

MORTALITY AND CANCER MORBIDITY IN WORKERS IN THE SWEDISH PVC-PROCESSING INDUSTRY

BY

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Vinyl chloride has proved to be the cause of scleroderma, Raynaud's disease, acro-osteolysis, liver damage and liver cancer (haemangiosarcoma)(7) in workers exposed to vinyl chloride monomer (VCM). This has been proved in investigations carried out in businesses producing polyvinyl chloride (PVC) (5,8). Studies using animal experiments have resulted in reports that inhalation of VCM has given rise to malignant tumours in different organs in rodents (6,9,18).

In Sweden, in 1974, two cases of haemangiosarcoma of the liver were confirmed in employees of a VCM and PVC-producing company (2). Subsequently, two further cases occurred in the same factory.

Studies (13,16) of different forms of cancer indicate that workers exposed to VCM in PVC-producing industries may run an increased risk of dying from forms of cancer other than haemangiosarcoma of the liver. Earlier, an increased rate of mortality from heart/vessel diseases(1) was also observed in employees of the PVC-producing industry.

This retrospective cohort study was carried out with the purpose of surveying the pattern of morbidity and death in the PVC-processing industry. In general there is a lower level of exposure to VCM in the PVC-processing industry than in the production industry. There are ca. 5,000 people employed in production in the PVC-processing industry.

MATERIAL AND METHODS

For the investigation, information was collected from four PVC-processing enterprises. The four enterprises all use PVC which, following the addition of different chemicals, undergoes heat-treatment to produce, amongst other things, flooring, PVC-coated fabrics, pipes, and food packaging.

Collection of data

The following information was collected from lists of personnel employed with the enterprises :

Staff number

Name

Start and end of exposure (year and month)

Class of exposure.

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The requirement for a person to be included in the original cohort is at least 3 months' employment, between 1945 and 31.12.74. Exposures are classified as follows: Class 3 (high): working in the blending department; Class 2 (medium): heat-treatment machines; Class 1 (low): other production departments.

The collected data was transferred to punched cards and magnetic tape for statistical processing. The magnetic tape was compared, at the Central Office for Statistics (SCB), with the country's total population and with the "death tape" for the period 1961-76, and checked against the cancer register. The number of persons who could not be found was checked at the State Tax Dept. In all, 2073 persons were included in the original cohort. 103 persons had dropped out (5%), of whom 70 have gone abroad, 5 appear in the State Tax Dept.'s register of missing persons and 28 could not be traced.

Study cohorts

For statistical purposes, the resulting cohort of 1970 persons was divided into a number of sub-cohorts (study cohorts):

1. All persons with at least 0 months exposure. Follow-up period from beginning of exposure up to 1976 inclusive.
2. All persons with at least 6 months' exposure, excluding those who left before 1961. Follow-up period from beginning of exposure, but not earlier than 1961, up to 1976 inclusive.
3. All persons with at least 6 months' exposure, beginning not earlier than 1961. Follow-up period from beginning of exposure up to 1976 inclusive.
4. All persons with at least 2 years' exposure. Follow-up period from two years after beginning of exposure, but not earlier than 1961, and up to 1976 inclusive, but not more than 10 years after end of exposure.
5. All persons with at least 2 years' exposure. Follow-up period from 10 years after beginning of exposure, but not earlier than 1961, and up to 1976 inclusive.

The last two study cohorts were selected in order to investigate whether there are any differences in the cause-of-death pattern with regard to how long after the beginning of exposure death occurs. The object of the first of the study cohorts is to shed light on the cause of death occurring relatively early - e.g. accident caused by the work. The object of the others is to shed light on any causes of death occurring after a fairly long period. For example, tumours caused by exposure at work often have a long incubation period, as a rule 5-10 years or longer.

Statistical methods

The final analysis was carried out on the basis of two methods. In Method A the observed and anticipated number of deaths/cases of cancer (cancer incidence) was calculated on the basis of the calendar year, and in Method B, the observed/anticipated annual risk of death was calculated on the basis of the risk year.

