Radiat Environ Biophys (2003) 42:129–135
DOI 10.1007/s00411-003-0198-3

ORIGINAL PAPER

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Lung cancer mortality among nuclear workers of the Mayak facilities in the former Soviet Union

An updated analysis considering smoking as the main confounding factor

Received: 28 February 2003 / Accepted: 28 April 2003 / Published online: 8 July 2003

Abstract A new analysis of lung cancer mortality in a cohort of male Mayak workers who started their employment in the plutonium and reprocessing plants between 1948 and 1958 has been carried out in terms of a relative risk model. The follow-up has been extended until 1999, moreover a new dosimetry system (DOSES2000) has been established. Particular emphasis has been given to a discrimination of the effects of external γ-exposure and internal α-exposure due to incorporated plutonium. This study has also utilized and incorporated the information from a cohort of Mayak reactor workers, who were exposed only externally to γ-rays. The influence of smoking as the main confounding factor for lung cancer has been studied. The baseline lung cancer mortality rate was not taken from national statistics but was derived from the cohort itself. The estimated excess relative risk for the plutonium α-rays was 0.23/Sv (95%CI: 0.16–0.31). The resulting risk coefficient for external γ-ray exposure was very low with a statistically insignificant estimate of 0.058/Sv (95%CI: –0.072–0.20). The inferred relative risk for smokers was 16.5 (95%CI: 12.6–20.5).

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Introduction

As outlined in a number of earlier publications [1, 2, 3, 4, 5, 6, 7, 8, 9], several thousand nuclear workers were subjected to major radiation exposures in the Mayak plutonium production facilities of the former Soviet Union, particularly in the 1950s. All workers in the reactors and in the plutonium and radiochemical plants were exposed to external γ-radiation during their period of employment at Mayak. The radiochemical and plutonium workers were also exposed internally to α-rays from incorporated plutonium. In contrast to the external γ-rays the internal exposures continued after termination of work. Included in the cohort are all workers hired between 1948 and 1958, for whom plutonium body burdens are determined and for whom smoking information is available. As reported earlier, increases in cancer incidence and mortality rates have been noted, however, the significant excess of lung cancer mortality is most striking.

Characteristics of the cohort

Between 1948 and 1958, which was the period of highest exposures, a total of 8,927 male workers were hired at Mayak. In the present study lung cancer mortality among a cohort of 4,212 male Mayak nuclear workers is analysed, 3,132 (74%) of these workers being smokers. An earlier study [9] comprised 3,841 workers—with follow-up until the end of 1995—and included 191 lung cancer cases. The follow-up has now been extended through 1999 and the total of lung cancer deaths is now 219 (among 1,921deaths). The cohort includes all 1,339 radiochemical and 676 plutonium workers from the group of workers with early employment for whom urinary excretion measurements have been performed to determine the plutonium incorporation. It also includes 2,197 reactor workers for whom individual external dose-measurements are available. Lack of smoking information

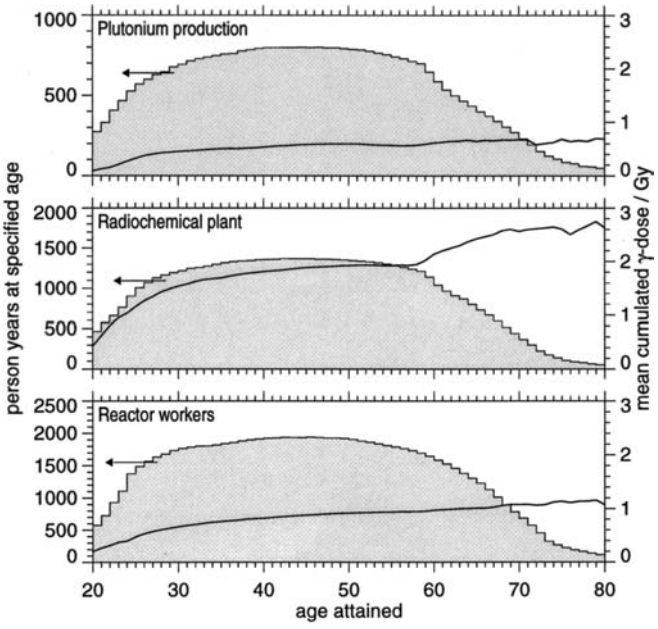

Fig. 1 Mean cumulated absorbed γ-dose up to specified age, for plutonium (*upper panel*), radiochemical (*middle panel*), and for reactor workers (*lower panel*). The grey shaded areas give the person years, i.e. the number of cohort members under employment at specified age

