	20.5[d]	21.2[d]
Time since first employment (years)	<20	1.0	1.0	1.0	1.0
	20–29	0.74	2.8[c]	2.8	4.9
	30–39	0.47	4.9[d]	2.4	6.6[c]
	40–49	0.22[d]	4.8[d]	3.1	13.9[d]
	50+	0.11[d]	2.4	3.4	24.7[d]

[a] From Kaldor *et al.* (1986). Due to editing in progress, these analyses are based on a slightly modified version of the data given in Appendices VII and VIII. There are therefore some minor differences between this table and Table 4.25.

[b] Relative to the rate in the baseline category, which is arbitrarily fixed as 1.0

[c] Significantly different from the baseline at the 0.05 level of significance (two-tailed)

[d] Significantly different from the baseline at the 0.01 level of significance (two-tailed)

given the exposure index, is slight for both cancers. For age at first employment and time since first employment, however, the estimates are strikingly different for the two cancers.

The SMR for lung cancer varies little with age at first employment but decreases sharply with time since first employment – variables that can be considered as surrogates for age at first exposure and time since last exposure. The EMR, as a function of time since first employment, rises to a plateau then remains roughly constant. This behaviour of the SMR and the EMR corresponds well to that of a late-stage agent, as described in Table 6.6. There is some inconsistency with the behaviour of the EMR with age at first employment, which does not show the steady rise with age expected of a late-stage agent. The explanation may lie in changing underlying rates for lung cancer, since the relevant period is one in which the rate for lung cancer was increasingly rapidly. Those older at first employment would tend to have lower baseline rates.

For nasal sinus cancer, the EMR rises rapidly with time since first employment; the SMR rises initially and then plateaus. This behaviour corresponds to that of an early-stage agent. Both the EMR and SMR, however, rise steadily, the former more rapidly, with age at first employment, behaviour directly contrary to that predicted for

an early-stage agent. This inconsistency may have arisen because age at first employment is still confounded with degree of exposure, even though an exposure index has been fitted in the model. In epidemiological data of this type, in which no concurrent measure of exposure is available, the retrospective construction of exposure indices may introduce problems of its own, and certainly cannot be guaranteed to summarize fully different exposures among individuals.

This example demonstrates that one cannot expect epidemiological observation to conform closely to the constraints of simple models, due, for example, to the effect of other variables for which there is no information, or to the inadequacy of exposure information for the variable of interest. The purpose of introducing multistage concepts is not to describe completely the complexities actually observed, but to explain, in terms of a fairly simple model of the carcinogenic process, major differences in behaviour.