Method A

For each person, a calculation is carried out of the "annual contribution to the anticipated number of deaths" by dividing each individual's death expectation by a small part of each calendar year, in accordance with the formula :

$$e_{xy} = q_{xy} \times p_{x-1,y-1} \times \dots \times p_{ab}$$

where e_{xy} is the contribution to the anticipated number of deaths during year x at the age of y and q_{xy} is the risk of death throughout the country for those who were y years old during year x . The survival probability is $p_{xy} = 1 - q_{xy}$. However, for the first risk year, the survival probability is calculated as $p_{ab} = 1 - \frac{1}{2}q_{ab}$, as it can be reasonably assumed that on average exposure began in the middle of the year.

The individual e_{xy} has been added up to E where E_{xy} is the anticipated number of deaths during year x amongst those who are (or would have been) aged y . Corresponding sums have been carried out for the observed number of deaths. By taking all ages into account for a certain year, the expected/observed number of deaths that year is obtained.

As each annual total consists of a relatively small number, as time goes on, the years have been added to each other (accumulated) to give a better picture of the development. The accumulated annual sums show the development up to and including the year to which the sum relates. In order to facilitate comparison of different sub-groups, the accumulated sums have been converted to percentages of the number of persons included in the follow-up up to the present.

The expected number of deaths from a specific cause, e.g. heart infarction, has been calculated by multiplying E_{xy} by the proportion of deaths from heart infarction in relation to all deaths throughout the country during year x at age y . The numbers thus obtained have been added up for two periods, 1961-1968 and 1969-1976. The reason for division into these particular periods is a thorough revision of the cause-of-death classification which was first applied in 1969.

To examine whether the total number of deaths deviates from the expected figure to an extent too great to be attributed to chance, an χ^2 test has been used. The observed distribution of deaths amongst different causes was checked against that expected by means of an χ^2 test.

Calculations were carried out in the same way for the incidence of cancer, except that the following formula was used :

$$e_{xy} = r_{xy} \times s_{x-1,y-1} \times \dots \times s_{ab} \times p_{x-1,y} \times \dots \times p_{ab}$$

where r_{xy} constitutes the risk of a tumour being diagnosed at age y during year x , $s_{xy} = 1 - r_{xy}$ and p_{xy} denotes survival probability. This somewhat more complicated formula takes into account the fact that a person's risk of cancer at a certain time is calculated with reference to the probability of his surviving up to that time.

Method B

The beginning of exposure or the time when the risk is seen as starting constitutes the starting point (time = 0) and time is calculated in risk years. The observed risk of death during a risk year ($x, x+1$) is calculated in accordance with the formula $q_x = 1 - p_x$, where p_x is the probability of surviving the current risk year, provided that the person concerned survived the previous year (ref 3) :

$$p_x = \left[\frac{-1/2d'_x + \sqrt{\frac{1}{4}d'^2_x + 4(N_x - 1/2n_x)(s_x + 1/2w_x)}}{2(N_x - 1/2n_x)} \right]^2$$

In the formula, N is the number of persons alive at the beginning of risk year x , s_x is the number of persons who survived the risk year ($= N_x + 1$), whilst w_x is the number of persons who dropped out of the follow-up during a risk year, as the closing date (31.12.76) occurred during their risk year. d is the number of persons who would have dropped out of the cohort but died, and n_x is the sum of w_x and d'_x .

The expected risks for each risk year have been calculated as the average value of the risks of death mentioned in Method A above, q_{xy} since account was taken of when the follow-up started. For a person whose follow-up started in year a and who was b years old, the risk during the first follow-up year was calculated as $q_0 = 1/2 q_{ab} + 1/2 q_{a+1,b}$. The average risk during the first risk year was calculated as the average value of all such risks q_0 .

The development over the period is illustrated by calculating the accumulated probabilities of survival on the basis of the observed and expected annual probabilities. The formula

$$P_{0x} = P_0 \times P_1 \times \dots \times P_{x-1}$$

expresses the probability of surviving from the beginning of the follow-up until a point in time x .