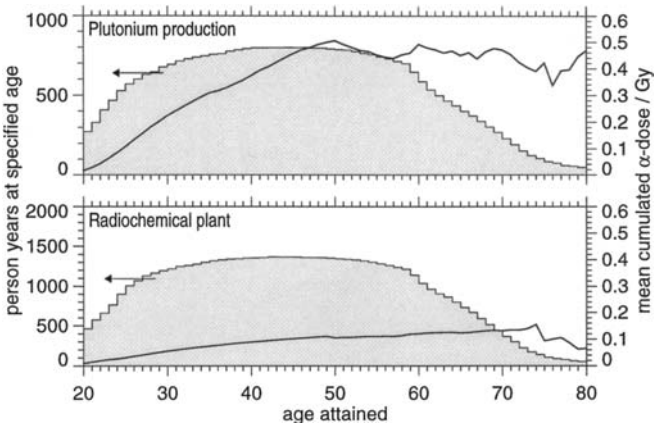

Fig. 2 Mean cumulated absorbed α-dose up to specified age, for plutonium (*upper panel*) and for radiochemical workers (*lower panel*). The grey shaded areas give the person years, i.e. the number of cohort members under employment at specified age

led to the exclusion of 438 workers who had been included in the preceding study [9].

Smoking information has been collected from individual workers records and the analysis accounts for smoking as the main confounding risk factor.

The vital status of all 4,212 workers in the study cohort has been determined, and for the deceased the causes of death, documented in the official death registry, have been checked in terms of the individual patient data sheets. The doses from external γ-exposures have been derived from film-badge dosimetry. For the assessment of internal α-doses a modified biokinetic model for the estimation of accumulation of plutonium in the lungs has been developed on the basis of a large set of urinary excretion data. As detailed in the published reports [10, 11, 12, 13, 14, 15] the model differs from the ICRP assumptions [16], particularly due to its somewhat larger retention times. The individual exposure history in terms of annual doses (external and where applicable, internal) of all the 4,212 workers in the study group has been reconstructed. In particular it needs to be pointed out that for the internal exposures due to incorporated plutonium the more recently developed dosimetry system DOSES 2000 [13, 14, 15] was utilized.

The mean accumulated absorbed dose to the lungs up to specified age illustrates, in Figs. 1 and 2, the trend of the external and internal exposures for each of the subcohorts. The reactor workers were exposed to γ-rays only. The radiochemical workers received the highest γ-doses and, in addition α-doses, mainly from incorporated $PuNO_3$. The plutonium workers were subject to external γ-exposures and received the highest α-doses because they incorporated predominantly PuO_2 which is less soluble than $PuNO_3$ and is, therefore, removed more slowly from the respiratory tract.

Table 1 gives essential characteristics of the cohort. An analysis of an extended cohort which includes 1,732

Table 1 Essential characteristics of the cohorts (through end of 1999), year of 1st employment 1948–1958

	Reactor	Radiochemical plant	Plutonium production
Number of workers	2,197	1,339	676
Number of lung cancer deaths	92	77	50
Fraction of deaths due to lung cancer	8.3%	13.5%	18.6%
Number of workers alive in 1999	1,114 (50.7%)	770 (57.5%)	407 (60.2%)
Person years at risk	78,813[a]	19,474[b]	11,003[b]
Mean duration since 1st year of employment	35.9 years	41.9 years	41.3 years
Mean cumulated α-dose		0.140 Gy	0.450 Gy
Mean cumulated γ-dose	0.904 Gy	1.973 Gy	0.510 Gy
Collective α-dose		186.93 Gy	301.40 Gy
Collective γ-dose	1986.34 Gy	2641.26 Gy	344.56 Gy
Mean duration of work	15.8 years	29.1 years	17.9 years

[a] Person years calculated since year of 1st employment.
[b] Person years calculated since year of 1st urinary sampling

female workers is presented in the Appendix. Among the female workers there were only 57 (3.3%) smokers and 19 lung cancer cases among 381 deaths.