If no discrepancy is found between observed and expected risk, the observed and expected risks for each risk year should be equally great. In order to illustrate whether there are changes over the period, the observed risk series has been established by a 3-part sliding average, i.e. the risk for year 2 is the average value for the years 1-3, the risk for year 3 is the average value of the risks for years 2-4 etc. The series established in this way has been divided by the expected risks, year for year, thus obtaining a risk quota. If no discrepancies are found, this risk quota will be ca. 1, or, expressed as a percentage, 100. An increasing series indicates a risk increasing with exposure, and a series which is constant at first, but after some years begins to increase, indicates that the exposure must reach a certain level before there can be a question of an increase in risk.

RESULT

The original cohort was relatively young at the beginning of exposure. Age distribution into different classes of exposure is shown by Table 1. There are certain differences between the classes of exposure. In Class 1 (low), 41.7 % were younger than 35 years at the beginning of exposure, in Class 2 (medium), 47.7 %, and in Class 3 (high), 50.6 %. The duration of exposure also differs according to the Class of exposure (Table 2).

It should however be noted that the table includes cases still subject to exposure on the last date for inclusion in the cohort (31.12.74), which explains a certain tendency towards short periods of exposure. Notwithstanding this, Exposure Class 3 includes longer periods of exposure on average.

The cohort as a whole shows up no noteworthy increase in the total risk of death compared with the average for the country, nor was there any indication of this in the sub-groups comprising the study cohorts.

Study cohort 1, which includes all those with at least 6 months' exposure, and with the risk calculated from the beginning of exposure, is somewhat remarkable insofar as the expected number of deaths is significantly higher than that observed in 1964 (Fig. 1). Further comments on this are contained in the discussion. Study cohort 2 (Tables 3 and 4, Fig. 2) includes persons with at least 6 months' exposure, excluding those who left before 1961. The calculation of the risk is carried out from the beginning of exposure, but not earlier than 1961, and up to the end of the follow-up period (1976). The number of deaths observed is somewhat lower than expected - in Exposure Class 2 much lower. Classes 2 and 3 are relatively small and with this type of analysis are subject to random developments. To prevent chance developments affecting the result, the classes have been combined; this applies to all the study cohorts. Table 4 shows the distribution amongst different causes of death. The observed and expected number of deaths during the period 1961-68 is relatively small - only a few cases, and as the cause-of-death classification was changed in 1969, as mentioned previously, the period 1961-68 is not shown separately. The picture is broadly the same as for the period shown - 1969-76. Table 4 shows that the observed number of deaths, in particular from tumours of the digestive organs, heart infarction and accidents etc. is somewhat higher than expected. However the discrepancies are not significant. Study cohort 3 (Tables 5 and 6, Figs. 3-5) which apply to those who started in 1961 or later but who otherwise fulfil the same criteria as study cohort 2, shows a similar picture.

An analysis of Study Cohort 3 in accordance with method B (Figs 4-5) indicates that the annual risk during the first years of exposure is somewhat lower than expected, but after ca. 10 years there is an increase in risk, so that the observed risk is higher than expected.

In study cohort 4 (Table 7) which relates to the period of continuous exposure or a relatively short time after the end of the exposure, i.e. the "short-term perspective", there is an increased risk of death from heart infarction. In this case the risk from other causes is somewhat lower than expected.

Finally, in study cohort 5 (Table 8) there is an indication of an increase in the risk of death as regards tumours, but also heart infarction. Discrepancies between the observed and expected number is however not statistically established at the 5 % level.

The result with regard to mortality can be summarised as follows : Taken as a whole, there is no apparent increase in mortality in the study cohorts. On the other hand, there are indications of a shift in the cause-of-death pattern as compared with the average for the country. This shift is chiefly expressed by the fact that the number of heart infarctions is evidently higher during continuous exposure or within a relatively short time after exposure ended. There is also an indication that the risk of death from tumours can be increased amongst persons, with a long incubation period (Tables 7 and 8).