Evaluation of the model

The relative risk model

The utilization of a relative risk model has been a common feature in various previous studies on radiation-induced lung cancer [17, 18, 19, 20, 21, 22, 23, 24, 25]. The simplest equation relates to a one-time exposure:

$$r(a,e,D) = r_0(a) \cdot (1 + \Delta rr(a,e,D)) \quad (1)$$

where a is attained age, e is age at exposure, $r_0(a)$ is the spontaneous lung cancer mortality rate at age a, D is the cumulated absorbed dose to the lung, $r(a,e,D)$ the resulting lung cancer mortality rate at age a, and $\Delta rr(a,e,D)$ the excess relative rate.

Dose dependence

As the members of the cohort were continuously exposed, their excess lung cancer rate, $\Delta rr(a,e,D)$, at a specified age attained, need not simply depend on the cumulated absorbed dose, D, but on a suitable summation of doses received. In some of the earlier analyses, especially in those of underground miners exposed to radon progenies, the summation included weighting factors dependent on time since exposure. In the present analysis, a straight summation is employed which is subject merely to a time lag. This is in line with the previous study and reflects the fact that for the continued exposure from plutonium there are less temporal variations of exposure. With an assumed minimum latency period (*lag*), t_0, of 5 years, the dose, $D(a)$, at age a is accordingly set equal to the lung dose accumulated up to the age, $a-5$ years. It can be termed the *lagged accumulated dose* at age a.

The initial formulation of the relative risk model includes a linear-quadratic dependence in dose:

$$f(D(a)) = \alpha \cdot D(a) + \beta \cdot D(a)^2 \quad (2)$$

The computations are performed with separate linear-quadratic terms as in Eq. 2 for the α-rays and for the γ-rays:

$$\Delta rr(a,e,D) = f_{Pu}(D_{Pu}(a)) + f_\gamma\left(D_\gamma(a)\right) \quad (3)$$

Influence of smoking

Interaction between radiation and smoking can be described either by an additive or a multiplicative model [19]. The formulae are given in Eqs. 4 and 5. The variable s is categorical and takes the values 0 for non-smokers and 1 for smokers:

Additive model:

$$r(a,e,D) = r_0(a) \cdot \left(1 + \alpha_\gamma \cdot D_\gamma(a) + \alpha_{\mathrm{Pu}} \cdot D_{\mathrm{Pu}}(a) + \beta_\gamma \cdot D_\gamma(a)^2 + \beta_{\mathrm{Pu}} \cdot D_{\mathrm{Pu}}(a)^2 + \eta \cdot s\right) \quad (4)$$

Multiplicative model:

$$r(a,e,D) = r_0(a) \cdot \left(1 + \alpha_\gamma \cdot D_\gamma(a) + \alpha_{\mathrm{Pu}} \cdot D_{\mathrm{Pu}}(a) + \beta_\gamma \cdot D_\gamma(a)^2 + \beta_{\mathrm{Pu}} \cdot D_{\mathrm{Pu}}(a)^2\right) \cdot (1 + \eta \cdot s) \quad (5)$$

Exploratory computations to derive a specific model

For the analysis of increased lung cancer rates due to radiation, the quantification of the background rates is most important. Since national lung cancer mortality rates need not be an adequate choice, an internal estimate of the background lung cancer rate, $r_0(a)$, has been employed in the present analysis. Different analytical expressions and, in addition, non-parametric estimates have been explored. They resulted in essentially the same attribution to background and excess rates. A comparatively simple analytical expression with three free parameters was selected as the preferred choice for the spontaneous rate (time unit: year):

$$r_0(a) = k \cdot \exp\left(c_1 \cdot \ln(a/60) - c_2 \cdot (\ln(a/60))^2\right) \quad (6)$$

As stated a latency period, t_0, of 5 years has been assumed and the influence of smoking was included in the model either through an additive or a multiplicative dependence (see Eqs. 4 and 5). Utilization of the additive model resulted in a very poor fit, compared to the multiplicative model.

With regard to the γ-ray component, computations were initially performed with a linear-quadratic dose dependence (see Eq. 2). The best estimate included a negative quadratic coefficient, but the likelihood was not appreciably decreased when the coefficient was set equal to zero. A simple linear dose dependence was, therefore, chosen for the γ-ray component.