With regard to cancer morbidity there is no definite increase in study cohort 2 (Table 9 and Fig. 6). With regard to tumours of the digestive organs, 11 cases were observed, as against 8.5 expected. The differences are not statistically established. One of the 11 cases of tumour was cancer of the liver.

DISCUSSION

A noteworthy finding of the analysis of the total mortality for the cohort (Fig. 1) is the fact that the number of deaths at the beginning of the observation period (1947-64) is significantly lower than that to be expected in relation to the average for the country. This

discrepancy is so great that it cannot simply be attributed to chance, nor can it be wholly ascribed to the so-called "healthy worker effect". Theoretically it is of course possible that with regard to mortality and connected factors, the selected cohort differs considerably from the population of the country as a whole. However a more likely explanation is that the list of persons available in the company concerned at the time of this investigation was incomplete with regard to persons employed during an earlier period. A list of persons from which for example in the mid-1960s persons who left its employ before 1960 were removed, may result in the above-mentioned discrepancy. The company concerned has stated that, to its knowledge, no such "thinning out" was carried out.

Should this "thinning out" have taken place after all, this would have resulted in a loss of persons with a long observation period at the time of the follow-up. In this investigation the risk calculations have been restricted so that they begin no earlier than 1961. This means limiting the analysis to the group of surviving employees, beginning in 1961 so that the risk of a loss can certainly be eliminated. However this restriction means that the analysis is weakened, as sections of the cohort with long follow-up periods are excluded. This principally means that there is less possibility of detecting an increased incidence of cancer, should one exist.

Heart-infarction mortality (ICD 410.90) is increased in the cohort. This increase appears most clearly in the category of the total cohort with at least 2 years' employment, where the analysis is concerned with the period following two years from the beginning of employment and extending to a maximum of five years after termination of employment. It thus deals with those deaths from heart infarction which, with regard to time, occur relatively close to the period of employment. It is not possible on the basis of such observations to draw the conclusion that the increase is caused by exposure to vinyl chloride. The observed increase in mortality from heart infarction is however so marked, that in combination with known facts concerning vinyl chloride's toxic properties, it must be taken into account.

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There is no reason to assume that varying diagnostics, standards or practice in the filling-in of death certificates alone can provide an explanation. Disregarding the possibility of a chance local phenomenon, a natural conclusion is therefore that the increased frequency can be ascribed to either a selection of individuals susceptible to risk, or an outbreak of risk factors in the employee's immediate environment. In theory, a combination of these is, of course, also possible.

In this connection it should be noted that many risk factors in the case of heart infarction are connected with environment in the sense that they constitute part of the life style in the present-day social environment of an industrialised country. Cigarette smoking, physical inactivity, overweight, high blood-lipid content thus constitute environmental factors which are connected with social behaviour. It is a well-known fact that the risk of coronary heart disease varies according to the total risk factors amongst other things. Other risk factors which may be mentioned include hereditary characteristics and high blood pressure. In this connection it should be remembered that the causes of coronary disease include many factors, and in this respect the disease is connected with environment. It should also be borne in mind that the total risk increases when several risk factors, known or unknown, are combined (15,17).

It has not been possible to establish the distribution of such already known risk factors for coronary disease in the cohort examined in comparison with the population of the country in general. No continued analysis of the question of causal relationship between immediate environment and heart-disease morbidity can therefore be carried out within the context of this study.

In this study, exposure classes 2 and 3 constitute sub-cohorts which are too small to give rise to meaningful discussion of heart-infarction risks in relation to different levels of exposure within the processing industry. In this connection account should also be taken of the fact that the exposure classes in the study are based on interviews with employees concerned with the work environment between ten and fifteen years ago. If thus deals with an environment which has since undergone changes. There are no objective classification criteria with regard to exposure, e.g. in the form of environmental measurements. The distribution into exposure classes is therefore impaired by uncertainty.

Class - Risk factors for heart

Can't do this
which is probably
hazardous to
when to get an
never why not alone
ACM?