For the α-particle exposures, too, a linear-quadratic dose dependence as in Eq. 2 was tested. The best estimate was obtained with a positive quadratic coefficient, but a vanishing quadratic component provided very nearly the same quality of the fit. A purely quadratic dependence on α-ray dose resulted in a poor fit (see Table 2). Again, a simple linear dose dependence was chosen for the α-ray component. All computations were performed by regression with maximum likelihood methods [26, 27, 28].

In line with the above considerations the following model has been employed:

$$r(a,e,D) = r_0(a) \cdot \left(1 + \alpha_\gamma \cdot D_\gamma(a) + \alpha_{\mathrm{Pu}} \cdot D_{\mathrm{Pu}}(a)\right) \cdot (1 + \eta \cdot s) \quad (7)$$

Table 2 Log-likelihood (*LL*) values for models linear, linear-quadratic and purely quadratic with regard to internal α-particle exposures, male workers only (A likelihood ratio test was employed to discriminate between different models. A difference in the maximized log-likelihood statistics for two nested models, one additional parameter, of at least 1.92 indicates a significant improvement of the fit, e.g. a linear compared to a linear-quadratic model results in an increase of the log-likelihood of only 0.2, thus the quadratic component does not improve the quality of the fit)

Model	–LL
Linear	1322.7
Quadratic	1335.0
Linear-quadratic	1322.5

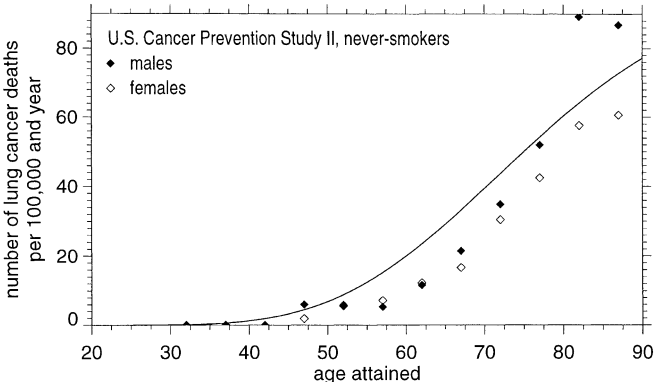

Fig. 3 Spontaneous lung cancer incidence, estimated from the data (*solid line*) and from US study (*diamonds*) among never-smokers (US Cancer Prevention Study II), for males and females

Numerical results

The inferred background lung cancer rate, $r_0(a)$, is shown in Fig. 3 (solid line). According to Eq. 7 this is the rate for non-smokers. It is compared to the cumulative lung cancer mortality for never-smokers in the US (diamonds) in Fig. 3, for males and females (US Cancer Prevention Study II) [19]. The comparison is, of course, subject to the uncertainty of the US data for never-smokers and also to the qualification that the non-smokers in the study cohort need not all be never-smokers. However, the general agreement with the US data is notable.

The model parameters (and 95% confidence limits) that are obtained for the chosen model Eq. 7, i.e. the numerical values of α_γ, α_{Pu} and η, are given in Table 3.

The numerical values for the three added parameters, k, c_1 and c_2, in the expression of Eq. 6 for the spontaneous lung cancer mortality, $r_0(a)$, are k=0.20×10^{-3} (±0.016×10^{-3})/year, c_1=5.07 (±0.47) and c_2=–4.29 (±2.11), the numbers in parentheses being standard errors.

For the γ-ray exposures the estimated excess relative risk is 0.058/Gy with large uncertainty. The estimate is statistically not significant, since the 95% confidence range includes the value zero.

For the α-ray exposure the estimated excess relative risk for lung cancer is 4.50/Gy (95%CI: 3.15–6.10). The estimated excess relative risk due to smoking is 15.3 (95%CI: 11.6–19.5).

Table 3 Excess relative risk and 95% confidence bounds for external γ-ray exposure, internal α-ray exposure and smoking, male workers only.