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Animal tests have shown that the toxicity picture in rodents with chronic exposure to VCM involves blood vessels. In addition to haemangiosarcoma of the liver and other organs (6,9), inhalation of VCM also seems to lead to telangiectasis (6) of the liver in mice, which may lead to death in haemocoel[?]. Changes in sinus cells have been observed in liver biopsies of VCM-exposed workers (14). Capillary changes in the skin of the fingers have also been observed (10,11,12) both in VCM-exposed workers with other diseases involving vessels, such as acro-osteolysis, Raynaud's disease and scleroderma and in VCM-exposed workers without such diseases. An over-representation of cases of death from heart/vessel diseases has also been observed in a study of the PVC-manufacturing industry (1). Animal experiments and earlier medical studies of people exposed to VCM thus support the assumption that the increased risk of heart infarction observed in this study could be ascribed to VCM exposure.

With regard to tumour mortality and morbidity, the result is unclear. There are certain indications of an increase but the differences have not been established by statistics. Two possibilities can be considered here :

1. There is in reality no increase in the risk of tumours.
2. There is an increased risk of tumours in the works itself. The result neither confirms nor denies this. Tumours only appear after a long incubation period. The majority of the persons included in the study did not begin their exposure until the 60s or 70s, and could therefore not be followed up for a sufficiently long time. A careful follow-up of this cohort during the coming 5-year period should considerably clarify this question.

In this connection it is interesting that in a recently published mortality study (4) of over 4300 deaths in the American PVC-processing industry there is an over-representation of cancer mortality (all cancer), and in particular cancer of the stomach/intestines in both sexes.

SUMMARY

Personnel lists were collected from four PVC-processing enterprises for production workers with at least 3 months' employment between 1945 and 31.12.1974. Of 2073 persons, 103 could not be followed up, e.g. because they had gone abroad. The remaining cohort of 1970 individuals was analysed and compared with the population of the country with regard to mortality in different diseases and to cancer morbidity.

The risk of death from heart infarction was higher in the cohort. This increase is shown most clearly in the sub-cohort with at least 2 years' exposure, where the analysis was concerned with events occurring during exposure or shortly after. The risk of heart infarction in connection with vinyl-chloride exposure is discussed in relation to earlier studies of the effect of vinyl chloride on vessels. There is also an indication of an increased risk of morbidity and mortality in connection with tumours of the digestive system. This has not been established by statistics. A future follow-up of this study is necessary to clarify whether there is any increased risk of tumours in the PVC-processing industry.

Key words : Retrospective cohort study, vinyl chloride, PVC-processing industry, cancer, tumours of the digestive system, heart infarction.

References :

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Exposure Class

Age	1	2	3	1-3
-19	1.6	2.0	8.9	2.1
20-24	7.5	14.6	14.3	9.2
25-29	13.5	15.7	21.4	14.4
30-34	19.1	15.4	17.0	18.3
35-39	17.0	13.2	10.7	15.9
40-44	13.7	12.6	9.8	13.3
45-49	11.1	12.6	8.9	11.3
50-54	8.0	7.8	5.4	7.8
55-59	5.1	3.9	1.8	4.7
60-64	2.6	2.0	1.8	2.4
65-	0.7	0.3	0.0	0.6
No. of persons	100 % (1501 st)	100 % (357 st)	100 % (112 st)	100 % (1970 st)

Table 1. Age distribution in the original cohort at the beginning of exposure (%).

Exposure Class

Months	1	2	3	1-3
-5	13.1	0.3	0.0	10.1
6-23	38.4	8.4	8.9	31.3
24-59	25.0	17.4	10.7	22.8
60-119	15.3	45.7	15.2	20.8
120-	8.2	28.3	65.2	15.1
	100 %	100 %	100 %	100 %

Table 2. Exposure-period distribution in the original cohort (%).