Exposure	Excess relative risk
α_γ/Gy	0.058 (–0.072, 0.20)
α_{Pu} /Gy	4.50 (3.15, 6.10)
η	15.3 (11.6, 19.5)

Table 4 Observed and calculated, from the model, numbers of lung cancer cases, male workers only

Criteria	No. of lung cancer cases
Observed	219
Spontaneous	12
γ-Excess + smoking	12
α-Excess + smoking	55
γ-Excess	1
α-Excess	4
Smoking	140

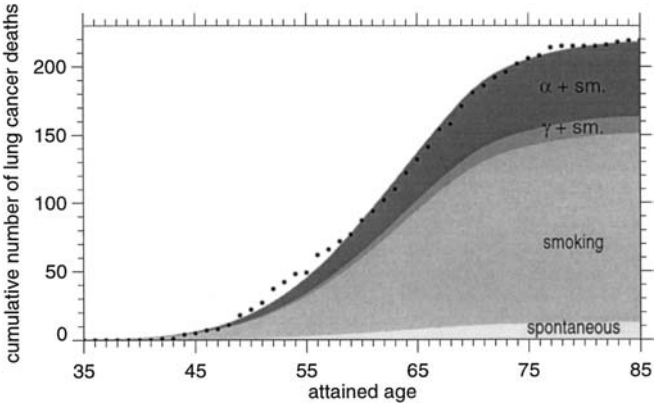

Fig. 4 Observed cumulative numbers of lung cancer cases among male workers, vs age attained (*dotted line*) and the numbers that correspond to the model with the best fit parameters for the entire cohort. These are broken up into the numbers assigned to background, to smoking alone (i.e. assuming that no radiation exposure had occurred), to γ-exposures and smoking, and to plutonium α-rays and smoking (*differently shaded areas*)

Table 4 gives the numbers of cases attributed to background, to γ-rays, to α-rays and to smoking based on the model calculations. Out of a total of 219 lung cancer cases, the model attributes 12 (5.5%) to background, 67 (30.5%) to the radiation exposure in combination with smoking, and 140 (64%) to smoking alone. Among the 67 lung cancers attributed to irradiation, 12 (5.5%) cases are ascribed to the γ-exposures and the interaction with smoking, while 55 (25%) are attributed to α-radiation from plutonium and smoking. If only radiation is considered as the risk factor, i.e. one assumes that the cohort comprises non-smokers, 4 cases are attributed to α-radiation and 1 case to the γ-exposures.

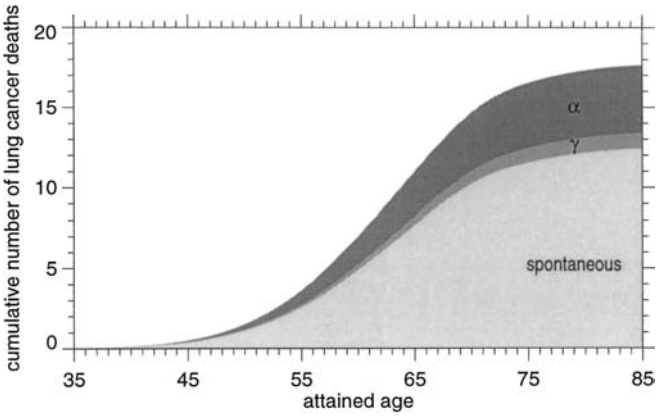

Fig. 5 Cumulative numbers of lung cancer cases that would have occurred according to the model calculations among the male workers, if there had been no smoking in the cohort. The numbers are broken up into the contributions assigned to background, to γ-exposures, and to plutonium α-rays (*differently shaded areas*)

To visualize the magnitude of the attributed effects, Fig. 4 shows the observed cumulative numbers of lung cancer cases, vs age attained (dotted line) and the numbers that correspond to the model calculations with the best fit parameters for the entire cohort. These are broken up into the numbers assigned to background, to smoking alone (i.e. assuming that no radiation exposure occurred), to γ-exposures and smoking, and to plutonium α-rays and smoking (differently shaded areas). Figure 5 gives the numbers that would have resulted according to the model calculations for radiation exposure alone (i.e. if all cohort members had been non-smokers). The spontaneous lung cancer mortality is, of course, the same as in Fig. 4.

Discussion

The present study shows, in line with earlier publications on Mayak nuclear workers, a marked dependence of the lung cancer mortality on the α-particle exposure due to incorporated plutonium. There is no suggestion of a departure from linearity or of a threshold.

The calculations have been performed in terms of a relative risk model with a multiplicative interaction between radiation and smoking. The spontaneous lung cancer mortality rate has not been taken from national statistics, but was estimated from the cohort itself. The model predicts 12 spontaneous lung cancer cases in the cohort, i.e. 0.62% out of a total of 1,921 deceased workers. This value corresponds well with an estimated percentage of 0.5–1.0% of lung cancer deaths among all causes of death for non-smokers in Western populations, see e.g. [30].