Cohort	No.	No. of deaths		Quota	Approx. 95 % conf. interval
		Obs.	Exp.		
Exp. klass 1	1303	53	55.5	0.95	± 0.26
Exp. klass 2	356	14	21.9	0.64	± 0.34
Exp. klass 3	112	6	10.3	0.70	± 0.47
Exp. klass 1-3	1771	73	87.8	0.84	± 0.19

Table 3. Expected and observed number of deaths as at 31.12.76 amongst those with at least 6 months' exposure, excluding those who left before 1961. Calculation of risk from the beginning of exposure, but not before 1961. Study cohort 2 (1771 persons).

	Observed	Expected	Quota
Malignant tumours 140-209	17	14.0	1.21
Tumours of the digestive system 150-159	8	4.9	1.63
Heart and vessel diseases VII	22	24.3	0.91
Heart infarction 410.90	15	10.0	1.49
Accidents, suicide etc. XVII	13	9.2	1.42

Table 4. Expected and observed number of deaths from certain causes during the period 1969-1976 in those with at least 6 months' exposure excluding those who left before 1961. Calculation of risk from the beginning of exposure, but not earlier than 1961. Study cohort 2 (1771 persons).

Cohort	No.	No. of deaths		Quota	Approx. 95 % conf. interval
		Obs.	Exp.		
Exp. Class 1	1139	43	41.2	1.04	± 0.31
Exp. Class 2	247	4	11.7	0.34	± 0.34
Exp. Class 3	42	1	1.8	not calcul- ated	not calculated
Exp. Class 1-3	1428	48	54.7	0.88	± 0.25

Table 5. Expected and observed number of deaths as at 31.12.76 in those with at least 6 months' exposure beginning not earlier than 1961. Calculation of risk from beginning of exposure. Study cohort 3 (1428 persons).

	Observed	Expected	Quota
Malignant tumours 140-209	9	9.7	0.93
Tumours of the digestive system 150-159	4	3.3	1.20
Heart and vessel diseases VII	16	16.2	0.99
Heart infarction 410.90	14	11.2	1.25
Accidents, suicide etc. XVII	11	7.3	1.51

Table 6 . Observed and expected number of deaths from certain causes during the period 1969-1976 amongst those with at least 6 months' exposure beginning 1961 or earlier. Calculation of risk from the beginning of exposure. Study cohort 3 (1428 persons).

	Observed	Expected	Quota
Malignant tumours 140-209	5 (9)	7.4 (8.9)	0.68 (1.01)
Tumours of the digestive system 150-159	2 (4)	2.6 (3.2)	0.78 (1.27)
Heart and vessel disease	15(16)	12.7(15.8)	1.18 (1.01)
Heart infarction	11(12)	5.4 (6.6)	2.03*(1.82*)
Accidents, suicide etc. XVII	4 (5)	4.6 (5.1)	0.87 (0.97)

* $p < 0.05$

Table 7. Observed and expected number of deaths from certain causes during the period 1969-76 amongst those with at least 2 years' exposure beginning not earlier than 1961. Calculation of risk from beginning of exposure. Study cohort 3 (1428 persons).

	Observed	Expected	Quota
Malignant tumours 140-209	9	6.0	1.51
Tumours of the digestive system 150-159	4	2.2	1.85
Heart and vessel diseases VII	12	11.1	1.08
Heart infarction 410.90	8	4.5	1.77
Accidents, suicide etc. XVII	2	2.5	0.79

Table 8. Observed and expected number of deaths from certain causes during the period 1969-76 in those with at least 2 years' exposure. The calculation of risk is carried out from ten years after the beginning of exposure. Study cohort 5 (680 persons).

	Observed	Expected	Quota
Malignant tumours (total)	51	44.6	1.14
Tumours of the digestive system (150-159)	11	8.5	1.29

Table 9. Observed and expected number of cancer cases during the period 1961-76 in those with at least 6 months' exposure excluding those who left before 1961. Risk calculation from the beginning of exposure, but not earlier than 1961. Study cohort 2 (1771 persons)

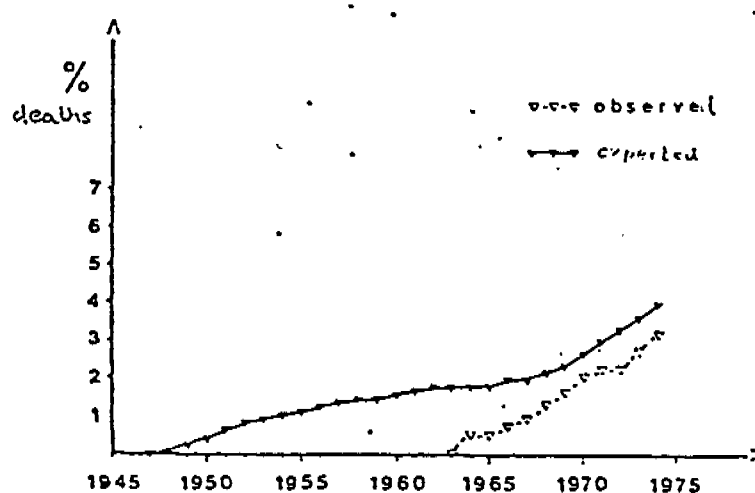


Fig. 1

Accumulated proportion of deaths in %. Expected value calculated from beginning of exposure. Study cohort 1 (1970 persons).

The percentage for a given year has been calculated as

$$100 \times \frac{\text{number of persons dying up to the given year inclusive}}{\text{number of persons beginning exposure up to the given year inclusive}}$$

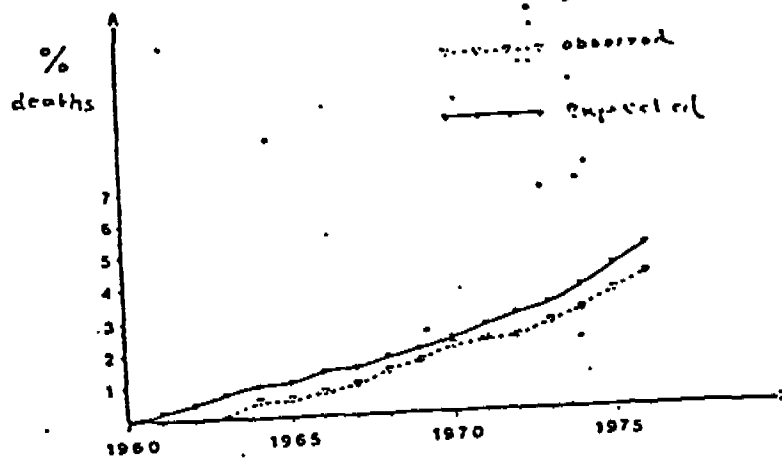


Fig. 2

Accumulated proportion of deaths in %. Expected value calculated from 1961 inclusive. Study cohort 2 (1771 persons).

The percentage for a given year is calculated as in Fig. 1. (This also applies to Fig. 3 and Fig. 6, which relates to cases of cancer).

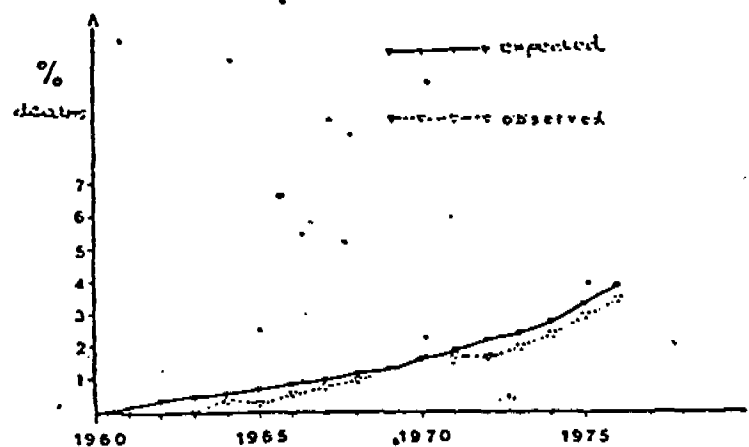


Fig. 3

Accumulated proportion of deaths in % of those whose exposure began in 1961 or later. Study cohort 3 (1428 persons)