For the γ-ray component, the present analysis suggests a very low excess relative risk for lung cancer mortality of 0.058/Gy, with a 95% confidence range of –0.072/Gy to 0.20/Gy. For γ-rays the unit Gy can, of course, be replaced by Sv. The estimated excess is statistically insignificant since the value zero is included in the confidence range. A comparison to the value *ERR*=0.34/Sv, for males, from the follow-up of the A-bomb survivors shows that the present estimate is significantly lower. As noted earlier [31] there were a number of studies on cohorts exposed for medical reasons that suggest little or no excess relative risk for lung cancer after low or protracted photon doses.

For male workers, the excess relative risk per unit absorbed dose in the lungs due to the plutonium α-rays is, according to the present analysis, 4.50/Gy with a 95% confidence range of 3.15/Gy–6.10/Gy. With the radiation weighting factor of 20 for α-rays, this corresponds to an excess relative risk per unit organ equivalent dose of 0.23 (0.16, 0.31)/Sv. This value is substantially less than the estimate of 12.2/Gy, or 0.6/Sv, obtained in an earlier analysis [9]. While in the previous study 191 lung cancer cases were observed in the cohort, 219 cases are included in the present analysis. However, the majority of these additional cases has occurred among reactor workers without plutonium body burden. Consequently it increased the factor k in Eq. 6 rather than the dose coefficients, which leads to a reduction of the estimated excess relative risk with regard to plutonium α-rays. In this context it must be noted that a correlation between smoking and α-ray dose cannot be excluded since workers used to remove their breathing masks during work while they were smoking. Additional studies have to be performed to investigate these complexities.

The *ERR*=0.23/Sv per dose equivalent to the lung due to the plutonium α-rays is smaller than the value of 0.34/Sv that was derived from the lung cancer mortality of the male A-bomb survivors [32]. It is also smaller, although without 95% significance, than the value 0.48/Sv derived from the lung cancer incidence among the male A-bomb survivors [33].

The statistical uncertainty of the estimated excess relative risk for γ-rays permits—in terms of the internal analysis—only a very uncertain internal estimate of the low dose relative biological effectiveness (RBE) of the plutonium α-rays. Consequently there was no attempt here to employ such an estimate.

Additional computations have also been performed for an extended cohort which includes female workers. The findings are given in the Appendix. The results differ little from those for the male cohort alone.

The inferred relative risk of 16.3 (95%CI: 12.6–20.5) for smoking is somewhat larger than the value of about 12 which is usually assumed. It corresponds, according to Western experience, to the consumption of about two packs of cigarettes per day [34]. It needs to be noted that many of the Russian workers smoked strong cigarettes, usually without filters and in large quantities.

Both for α-rays and γ-rays the results of the analysis are consistent with linear dose dependence. The linear dose dependence for α-rays is in line with the results of several preceding studies [7, 8, 9]. This conflicts strongly with the findings of a case control study on Mayak

workers [29], which has also utilized smoking information and has provided a pure quadratic dependence on absorbed lung dose or on plutonium body burden, with a threshold at 0.8 Gy. To clarify this discrepancy a new analysis in terms of a case control study nested in the present cohort has been performed. Its results will be published separately.

Appendix

Tables 55, 6 and 7 present the results of the analysis of an extended cohort which comprises 4,212 male and 1,732 female workers with 238 observed lung cancer cases. The findings are consistent with the results given in the main section.

Table 5 Log-likelihood (*LL*) values for models linear, linear-quadratic and purely quadratic with regard to internal α-particle exposures, male and female workers

Model	–LL
Linear	1418.4
Quadratic	1436.1
Linear-quadratic	1418.3

Table 6 Excess relative risk and 95% confidence bounds for external γ-ray exposure, internal α-ray exposure and smoking, male and female workers

Exposure	Excess relative risk
α_γ/Gy	0.007 (-0.093, 0.12)
α_{Pu} /Gy	4.55 (3.32, 5.98)
η	17.2 (13.6, 21.2)

Table 7 Observed and calculated, from the model, numbers of lung cancer cases, male and female workers

Criteria	No. of lung cancer cases
Observed	238
Spontaneous	18
γ-Excess + smoking	2
α-Excess + smoking	63
Smoking	155

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