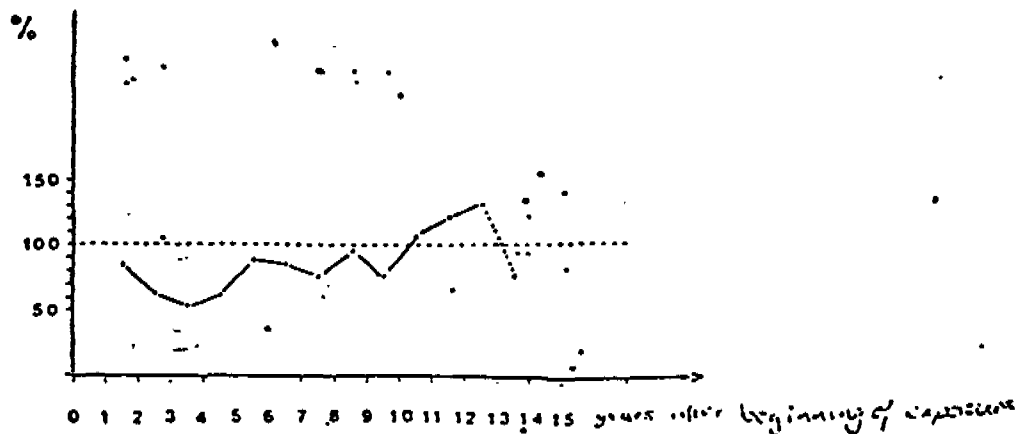


Fig. 4 The observed risk of death per risk year at different times after the beginning of exposure as a percentage of the corresponding expected risk in those whose exposure began in 1961 or later. Study cohort 3 (1428 persons).

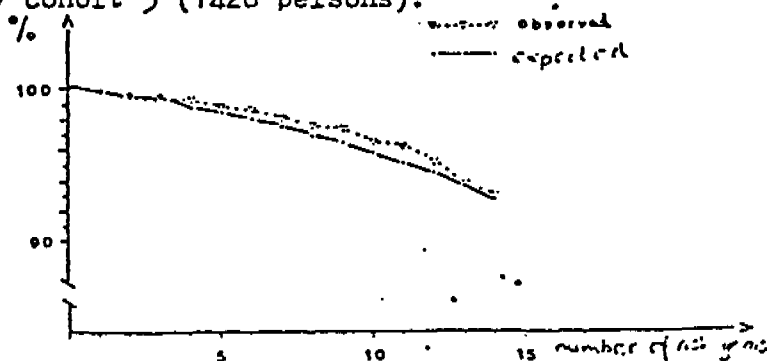


Fig. 5 Accumulated survival probability in % for those whose exposure began in 1961 or later and who have at least 6 months' exposure. Study cohort 3 (1428 persons):

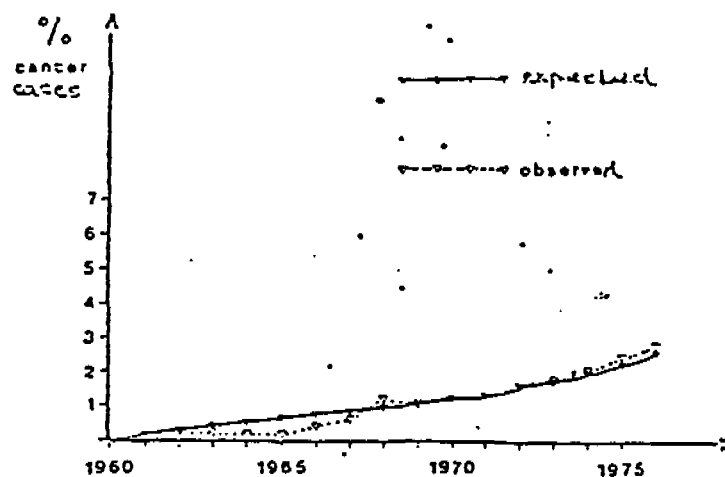


Fig. 6 Accumulated proportion of cancer cases in %. Study cohort 2 (1771 persons).